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Desymmetrisation of a *meso*-*N*-hydroxyimide via a chiral Lossen reaction

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Abstract

N-[(1*S*)-10-Camphorsulphonyloxy]norborn-5-ene-*endo*-2,3-dicarboximide **2** underwent a Lossen type reaction with dicyclohexylmethylamine to furnish *endo*-2-methoxycarbonyl-*endo*-3-(methoxycarbonyl-amino)norborn-5-ene **3**, in 84% yield and 33% e.e. (by NMR).

The desymmetrisation of *meso* compounds offers an attractive avenue in asymmetric synthesis.[1,2] These position-selective processes may be viewed as 'internal kinetic resolutions' in the sense that the *meso* compounds are 'internal racemates'; however, as desymmetrisation can in principle effect a total conversion to the chiral product, it is more advantageous than resolution. Reported herein is a novel desymmetrisation strategy applied to a hitherto neglected set of reactions in asymmetric synthesis (the Hofmann–Curtius–Lossen[3] family involving migration to electron deficient nitrogen).

Among the above, in fact, only the Lossen reaction[3] offers a window of opportunity for asymmetric synthesis: in the general case, the kinetic resolution of a chiral hydroxamic acid may be envisaged, but the desymmetrisation of an appropriate *meso* system would be better. The present work is based on the stereospecific Lossen-type reaction that has been observed in certain *N*-benzoyloxyimides upon treatment with trialkylamines.[4,5] In the present study, the chiral version was developed in the norbornene-fused *N*-hydroxyimide **1**, which was activated towards the Lossen reaction via the (1*S*)-10-camphorsulphonate **2** (Scheme 1).

The Lossen reaction was attempted on **2** in methanol solution with two equivalents of either triethylamine or dicyclohexylmethylamine (DCMA), at either rt or −78°C. The product was identified as the norbornene ester carbamate **3**. The best e.e. for **3** (33%) was observed with dicyclohexylmethylamine at −78°C (Table 1; the results apparently indicate that DCMA is more reactive and less selective than Et_3N). A consideration of the reported[4] mechanism for the analogous Lossen reaction of *N*-benzoyloxyphthalimide reveals that a minimum of two equivalents of the trialkylamine is required—as was also confirmed in the present case.

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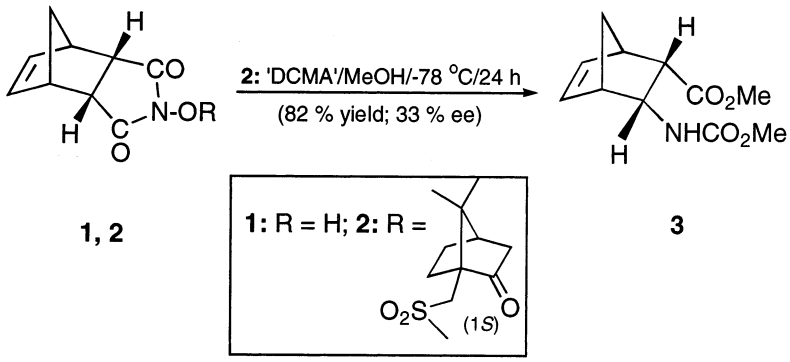

Scheme 1.

The above e.e. value of **3** was determined by a chiral shift reagent NMR study. Thus, in the presence of 0.6 equivalents of $Eu(hfc)_3$ in $CDCl_3$, the normally juxtaposed singlet resonances of the two ester methyl groups at δ 3.63 resolved: the carbamate signal shifted 5 ppm downfield and further resolved into two singlets, which were of equal intensity in racemate **3**. (It is assumed that the carbamate group is the site of the chelation with the $Eu(hfc)_3$.) However, in **3** obtained via the above chiral Lossen reaction, the relative intensities of the resolved carbamate signals indicated an e.e. value of 33%. Although this is but modest and the absolute configuration of the predominant enantiomer of **3** is yet unknown, the viability of the above approach has

Table 1
The Lossen reaction[a] on the (+)-camphorsulphonate **2** to furnish the ester carbamate **3**

Base	Temp. (°C)	Time (h)	Yield (%)	E.e. (%)
Et_3N	25	2	70	18
Et_3N	−78	24	No reaction	–
DCMA	25	2	98	0
DCMA	−78	24	84	33

[a] The camphorsulphonate **2** was prepared from **1**, (1*S*)-(+)-camphorsulphonyl chloride and pyridine (1.0 mmol each) in CH_2Cl_2 (10 ml) at 0°C for 20 h; the usual work-up was followed by silica gel column chromatography (eluent: 15% EtOAc in hexanes) to obtain pure **2**. A mixture of **2** (0.5 mmol) and the trialkylamine (1.0 mmol) in absolute MeOH (5 ml) was stirred under the indicated conditions. Evaporation of the volatiles and silica gel chromatography (eluent: 20% CH_2Cl_2 in hexanes) furnished **3** as a colourless liquid. Selected data: camphorsulphonate **2**: mp 165–167°C (dec.); $[\alpha]_D^{25}$ +5.00 (c=4, $CHCl_3$); IR 1790, 1730 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 0.88 (3H, s, camphor C_7-*Me*), 1.08 (3H, s, camphor C_7-*Me*), 1.38–2.58 (9H, m, saturated and allylic C*H*), 3.23–4.04 (6H, m, C*H* α to CO and SO_2), 6.18 (2H, br. s, C=C*H*); HRMS 394.1321 (calcd for $C_{19}H_{23}NO_6S$, 394.1324). Ester carbamate **3** (colourless liquid): IR 3400, 1720 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$) δ 1.30–1.60 (2H, m, C_7H), 3.04–3.30 (3H, m, C*H* α to CO, NH and C=C), 3.62 (3H, s, carbamate Me), 3.64 (3H, s, ester Me), 4.60 (1H, m, allylic C*H* β to NH), 5.30 (1H, br. m, NH), 6.10–6.25 (1H, m, C=C*H*), 6.32–6.45 (1H, m, C=C*H*). HRMS 226.1100 (calcd for $C_{11}H_{16}NO_4$ 226.1080). The shift reagent studies were performed with tris[3-(heptafluoropropylhydroxymethylene)-D-camphorato]europium(III) [$Eu(hfc)_3$, from the Aldrich Chemical Co.], which was added in increments of 0.2 equiv. to an NMR sample of **3**; at 0.6 equiv. the carbamate methyl singlet signal had resolved into two peaks at δ 8.50 and 8.80 in a 1:2 ratio. The $[\alpha]_D^{28}$ (c=3, $CHCl_3$) values obtained were −0.027 (18% e.e. by NMR) and −0.067 (33% e.e by NMR).

been demonstrated. (The chiral framework of **3** is of interest as a peptide β-sheet inducer.[1]) Further work to extend and improve the above results is planned.

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