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Asymmetric total synthesis of (+)- and (−)-clusianone and (+)- and (−)-clusianone methyl enol ether via ACC alkylation and evaluation of their anti-HIV activity

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ABSTRACT

The total asymmetric synthesis of (+)- and (−)-clusianone and (+)- and (−)-clusianone methyl enol ether is reported. Asymmetric induction is achieved through the use of ACC alkylation, providing the key intermediates with an er of 99:1. The four synthetic compounds were evaluated for their anti-HIV activity. Both (+)- and (−)-clusianone displayed significant anti-HIV activity.

Viral infections are a pervasive form of disease that range from the common cold to much more deadly forms such as AIDS. 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 antiviral agents. (+)-Clusianone (**1**) (Fig. 1) is a member of a large class of biologically active natural products termed the polycyclic polyprenylated acylphloroglucinols (PPAPs).[3] (+)-Clusianone has been shown to possess antiviral activity against both HIV ($EC_{50} = 0.020 \pm 0.003$ μM),[4] and Epstein–Barr virus (17.4 ± 1.2% of cells were EBV-EA positive in the presence of 32 nmol of 1).[5] As such, it is a compelling target for further biological investigation as an antiviral agent. Unfortunately, no asymmetric total synthesis is available, as is necessary for further biological testing and medicinal chemistry efforts.

Not only do PPAPs generally exhibit biological activity, but they also possess intriguing structures.[3] Consequently, they have attracted considerable interest from the synthetic community. Despite the impressive advances culminating from the synthetic work carried out to date on the PPAPs, asymmetric total syntheses are rare.[6] In the case of clusianone, total syntheses have been reported by Danishefsky,[7] Simpkins,[8] Porco,[9] and Marazano.[10] However, only one synthesis of optically active (+)-clusianone has been reported,[6b] and this was achieved via chiral resolution of a late-stage synthetic intermediate.

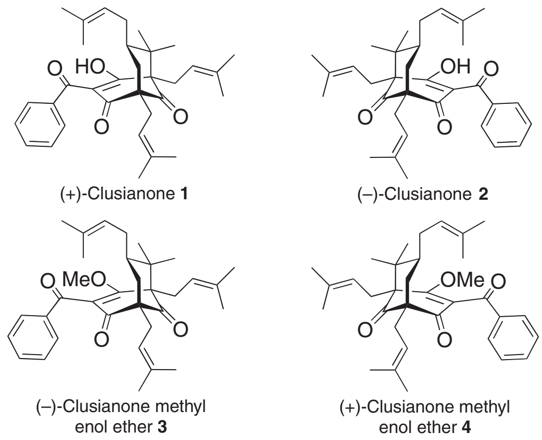
(+)-Clusianone **1**
(−)-Clusianone **2**
(−)-Clusianone methyl enol ether **3**
(+)-Clusianone methyl enol ether **4**

Figure 1. The clusianones and their methyl enol ethers.

We recently described a new method for the asymmetric α-alkylation of ketones utilizing chiral *N*-amino cyclic carbamate (ACC) auxiliaries (cf. **9** and **10**, Scheme 1).[11] ACC auxiliaries react readily with ketones to afford the corresponding hydrazones (**5**→**6**). These undergo rapid deprotonation to the azaenolates, which can be alkylated on up to a multi-gram scale with excellent

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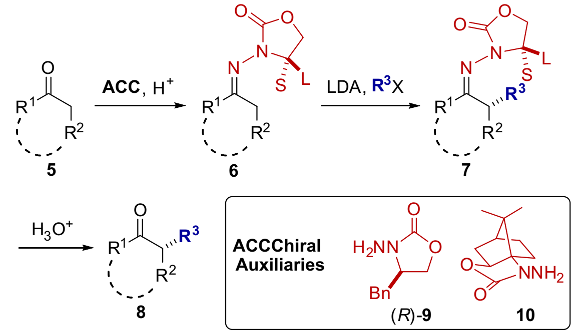
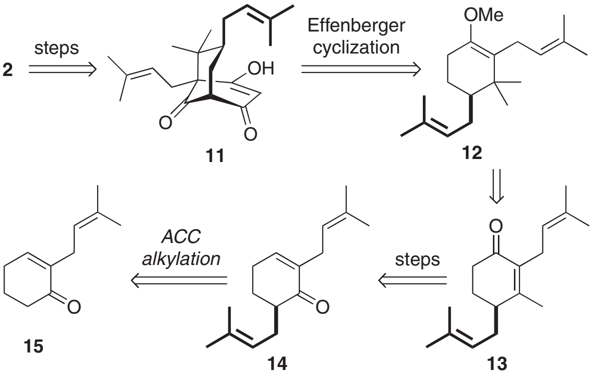


Scheme 1. Asymmetric ACC α-alkylation of ketones.

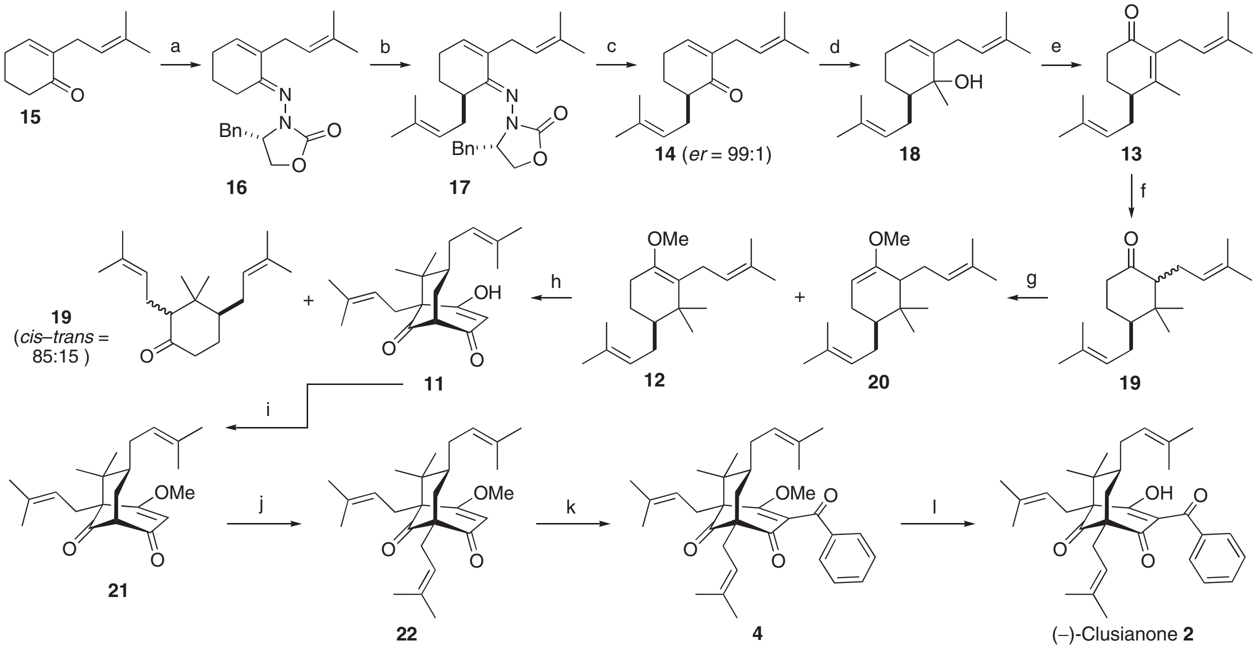


Scheme 2. Retrosynthetic analysis of 2.

stereoselectivity and yield (**6**→**7**). Moreover, the auxiliaries can be recovered quantitatively and recycled. We realized that this enantio-selective alkylation method could provide the basis for an efficient asymmetric total synthesis of the clusianones. In an earlier communication,[12] we described the first asymmetric total synthesis of (+)-clusianone (**1**) and its methyl enol ether (**3**). In what follows we describe the extension of this synthetic strategy to the first asymmetric total synthesis of (−)-clusianone (**2**) and its methyl enol ether (**4**). Whereas some PPAPs have been isolated in both their (+)- and (−)- forms, clusianone has not, so this constitutes the first report of (−)-clusianone. We also report our initial biological investigation of compounds **1–4** with regard to their anti-HIV activity. To our knowledge, this is the first instance in which the two enantiomers of a PPAP have been tested in the same biological assay.

Our general retrosynthetic plan is summarized in Scheme 2 by reference to (−)-clusianone (**2**), and is analogous to that used previously by us for the synthesis of (+)-clusianone (**1**).[12] We would engage optically pure enol ether **12** in a diastereoselective Effenberger cyclization[13] to generate the advanced bicylic intermediate **11**, as done by Simpkins in his synthesis of racemic clusianone.[8a] This would be elaborated to optically pure **2** using established procedures.[8a] Conjugate addition and enol ether formation would provide access to **12** from **13**. The preparation of **13** would be effected by 1,2-methylation of α,β-unsaturated ketone **14**, followed by a Babler–Dauben[14] oxidation of the resulting tertiary allylic alcohol. Synthesis of the key optically pure intermediate **14** would be achieved via enantioselective ACC alkylation,[11] beginning from known enone **15**.

We began our studies by preparing enone **15** using a combination of literature procedures,[10,15,16] which was then subjected to enantioselective ACC alkylation. To begin this process, compound **15** was converted to hydrazone **16** by acid mediated condensation with ACC auxiliary (*S*)-**9**.[17] Once formed, **16** was subjected to LDA-mediated prenylation, giving **17** in excellent yield, and as a single diastereomer, as judged by ^{1}H and ^{13}C NMR analysis. Auxiliary removal from prenylated hydrazone **17** was achieved hydrolytically by treatment with *p*-TsOH·H_2O in acetone/H_2O, producing the key synthetic intermediate **14** in 80% yield. Analysis of synthetic **14** by chiral HPLC revealed an enantiomer ratio of 99:1 indicating that minimal, if any, epimerization occurred during removal of the ACC auxiliary.



Scheme 3. Synthesis of (−)-clusianone (**2**). Reagents and condition: (a) (*S*)-**9**, *p*-TsOH·H_2O, CH_2Cl_2, reflux, 95%; (b) LDA, THF, −78 °C, then prenyl bromide, to 0 °C, 90%; (c) *p*-TsOH·H_2O, acetone, H_2O, 80%; (d) MeMgBr, Et_2O, −78 °C to rt, 88%; (e) PCC, 3 Å MS, CH_2Cl_2, 67%; (f) MeMgBr, CuBr·SMe_2, TMSCl, HMPA, then 10% HCl, 88%; (g) *t*-BuOK, DMSO, then Me_2SO_4, 63%; (h) malonyl dichloride, Et_2O, −20 °C, then KOH, $BnEt_3NCl$, H_2O, 35%; (i) $(MeO)_3CH$, *p*-TsOH·H_2O, MeOH, 50 °C, 60%; (j) LDA, THF, −78 °C, then prenyl bromide, 90%; (k) LTMP, THF, −78 °C, then BzCl, 65%; (l) LiOH, dioxane, H_2O, 90 °C, 79%.