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Strigol Synthetic Studies
The First Synthetic Approach that Allows Control of C-2′ Configuration

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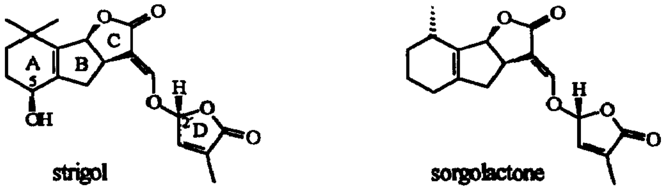
Abstract - A phenylthio group has been used to control stereoselective bond formation at C-2′.

Germination of seeds of root parasitic flowering plants of the genera *Striga*, *Alectra* (Scrophulariaceae), and *Orobanche* (Orobanchaceae) is stimulated by substances from their host plants. Prominent examples are strigol and sorgolactone.[1]



strigol sorgolactone

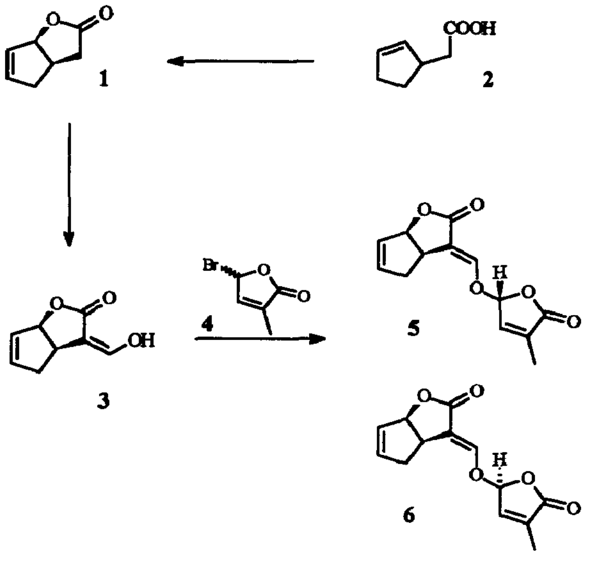
Scheme 1

Very specific interactions between the stimulant and the binding site(s) at the seed seem to exist. For *Orobanche crenata* seeds it has been found that the absolute configuration at C-2′ is of major importance as far as seed germination potency is concerned.[1]

Non-racemic samples of strigol, its stereoisomers, and of structural analogues have been obtained both by resolution[2,3,4,5] and by asymmetric synthesis.[6,7] However, for one stereochemical problem no solution has previously been found, namely control of the configuration at C-2′. In all cases reported so far, a synthetic intermediate of type 1 was converted into a hydroxymethylene derivative 3 which was in turn coupled with racemic, configurationally unstable bromo lactone 4 to give a 1:1-mixture of 2′-epimers such as 5 and 6.[3,4,7,8,9,10]

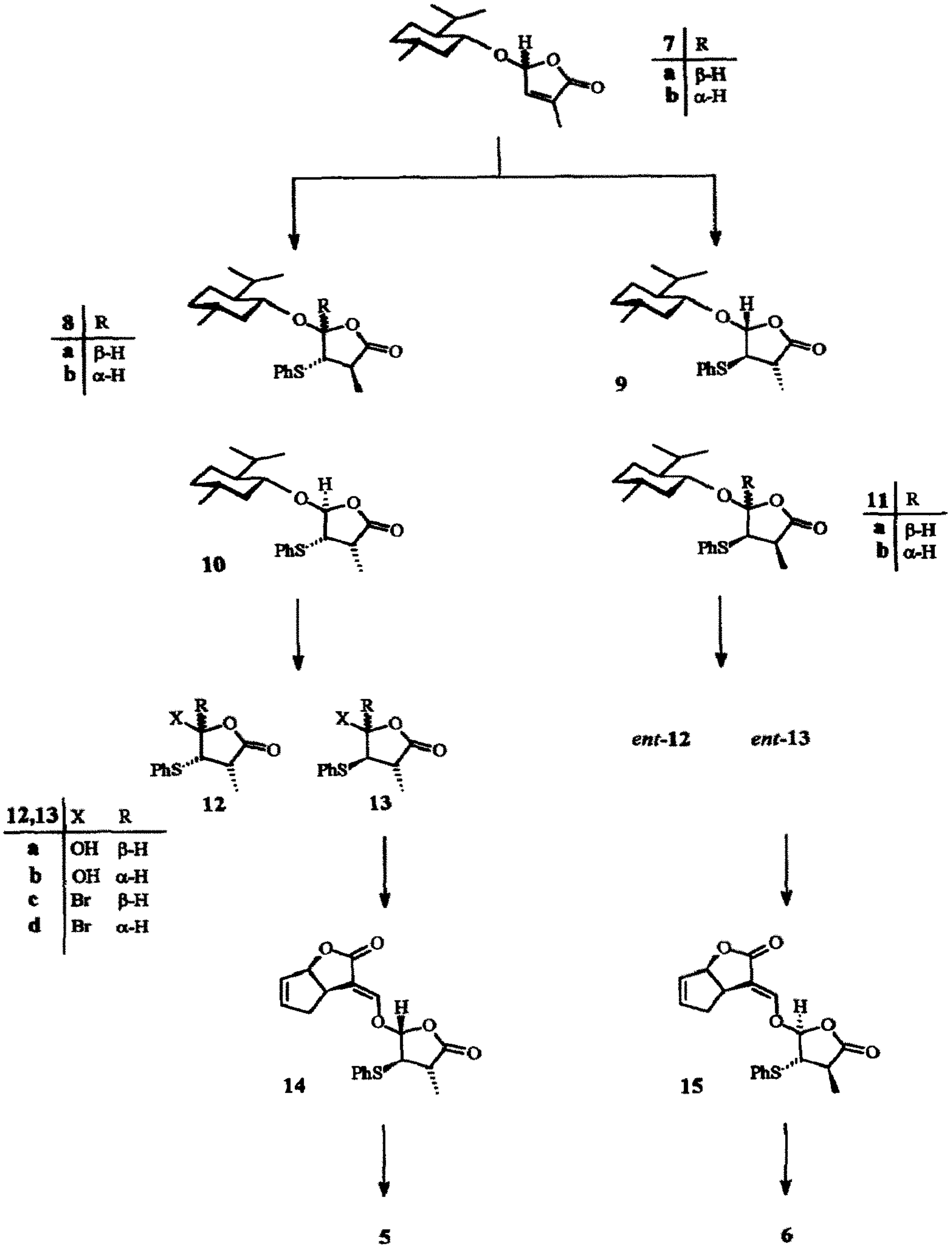
It is the purpose of this publication to discuss preliminary results which indicate that this difficulty can be mastered. The stereohomogeneous strigol analogue GR 28 (5) and its 2′-epimer 6 have been obtained stereoselectively. The precursors and reference samples were prepared starting from *rac*-2 which was cyclized with cat. Pd(OAc)$_2$[11] to provide *rac*-1.[12] Resolution of *rac*-1 was achieved by cellulose triacetate chromatography. 1[13] was then converted to 5[13] and 6[13] via 3. Similarly, *ent*-5 and *ent*-6 were obtained from *ent*-1. The relative configuration at C-2′ in 5 and 6 rests on X-ray analysis.[12] The absolute configuration was determined by means of circular dichroism. The CD spectrum of **5** is almost superimposable to that of strigol[12] and that of **6** is practically identical with that of 2'-epistrigol.[12]

We reasoned that control at C-2'should be possible making use of Feringa'*s* work.[14] Thus, **7a** and **7b** were obtained and separated as described.[15] Treatment of **7a** with thiophenol yielded **9** and **11a**. In later experiments it turned out to be more convenient to treat the mixture of **7a** and **7b** with thiophenol and separate adducts **8b**, **10**, **9**, and **11a** chromatographically. Configurational assignment of **11a** and **9** was achieved by X-ray analysis.[16] As already published by Feringa,[14] thiophenol adds trans to the menthyloxy group of **7a**. Protonation of the intermediate anion is then almost stereo-random, addition of the proton opposite to the phenylthio group being slightly preferred. The determination of the configuration of these compounds turned out to be quite complicated since they adopt different conformations in solution and in the crystalline state. According to the X-ray analysis[16] **9** adopts a ^4E-conformation in the crystal. From the torsional angles as calculated from the X-ray structure, (3'-H)C-3' - C-4'(4'-H) = -98.4° and (4'-H)C-4' - C-5'(5'- H) = 99.4°, one would expect narrow multiplets for all ring protons in the ^1H NMR spectrum. This is, however, not the case: $J_{4',5'}$= 4.0 Hz and $J_{3',4'}$= 7.5 Hz are observed. Obviously, in solution the 5-membered ring adopts a twist conformation with the large substituents in pseudo-equatorial position. Similar results have been obtained for **11a**. In **9** a NOE between 3'-H and 5'-H demonstrates the cis relation between these protons. In **11a** this NOE signal is lacking. The configurations as depicted in **10** and **8b** were assigned by comparison of the ^1H NMR spectra with those of **9** and **11a**, again a NOE between 3'-H and 5'-H proved these two protons to be cis in **8b**. The auxiliary menthyl group was removed from **10** and **11a**, respectively, by acid hydrolysis. In each experiment a mixture of compounds was formed which contained more components than expected. We were unable to separate these mixtures. However, when the hydrolysis products of **11a** were treated with (-)-menthol in the presence of p-toluenesulfonic acid, four compounds were formed. Two of them could be readily identified to be **11a** and **8b**. According to spectral data the other compounds were **11b** and **8a**. The formation of **8a** and **8b** can be explained assuming the hydrolysis products *ent*-**12a** and *ent*-**12b** to



Scheme 2

be in equilibrium with the ring opened aldehyde, the α-position of which is of course stereo-labile. Similary, from **10** the hydrolysis products **12a**/**12b** and **13a**/**13b** were formed. The observed stereoisomerization at C-3′



Scheme 3

has, of course, to be avoided, if this approach were to become a useful way to stereohomogeneous strigol-type compounds, as the phenolthio group is intended to stereodirect bond formation at C-2'.[17]

In order to probe the stereodirecting properties of the C-3'substitutent, the mixture containing **12a/12b** and **13a/13b** was treated with CBr_4/PPh_3.[18] Three bromo derivatives could be isolated. The most readily isolated compound which also turned out to be the most stable one, was assigned structure **13d** on the basis of H,H coupling constants ($J_{3,4}$= 12.0 Hz and $J_{4,5}$= 4.6 Hz, for comparison, see[19]). This compound (note the inverted configuration at C-3' when compared with **10**) was coupled with non-racemic **3** in the presence of silver carbonate. However, this promotor turned out to be quite unsuitable as far as rate and yield of the reaction were concerned. A very slow reaction occurred and a mixture of compounds was formed. After 14d **14** was isolated in 16% yield alongside with a rearrangement product.[20] Oxidation of **14** with mCPBA followed by elimination in the presence of Et_3N yielded stereohomogeneous **5** in 79% (based on **14**).

Because of the difficulties experienced with Ag_2CO_3 recourse was made to Ag silicate.[21] Treatment of *ent*-**13c** with **3** in the presence of Ag silicate yielded coupling product **15**[22] (30% after 50h). Again, oxidation and elimination proceeded smoothly to furnish **6**. The properties of both **5** and **6** (including $[\alpha]_D$ values) were identical with those of reference samples prepared as summarized in Scheme 2.

In conclusion, for the first time it was possible to control the configuration at C-2' in strigol type compounds although the methods certainly needs improvement. Work along theses lines including a cycloaddition/cycloreversion variant is in progress.

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[13] $[\alpha]_D$ values: **1**: -131.3 (c 1.0, CH_2Cl_2), **5**: 130.9 (c 0.6, $CHCl_3$), **6**: 28.6 (c 0.6, $CHCl_3$).

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