Central to axial chirality transfer *via* double bond migration: asymmetric synthesis and determination of the absolute configuration of axially chiral 1-(3′-indenyl)naphthalenes

Robert W. Baker,* Trevor W. Hambley, Peter Turner and Brian J. Wallace

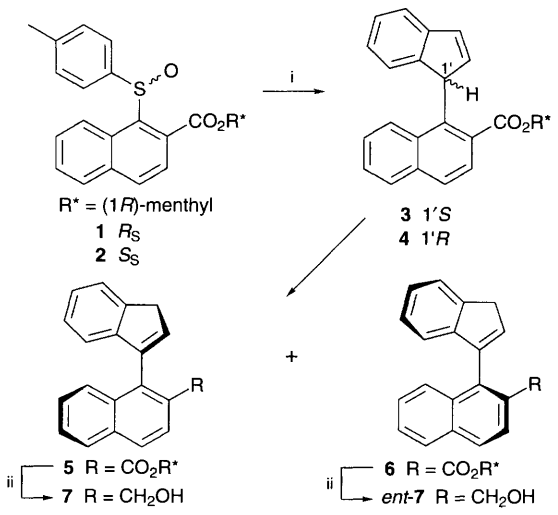
School of Chemistry, The University of Sydney, NSW 2006, Australia

(1*R*)-Menthyl (*R*)- and (*S*)-1-(1′-indenyl)naphthalene-2-carboxylates 3 and 4 are stereoselectively isomerised to the (1*R*)-menthyl (*S*)- and (*R*)-1-(3′-indenyl)naphthalene-2-carboxylates 5 and 6, respectively, on treatment with triethylamine, the relative configuration of 5 being established by a single crystal X-ray study; the sense of chirality transfer is reversed on LAH reduction of 3 and 4, stereoselectively furnishing (*R*)- and (*S*)-1-(3′-indenyl)naphthalene-2-methanol *ent*-7 and 7, respectively, *via* an intramolecular deprotonation reaction.

Molecular rearrangements that destroy one chiral element while simultaneously creating a new one are well known in the case of sigmatropic rearrangements.[1] However, rearrangements involving transfer of central chirality to axial chirality due to atropisomerism have not, to the best of our knowledge, been described previously. Although not a rearrangement, central to axial chirality transfer has been demonstrated in the oxidation of centrally chiral 4-(1′-naphthyl)-1,4-dihydroquinolines to axially chiral 4-(1′-naphthyl)quinolines.[2] Another related example of central to axial chirality transfer is the stereoselective oxidation of 3-[methyl(α-menthylbenzyl)carbamoyl]-1,2,4-trimethyl-1,4-dihydroquinoline to the corresponding quinolinium ion, which possesses axial chirality due to hindered rotation about the C_3–$C_{carbonyl}$ single bond.[3] In these transformations chirality transfer is the result of differing reactivities or equilibrium distributions of ground state conformations about the incipient chiral axis. Here we describe rearrangements in which double bond migration leads to the stereoselective conversion of central into axial chirality, with the highest selectivities obtained when migration is facilitated by an intramolecular deprotonation reaction.

We recently described an enantioselective synthesis of asymmetrically substituted 9-(1′-naphthyl)fluorenes *via* ligand coupling reactions of 1-naphthyl sulfoxides and reported that the corresponding fluorenyl carbanions retain axial chirality.[4] As an extension of this work, the reaction of the previously described[4] (1*R*)-menthyl (*R*)-(1-*p*-tolylsulfinyl)naphthalene-2-carboxylate **1** with indenyllithium was examined (Scheme 1). Reaction of **1** with 1.2 equiv. of indenyllithium for 5 min in THF at 0 °C afforded the 1-(1′-indenyl)naphthalene **3**† in 88% yield and 59% de,‡ accompanied by a mixture of the atropisomers **5** and **6** in a combined yield of 9%. Reaction of the epimeric (*S*)-sulfoxide **2**[4] with indenyllithium afforded the 1-(1′-indenyl)-naphthalene **4** in 86% yield and 57% de,‡ accompanied by a mixture of the atropisomers **5** and **6** in a combined yield of 9%. Thus, the chirality of the menthyl moiety has no significant influence on the stereoselectivity of the coupling reaction. Atropisomers **5** and **6** were separable by preparative HPLC, possessing moderate stability in solution at room temperature (half-life for interconversion *ca.* 25 h at 25 °C). The rate of interconversion of **5** and **6** (ultimately affording a 50:50 mixture) was determined by ^{1}H NMR analysis at 327 K,§ providing a barrier to rotation $\Delta G^{\ddagger}_{327}$ = 106 kJ mol^{-1}. Recrystallisation of **5** from aqueous acetone at −20 °C furnished suitable crystals for X-ray crystallographic analysis (Fig. 1),¶ thus allowing inference of the (*S*) absolute configuration at the chiral axis. Reduction of **6** (99% de‖) with an excess of LAH in diethyl ether solution afforded (*S*)-1-(3′-indenyl)-naphthalene-2-methanol **7** of 97% ee** in quantitative yield (Scheme 1). Similarly, reduction of **4** (98% de‖) afforded (*R*)-1-(3′-indenyl)naphthalene-2-methanol *ent*-**7** of 98% ee** in 96% yield. The rate of racemisation of **7** in refluxing benzene solution was determined by HPLC analysis,** providing a barrier to rotation $\Delta G^{\ddagger}_{353}$ = 112 kJ mol^{-1}.

The formation of **5** and **6** during the coupling reactions occurs through isomerisation of **3** and **4** by the excess of indenyllithium employed. Re-exposure of **3** (59% de‡) to indenyllithium (1.5 equiv., *ca.* 0.02 mol dm^{-3}) in THF solution at 0 °C for 1 h resulted in 56% conversion to a mixture of **5** and **6** in which there was a slight excess of **5** (18% de‖). Exposure of **3** (59%



Scheme 1 *Reagents and conditions*: i, indenyllithium (1.2 equiv.), THF, 0 °C, 5 min; ii, LAH (5 equiv.), diethyl ether, 0 °C, 30 min

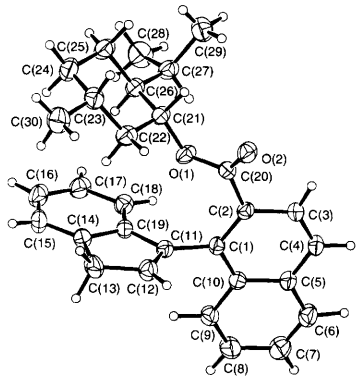
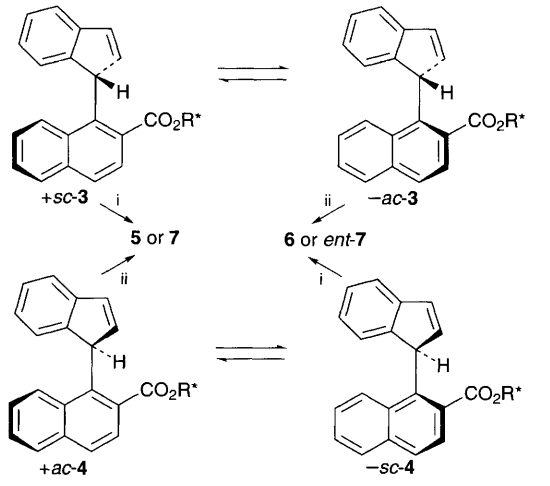


Fig. 1 ORTEP[8] plot of (1*R*)-menthyl (*S*)-1-(3′-indenyl)naphthalene-2-carboxylate **5**, with crystallographic numbering; 25% thermal elipsoids are shown for non-hydrogen atoms

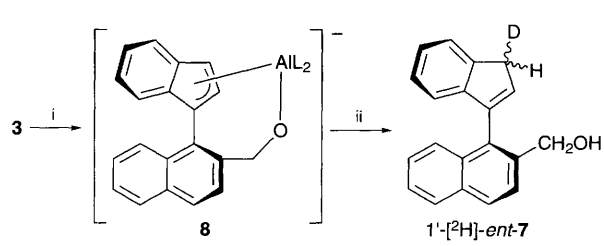
de‡) to triethylamine (5 equiv., *ca.* 0.07 mol dm^{-3}) in dichloromethane solution at 20 °C for 2 h resulted in 17% conversion to a mixture of **5** and **6** in which there was a significant excess of **5** (46% de‖). Isomerisation of **4** (57% de‡) with triethylamine under the same conditions resulted in 17% conversion to a mixture of **5** and **6** in which there was a significant excess of **6** (54% de‖). Longer reaction times with either indenyllithium or triethylamine eventually leads to the complete conversion of **3** or **4** into a mixture of **5** and **6**. However, given the slow interconversion of **5** and **6** at room temperature, a gradual reduction of diastereomeric excess was observed in the reaction with triethylamine.

Assuming free rotation about the $C_{(1)}$–$C_{(1')}$ bond does not occur in the indenyl carbanion intermediates,[4] formation of **5** will occur *via* isomerisation of the *+sc* rotamer of **3** or the *+ac* rotamer of **4**, while formation of **6** will occur *via* isomerisation of the *−ac* rotamer of **3** or the *−sc* rotamer of **4** (Scheme 2). The observed stereoselectivities for the isomerisation of **3** and **4** with triethylamine indicate that isomerisation is favoured *via* the rotamers in which the bulky menthoxycarbonyl group is *anti* to the abstracted hydrogen at C-1′, *i.e.* *+sc*-**3** and *−sc*-**4**. In addition to chirality transfer from C-1′, the chirality of the menthyl moiety has an influence on the stereoselectivity of isomerisation, as evident from the differing selectivities for the isomerisation of **3** and **4**.

When **3** (59% de‡) was treated with an excess of LAH in diethyl ether solution it was found that, in addition to reduction of the ester group, double bond migration had occurred to afford alcohol *ent*-**7** of 58% ee** in 92% yield. Evidence for the intermediacy of the (indenyl)aluminate **8** (Scheme 3) was obtained by quenching the reaction with *ca.* 2 mol dm^{-3} DCl in D_2O solution. By ^1H NMR analysis the recovered alcohol *ent*-**7** contained 89% deuterium at C-1′, with the substitution occurring with 90% de†† (the stereochemistry of deuterium substitution has yet to be established). Reduction of either **5** or **6** with LAH followed by DCl/D_2O quench did not lead to the incorporation of deuterium at C-1′; presumably the geometry of the aluminate intermediate is not favourable for intramolecular deprotonation and intermolecular deprotonation does not take place. The reduction of **4** (57% de‡) with an excess of LAH in diethyl ether solution afforded **7** of 55% ee** in 91% yield. The high stereoselectivity for the conversion of **3** and **4** into *ent*-**7** and **7**, respectively, is readily rationalised by the involvement of an (indenyl)aluminate intermediate formed through intramolecular deprotonation, since this process can only take place *via* one rotamer: the *−ac* rotamer in the case of **3**, and the *+ac* rotamer in the case of **4** (Scheme 2).



Scheme 2 *Reagents and conditions*: i, NEt_3 (5 equiv., *ca.* 0.07 mol dm^{-3}), CH_2Cl_2, 20 °C, 2 h; ii, LAH (5 equiv.), diethyl ether, 0 °C, 30 min



Scheme 3 *Reagents and conditions*: i, LAH (5 equiv.), diethyl ether, 0 °C, 30 min ($-H_2$); ii, *ca.* 2 mol dm^{-3} DCl in D_2O

Footnotes

† New compounds gave satisfactory elemental analyses or high resolution mass spectral molecular ions and spectra (MS, IR, ^1H and ^{13}C NMR) in accord with the assigned structures.

‡ Diastereomeric purity was determined by the ^1H NMR (400 MHz) signals at δ(C_6D_6) 6.78 and 6.72 (each dd, *J* 5.4, 1.9 Hz), respectively, for **3** and **4**. The assignment of relative configuration to **3** and **4** has been made on the basis of the proposed intramolecular deprotonation mechanism for chirality transfer.

§ Interconversion of **5** and **6** was followed by the ^1H NMR (400 MHz) signals at δ([$^2H_8$]-toluene) 6.16 and 6.26 (each dd, *J* 2.0, 2.0 Hz), respectively, for **5** and **6**. Temperature calibration was based on the chemical shift difference between the OH and methylene signals in the ^1H NMR spectrum of ethylene glycol.

¶ *Crystal data* for **5**: $C_{30}H_{32}O_2$, *M* = 424.58, colourless prism 0.30×0.22×0.20 mm, orthorhombic, space group $P2_12_12_1$ (#19), *a* = 13.505(2), *b* = 16.746(1), *c* = 10.769(1) Å, *V* = 2435.5(4) $Å^3$, D_c (*Z* = 4) = 1.158 g cm^{-3}, μ(Cu-Kα) = 5.47 cm^{-1}, λ(Cu-Kα) = 1.54178 Å, *F*(000) = 912 electrons. Ranges of *hkl* 0–15, 0–19, 0–12; 4–130° 2θ, *N* = 2523, *N*(unique) = 2368 (R_{int} = 0.145), N_o = 1966 [$I > 3.00\sigma(I)$], N_{var} = 417, *R* = 0.043, R_w = 0.040, residual electron density -0.15 to 0.15 e $Å^{-3}$. Data collected at 21 °C with a Rigaku AFC7R diffractometer employing graphite monochromated Cu-Kα radiation generated from a 12 kW direct drive rotating anode. All calculations were performed using the TEXSAN[5] crystallographic software package. The structure was solved by direct methods[6] and expanded using Fourier techniques.[7] The non-hydrogen atoms were refined anisotropically with full matrix least squares, while the hydrogen atoms were located and refined isotropically. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC). See Information for Authors, Issue No. 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 182/248.

‖ A 4.6 × 250 mm column (Zorbax 5μ silica, Jones) was used with 0.4% ethyl acetate–hexane as eluent at a flow rate of 1.5 ml min^{-1}, detection 254 nm, t_R: 23.1 min for **5** and 20.1 min for **6**.

** A 10×250 mm column (Pirkle Type 1A, Regis) was used with 5% propan-2-ol–hexane as eluent at a flow rate of 3.0 ml min^{-1}, detection 254 nm, t_R: 31.3 min for **7** and 29.6 min for *ent*-**7**.

†† Diastereomeric purity was determined by the ^1H NMR (400 MHz) signals at δ(C_6D_6) 3.26 and 3.21 (each br m), respectively, for H-1′ of the major and minor diastereomers of 1′-[^2H]-*ent*-**7**. Signals for (H-1′)$_2$ for residual *ent*-**7** appear at δ 3.30 and 3.21 (each dd, *J* 24.0, 2.0 Hz).

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