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Asymmetric Synthesis of Axially Chiral 1-(2'-Methyl-3'-indenyl)naphthalenes *via* Prototropic Rearrangements of Stable Rotamers of 1-(2'-Methyl-1'-indenyl)naphthalenes

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Abstract: Reaction of methyl (*R*)-1-(*p*-tolylsulfinyl)naphthalene-2-carboxylate **2** with 2-methylindenyllithium affords the *-ac* rotamer of methyl (*S*)-1-(2'-methyl-1'-indenyl)naphthalene-2-carboxylate **6** in 63% ee. Heating *-ac*-**6** at 80 °C leads to the formation of an 18:1 mixture of *-ac*:*+sc*-**6** rotamers, with a barrier to atropisomerisation of $\Delta G^{\ddagger}_{353}$ = 28.4 kcal mol^{-1} (*+sc* to *-ac*). Prototropic rearrangements of the rotamers of 1-(2'-methyl-1'-indenyl)naphthalenes to 1-(2'-methyl-3'-indenyl)naphthalenes occur with retention of the axial stereogenic element.

As part of a project examining the asymmetric synthesis of planar chiral cyclopentadienylmetal complexes through the use of axially chiral chelating cyclopentadienyl ligands,[1, 2] we recently described a stereoselective synthesis of axially chiral 1-(3'-indenyl)naphthalenes *via* central to axial chirality transfer during prototropic rearrangements of 1-(1'-indenyl)naphthalenes.[3] It was proposed that the sense of chirality transfer in these rearrangements was dependent on the relative reactivities of interconverting rotational isomers about the naphthalene-indene bond. Thus, isomerisation of the (*S*)-1-(1'-indenyl)naphthalene **3** (obtained in 59% de through reaction of the (*R*)-sulfoxide **1** with indenyllithium, Scheme) with triethylamine proceeded preferentially through the *+sc* rotamer, affording the (*S*)-1-(3'-indenyl)naphthalene **11** (46% de), whilst isomerisation during the course of lithium aluminiumhydride (LAH) reduction proceeded through the *-ac* rotamer, affording the (*R*)-1-(3'-indenyl)naphthalene **7** (58% ee). In the former reaction the indene 1-H is presumably more sterically accessible to the base in the *+sc* rotamer, while in the latter reaction it was shown that isomerisation during reduction proceeds through an intramolecular deprotonation reaction, which can only take place through the *-ac* rotamer. Since the 1-(3'-indenyl)naphthalenes **7** and **11** had only low to moderate thermal stability with respect to atropisomerisation, it was decided to raise the barriers to rotation further by introducing a methyl substituent at the indene 2-position. In this Letter we report that the resulting 1-(2'-methyl-1'-indenyl)naphthalene compounds exhibit the rare phenomenon of atropisomerism owing to hindered rotation about an sp^3—sp^2 bond[4] and that subsequent prototropic rearrangements to the 1-(2'-methyl-3'-indenyl)naphthalenes occurs with retention of the axial stereogenic element.

Reaction of the (*R*)-sulfoxide **1**[1, 2] (Scheme) with 2-methylindenyllithium (1.2 equiv.) in THF solution during 30 min at 0 °C furnished the (*S*)-1-(2'-methyl-1'-indenyl)naphthalene **4** in 50% yield and 70% de (^{1}H NMR analysis). Treatment of **4** with triethylamine (1:1 NEt_3/benzene, reflux, 60 h) afforded the (*R*)-1-(2'-methyl-3'-indenyl)naphthalene **8** in 97% yield and 65% de (^{1}H NMR analysis), while treatment of **4** with excess LAH (ether, 0 °C, 20 min) afforded the (*R*)-1-(2'-methyl-3'-indenyl)naphthalene **9** in quantitative yield and 70% ee (HPLC analysis, Pirkle Type 1A, Regis), *i.e.* the sense of "chirality transfer" was no longer reversed as previously observed in the case of the 1-(1'-indenyl)naphthalene **3**, and the rearrangements under both conditions appeared to be taking place preferentially *via* the *-ac* rotamer. In order to gain an insight into the reasons for this change in behaviour, calculations of the barriers to rotation in the 1-(1'-indenyl)naphthalene systems were made using the simplified methyl esters (Scheme). The calculations[5] on the 1-(1'-

0040-4039/98/$ - see front matter
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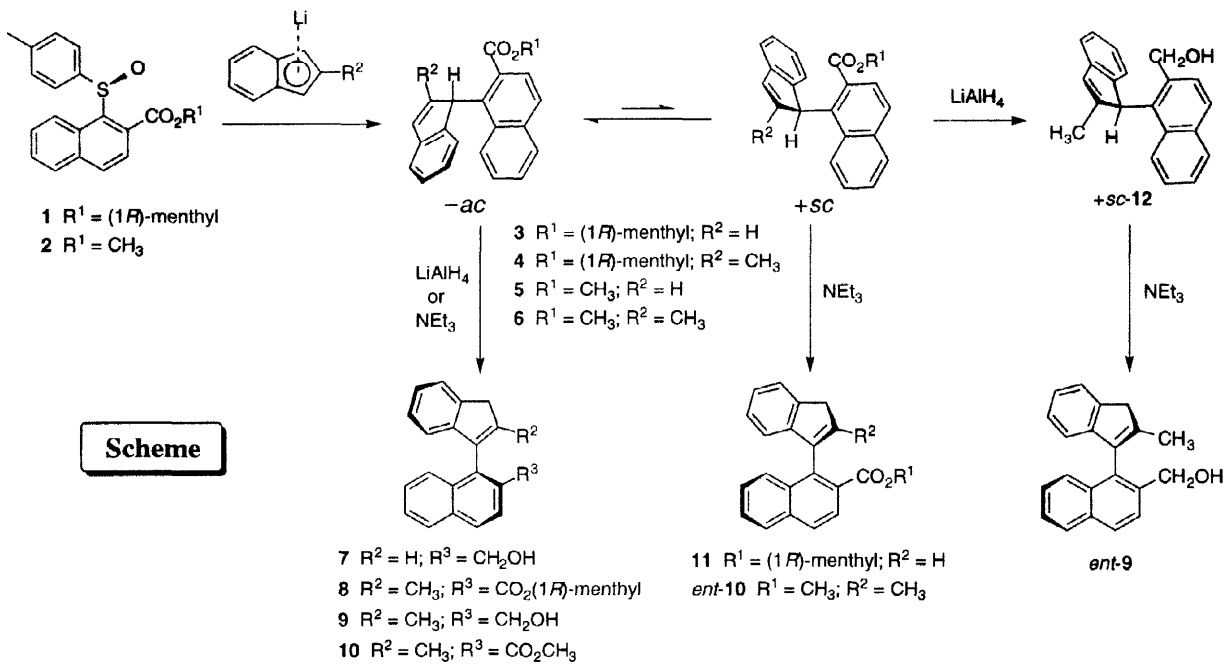
indenyl)naphthalene **5** [$\Delta H^{\ddagger}_{calc}$ = 15.0 kcal mol^{-1} (*-ac* to *+sc*); $\Delta H^{\ddagger}_{calc}$ = 12.7 kcal mol^{-1} (*+sc* to *-ac*)] supported our previous proposal that interconversion of the rotamers should be rapid relative to the rate of rearrangement, while the calculated barriers were considerably higher in the case of the 1-(2'-methyl-1'-indenyl)naphthalene **6** [$\Delta H^{\ddagger}_{calc}$ = 24.4 kcal mol^{-1} (*-ac* to *+sc*); $\Delta H^{\ddagger}_{calc}$ = 18.9 kcal mol^{-1} (*+sc* to *-ac*)]. Nevertheless, contrary to expectations from the calculations, there was no evidence for hindered rotation in the ^{1}H NMR spectra of either **3** or **4** in the temperature range -80 to 80 °C, nor were atropisomers evident (^{1}H NMR and HPLC analysis) after prolonged heating in toluene solution under reflux. The calculations did suggest, however, that there may be a significant thermodynamic bias in favour of the *-ac* rotamer which might preclude observation of the minor *+sc* rotamer. Consequently, it was decided to replace the bulky menthyl ester of compounds **3** and **4** with a methyl ester in which the bias in favour of the *-ac* rotamer may not be as pronounced.



Scheme

The (*R*)-sulfoxide **2** was prepared in 56% yield through reaction of the 2-lithio derivative of (*R*)-1-(*p*-tolylsulfinyl)naphthalene[6] with methyl chloroformate in THF solution at -78 °C during 5 h. Reaction of **2** (Scheme) with indenyllithium (1.0 equiv.) in THF solution during 5 min at 0 °C furnished the (*S*)-1-(1'-indenyl)naphthalene **5** in 36% yield together with the corresponding 1-(3'-indenyl)naphthalene in 6% yield (longer reaction times eventually leads to complete isomerisation of **5**). The enantiomeric excess of **5** was unable to be determined directly, however, on reduction with excess LAH (ether, 0 °C, 20 min) the (*R*)-1-(3'-indenyl)naphthalene **7** was isolated in quantitative yield and 21% ee (HPLC analysis, Pirkle Type 1A, Regis). Given that LAH reduction of the menthyl ester **3** proceeds with essentially complete retention of stereochemical purity, it follows that the enantiomeric excess of **5** is also 21% [because of the low barrier to rotation anticipated[3] for the 1-(3'-indenyl)naphthalene isomer of **5**, no attempt was made to determine its ee]. The ^{1}H NMR ($CDCl_3$) spectrum of **5** now revealed the presence of two rotameric forms in a ratio of 9:1. The minor rotamer was assigned as *+sc* since the signal for the methyl group (δ_H 3.08) was significantly shielded with respect to that of the *-ac* rotamer (δ_H 3.89) by the magnetic anisotropy of the indene moiety. Conversely, in the *-ac* rotamer the signal for the naphthalene 8-H (δ_H 6.84) was significantly shielded with respect to that of the *+sc* rotamer (δ_H 8.46). The barrier to rotation in **5** was determined by saturation transfer experiment[7] to be $\Delta G^{\ddagger}_{333}$ = 19.6 kcal mol^{-1} (*-ac* to *+sc*).

Reaction of **2** (Scheme) with 2-methylindenyllithium (1.2 equiv.) in THF solution during 5 min at 0 °C furnished the (*S*)-1-(2'-methyl-1'-indenyl)naphthalene **6** in 47% yield and 63% ee [HPLC analysis, Chiralpak OT(+), Daicel] together with the (*R*)-1-(2'-methyl-3'-indenyl)naphthalene **10** in 3% yield (again, longer

reaction times eventually leads to complete isomerisation of **6** to **10**). The enantiomeric excess **10** was unable to be determined directly, however, reduction with excess LAH (ether, 0 °C, 20 min) furnished the (*R*)-1-(2'-methyl-1'-indenyl)naphthalene **9** in quantitative yield and 63% ee. The ^{1}H NMR spectrum of **6** indicated the presence of only a single rotamer, however, on heating **6** for 2 days in benzene solution under reflux the ^{1}H NMR ($CDCl_3$) spectrum revealed that a second minor rotamer had been formed in a ratio of 18:1 (heating for longer periods does not alter this ratio). As in the case of **5**, the minor rotamer was assigned as *+sc* since the signal for the methyl group (δ_H 3.19) was significantly shielded with respect to that of the *-ac* rotamer (δ_H 4.03), while in the *-ac* rotamer the naphthalene 8-H (δ_H 7.06) was significantly shielded with respect to that of the *+sc* rotamer (δ_H 8.53). This assignment was confirmed by single-crystal X-ray diffraction analysis of *-ac*-**6**.[8]

The rotamers of **6** were chromatographically separable and the rate of conversion of *+sc*-**6** back to an equilibrium mixture in refluxing benzene solution was determined (HPLC analysis), providing a barrier to rotation $\Delta G^{\ddagger}_{353}$ = 28.4 kcal mol^{-1} (*+sc* to *-ac*). Treatment of *-ac*-**6** (63% ee) with triethylamine (1:1 NEt_3/benzene, 25 °C, 10 days) furnished the (*R*)-1-(2'-methyl-3'-indenyl)naphthalene **10** in 96% yield which, following LAH reduction, quantitatively afforded the (*R*)-1-(2'-methyl-3'-indenyl)naphthalene **9** in 63% ee. Treatment of *-ac*-**6** with excess LAH (ether, 0 °C, 20 min) also afforded the (*R*)-1-(2'-methyl-3'-indenyl)naphthalene **9** in quantitative yield and in 63% ee. Treatment of *+sc*-**6** (presumably also of 63% ee; the ee could not be determined directly) with triethylamine (1:1 NEt_3/benzene, 25 °C, 24 h) afforded the (*S*)-1-(2'-methyl-3'-indenyl)naphthalene *ent*-**10** in 96% yield which, following LAH reduction, quantitatively afforded the (*S*)-1-(2'-methyl-3'-indenyl)naphthalene *ent*-**9** in 63% ee. When *+sc*-**6** was treated with excess LAH (ether, 0 °C, 20 min) reduction was not accompanied by rearrangement and the (*S*)-1-(2'-methyl-1'-indenyl)naphthalene *+sc*-**12** was obtained in 98% yield. The enantiomeric excess of *+sc*-**12** was unable to be determined directly, however, on treatment with triethylamine (1:1 NEt_3/benzene, 25 °C, 3 days) the (*S*)-1-(2'-methyl-3'-indenyl)naphthalene *ent*-**9** was isolated in quantitative yield and 63% ee. The formation of *+sc*-**12** verifies our previous proposal[3] that isomerisation during reduction proceeds through an intramolecular deprotonation reaction, generating a chelated (indenyl)aluminate intermediate, and this can only take place through the *-ac* rotamer.

The differences in behaviour noted above for the rearrangement reactions of **3** and **4** can now be accounted for. Thus, while existing almost exclusively as the *-ac* rotamer (as evident from the ^{1}H NMR chemical shifts for the menthyl 1-H and naphthalene 8-H), facile rotation about the naphthalene-indene bond in **3** allows access to the more reactive *+sc* rotamer during the triethylamine catalysed rearrangement. However, in the triethylamine catalysed rearrangement of **4** (which is synthesised exclusively as the *-ac* rotamer), rotation about the naphthalene-indene bond does not occur, or is at least considerably slower than the rate of rearrangement of the *-ac* rotamer, leading to the substantial retention of the axial stereogenic element. The stereochemical outcome of the rearrangements of the rotamers of 1-(2'-methyl-1'-indenyl)naphthalenes is analogous to the retention of the axial stereogenic element in fluorenyl carbanions derived from the rotamers of asymmetrically substituted 9-(1'-naphthyl)fluorenes which we have recently reported.[1, 2]

As expected, the 1-(2'-methyl-3'-indenyl)naphthalenes have considerably higher thermal stability with respect to atropisomerisation than the 1-(3'-indenyl)naphthalenes described previously.[3] Although we have yet to determine the barriers to rotation, heating of the 1-(2'-methyl-3'-indenyl)naphthalene **4** in toluene solution under reflux for 24 h did not result in any detectable epimerisation. The absolute configurations of the 2-methylindene compounds prepared have been determined by CD spectroscopy. Thus, comparison of the CD spectrum of (*S*)-1-(3'-indenyl)-2-naphthalenemethanol *ent*-**7** (the absolute configuration having been previously determined[3]) with that of 1-(2'-methyl-3'-indenyl)-2-naphthalenemethanol **9** (Figure 1), indicates that **9** has the *R* absolute configuration, both compounds displaying Cotton effects at similar wavelengths (*ca.* 200, 230, 240 and 270 nm) but with opposite signs. The CD spectra of the rotamers *-ac*-**6** and *+sc*-**6** (Figure 2) also show Cotton effects at similar wavelengths (*ca.* 205, 230 and 255 nm) but with opposite signs, *i.e.* the CD spectra largely reflect the axial rather than the central stereogenic element of the compounds. Comparison of the signs of the Cotton effects of the rotamer *-ac*-**6** with those of the three lowest wavelength Cotton effects of **9** suggests an absolute configuration which is entirely consistent with the assignment of configuration based on the intramolecular deprotonation mechanism for rearrangement accompanying LAH reduction. Having established that 1-(2'-methyl-3'-indenyl)naphthalenes display high configurational stability, we are currently

exploring the preparation of a range of chelating ligands based on this system and examining their application to the asymmetric synthesis of planar chiral cyclopentadienylmetal complexes.

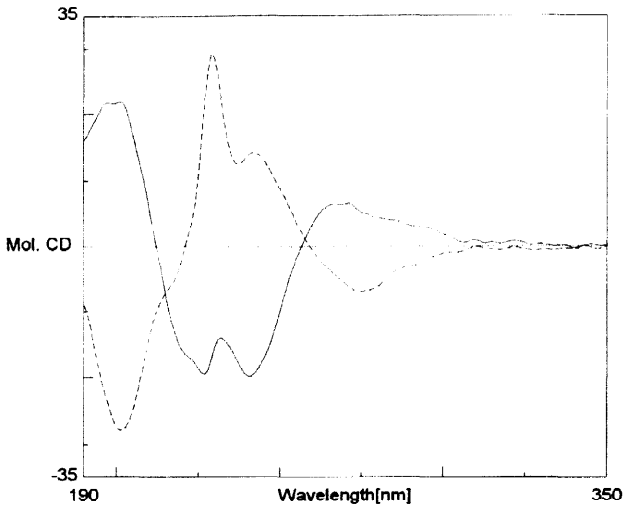


Fig. 1 CD spectra (acetonitrile) corrected to enantiomeric purity of ***ent*-7** (—) and **9** (- -)

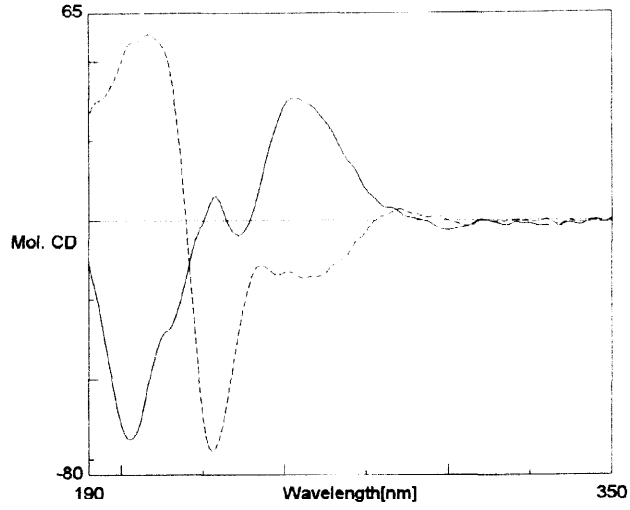


Fig. 2 CD spectra (acetonitrile) corrected to enantiomeric purity of *-ac*-**6** (—) and *+sc*-**6** (- -)

References and Notes

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4. For other examples of atropisomerism about an sp^3—sp^2 bond see: Ōki, M., *Top. Stereochem.*, 1983, **14**, 1, and references therein; Ōki, M., *The Chemistry of Rotational Isomers*, Springer-Verlag, Berlin, 1993, and references therein.
5. Structures were generated using SPARTAN 4.0 (Wavefunction, Inc, Irvine, CA, USA, 1995) and rotational barriers calculated by constraining the C2-C1-C1'-C2' dihedral angle at 10° increments around 360°. Structures at each step were initially minimised using the Sybyl force field and then optimised using AM1. The obtained structures with a minimum energy were then further optimised with AM1 without constraints, and the energy barriers calculated by subtracting the minimum from the maximum energy structures. For both **5** and **6** the minimum energy pathway for interconversion of the rotamers involved passage of the naphthalene ester substituent over the indene 7-position, with the barriers for the alternative pathway (ester over indene 2-position) being 3.7 and 2.4 kcal mol^{-1}, respectively, higher in energy.
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7. Martin, M.L., Delpuech, J.-J., and Martin, G.J., *Practical NMR Spectroscopy*, Heyden, London, Philadelphia, Rheine, 1980, p. 315.
8. The single-crystal X-ray diffraction analysis of *-ac*-**6** will be reported elsewhere.