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Asymmetric Synthesis of Overcrowded Alkenes by Transfer of Axial Single Bond Chirality to Axial Double Bond Chirality**

Edzard M. Geertsema, Auke Meetsma, and Ben L. Feringa*

Sterically overcrowded alkenes have attracted considerable interest in view of their unique photochromic and thermochromic properties. In addition the beautiful architecture of these structures is as fascinating as their potential applications. Although they lack a stereogenic center they can exist as stable, optically active stereoisomers as a consequence of the presence of substituents that cause sufficient hindrance between the upper and lower half of the alkene and enforce a helical distortion to the entire molecule. Unsymmetrical cis and trans isomers of overcrowded alkenes were shown to act as chiroptical molecular switches suitable for reversible data storage while other applications include photomodulation of liquid-crystalline materials and thin polymer films. A practical synthetic route towards enantiomerically pure over-
crowded alkenes is still a challenging goal.\textsuperscript{[9]} Methodology has been developed for the synthesis of optically active biaryls in which control of the chirality of an axial single bond is achieved by the coupling of two aryl moieties to a chiral bridge.\textsuperscript{[6]} Based on a related principle we present the synthesis of stable enantiomers of an overcrowded alkene, which features axial double bond chirality, by using \((-\)-\textsuperscript{2,3}-\textsuperscript{O}-isopropylidene-\textsuperscript{1,4}-ditosylate ((SS)-1), (+)-(R)-1,1\textsuperscript{1}-binaphthol ((R)-2), and \((-\)-(S)-1,1\textsuperscript{1}-binaphthol ((S)-2) as chiral auxiliaries. In our most successful approach two halves of the envisioned alkene were first coupled to the binaphthol chiral bridge. A diastereoselective intramolecular coupling reaction then afforded the corresponding overcrowded alkenes. As no racemization was observed after removal of the chiral bridge this sequence implies the realization of the intriguing concept of conveying axial single bond chirality to stable axial double bond chirality. Moreover, we report for the first time the determination of the absolute configuration of enantiomerically pure bis-thioxanthylidenes as accomplished by X-ray analysis.

Initially we focussed on chiral template 1, which is derived from tartaric acid (Scheme 1). An earlier attempt by Yip et al. to prepare optically active bifluorenylidenes\textsuperscript{[7]} along these lines resulted in the complete loss of optical activity as a result of the product having a low barrier to racemization.

The preorganized system (SS)-4 was prepared from 7-methoxy-\textsuperscript{9}-exo-\textsuperscript{9}H-thioxanthene-2-carboxylic acid (3)\textsuperscript{[9]} and (SS)-1. An intramolecular copper-promoted gem-dichloride coupling reaction\textsuperscript{[9]} afforded the sterically overcrowded alkenes (SS,M)-5 (major product) and (SS,P)-5 (minor product) in 20% yield.\textsuperscript{[10]} This rather low yield is a result of the extensive formation of oligomers during the coupling reaction, which unfortunately could not be suppressed by working at high dilution. The newly formed alkene moiety is chiral as a consequence of its folded structure, which explains the formation of the two diastereoisomers. A diastereomeric excess of 60% was determined by \textsuperscript{1}H NMR spectroscopy. Recrystallization from acetone gave crystals of pure (SS,P)-5 that were suitable for X-ray analysis (Figure 1). The unique folded structure of the overcrowded alkene part of (SS,P)-5 is clearly visible and based on the 2S,3S configuration of the \textsuperscript{1}-threitol moiety a (P)-configuration for the diester moiety is established. The helical structure of (SS,P)-5 is quantified by torsion angles of 50.6 (C8-C30-C28-C29) and 59.2° (C30-C28). The major isomer (SS,M)-5 could not be obtained diastereomERICALLY pure, despite several attempts.

In order to develop a synthetically useful asymmetric route we employed (R)-2 and (S)-2 as chiral templates (Scheme 2 for (R)-2, the same procedure was applied for (S)-2). The diester (R)-6 was prepared from thioxanthone 3 and (R)-2 in two steps in nearly quantitative yield. More importantly the yield of the subsequent intramolecular gem-dichloride coupling reaction with Cu-bronze increased considerably and diastereoisomers (R,M)-7 (major product) and (R,P)-7 (minor product) were obtained in 54% yield in a 81.5:18.5 ratio (\textsuperscript{1}H NMR). Apparently the more rigid binaphthol-based chiral diester bridge of the tetrachloride derived from (R)-6 enforces a more favorable geometry to the two thioxanthene moieties and suppresses oligomer formation through intermolecular coupling. The diastereoisomers (R,M)-7 and (R,P)-7 were readily separated by column chromatography.

It should be emphasized that both a folded and twisted helical shaped structural moiety is present in the same molecule. The two diastereoisomers differ significantly in structure as is visualized in Scheme 2. Although the binaphthyl part is twisted and the thioxanthylidene is folded in both isomers, the formation of the “cross-coupled” product (R,M)-7 is strongly favored over the “linearly coupled” product (R,P)-7. Figure 2 shows an optimized space filling model\textsuperscript{[11]} of (R,M)-7 revealing a double-helix-type structure that is
reminiscent of the helical structure Nozaki et al. found for their double-helical oligo esters.\[^{[12]}\] The configurations of diastereoisomers \((R,M)\)-7 and \((R,P)\)-7 (and of diastereoisomers \((S,P)\)-7 (major product) and \((S,M)\)-7 (minor product) obtained from \((S\_2)\) were unequivocally established after removal of the chiral bridges of all obtained diastereoisomers \((S,S,P)\)-5 (minor product), \((R,M)\)-7, \((R,P)\)-7, \((S,P)\)-7, and \((S,M)\)-7). The overcrowded alkenes were liberated from their chiral bridge by reduction with LiAlH\(_4\) to provide enantiomers of thioxanthylidenes \((P\_cis)\)-8 and \((M\_cis)\)-8 with \(ee\) values of 96 ± 1 % as determined by chiral HPLC (Scheme 3). Based on the X-ray analysis of \((S,S,P)\)-5 the overcrowded alkene part has a \(P\) configuration, which leads to \((P\_cis)\)-8 after removal of the \(\alpha\)-treitol moiety. The analytical data of \((P\_cis)\)-8 (optical rotation, CD data, and retention times on chiral HPLC) obtained from \((S,S,P)\)-5 were correlated with those of the enantiomers of \(cis\)-8 obtained by reductive cleavage of the four diastereoisomers \((R,M)\)-7, \((R,P)\)-7, \((S,P)\)-7, and \((S,M)\)-7. The results are outlined in Table 1.

**Scheme 2.** Synthetic route towards optically active overcrowded alkenes 7 with \((R)\)-2 used as a chiral template. \(R\) and \(S\) denote the configuration of the binaphthol moiety whereas \(M\) (left-handed helix) and \(P\) (right-handed helix) define the helicity at the diester side of the overcrowded alkene part of the molecule.

**Scheme 3.** Cleavage of the chiral bridge (CB) from overcrowded alkenes 5 and 7. \(M\) (left-handed helix) and \(P\) (right-handed helix) define the helicity at the hydroxymethyl-side of 8.

**Table 1.** Stereochemical correlation and optical rotation data of 5, 7, and 8.

<table>
<thead>
<tr>
<th>Substrate</th>
<th>([\alpha]_D^{[a]})</th>
<th>Product</th>
<th>([\alpha]_D^{[b]})</th>
</tr>
</thead>
<tbody>
<tr>
<td>((S,S,P))-5 (minor)</td>
<td>+ 203</td>
<td>((P_cis))-8</td>
<td>- 92</td>
</tr>
<tr>
<td>((R,M))-7 (major)</td>
<td>- 101</td>
<td>((M_cis))-8</td>
<td>+ 91</td>
</tr>
<tr>
<td>((R,P))-7 (minor)</td>
<td>+ 120</td>
<td>((P_cis))-8</td>
<td>- 93</td>
</tr>
<tr>
<td>((S,P))-7 (major)</td>
<td>+ 100</td>
<td>((P_cis))-8</td>
<td>- 92</td>
</tr>
<tr>
<td>((S,M))-7 (minor)</td>
<td>- 120</td>
<td>((M_cis))-8</td>
<td>+ 91</td>
</tr>
</tbody>
</table>

[a] \(c = 1.00, \text{CHCl}_3\), [b] \(c = 0.50, \text{CHCl}_3\).

A racemization barrier \((\Delta^G)^\circ\) of 26.7 ± 0.5 kcal mol\(^{-1}\) (polarimetry) was determined for \(cis\)-8, which is in accordance with the observation that the enantiomers of \(cis\)-8 are stable at room temperature. A pair of identical CD spectra (except for the sign) were obtained for enantiomers \((P\_cis)\)-8 and \((M\_cis)\)-8. Seven maxima were observed for \((M\_cis)\)-8 (\(n\)-hexane/2-propanol 80/20) at wavelengths greater than 220 nm: \(\lambda_{\text{max}} (\Delta)\) 230 nm (−3.5), 238 (+17.3), 252 (−6.2), 269 (−25.3), 291 (−38.6), 313 (+18.4), 342 (+10.7). The CD absorptions as well as the \(\Delta\) values are in good agreement with those obtained for related optically pure overcrowded alkenes that were obtained previously by preparative chiral HPLC.\[^{[5]}\]

In conclusion, an asymmetric synthesis method, which includes the transfer of axial single bond chirality to axial double bond chirality, for stable optically active overcrowded alkenes has been developed. The determination of the absolute configuration of the major stereoisomer revealed an appealing double-helical structure.

**Experimental Section**

\((R,M)\)-7 and \((R,P)\)-7 (the same procedure was used for \((S,P)\)-7 and \((S,M)\)-7): Duster \((R)\)-6 (0.73 mmol) was refluxed overnight in oxalyl chloride (20 mL) under a nitrogen atmosphere. The excess of oxalyl chloride was evaporated under reduced pressure. The residue was dissolved in freshly distilled \(p\)-xylene (100 mL) and then activated Cu-bronze (15.90 mmol) was added. This mixture was refluxed overnight. After cooling, the mixture was filtered and the filtrate was concentrated in vacuo. Purification of the residue by silica gel column chromatography (CH\(_2\)Cl\(_2\)/n-hexane 3/1) gave \((R,M)\)-7 (44 % yield) and \((R,P)\)-7 (10 % yield) as yellow solids. \((R,M)\)-7: 1\(^H\) NMR (300 MHz, CDCl\(_3\), 25 °C): \(\delta = 8.02\) (d, \(\text{J}(\text{H,H}) = 9.15\) Hz, 2H, CH); 7.96 (d, \(\text{J}(\text{H,H}) = 8.42\) Hz, 2H, CH); 7.49–7.29 (m, 12H, CH); 7.18 (d, \(\text{J}(\text{H,H}) = 8.42\) Hz, 2H, CH); 7.07 (m, 2H, CH); 6.77 (m, 2H, CH); 6.42 (d, 2H, CH).
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Keywords: alkylens · asymmetric synthesis · biaryl · chirality · helical structures


[8] Compound 3 was prepared from 4-methoxybenzenethiol and 4-bromoisothiocyanate in a two-step procedure.


[10] The chirality of this type of helical-shaped distorted alkenes is described by the helicity rule, with P (plus) for a right-handed helix and M (minus) for a left-handed helix, see for example, R. S. Cahn, C. K. Ingold, V. Prelog, Angew. Chem. 1966, 78, 413; Angew. Chem. Int. Ed. Engl. 1966, 5, 385.

[11] The model of (R,M)-7 was constructed by using Quanta97/CHARMM, which is a product of Molecular Simulations Inc., San Diego, USA. Internet: http://www.msi.com. Dr. Franck Schoenbeek is acknowledged for his assistance.


Influence of Perfluoroarene–Arene Interactions on the Phase Behavior of Liquid Crystalline and Polymeric Materials**

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Supramolecular chemistry, the chemistry of noncovalent intermolecular interactions such as hydrogen bonds, ionic interactions, metal–ion interactions, or the hydrophobic effect, is essential for processes in biological and synthetic systems, such as molecular recognition, catalysis, transport,