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

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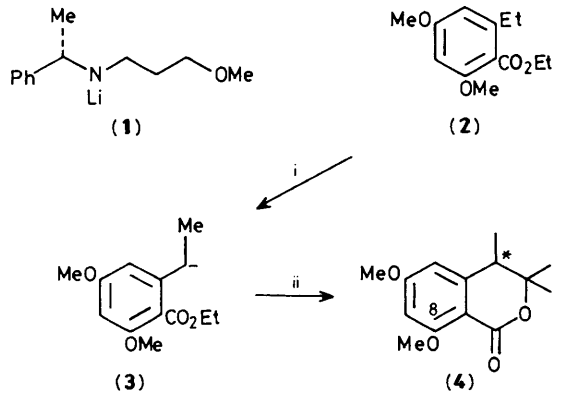
The carbanion (**3**), generated using the chiral lithium amide base (**1**), undergoes enantioselective addition to acetaldehyde and acetone with a high degree of asymmetric induction at the nucleophilic centre; the reaction with acetaldehyde is exploited in an enantioselective synthesis of (+)-citrinin (**10**).

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.

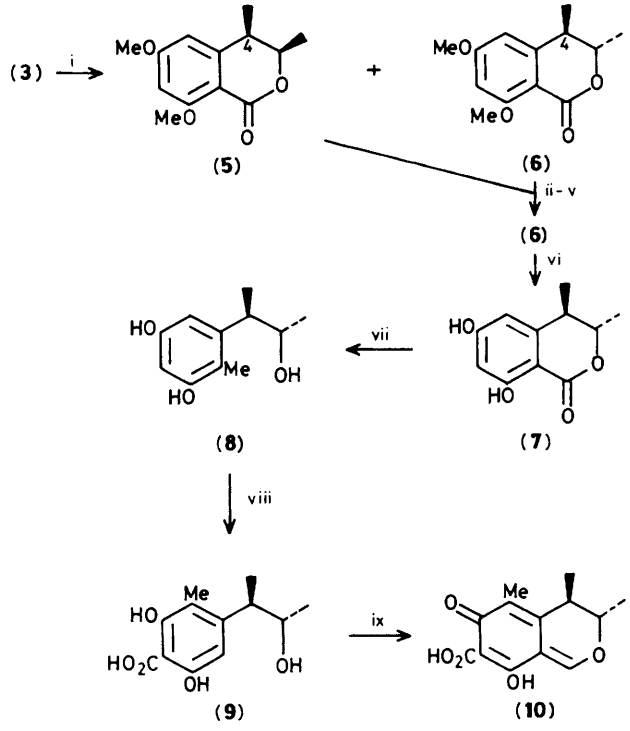
In a model study, the toluate ester (**2**)[2] was treated with the chiral lithium amide (**1**) in tetrahydrofuran (THF) at −78 °C, and the resulting orange anion was quenched with an excess of the acetone after 30 min, to give the lactone (**4**)† in 51% yield (Scheme 1). In the ^{1}H n.m.r. spectrum (100 MHz) obtained in the presence of the chiral shift reagent Eu(tfc)$_3$ [tfc = 3-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, ^{1}H 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.



Scheme 2. *Reagents:* i, MeCHO; ii, LiOH(aq.); iii, freeze dry; iv, pyridinium dichromate, dimethylformamide; v, $NaBH_4$, MeOH; vi, BBr_3, CH_2Cl_2; vii, $(MeOCH_2CH_2)_2AlH_2Na$, xylene, reflux; viii, CO_2, $KHCO_3$, glycerol, 150 °C; ix, $(EtO)_3CH$.

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 Eu(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 Eu(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 dihydroxylactone (**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° (*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° (*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: carboxylation[7] gave the acid (**9**) in 45% yield, which was then treated with neat triethylorthoformate[8] to give (+)-citrinin (**10**) in 48% yield after recrystallisation. The (+)-citrinin, $[\alpha]_{546}^{22}$ +45.8° (*c* 0.435 in EtOH), was optically pure and showed identical spectral characteristics (^{1}H n.m.r., i.r., u.v., and mass) to natural (−)-citrinin, $[\alpha]_{546}^{22}$ −46.0° (*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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References

1 A. C. Regan and J. Staunton, *J. Chem. Soc., Chem. Commun.*, 1983, 764.
2 T. A. Carpenter, G. E. Evans, F. J. Leeper, J. Staunton, and M. R. Wilkinson, *J. Chem. Soc., Perkin Trans. 1*, 1984, 1043.
3 J. A. Barber, J. Staunton, and M. R. Wilkinson, *J. Chem. Soc., Perkin Trans. 1*, 1986, in the press.
4 D. H. Johnson, A. Robertson, and W. B. Whalley, *J. Chem. Soc.*, 1950, 2971.
5 A. C. Hetherington and H. Raistrick, *Proc. Roy. Soc. (London) B*, 1931, **220**, 269.
6 J. P. Brown, N. J. Cartwright, A. Robertson, and W. B. Whalley, *J. Chem. Soc.*, 1949, 859.
7 N. J. Cartwright, A. Robertson, and W. B. Whalley, *J. Chem. Soc.*, 1949, 853.
8 T. S. Gore, R. V. Talavdekar, and K. Venkataraman, *Curr. Sci.*, 1950, **19**, 20.