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The Synthesis of *trans*-Carbovir *via* the Ramberg-Bäcklund Reaction

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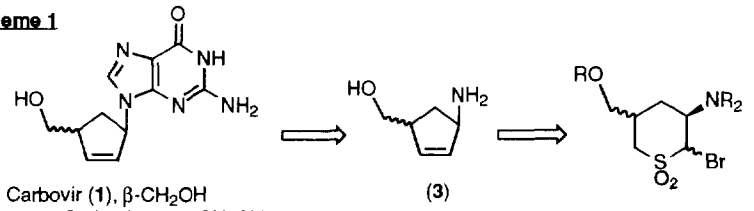
Abstract: A novel Ramberg-Bäcklund approach to the synthesis of 1-amino-4-substituted cyclopentenes is described and applied to prepare the *trans*-isomer of the carbocyclic nucleoside carbovir.

The fraudulent nucleoside carbovir (**1**) was prepared for the first time in 1988 and shown to have similar potency to AZT in inhibiting viral reverse transcriptase of the Human Immunodeficiency Virus (HIV).[1] Furthermore carbovir is less toxic and has a longer half life than AZT, which makes it an interesting target for the synthetic organic chemist.[2] We have been exploring the synthetic utility of the Ramberg-Bäcklund reaction for the preparation of cyclopentenes of biological interest.[3] We therefore investigated the approach to carbovir, and its *trans*-isomer (**2**), shown in retrosynthetic form in Scheme 1. This novel Ramberg-Bäcklund approach to the synthesis of 1-amino-4-substituted cyclopentenes (**3**) proved successful and has been employed to prepare *trans*-carbovir (**2**). To our knowledge this is the first reported synthesis of *trans*-carbovir, although other *trans*-nucleosides are known and have been shown to possess interesting biological activity.[4]

Scheme 1



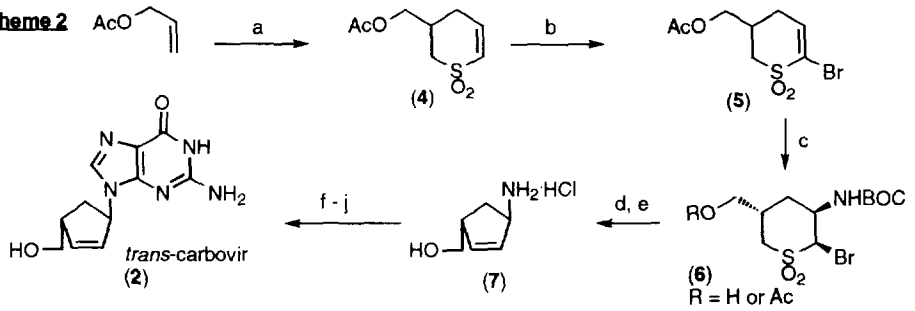
Carbovir (**1**), β-CH_2OH
trans- Carbovir (**2**), α-CH_2OH

(**3**)

The key Ramberg-Bäcklund precursor was prepared by the sequence outlined in Scheme 2. The 2,3-dehydro-thiane dioxide (**4**) was prepared in low yield[5] by a Diels-Alder reaction of allyl acetate and thioacrolein, which was generated *in situ* from diallyl sulfoxide as described by Block *et al.*,[5] followed by efficient oxidation using sodium perborate.[6,7] Addition of bromine and elimination of HBr gave the Michael acceptor (**5**).[8] Concentrated aqueous ammonia in 1,4-dioxane provided the best procedure for the introduction of nitrogen into the 3-position and, after carbamate formation, gave the single diastereoisomer (**6**). High field NMR and NOE studies indicated the stereochemistry shown with the NHBOC group axial. Ramberg-Bäcklund reaction under mild conditions[3] proceeded efficiently and deprotection gave cyclopentene (**7**). The *cis*-isomer of (**7**) is a key precursor to carbovir (**1**).[1a,2a,2b] In a similar manner (Scheme 2), (**7**) was transformed into *trans*-carbovir (**2**). The guanine unit was constructed using the Traube method.[9] Hydrochloride (**7**) was first reacted with 2-amino-4,6-dichloropyrimidine. Diazotisation with 4-chlorobenzene-diazonium chloride, reduction with zinc, ring closure and hydrolysis then provided *trans*-carbovir, which has been fully characterised[10] and the stereochemistry confirmed by NOE studies.

We are currently exploring the scope of this new procedure for the preparation of substituted aminocyclopentenes and modifying the sequence to allow *cis*-isomers to be prepared. The chemistry is also being employed to prepare novel carbocyclic nucleosides for biological screening.

Scheme 2



(a) (i) 0.2 eq. diallyl sufoxide, 104°C, neat. (ii) $NaBO_3$, AcOH. (b) (i) Br_2, CH_2Cl_2; (ii) Et_3N, 83 %.
(c) (i) aq. NH_3/1,4-dioxane, 3h; (ii) BOC_2O, 87 %. (d) 2.2 eq ^tBuOK, THF, -78°C, 77 %.
(e) HCl, MeOH, quant. (f) 2-Amino-4,6-dichloropyrimidine, Hünigs base, BuOH, Δ, 77 %.
(g) *p*-$ClPhN_2^+$ Cl^-, NaOAc, AcOH, 42 %. (h) Zn, AcOH, H_2O, 79 %. (i) $HC(OEt)_3$, HCl, 62 %.
(j) 0.33 *M* NaOH, Δ, quant.

Acknowledgement
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References and Notes

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4. Russ, P. L.; Hegedus, L.; Kelley, J. A.; Barchi, J. J., Jr; Marquez, V. E., *Nucleosides & Nucleotides*, 1992, **11**, 351.
5. Block, E.; Zhao, S. H., *Tetrahedron Lett.*, 1990, **31**, 5003. Compound (**4**) was obtained together with its regioisomer (removed by chromatography) in 10-15% combined yield based on diallyl sulfoxide over the 2 steps.
6. McKillop, A.; Tarbin, J. A., *Tetrahedron Lett.*, 1983, **24**, 1505.
7. All new compounds gave spectral and analytical/mass spectrometric data fully consistant with the proposed structures.
8. Michael addition of ammonia to α,β-unsaturated sulfones related to (**4**) required 5 days for the reaction to go to completion.
9. Traube, W., *Chem. Ber.*, 1900, **33**, 3035; Borthwick, A.D. and Biggadike, K., *Tetrahedron*, 1992, **48**, 571.
10. δ_H (500 MHz; CD_3OD) 7.61 (1H, s, 8-H), 6.23 (1H, dt [ddd], J 1.9, 1.9, 5.6 Hz, 2'-H), 5.93 (1H, dt [ddd], J 2.2, 2.2, 5.6, 3'-H), 5.52-5.56 (1H, m, 1'-H), 3.58 (1H, dd, J 6.3, 10.7, OCH_a), 3.55 (1H, dd, J 6.3, 10.7, OCH_b), 3.19-3.22 (1H, m, 4'-H), 2.30 (1H, ddd, J 5.3, 8.6, 13.9, 6'-H_a), 2.05 (1H, ddd, J 4.0, 8.6, 13.9, 6'-H_b); δ_C (500 MHz; CD_3OD) 159.5 (C-6), 155.2 (C-2), 152.7 (C-4), 140.5 (C-2'), 137.4 (C-8), 130.8 (C-3'), 117.9 (C-5), 66.0 (OCH_2), 61.0 (C-1'), 49.1 (C-4'), 36.0 (C-6'); (Found (FAB): *M* + *H*, 248.1148. $C_{11}H_{14}N_5O_2$ requires 248.1148), ν_{max} (KBr) 3349, 3126, 2931, 1691, 1608 cm^{-1}; m.p. 220°C (decomp.).

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