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Axial chirality in xanthene-4,5-dicarboxamides: 1,9-stereocontrol mediated by remote interactions between conformationally constrained amide groups

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Abstract

Tertiary 9,9-dimethylxanthene-4,5-dicarboxamides have a C_2-symmetric, axially chiral ground state due to remote interactions between the conformationally constrained tertiary amide substituents. Double ortholithiation–alkylation blocks amide rotation, and the 3,6-dialkylated products are chiral, existing as a pair of enantiomeric C_2-symmetric atropisomers. Double lateral lithiation–electrophilic quench introduces a pair of 1,9-related stereogenic centres—each under the control of one of the conformationally constrained amides—with complete diastereoselectivity.

The tertiary amide groups of benzene-1,2-dicarboxamides[1] and benzene-1,2,3-tricarboxamides[2] align themselves anti-parallel to avoid steric interactions between their NR_2 groups. In a previous publication, we described how this conformational preference may be exploited to relay stereochemistry around an aromatic ring.[1] A series of directed *ortho*[3] and lateral[4] lithiations led to the synthesis of **1**, which bears 1,6-related stereogenic centres lying *para* across an aromatic ring. Information about the stereochemistry of the first-formed stereogenic centre was communicated to the second through the pair of conformationally interlocked amide substituents.

We now report that pairs of tertiary amide substituents which are much further apart can retain a similar type of conformational communication, even when they are attached to quite separate aromatic rings. The amide groups in question lie at the 4 and 5 (‘*peri*’) positions of a xanthene—a ring system chosen for the ease with which it undergoes regioselective functionalisation by directed metallation.

Secondary xanthene-4,5-dicarboxamides had been made previously by Rebek[5] using an electrophilic bromination–halogen/metal exchange sequence. We decided to try a more direct route using the directed 4,5-dilithiation of 9,9-dimethylxanthene reported by Haenel[6] in the synthesis of Xantphos-type ligands.[7] Dimethylation of xanthone **2** was achieved with trimethylaluminium,

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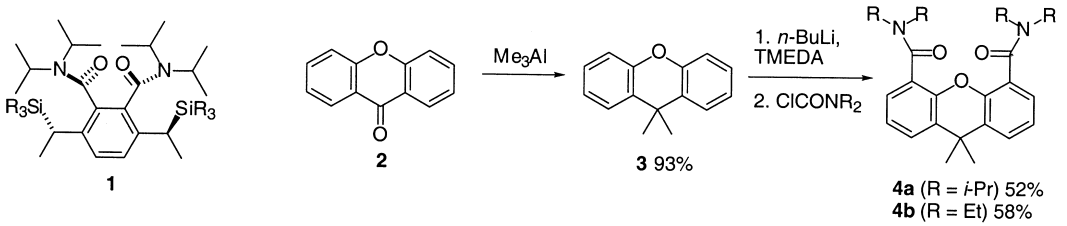
and the 9,9-dimethylxanthene **3** was doubly lithiated using *n*-BuLi in refluxing TMEDA.[6,8] The 4,5-dilithioxanthene was converted to the *N*,*N*,*N*,*N*-tetraethyl and tetraisopropyl xanthene-4,5-dicarboxamides **4a** and **4b** by reaction with the appropriate *N*,*N*-dialkylcarbamoyl chlorides (Scheme 1).



Scheme 1. Synthesis of xanthene-4,5-dicarboxamides

Ortho-substituted aromatic tertiary amide groups lie perpendicular to the ring,[9] allowing the xanthene-4,5-dicarboxamides to exist as either of two conformers (Fig. 1: *syn* or *anti*). Such conformers would interconvert too rapidly to be separated,[10] but should be separately discernible by NMR even at room temperature, and certainly on cooling. However, the NMR spectra of **4a**–**4c** showed only a single set of sharp peaks at 25°C, suggesting the presence of a single conformer in solution. Moreover, the 9,9-dimethyl group in both **4a** and **4b** was a 6H singlet in $CDCl_3$, C_6D_6 and $(CD_3)_2SO$, indicating that this single conformer has *anti* stereochemistry: the *anti* conformer has homotopic 9-methyl groups; in the *syn* diastereoisomer the 9-methyl groups are diastereotopic. Further evidence that **4a** exists as the *anti* conformer was provided by its ^{1}H NMR spectrum in the presence of 4 equiv. of Pirkle's chiral solvating agent (*R*)-TFAE [(*R*)-2,2,2-trifluoro-1-(9-anthryl)ethanol].[11,12] Two clear sets of signals became apparent, arising from the pair of enantiomeric conformers made diastereoisomeric by the chiral solvating agent. Only the *anti* conformer is chiral: the *syn* conformer has a plane of symmetry.

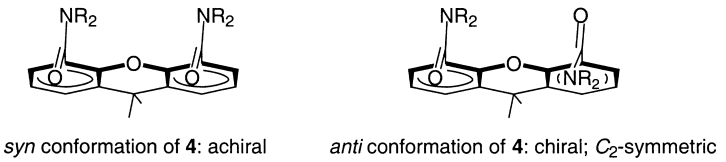


Figure 1. Conformations of a xanthene-4,5-dicarboxamide

The barrier to interconversion of the enantiomeric conformers of **4a** $\Delta G^{\ddagger}$ was estimated as 80 kJ mol^{-1} using variable temperature NMR spectroscopy in $(CD_3)_2SO$.[13]

Confident that the amide groups of **4** were in communication, despite their remoteness, we treated **4a** and **4b** with *s*-BuLi (5 equiv.) and excess ethyl iodide,[1,3,14] obtaining the bis-ethylated products **5**. Each amide group of **5** is now doubly *ortho*-substituted, and would be expected to rotate around the Ar–CO axis only very slowly—2,6-disubstituted benzamides usually exhibit atropisomerism at room temperature.[10] In principle, therefore, two diastereoisomers of **5** are possible: one *meso*, one a racemic pair. However, the *gem*-dimethyl group of both **5a** and **5b** still appeared as a 6H singlet; (*R*)-TFAE gave doubling of the signals of **5a**; and an X-ray crystal structure (Fig. 2) of **5a** confirmed that it was the C_2-symmetric, axially chiral atropisomer.

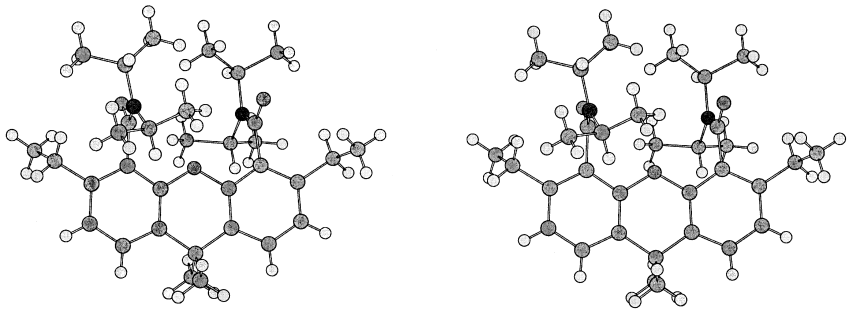
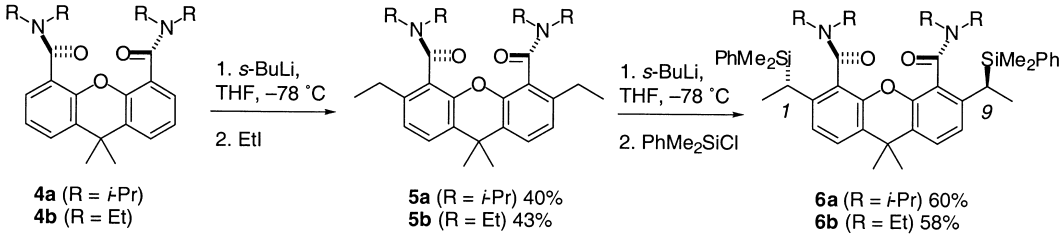


Figure 2. X-Ray crystal structure of **5a** (stereo views)

Atropisomeric amide groups are known to direct the stereoselectivity of lateral lithiation reactions,[1,14,15] and from **5** we had the opportunity to demonstrate the simultaneous stereocontrolled construction of 1,9-related stereogenic centres. Compounds **5a** and **5b** were treated with excess *s*-BuLi and then excess $PhMe_2SiCl$ (Scheme 2). Each reaction yielded a single diastereoisomer of a crystalline product **6a** or **6b**. The X-ray crystal structure of **6a** is shown in Fig. 3: it clearly shows the *anti* arrangement of the atropisomeric amide groups, in addition to the overall 1,9-*anti* relationship of the two new silyl substituents.



4a (R = *i*-Pr)
4b (R = Et)

5a (R = *i*-Pr) 40%
5b (R = Et) 43%

6a (R = *i*-Pr) 60%
6b (R = Et) 58%

Scheme 2. Control over 1,9-related stereogenic centres

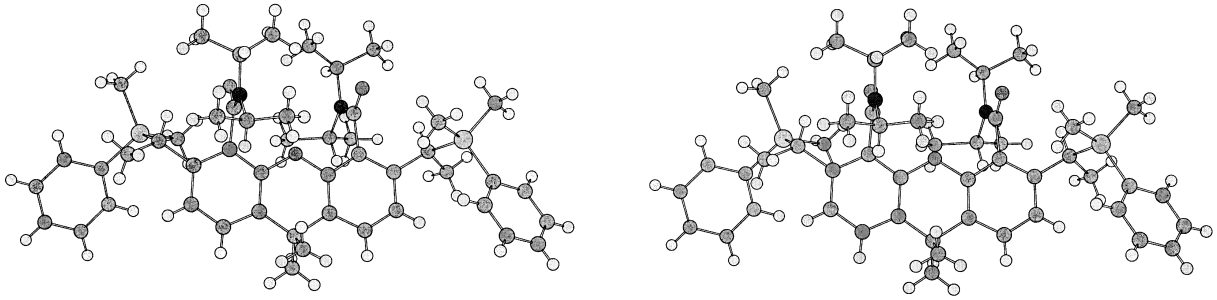
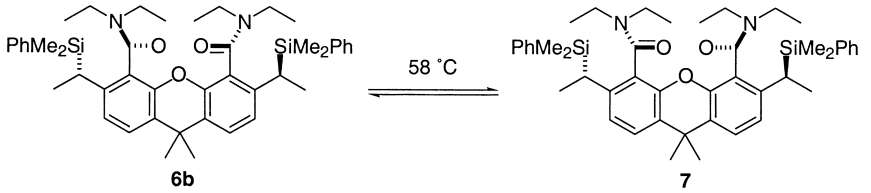


Figure 3. X-Ray crystal structure of **6a** (stereo views)

While **6a** was conformationally stable, we found, to our surprise, that **6b** was not. Failure to keep the reaction mixture cold during the work-up of **6b** led to formation of significant amounts of another C_2-symmetric diastereoisomer which we presume to be **7** (^{1}H NMR shows a 6H singlet

for the *gem*-dimethyl groups). **6b** could be equilibrated to a 1:1 mixture of **6b** and **7** (Scheme 3) by heating in solution at 58°C overnight. The difference in conformational stability between **6a** and **6b** is probably thermodynamic in origin. The known[1,10,13,16] thermodynamic preference for *syn* over *anti* stereochemistry with N*i*-Pr_2 amides bearing chiral *ortho*-substituents is weaker with the less sterically demanding NEt_2 amides—it is unlikely that the change from *i*-Pr to Et would lead to such a marked increase in *kinetic* propensity to epimerise.[10]



6b **7**

Scheme 3. Epimerisation of a *N*,*N*,*N*′,*N*′-tetraethyl xanthene-4,5-dicarboxamide

The diastereoselective syntheses of **6** confirm the ability of remotely related amide groups to relay stereochemistry over remarkably long distances.[17] We are currently investigating similar structures with a view to controlling even more remote stereochemical relationships using iterative methods.

Crystal data for **5a**: colourless block, 0.55×0.35×0.25 mm; $C_{33}H_{48}N_2O_3$; $M_r = 520.73$; monoclinic, space group *P*21/a (#14); $a = 12.38(4)$ Å, $b = 15.579(3)$ Å, $c = 16.632(5)$ Å; $\beta = 98.27(13)°$; $V = 3173(10)$ Å^3; $Z = 4$; data recorded at 293(2) K, 25 reflections used. Crystallographic data deposited with the Cambridge Crystallographic Data Centre, Cambridge, UK, reference CCDC 144175.

Crystal data for **6a**: colourless table, 0.50×0.35×0.20 mm; $C_{49}H_{68}N_2O_3Si_2$; $M_r = 789.23$; triclinic, space group $P\hat{1}$ (#2); $a = 12.903(3)$ Å, $b = 19.1375(3)$ Å, $c = 10.321(2)$ Å; $a = 91.29(2)°$, $\beta = 101.71(2)°$, $\gamma = 77.60(2)°$; $V = 2436.6(11)$ Å^3; $Z = 2$; data recorded at 296.2 K, 25 reflections used. Crystallographic data deposited with the Cambridge Crystallographic Data Centre, Cambridge, UK, reference CCDC 144232.

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