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A novel asymmetric route to succinimides and derived compounds: synthesis of the lignan lactone (+)-hinokinin

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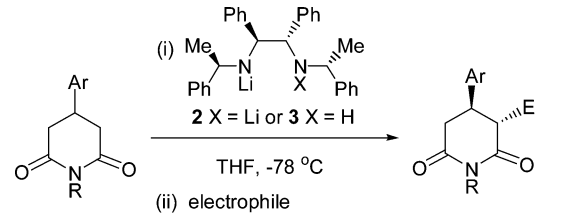
A novel approach to chiral succinimides and derived compounds has been developed that involves chiral lithium amide desymmetrisation of an *N-ortho-tert*-butylphenyl succinimide to generate a putative atropisomeric intermediate enolate, alkylation of which enables access to the lignan lactone (+)-hinokinin.

Previously we have demonstrated a range of applications of chiral base chemistry in which prochiral starting materials are converted into useful chiral (non-racemic) products by a process dubbed 'asymmetric deprotonation'.[1] Most recently the focus of this work has been the asymmetric transformation of various types of cyclic imide, especially ring-fused succinimides and certain types of glutarimide.[2] For example, asymmetric substitution of glutarimide **1**, by deprotonation with *bis*-lithium amide base **2**, gave a range of substituted products **4**, one of which was converted into the drug substance paroxetine, (Scheme 1).

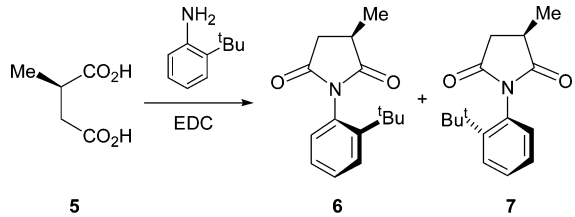
In much of this chemistry the use of diamine derived base **2**, or the corresponding mono-lithiated derivative **3** has proved crucial for optimal chemical yield or enantioselectivity.[3]

A further possibility for the application of the asymmetric deprotonation strategy to the synthesis of chiral imides became apparent to us following a report by Taguchi and co-workers.[4] As part of this study, chiral pool access to atropisomeric imides **6** and **7** was reported, starting from (*R*)-2-methylsuccinic acid **5**, Scheme 2.

One of the diastereomeric imide products **6** was converted into the corresponding maleimide, which was shown to undergo a highly stereocontrolled Diels–Alder reaction.[5] Prompted by these findings we initiated studies aimed at applying the kind of desymmetrisation shown in Scheme 1 to the asymmetric synthesis of atropisomeric intermediates such as **6** and **7**, the results of which are described herein.



Scheme 1



Scheme 2

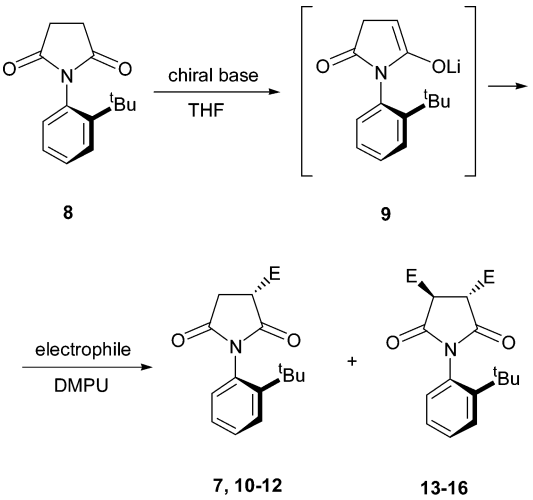
At the outset we envisaged desymmetrisation of the parent succinimide **8**, having an *N-ortho-tert*-butyl substituent, as shown in (Scheme 3).[6]

A chiral base was anticipated to select between a pair of enantiotopic protons on the face of the succinimide **8** *anti* to the bulky *tert*-butyl substituent, thus generating an enolate **9** possessed of a chiral C–N axis. Subsequent face selective electrophilic quench would then furnish a chiral succinimide product **7**, **10–12** (see later for nature of E).

Preliminary experiments using *bis*-lithium amide **2** provided mainly the doubly substituted products **13–16**, which were isolated in good yield, predominantly as the *trans* isomer shown. This result demonstrated that the steric effect of the first installed substituent could over-ride the influence of the remote *tert*-butyl group, and thus avoid the second alkylation returning a *meso* product.[7] However, the products from these reactions proved to be almost racemic, a result that suggests the intermediacy of symmetrical imide dianions, as documented by Garratt and co-workers.[8]

To avoid this problem we utilised the mono-lithiated base **3** to deprotonate **8**, and then effected alkylation using reactive alkyl halides and DMPU, Table 1.†

In each case a mono-alkylated product was obtained as the main product, principally as the *anti* isomer shown, although small amounts of the corresponding *syn* isomer (not shown) were also isolated.‡ The chemical yields are moderate, which reflects the



Scheme 3

Table 1 Alkylation of **8** to give **7** and **10–12** according to Scheme 3

Entry	Electrophile	Product and yield (%)	Product ee (%)	By-product and yield (%)
1	Methyl iodide	**7** 56[a]	85	**13** 0
2	Allyl bromide	**10** 55	94	**14** 7
3	Benzylbromide	**11** 50	92	**15** 6
4	Piperonyl bromide	**12** 40	95	**16** 7

[a] The methylated imide corresponds to the enantiomer of **7** in Scheme 2

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difficulty in controlling the alkylations of the somewhat unstable imide enolate, and have not been fully optimised. As in the previous glutarimide work, illustrated in Scheme 1, the enantiomeric excess of the monoalkylated product appears to be slightly enhanced in runs where some dialkylation is evident. This effect is due to a kinetic resolution of the first formed product being superimposed on the initial asymmetric deprotonation.[9] Thus, in the case of MeI as electrophile, the ee of the monoalkylated product **7** is a little lower than for the other electrophiles, since no over-alkylation occurred.

The absolute configuration of methylated product (−) **7** (entry 1) was correlated with the enantiomeric imide synthesized previously by Taguchi and co-workers, generated as shown in Scheme 2. The absolute configuration of product **12** was also proved by subsequent transformations, as described below.

It appeared to us that this novel imide alkylation could provide useful access to a range of target molecules, and we were particularly attracted to a very simple idea for preparing certain lignan dibenzyl lactones.[10] Initially, we established the viability of such a process by the three step sequence shown in Scheme 4, using racemic imide **11**.

A second benzylation of imide **11** served to generate **15**, identical to the product that we had obtained previously (Scheme 3), and subsequent borohydride reduction then furnished the hydroxyamide **17**. Treatment of this amide with sulfuric acid, according to a procedure that we had used previously,[11] then gave the desired racemic dibenzyl lactone **19**, albeit in moderate yield.

We then conducted an analogous sequence of reactions, starting with imide (+)-**12** of 95% ee, bearing a piperonyl substituent, which is characteristic of a number of naturally occurring lignan lactones. Introduction of a further piperonyl unit was accomplished by enolate alkylation, and reduction and cyclisation then gave (+)-hinokinin **20**, which is the enantiomer of a well-known lignan natural product. Our spectroscopic data for this compound were in accord with those reported previously,[12] and analysis by HPLC indicated that the enantiomeric excess of this compound was at the same level (95% ee) as that of the initially formed chiral intermediate (+)-**12**.

In summary, a conceptually novel approach to the synthesis of chiral imides, and derived systems, has been demonstrated, which uses a new chiral base desymmetrisation as the pivotal step. A new and concise synthesis of the lignan lactone hinokinin serves as a preliminary demonstration of the potential of the new method.

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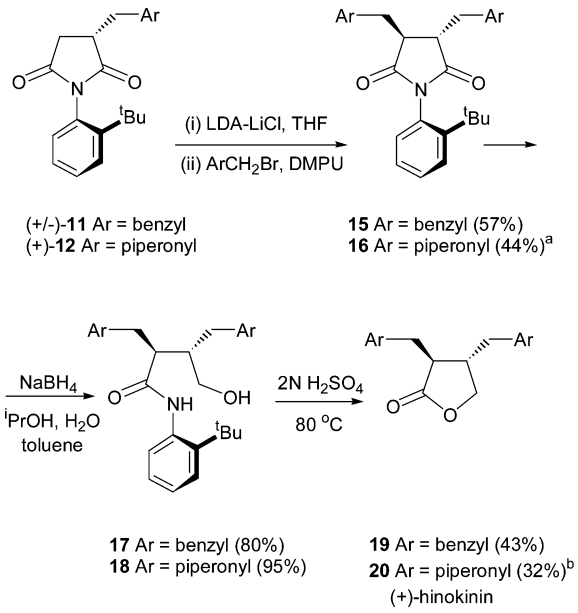

a - 73% based on recovered starting material

b - a 62% yield was obtained in the racemic series

Scheme 4

Notes and references

† *Preparation* of (+)-**12**: A solution of chiral lithium amide base **3** (2.44 mmol) in THF (5 mL) at −78 °C was added by cannula to a solution of imide **8** (400 mg, 1.73 mmol) in THF (40 mL) at −78 °C. After 1 h DMPU (0.29 mL, 2.42 mmol) was added, followed by piperonyl bromide (3.72 g, 17.3 mmol) in THF (4 mL), and the reaction mixture stirred at −78 °C for a further 2 h. Usual workup (saturated aqueous NH_4Cl solution and EtOAc extraction), followed by chromatographic purification gave firstly the *bis*-adduct **16** (R_f 0.65, 7 : 3 EtOAc/petroleum ether) as a white solid (60.0 mg, 0.12 mmol, 7%); followed by imide **12** (R_f 0.6, 7 : 3 EtOAc/petroleum ether) as a solid (250 mg, 0.68 mmol, 40%), m.p. 143–145 °C, $[\alpha]_D^{23}$ +86.7 (*c* 0.5, $CHCl_3$); ν_{max} ($CHCl_3$)/cm^{-1} 2972, 1711, 1602, 1490, 1444, 1382, 1041; δ_H (500MHz, $CDCl_3$) 1.32 (9H, s, $C(CH_3)_3$), 2.67 (1H, dd, *J* 18.7, 4.8, 4-H_A), 2.90 (1H, dd, *J* 18.7, 9.7, 4-H_B), 3.09 (1H, dd, *J*, 13.9, 7.2, 1′-H_A), 3.13 (1H, dd, *J*, 13.9, 4.8, 1′-H_B), 3.28 (1H, dddd, *J* 9.7, 7.2, 4.8, 4.8, 3-H), 5.98 (2H, m, OCH_2O), 6.61 (1H, dd, *J* 7.5, 1.3, Ar-*H*), 6.69 (1H, dd, *J* 7.8, 1.3, Ar-*H*), 6.74 (1H, d, *J* 1.3, Ar-*H*), 6.80 (1H, d, *J* 7.8, Ar-*H*), 7.27 (1H, ddd, *J* 7.5, 7.2, 1.1, Ar-*H*), 7.40 (1H, ddd, *J* 7.8, 7.2, 1.3, Ar-*H*), 7.59 (1H, dd, *J* 7.8, 1.1, Ar-*H*); δ_C (125 MHz, $CDCl_3$) 31.7 (CH_3), 33.4 (CH_2), 35.7 (C), 35.8 (CH_2), 41.7 (CH), 101.2 (CH_2), 101.7 (CH), 109.7 (CH), 122.6 (CH), 127.5 (CH), 128.9 (CH), 129.9 (CH), 130.3 (2 × C), 130.7 (CH), 146.9 (C), 148.0 (C), 148.2 (C), 176.6 (C=O), 179.6 (C=O); *m*/*z* (EI) (Found M^+, 365.1628. $C_{22}H_{23}NO_4$ requires *M*, 365.1627). The ee of **12** (95%) was determined by HPLC analysis using a Chiracel OD column [25 cm × 0.46 cm i.d.; 8% *i*-PrOH in hexane; flow rate, 1.0 mL min^{-1}; (−)-12; t_R = 35.2 min, (+)-12; t_R = 41.3 min].

‡ This by-product amounted to: 14% (**7**); 4% (**10**); 7% (**11**), and could not be isolated for **12**. We expect that MeI represents a worst case, and that the observed level of facial selectivity (*ca.* 10 : 1) will be adequate for synthesis using most (bulkier) electrophiles.

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7 This result is in contrast to a related alkylation of an amino-substituted succinimide, see K. Kishikawa, I. Tsuru, S. Kohmoto, M. Yamamoto and K. Yamada, *Chem. Lett.*, 1994, 1605.

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9 See reference 2a for a range of examples of this kind of kinetic resolution.

10 (*a*) R. S. Ward, *Nat. Prod. Rep.*, 1999, **16**, 75; (*b*) For examples of asymmetric approaches, see J. W. Bode, M. P. Doyle, M. N. Protopopova and Q-L. Zhou, *J. Org. Chem.*, 1996, **61**, 9146; (*c*) N. Kise, T. Ueda, K. Kumada, Y. Terao and N. Ueda, *J. Org. Chem.*, 2000, **65**, 464; (*d*) S. Kamlage, M. Sefkow, B. L. Pool-Zobel and M. G. Peter, *Chem. Commun.*, 2001, 331.

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12 (+)-Hinokinin was made previously by Doyle and co-workers (ref. 10b) using an asymmetric C–H insertion process that gave *ca.*, 95% ee. They report $[\alpha]_D$ +29.4 (*c* 0.9, $CHCl_3$) for the final product, whereas we observed $[\alpha]_D$ +26.9 (*c* 0.7, $CHCl_3$).