

Asymmetric Synthesis of (+)-Citrinin using an *ortho*-Toluate Carbanion generated by a Chiral Base

Andrew C. Regan and James Staunton*

University Chemical Laboratory, Lensfield Road, Cambridge CB2 1EW, U.K.

The carbanion (**3**), generated using the chiral lithium amide base (**1**), undergoes enantioselective addition to acetaldehyde and acetone with a high degree of asymmetric induction at the nucleophilic centre; the reaction with acetaldehyde is exploited in an enantioselective synthesis of (+)-citrinin.

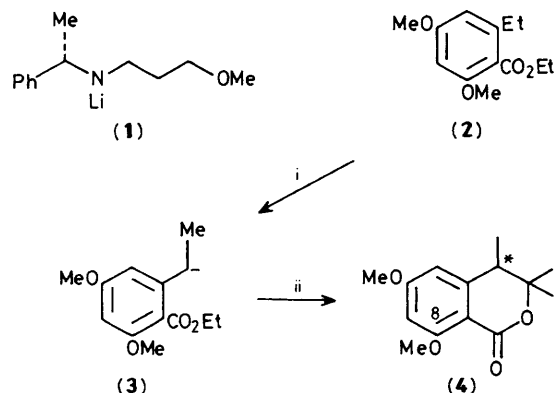
We have previously reported that the indicated enantiomer of the chiral lithium amide (**1**) can be used to generate an *ortho*-toluate carbanion, which then adds to acetaldehyde to give the polyketide isocoumarin derivative mellein methyl ether in 53% enantiomeric excess (e.e.).¹ In that reaction, the new asymmetric centre is formed at the electrophilic carbon atom of the aldehyde. We now report an extension of the work to reactions in which a new chiral centre is created at the nucleophilic centre of an *ortho*-toluate type carbanion. One of the reactions was used in an asymmetric synthesis of (+)-citrinin.

In a model study, the toluate ester (**2**)² was treated with the chiral lithium amide (**1**) in tetrahydrofuran (THF) at -78°C , and the resulting orange anion was quenched with an excess of the acetone after 30 min, to give the lactone (**4**)[†] in 51% yield

(Scheme 1). In the ^1H n.m.r. spectrum (100 MHz) obtained in the presence of the chiral shift reagent $\text{Eu}(\text{tfc})_3$ [$\text{tfc} = 3\text{-trifluoromethylhydroxymethylene-(-)-camphorato}$] there was excellent baseline separation of the two signals due to the 8-methoxy group; from their relative integrals it was apparent that (**4**) was produced in 72% e.e. A control n.m.r. experiment was carried out using racemic (**4**), prepared using lithium di-isopropylamide (LDA) in place of (**1**).

Encouraged by this reaction, in which there was a substantially higher degree of asymmetric induction than had been obtained in the synthesis of mellein methyl ether, we embarked upon an enantioselective synthesis of the polyketide antibiotic citrinin (**10**). In a synthesis of racemic citrinin recently reported from this laboratory,³ the anion (**3**), generated using LDA as base, was acetylated with acetyl chloride, and the resulting ketoester was reduced diastereoselectively to give the *threo*-lactone (**6**) as a key intermediate. In the equivalent sequence of reactions, using the chiral amide (**1**) in place of LDA, the lactone (**6**)

[†] For all new compounds, ^1H n.m.r., i.r., and mass spectra, as well as microanalysis and/or mass measurement were consistent with the assigned structures.



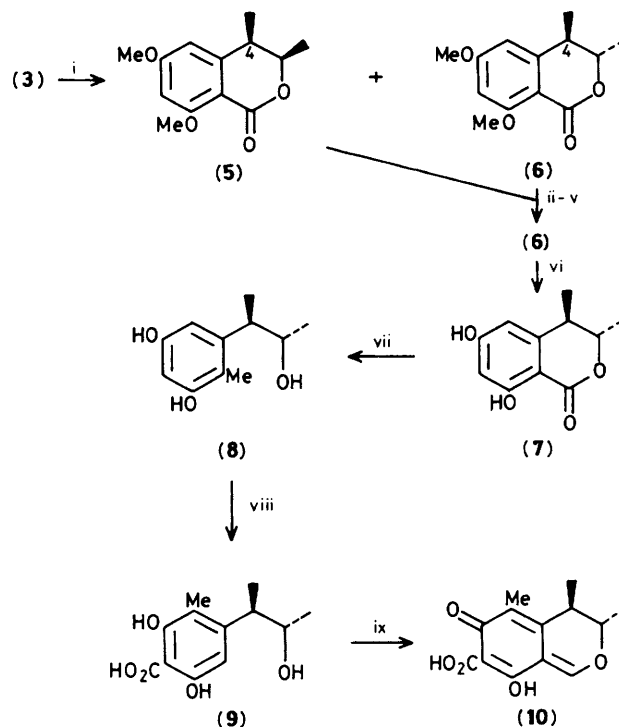
Scheme 1. Reagents: i, (1), THF, -78°C ; ii, Me_2CO .

was similarly produced, but with a negligible degree of asymmetric induction, as judged by the relative intensities of the 8-methoxy resonances in an n.m.r. spectrum (100 MHz), obtained in the presence of the chiral shift reagent $\text{Eu}(\text{hfc})_3$ [hfc = 3-heptafluoropropylhydroxymethylene-(-)-camphorato].

We therefore resorted to a modified strategy for the enantioselective synthesis (Scheme 2), in which the anion (3) generated, as above, with the chiral amide base (1), was treated with an excess of acetaldehyde at -110°C to give a mixture of the diastereoisomeric lactones (5) and (6) (51% total yield). Although the ratio of diastereoisomers (3:1) was unfavourable for direct use in the planned citrinin synthesis, both (5) and (6) were produced with a useful degree of enantioselectivity (70 and 74% e.e. respectively), as judged by the intensities of the 8-methoxy signals in an n.m.r. spectrum (100 MHz), obtained in the presence of $\text{Eu}(\text{hfc})_3$. Consequently, the mixture of lactones was stereoselectively converted into the desired *threo*-lactone (6) by a three-step sequence. First, the lactone mixture was hydrolysed to give the corresponding alcohols. These were then freeze-dried, prior to oxidation with pyridinium dichromate in dimethylformamide. Stereoselective reduction of the resulting ketone, with sodium borohydride in methanol, gave (6) in 59% overall yield. Its e.e. as measured by the n.m.r. spectrum was 70%, which proves that negligible racemisation has occurred in the sequence, and also that the major enantiomers of the lactones (5) and (6) produced above have the same absolute configuration at C-4.

The optically active lactone (6) was then demethylated with boron tribromide in dichloromethane to give the dihydroxy-lactone (7), which was reduced with sodium bis(2-methoxyethoxy)aluminium hydride in refluxing xylene to give (+)-'Phenol A' (8)⁴ in 59% yield. As expected on the basis of the known differential solubilities of the (-)-enantiomer and racemate of (8) in chloroform,⁵ a single recrystallisation from chloroform afforded (8), $[\alpha]_{546}^{22} +43.3^{\circ}$ (*c* 0.998 in EtOH), which was judged to be 97% optically pure, based on comparison with the optical rotation, $[\alpha]_{546}^{24} -44.6^{\circ}$ (*c* 1.005 in EtOH), measured for (-)-'Phenol A' obtained by degradation of natural citrinin.⁶

The almost enantiomerically pure (8) was then converted into (+)-citrinin (10)⁴ using known chemistry: carboxylation⁷ gave the acid (9) in 45% yield, which was then treated with neat triethylorthoformate⁸ to give (+)-citrinin (10) in 48% yield after recrystallisation. The (+)-citrinin, $[\alpha]_{546}^{22} +45.8^{\circ}$



Scheme 2. Reagents: i, MeCHO ; ii, $\text{LiOH}(\text{aq.})$; iii, freeze dry; iv, pyridinium dichromate, dimethylformamide; v, NaBH_4 , MeOH ; vi, BBr_3 , CH_2Cl_2 ; vii, $(\text{MeOCH}_2\text{CH}_2)_2\text{AlH}_2\text{Na}$, xylene, reflux; viii, CO_2 , KHCO_3 , glycerol, 150°C ; ix, $(\text{EtO})_3\text{CH}$.

(*c* 0.435 in EtOH), was optically pure and showed identical spectral characteristics (^1H n.m.r., i.r., u.v., and mass) to natural (-)-citrinin, $[\alpha]_{546}^{22} -46.0^{\circ}$ (*c* 0.432 in EtOH). Hence we have synthesised the unnatural enantiomer of citrinin, but an advantage of our strategy is that both enantiomers of the chiral amine (1) are readily available, so that both enantiomers of the natural product are equally accessible.

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