Asymmetric Synthesis of Structural Analogues of (+)-Clusianone via Enantioselective ACC Alkylation

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ABSTRACT

The asymmetric total synthesis of four structural analogues of (+)-clusianone from a common advanced intermediate is described. Asymmetric induction is achieved through the use of enantioselective ACC alkylation, providing the common advanced intermediate with an *er* of 99:1.

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Viral infections are a common and problematic form of disease. As with antibiotics,¹ current antiviral therapies are becoming less effective due to the development of resistant strains.² Consequently, there is an urgent need for new anti-viral agents. (+)-Clusianone (**1**) (Figure 1) is a member of a large class of biologically active natural products termed polycyclic polyprenylated acylphloroglucinols (PPAPs).³ (+)-Clusianone has been shown to possess antiviral activity against both HIV ($EC_{50} = 0.020 \pm 0.003 \mu\text{M}$),⁴ and Epstein-Barr virus ($17.4 \pm 1.2\%$ of cells were EBV-EA positive in the presence of 32 nmol of **1**).⁵ We recently completed the first asymmetric total synthesis of (+)-clusianone⁶ using an enantioselective ketone α -alkylation method that we have been developing in our laboratory.⁷ Subsequently, this route was used in the preparation of (–)-clusianone as well.^{8–10} The synthetic route that we developed to access (+)- and (–)-clusianone was designed to be amenable to the synthesis of a diverse array of structural analogues, for eventual testing as anti-viral agents.¹¹ Herein we describe the initial realization of this objective through the asymmetric total synthesis of four analogues of (+)-clusianone.

For our initial studies on analogue preparation, we choose to focus on two diversity points, namely the C-1 bridgehead position, and the C-3 position. Doing so would allow us to rapidly generate analogues from the common advanced intermediate **8** (Scheme 1), which we had previously⁶ established could be readily prepared with an *er* of 99:1, via enantioselective ACC ketone α -alkylation.⁷ We anticipated that **8** would undergo bridgehead alkylation^{9a,c} with various alkyl halides to give **7**, and

Figure 1. (+)-Clusianone (**1**) and structural analogues **2–5**.

this could then be treated with different acid chlorides to give the desired analogues (**6**).

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Scheme 1. General approach to C-1 and C-3 analogues from common advanced intermediate **8**.

The route that we had developed previously⁶ for the preparation of **8** had served us well in generating both (+)- and (–)-clusianone on a milligram test scale. However, in the context of the present proposed analogue studies we would need access to gram quantities of **8**, and in this regard our route was untested. Thus, we began our work by repeating our prior synthesis of **8**, but doing so on a scale that would eventually lead us gram quantities. The route began with the prenylation of 1,3-cyclohexadione (**9**) to give **10** (Scheme 2).¹² Conversion of **10** to β -chloro enone **11** was achieved using oxalyl chloride, and was followed by reduction to give enone **12**. With **12** in hand, we were positioned to conduct the enantioselective ACC alkylation sequence. During the course of earlier investigations on our ACC monoalkylation method¹³ we found that for ketones possessing at least two substituents at the α' -position, ACC auxiliary **13** gave extremely high (>98:2) levels of asymmetric induction and excellent yields. Thus, auxiliary **13** was chosen for use here and was condensed with enone **12** to generate hydrazone **14** as a single diastereomer in 95% yield. Hydrazone **14** was

Scheme 2. Synthesis of **16** via enantioselective ACC alkylation.

then alkylated in excellent yield by treatment with LDA followed by prenyl bromide. Removal of the auxiliary using *p*-TsOH·H₂O in acetone/H₂O produced intermediate **16** with excellent enantioselectivity (*er* = 99:1).¹⁴

Scheme 3. Synthesis of key intermediate **8**.

Conversion of ketone **16** to the key advanced intermediate **8** began with a methylation, carbonyl transposition sequence. This was achieved by treatment of **16** with MeMgBr to form tertiary allylic alcohol **17** as a mixture of diastereomers (Scheme 3). These were used without separation in the Babler-Dauben oxidation^{15,16} to produce enone **18**. This was then subjected to conjugate addition by the cuprate obtained from MeMgBr and CuBr·SMe₂ to establish the geminal dimethyl group, producing ketone **19**. Methyl enol ethers **20** and **21** were generated from **19** upon treatment with *t*-BuOK and Me₂SO₄, setting the stage for an Effenberger cyclization.¹⁷ Careful acid/base extraction was required following this transformation to separate the desired product (**22**) from **19**, and the latter was recycled to produce more of **20** and **21**. Methylation of crude cyclized product **22** gave **8** in 30% yield over the two steps (71% based on recovered **19**). Gratifyingly, we were able to prepare approximately 2 grams of **8** using the above route, confirming its ability to support analogue studies. We anticipate the further direct scale up will also be possible.

Having accessed advanced intermediate **8**, we were at a divergence point with regard to the synthesis of the four desired analogues (**2–5**) of (+)-clusianone. Continuation of the synthesis of each of these compounds began with the bridgehead allylation of **8**, which was achieved by treatment with LDA, followed by allyl bromide. The desired product (**23**) was obtained in excellent yield from this reaction. In an analogous fashion, methylated compound **24** was also obtained in excellent yield.

Scheme 4. Bridgehead alkylation of **8**.

Next, both **23** and **24** were individually subjected to treatment with both benzoyl chloride and 2,2-dimethylpropanoyl chloride, and the products of those reactions were then hydrolyzed using LiOH to give the desired analogues **2–4** (Scheme 5). Gratifyingly, in each case the desired compounds were obtained in very good yield over the two step process.

Scheme 5. Acylation of **23** and **24**.

In conclusion, we have developed an effective gram scale asymmetric synthetic strategy to advanced intermediate **8**, which, in principle, is amenable to the synthesis of a diverse array of structural analogues of clusianone. As an initial demonstration of this, we have prepared compounds **2–5**. A key transformation of this synthetic sequence is a highly enantioselective ($er = 99:1$) ketone α -alkylation sequence that is achieved using our enantioselective ACC α -alkylation method. Biological

evaluation of compounds **2–5** is underway and will be reported in due course.

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Supplementary data associated with this article can be found, in the online version, at X.

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Graphical Abstract

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