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Chirality transfer from a biphenyl axis to a spiro centre and its reverse: sequential self-immolation

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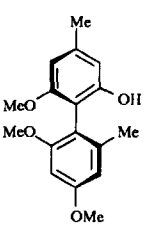
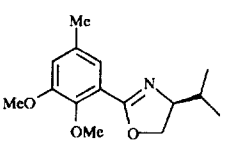
Abstract: Schmidt reaction of (*S*)-1-(2,4',6-trimethoxy-4,6'-dimethylbiphenyl-2-yl)ethanone **8** furnished the expected amide **9** (43%) accompanied by (*S*)-2,7'-dimethoxy-3',5',6-trimethylspiro[cyclohexa-2,5-diene-1,1'-(1*H*)isoindole]-4-one **12** (30%) which on reduction with zinc and acetic acid and subsequent methylation regenerated ketone **8**.

In connection with the synthesis[1] of the fungal bicoumarin desertorin C we required the phenol **1** in atropenantiomerically pure form. One of the abortive synthetic routes to this compound which we explored involved a Schmidt rearrangement which gave besides the expected product a compound in which self-immolative intramolecular chirality transfer from a biphenyl axis to a spiro centre had occurred. The synthesis and structural determination of this unusual product are the subjects of the present communication.

The oxazoline **2**, which was obtained in the conventional way from the appropriate benzoyl chloride[2] and (*S*)-valinol, was allowed to react in boiling THF with the Grignard reagent **3** which supplied a coupled product (88%) in which the diastereoisomeric ratio was 7.3:1 in favour of the diastereoisomer **4** as shown by the ^{1}H NMR spectrum of the derived methiodides.



1



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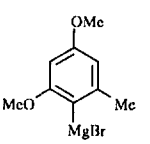

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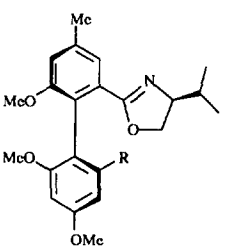

4 R = Me
5 R = CH_2OH

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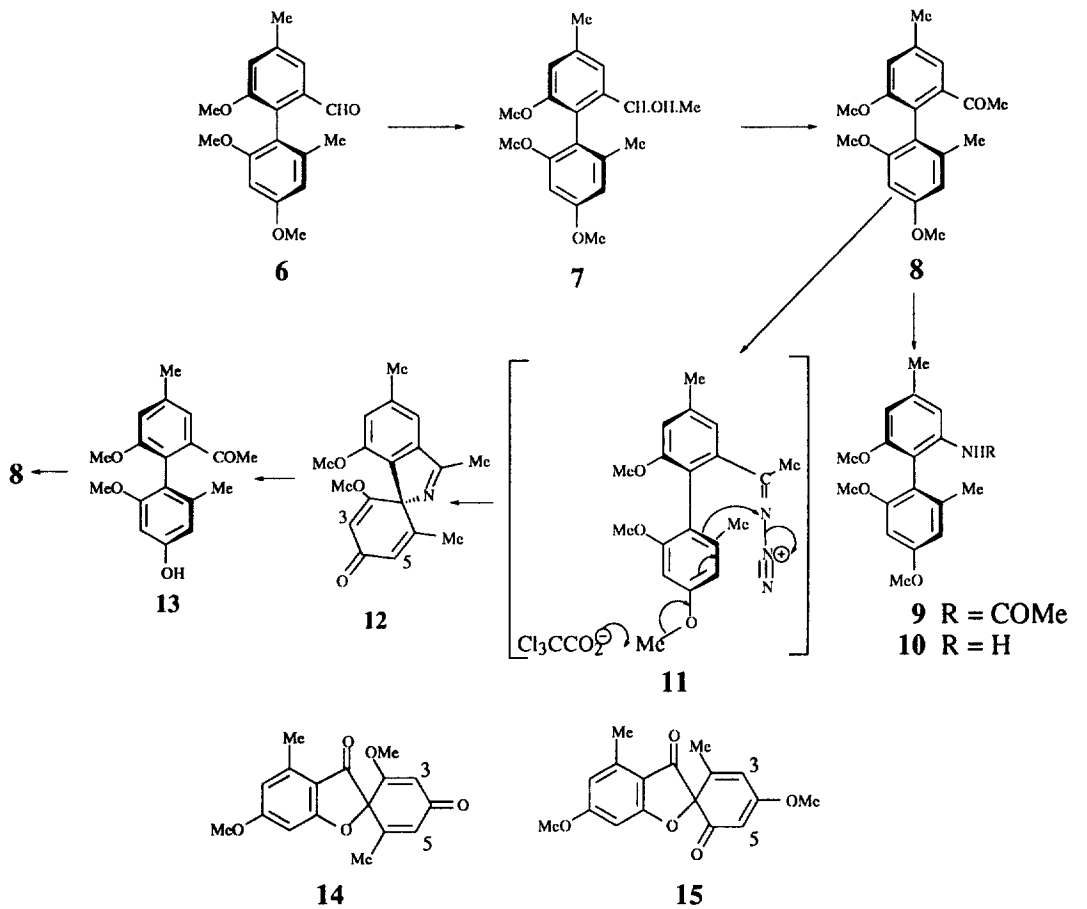
That the major diastereoisomer had the *S* axial configuration was predicted on mechanistic grounds[3] and confirmed by the similarity of its CD spectrum to that of pure **5**, synthesised in a similar manner and subjected to X-ray crystal structure determination.[4]

The mixture of oxazolines enriched in **4** was converted into the aldehyde **6** (52%) by sequential treatment of the derived methiodides (MeI, $MeNO_2$, 60°C) with sodium borohydride and oxalic acid. The enantiomeric ratio (e.r.) of the aldehyde was 6.1:1 as shown by the ^1H NMR spectrum of its sodium borohydride reduction product determined in the presence of (*S*)-1-(anthracen-9-yl)-2,2,2-trifluoroethanol. This aldehyde **6** was stable enough to thermal racemisation to be obtained enantiomerically pure, $[\alpha]_D^{20}$ – 92 (*c* 1.00, $CHCl_3$), m.p. 89-91°C, by four crystallisations from chloroform/light petroleum.



Treatment of the aldehyde **6** (e.r. 6.1:1) with methylmagnesium iodide in THF at –78°C – 25°C and oxidation of the resultant mixture (4.3:1) of epimeric alcohols **7** (91%) with PCC at 25°C gave the ketone **8** (83%), m.p. 80-82°C, $[\alpha]_D^{20}$ – 53 (*c* 1.30, $CHCl_3$).[5]

Schmidt rearrangement of the ketone **8** during 27h at 60°C with sodium azide in trichloroacetic acid gave the expected amide **9** (43%) which on hydrolysis furnished the amine **10**, m.p. 129-130°C, $[\alpha]_D^{20}$ – 33 (*c* 1.10, $CHCl_3$). No product of alkyl migration could be detected.[6] Another product (30%), m.p. 190-192°C, $[\alpha]_D^{20}$ 30 (*c* 0.62, $CHCl_3$),[7] was also isolated. Extensive ^1H and ^{13}C NMR spectral studies showed that it was the (*S*)-spiroisoindolylcyclohexadienone **12** derived by rearside attack (**11**, arrows) at the *ipso* position of the activated orcinol ring. That it was a cross-conjugated dienone rather than a linearly conjugated dienone followed from the magnitude (1.3 Hz) of $J_{3,5}$ in its ^1H NMR spectrum when compared to the dienones **14**[8] ($J_{3,5}$ 1.5 Hz) and **15**[9] ($J_{3,5}$ 2.2 Hz). Similar cross-conjugated spirocyclohexadienones, e.g. **14**, have been previously obtained from activated orcinol and phloroglucinol type rings by intramolecular *ipso* attack of an acylium ion.[8]

Further evidence for structure **12** came from cleavage of the spiro C-N bond with zinc and acetic acid (25°C), the resultant ketimine suffering hydrolysis, thereby yielding the ketone **13** (79%) readily converted by methylation (MeI, K_2CO_3, Me_2CO, 25°C) into the ketone **8** (82%), $[\alpha]_D^{20}$ – 55 (*c* 0.40, $CHCl_3$).

Attempts to determine the enantiomeric purity of the spiro compound **12** were frustrated since it migrated as a single band on HPLC on two different chiral columns[10] and the anthracenyl shift reagent was ineffective. In view of the stability of the aldehyde **6** to thermal racemisation and the mild conditions involved in the preparation of the ketone **8** the e.r. of this compound is likely to be 6.1:1. Since the specific rotation of the ketone **8** obtained at the end of the sequence is the same, within experimental error, as that of the initial ketone it may be concluded that little racemisation occurred throughout the sequence.

The cycle **8** → **12** → **8** thus involves the intramolecular transfer of biphenyl axial chirality to a spiro centre followed by the destruction of this centre and the recreation of the biphenyl axis. Such intramolecular processes which involve the intramolecular transfer of stereogenecity by the mutual destruction and creation of chiral elements have been termed self-immolative.[11] Examples in which the two chiral elements are a biaryl axis and a carbon centre are rare. Robinson recognised the first example of this process where the chiral centres of thebaine are transferred to the chiral axis of phenyldihydrothebaine. A few other examples of this type have since been discovered in natural products chemistry[13] and Meyers and Wettlaufer[14] have described an example of the transfer of a single chiral centre to a biaryl axis in a synthetic compound. The only work similar to the present of which we are aware is that of Ohno and his coworkers[15] in which an example of the self-immolative transfer of axial to central chirality and its reverse are described.

Notes and References

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4. The synthesis of compound **5** will be described in a full paper as will its X-ray structural determination which was performed by Assoc. Prof. A.H. White and Dr. B.W. Skelton.
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