The Enantioselective Synthesis of an Important Intermediate to the Antiviral, (−)-Carbovir

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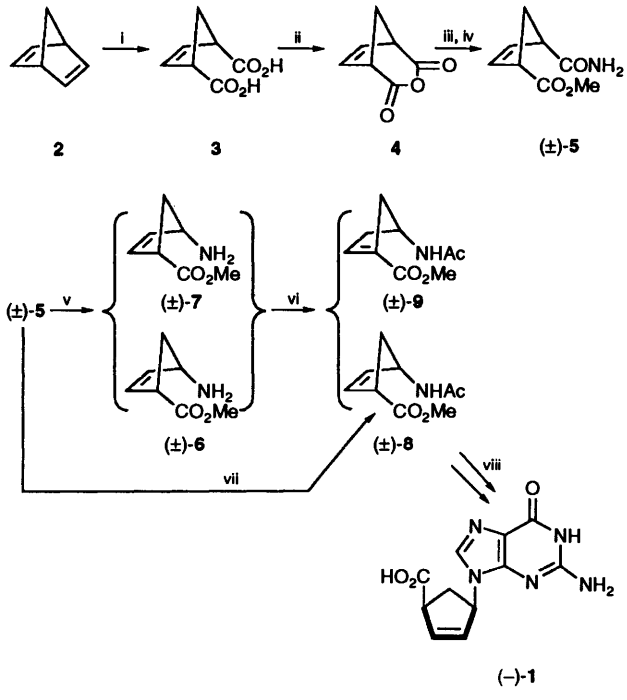
Two new routes to the important intermediate (−)-**8** for the carbocyclic-based nucleosides are reported. The intermediate (−)-**8** has also been synthesised in high enantiomeric excess *via* an enzymatic resolution of the racemic amide (+)-**8** or an enzymatic enantiotopic hydrolysis of the *meso* diester **12**.

Carbocyclic analogues of nucleosides, *e.g.* (−)-carbovir **1**, have been shown to be potent antiviral antibiotics, and (−)-carbovir is itself a potent inhibitor of HIV-1 *in vivo*.[1] There has been much interest in these compounds and many elegant syntheses of both racemic and homochiral **1** have appeared in the literature.[2] However, these routes were not amenable to large-scale production of **1** and its analogues, since they involved either unpleasant and possibly dangerous starting materials,[2a] expensive natural products as starting materials,[2b] or loss of product in side reactions. For the enantioselective synthesis of (−)-**1**, an enzymatic resolution was used which by its nature necessitates a loss of 50% of racemic material.[2d] We have investigated enantioselective routes to the key intermediate (−)-**8** which we hoped would address these areas. Here we report our enantioselective synthesis of (−)-**8** from either norbornadiene or cyclopentadiene which overcame some of the drawbacks of the earlier work.

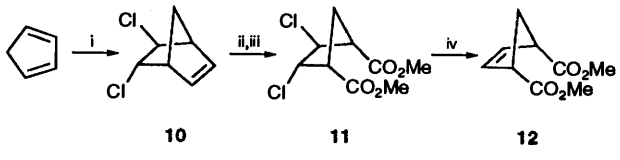
Careful ozonolysis of norbornadiene **2** followed by an oxidative work-up with silver oxide gave the *meso* diacid **3** in 40% yield (Scheme 1). The *meso* diacid **3** was converted into the amido ester **5** as shown in Scheme 1. Hofmann rearrangement of **5** with alkaline sodium hypochlorite (pH 13), followed by acetylation of the crude product mixture to assist recovery, gave a 13:1 ratio of the expected product (±)-**8** and the conjugated ester **9** in a combined overall yield of 55%. Using lead tetraacetate for the Hofmann rearrangement, the acetamido ester (±)-**8** was obtained directly in 84% yield; none of the conjugated ester **9** was detected under these conditions.

Alternatively, the addition of *trans*-dichloroethylene to cyclopentadiene at 200 °C and 16 bar, gave after 24 h, the adduct **10** in moderate yield (50%).[3] The double bond of **10** was cleanly cleaved with alkaline potassium permanganate to give after esterification the dichloro ester **11** in 70% yield. Similar yields were obtained using sodium periodate and catalytic ruthenium tetraoxide as oxidant. Treatment of **11** with zinc and copper [3:1 w/w ratio of Zn:**11**] in acetic acid at reflux gave the *meso* diester **12** in 98% yield (Scheme 2).

The enantioselective synthesis was carried out using two different methods (Scheme 3). Initially a straightforward resolution of the racemic acetamido ester (±)-**8** using naproxen esterase† gave the acetamido ester (−)-**8** (as the enantiomer shown) in 40% yield and an e.e. of 94% after a 7 h incubation.‡ The reaction was carried out at an esterase concentration of 5 g dm^{-3} and a substrate concentration of 100 g dm^{-3} in an aqueous buffer. However, after 7 h the activity of the enzyme decreased to approximately 15% of its original activity. The reasons for this decrease are not clear. The alternative and superior route to enantiomerically pure (−)-**8** would be *via* an enantiotopic hydrolysis of the *meso* diester **12** or an enantiotopic esterification of the *meso* diacid **3** to the enantiomerically pure monoester (−)-**14**. A range of esterases and lipases were screened initially for the enantiotopic hydrolysis of **12** and again naproxen esterase was found to be the best. The enzyme,

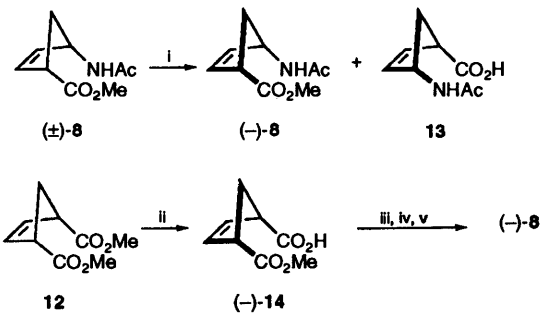


Scheme 1 *Reaction conditions and reagents:* i, O_3, −78 °C, 5 h, AgO; ii, DCC, CH_2Cl_2 40% from **2**; iii, NH_3; iv, $SOCl_2$, Na_2CO_3, MeOH, 70–80% overall from **4**; v, NaOCl, NaOH, pH 13; vi, Ac_2O, pyridine, 55% from (±)-**5**; vii, $Pb(OAc)_4$, AcOH, 1 h, reflux, (±)-**8** only 84%; viii, see ref. 2



Scheme 2 *Reaction conditions and reagents:* i, *trans*-1,2-dichloroethylene, 200 °C, 16 bar, 24 h, 40–50%; ii, alkaline, $KMnO_4$, 20 °C, 24 h; iii, MeOH, HCl, 2 h, reflux, 70% from **10**; iv, Zn–Cu, Et_2O, AcOH, 18 h, reflux, 98%

† This enzyme was kindly donated to us by Gist Brocades.
‡ The enantiomeric excess of (−)-**8** was determined by GC using a Chiralsil-valine column (50 m) and comparison with racemic (±)-**8**.



Scheme 3 *Reaction conditions and reagents:* i, naproxen esterase, 5 g dm^{-3}, 100 g dm^{-3} of (±)-**8**, 7 h, 40%, 94% e.e.; ii, naproxen esterase, 1 g dm^{-3}, 81.5 g dm^{-3} of **12**, 55%, 76% e.e.; iii, $SOCl_2$, NH_3; iv, as in Scheme 1, step vii, 75% overall from **14**; v, recrystallised twice from diethyl ether–hexane, > 95% e.e., 64% recovery

at a concentration of 1 g dm^{-3} and a substrate **12** concentration of 81.5 g dm^{-3}, gave the monoester (–)-**14** in 55% chemical yield and 76% e.e.* A time course experiment suggested that the actual yield of (–)-**14** was 70% after 2.5 h but the monoester was being further hydrolysed to the diacid **3**. The product from this hydrolysis was then converted into enantiomerically enriched amide (–)-**8** (76% e.e.) using the lead tetraacetate route (Scheme 3). It appears that racemic (±)-**8** exists as a conglomerate of (+)- and (–)-crystals, and thus may be amenable to a 'spontaneous' resolution by seeding, thus avoiding the use of enzymes. In this case recrystallisation of the enantiomerically enriched (±)-**8** from diethyl ether–hexane gave enantiomerically pure (–)-**8** after two crystallisations (64% recovery), which could be converted into (–)-carbovir **1**.[1,2a,2d]

Experimental†

meso-*Cyclopent*-4-*ene*-1,3-*dicarboxylic Acid* **3**.—A stirred solution of norbornadiene (9.2 g, 0.1 mol) in methanol (120 cm^3) was cooled to –75 °C. Ozone was passed through the cooled solution until 90–95% of the theoretical had been used (5 h reaction time). The residual ozone was purged from the reaction mixture, after which the latter was diluted with water (100 cm^3) and heated at 60 °C for 5 min. The solution was evaporated until its volume was approximately 40–50 cm^3, when any precipitated material was redissolved with a small amount of acetone. The resultant concentrate was cooled in ice and added over 10 min to freshly prepared silver oxide [from silver nitrate (60 g) and sodium hydroxide (14.2 g) and washed until neutral] in water (200 cm^3) at 0–5 °C. Aqueous sodium hydroxide solution (2 mol dm^{-3}) was added dropwise to the solution until it reached pH 10. It was then stirred for 10 min and filtered. The filtrate was carefully acidified with nitric acid to pH 1 and the resultant mixture was continuously extracted with ether for 16 h. The ether extracts were dried and evaporated to give the *meso* diacid **3** (6.2 g, 40%).

Hofmann Rearrangement of (–)-**5** (76% e.e.).—A solution of (–)-**5** (5.07 g, 0.03 mol, 76% e.e.) and lead tetraacetate (20 g, 0.045 mol) in glacial acetic acid (100 cm^3) was heated under gentle reflux for 90 min. The dark reaction mixture was evaporated under reduced pressure and the residue was diluted with water (100 cm^3) and dichloromethane (100 cm^3). The resultant mixture was stirred and carefully neutralised by addition to it of solid sodium hydrogen carbonate. Insoluble material was filtered off and washed with dichloromethane (2 × 20 cm^3). The combined filtrate and washings were dried and evaporated under reduced pressure to yield crude (–)-**8** (76% e.e.). The crude product was recrystallised from diethyl ether to give (–)-**8** (4.61 g, 84%, 76% e.e.) as a pale yellow solid.

General Method for Naproxen Esterase.—In a typical run the enzyme concentration was 1 g dm^{-3} and the initial concentration of the *meso* diester **12** was 81.5 g dm^{-3}. The transformation was performed at 37 °C in an incubator with Tris HCl buffer at pH 7.5. The pH was maintained at 7.5 during the course of the reaction by automatic titration of NaOH (0.2 mol dm^{-3}). After 4 h, or when the conversion was complete, the mixture was acidified to pH 1–2 with 2 mol dm^{-3} sulfuric acid or hydrochloric acid and the monoester (–)-**14** (76% e.e.) extracted with dichloromethane or ethyl acetate. The extracts were dried and evaporated under reduced pressure to give the monoester (–)-**14** (50–55% and 76% e.e.).

* The enantiomeric excess for (–)-**14** was determined by derivatisation with (*R*)-1-phenylethylamine and analysis of the diastereoisomers by GC.

† All compounds were either characterised by comparison to authentic samples or by spectroscopic analysis.

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Paper 4/02984D
Received 19*th May* 1994
Accepted 19*th May* 1994