Strigol-type germination stimulants: the C-2′ configuration problem

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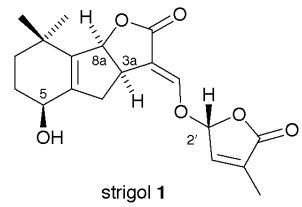
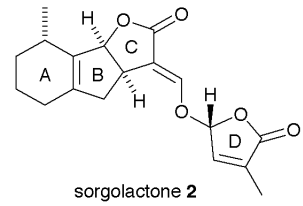
Germination of root parasites of the Scrophulariaceae and the Orobanchaceae is known to be induced by chemicals which are released from the roots of their host plants. An important class of germination stimulants are the strigolactones. Reviewed are (i) the connection of the configuration at C-2′ of the strigolactones and their seed germination potencies, (ii) methods for configurational assignment at C-2′, and (iii) stereocontrol at C-2′ in the synthesis of strigolactones.

Introduction

Root parasitic flowering plants of the genera *Striga*, *Alectra* (Scrophulariaceae) and *Orobanche* (Orobanchaceae) and their respective host plants use a very interesting system of chemical communication. It has long been known that germination of the seeds of the parasites is stimulated by compounds exuded from the roots of their host plant into the soil. Well-known stimulants are strigol (**1**) and its acetate (isolated from *Striga* hosts[1] and from cotton, *Gossypium hirsutum*,[2] a non-host), as well as sorgolactone (**2**, isolated from the root exudates of *Sorghum vulgare*,[3] a host for *Striga*). Recently, orobanchol, an isomer of strigol, has been isolated by Yokota *et al.* from root exudates of the host, *Trifolium pratense*. It is assumed that the secondary hydroxy group in orobanchol is attached to C-4.[4] Finally, from the root exudates of *Vigna unguiculata*[5] (host for *Striga* and *Alectra*) a compound, alectrol, has been isolated. A structure has been proposed for this compound that has recently been rejected.[6]

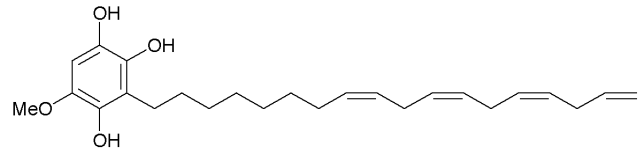


strigol **1**



sorgolactone **2**

It has been claimed that the true stimulants are in fact hydroquinones of type **3** (dihydrosorgoleone).[7] This suggestion will not be further discussed here. The present review will rather restrict itself to the problem of the strigol-type stimulants (also called strigolactones).



dihydrosorgoleone **3**

Structure–activity relationships

The exchange of chemical information indicated above raises basic questions, such as: (i) which structural features of the stimulants are essential to elicit a high seed germination potency; (ii) how is the chemical signal released from the host recognized by the seed; and (iii) how does the primary chemical signal initiate the biochemical processes that are involved in germination?

Whereas over the years an appreciable knowledge on the structure–activity relationships has accumulated (mainly driven by the desire to use this system for a novel approach of parasitic weed control), questions (ii) and (iii) are largely unanswered. Even the results of structure–activity investigations are not clear-cut. They indicate that very specific interactions exist between the stimulants and the binding site(s) at the seeds. However, it has been demonstrated that the interactions are species–dependent and may vary from test to test. Structure–activity relationships obtained from different test systems should, thus, be compared only with great care. The problem has been reviewed and discussed in detail by Zwanenburg and co-workers who also recommended a standard bioassay.[8]

In addition, the configuration at the various stereogenic centres of the stimulants is of great importance with respect to seed germination activity. Much of the older work was performed with mixtures of stereoisomers and is, thus, of

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limited value. As such, only results from single stereoisomers will be considered.

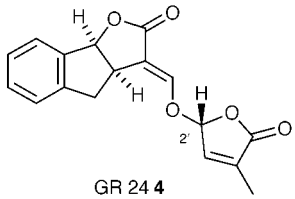
The first study with pure strigol isomers was published by Hauck and Schildknecht who found that strigol (**1**) was active (half-maximum germination) for *Striga asiatica*, *Orobanche aegyptiaca* at concentrations of 6×10^{-11} and 7×10^{-10} mol l^{-1}, respectively. The non-natural *ent*-strigol had to be 500 and 300 times more concentrated to be as active. For *Alectra vogelii*, however, *ent*-strigol was 20 times more active than the natural isomer.[9]

The Hauck study was complemented by work of Bergmann *et al.* showing that, in addition to the absolute configuration, the configuration at C-2′ is of major importance, at least as far as *Orobanche crenata* is involved (see Table 1).[10]

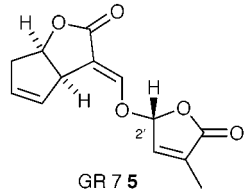
Table 1 Activity of strigol analogues in *O. crenata* seed germination bioassays: $c_{½}$ = concentration of half maximal stimulation of germination (ref. 10)

Compound	Configuration at C-2′	$c_{½}$/mol l^{-1}	$c_{½}$ (relative)
Strigol (**1**)	*R*	$8.5\ 10^{-8}$	1.0
ent-Strigol	*S*	$3.4\ 10^{-6}$	40.0
2′-*epi*-Strigol	*S*	$2.3\ 10^{-6}$	27.1
ent-2′-*epi*-strigol	*R*	$1.0\ 10^{-6}$	11.8
rac-GR24 (**4**)	*RS*	$3.4\ 10^{-7}$	
rac-2′-*epi*-GR24	*SR*	$3.4\ 10^{-6}$	

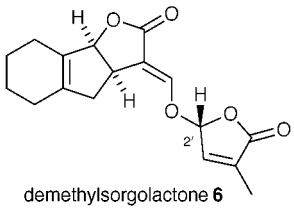
The largest collection of experimental results comes from Binne Zwanenburgś laboratory. Homogeneous stereoisomers in the GR7 (**5**),[11] GR24 (**4**),[12] demethylsorgolactone (**6**),[13] sorgolactone (**2**)[14] and Nijmegen 1 (**7**)[15] series have been



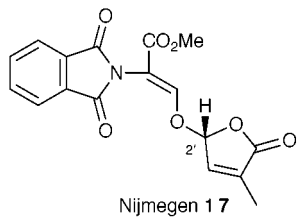
GR 24 **4**



GR 7 **5**



demethylsorgolactone **6**



Nijmegen 1 **7**

prepared. Tables 2 and 3 summarize the structure-activity results for GR7 and GR24. Similar results have been obtained for the other series.

Zwanenburg has stressed that in each experiment a reference compound should be used in order to get reliable results.[8] In most cases a mixture of GR 24 stereoisomers has been employed to serve this purpose. Using a mixture may be tolerated as long as one can be sure that only GR 24 itself (configuration as shown in formula **4**) is biologically active (as was found to be the case for *Striga hermonthica* and *Orobanche crenata*, see Table 3). It was also observed by the Nijmegen group that at higher concentrations differences between various stereoisomers are hidden because all of them are active. Zwanenburg solved this problem by defining a 'sensitive concentration' in each set of experiments in which differences for the stereoisomers are clearly visible (see Tables 2 and 3). Of course, the best solution for this problem is to determine an accurate dosage–activity curve in each case and extract an ED_{50} value (*cf.* the Hauck[9] and Bergmann[10] work described above).

From the results summarized here it follows that single stereoisomers differ greatly in their stimulating activities (under the proper conditions) which appears to permit the conclusion that germination stimulants are highly selectively recognized at the surface of the parasitic seeds. In almost all cases studied so far the correct configuration at C-2′ is of major importance.

Table 2 Germination percentages after exposure to solutions of GR7 (ref. 11)

Species	Compound	Configuration at C-2′	Germination (%) 1 mg l^{-1}	Germination (%) 0.01 mg l^{-1}
S. hermonthica	GR7 (5)	*R*	52.2 + 5.2	30.0 ± 4.1
S. hermonthica	2′*epi*-GR7	*S*	37.4 ± 4.9	—
S. hermonthica	*ent*-GR7	*S*	16.0 ± 5.2	—
S. hermonthica	*ent*-2′-*epi*-GR7	*R*	52.5 ± 4.4	—
S. hermonthica	GR24 (**4**)	[a]	61.3 ± 5.2	68.2 ± 4.9
O. crenata	GR7 (**5**)	*R*	76.6 ± 2.4	22.6 ± 2.4
O. crenata	2′-*epi*-GR7	S	26.0 ± 3.0	—
O. crenata	*ent*-GR7	*S*	3.1 ± 1.2	—
O. crenata	*ent*-2′-*epi*-GR7	*R*	76.4 ± 3.2	—
O. crenata	GR24 (**4**)	[a]	78.4 ± 3.7	13.3 ± 2.9

[a] Mixture of four stereoisomers.

The C-2′ stereochemical problem

Synthesis of strigol-type compounds is interesting for several reasons: (i) to understand the structure–activity relationships of this fascinating chemical communication system; (ii) to set the chemical basis for studying the biochemistry of the recognition and germination processes, respectively and (iii) to develop a novel method for parasitic weed control. Parasitic weeds of the genera *Striga*, *Orobanche* and *Alectra* cause severe damage to gramineous and leguminous crops in the Mediterranean and tropical areas of Africa and the eastern hemisphere. It is known that inducing germination in the absence of the host plant results in starvation of the seedlings after a short time. Thus, introducing a stimulant into the soil to induce germination of the parasitic weeds before planting the desired crop would represent a very selective method for parasitic weed control.[16]

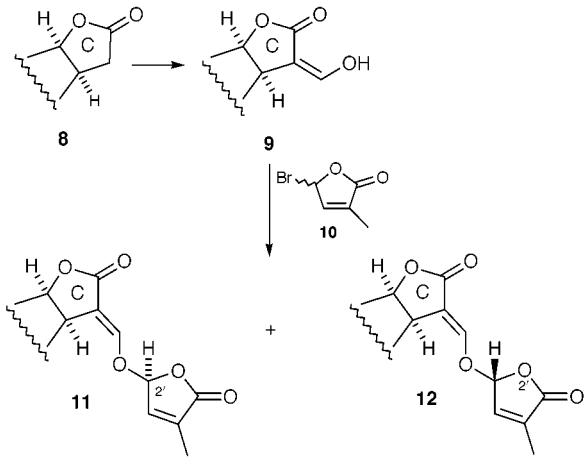
Table 3 Germination percentages after exposure to solutions of GR24 (ref. 12)

Species	Compound	Configuration at C-2′	Germination (%) 1 mg l^{-1}	Germination (%) 0.01 mg l^{-1}
S. hermonthica	GR24 (**4**)	*R*	56.2 ± 4.6	32.5 ± 4.5
S. hermonthica	2′-*epi*-GR24	*S*	40.8 ± 2.5	—
S. hermonthica	*ent*-GR24	*S*	4.0 ± 0.6	—
S. hermonthica	*ent*-2′-*epi*-GR24	*R*	54.2 ± 2.6	—
O. crenata	GR24 (**4**)	*R*	48.9±1.3	38.5 ± 0.4[a]
O. crenata	2′-*epi*-GR24	*S*	24.5 ± 1.1	17.2 ± 1.5[a]
O. crenata	*ent*-GR24	*S*	—	—[a]
O. crenata	*ent*-2′-*epi*-GR24	*R*	12.3 ± 0.6	4.1 ± 0.9[a]

[a] At 0.05 mg l^{-1}

Some of the synthetic analogues have as high a germinating activity as strigol. It is clear now that in each series of compounds only one of the stereoisomers is highly active. For many reasons it is, thus, desirable to use this one active isomer in pure form in the different research and application areas mentioned above.

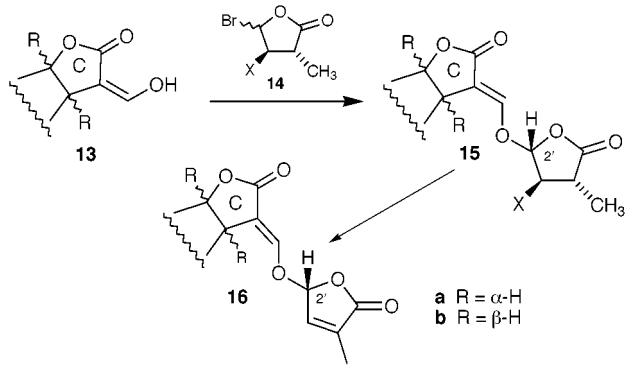
For the synthesis of stereohomogeneous strigol-type compounds four approaches have been employed. (i) Synthesis of a racemic ABC fragment *rac*-**8** (often in truncated form), subsequent formylation (*rac*-**8** → *rac*-**9**) and coupling to the racemic and stereolabile bromo (or chloro) lactone *rac*-**10** to yield the two racemic 2′-epimers *rac*-**11** and *rac*-**12** (Scheme 1). The final products had then to be resolved by a suitable method.[9,17]



Scheme 1

(ii) Synthesis of the enantiomerically pure ABC fragment **8**, formylation and coupling to racemic **10** to yield **11** and **12** as single stereoisomers.[11,12,18–20]

(iii) Synthesis of the ABC fragment in racemic form and coupling after formylation to a homochiral equivalent **14** of the halo butenolide **10** to yield one pair of stereoisomers (if **14** has appropriate stereodirecting properties) from which the desired compound **16a** is released, accompanied by a second stereoisomer **16b** (Scheme 2). In this approach the configuration at C-2′ is known in the final products.[12–15,21,22]



Scheme 2

(iv) Synthesis of the ABC fragment as a single enantiomer, formylation, coupling to **14**, and release of **16a** as a single stereoisomer with known configuration at all stereogenic centres.[22,23]

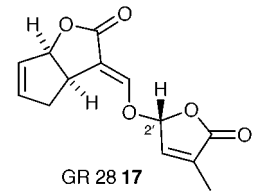
Routes (i) and (ii) may be called classical since all of the older syntheses were performed along these lines.[24] Clearly, after separation of the C-2′ epimers (in most cases easily achieved), the configuration at C-2' had to be determined. Configurational assignment at C-2′ is, however, hampered by the fact that obviously in all known examples the ^{1}H and ^{13}C NMR spectra of strigol-type C-2′ epimers are identical.[25]

In the following paragraphs methods are summarized which can be applied to determine the C-2′configuration. Then synthetic approaches will be reviewed that allow stereocontrol at C-2′. Such methods [routes (iii) and (iv), *vide supra*] have been developed only very recently.

Methods for configurational assignment at C-2′ of strigolactones

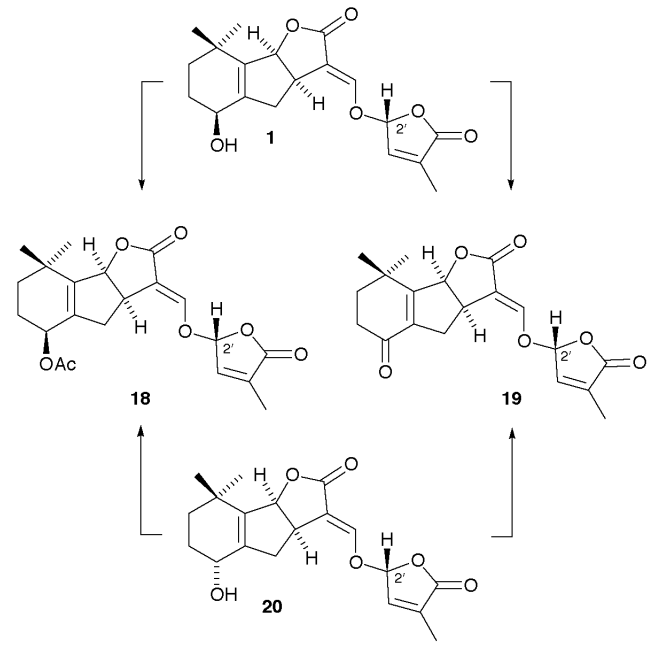
X-Ray analysis

For a long time X-ray analysis was the only means by which the configuration, especially that at C-2′, of strigol-type compounds could be established. X-Ray structures are now available of strigol (**1**),[17,26] its 5-epimer **20**,[25] 5-deoxystrigol,[27] of sorgolactone (**2**),[28] of analogues GR 7 (**5**),[29] GR 24 (**4**),[30] GR 28 (**17**)[25] and of compound Nijmegen 1 (**7**).[15]



Chemical correlation

With many reference compounds of known relative configuration now available (by X-ray analysis), configurational assignment at C-2′ by chemical correlation methods becomes feasable. Yet, this approach has been used very rarely. The C-2′ configuration of the 5-epimer of strigol (**20**) has been assigned by correlation. Thus, *rac*-**20** was converted to *rac*-**18** using the Mitsunobu procedure and the product was shown to be identical with a sample obtained from *rac*-strigol (**1**) by acetylation (Scheme 3). This correlation was secured by dichromate oxidation of both *rac*-**1** and *rac*-**20**, which furnished the same ketone *rac*-**19**. Analogously, the 2′-epimer of *rac*-**20** was correlated with the 2′-epimer of *rac*-strigol.[25]



Scheme 3

Circular dichroism

The relative and absolute configuration of sorgolactone (**2**) has tentatively been assigned on the basis of the similar CD spectra

of **2** and strigol (**1**).[3] The configuration of strigol is known from X-ray studies.[17,26] The configurational assignment of sorgolactone was recently confirmed by synthesis.[28,31] Fig. 1 displays

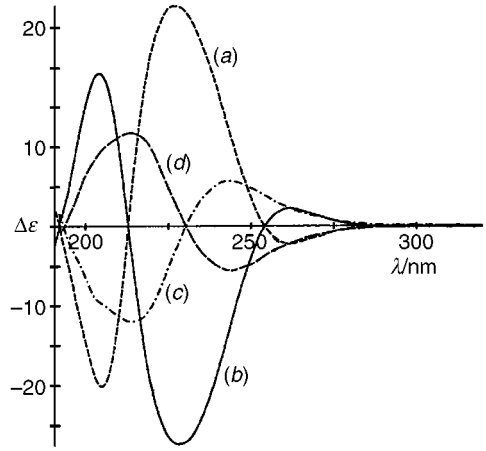
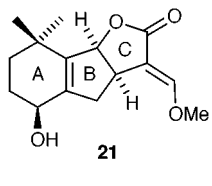
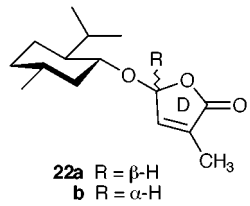


Fig. 1 CD spectra of (*a*) **1**, (*b*) *ent*-**1**, (*c*) 2′-*epi*-**1** and (*d*) *ent*-2′-*epi*-**1**.

the CD spectra of strigol (**1**), its 2′-epimer, and their enantiomers. The CD curves are, of course, sum curves of the different chromophores present in **1** and its stereoisomers. Frischmuth *et al.*[25] studied the CD spectra of **21** and *ent*-**21**, as well as of



21



22a R = β-H
b R = α-H

Feringa's compounds **22a** and *ent*-**22a**[32] which are reference compounds for the ABC and D parts, respectively, of the strigol isomers. It was found that the CD spectra of the strigol isomers can reasonably well be constructed from the CD spectra of the appropriate ABC and D models, indicating that (to a first approximation) there is no electronic interaction between the two chromophoric systems and, in addition, that the conformations of the 2′-epimers are similar. Thus, the configuration at C-2′ of a pair of C-2′ epimers can be obtained from their CD difference spectrum in which the contribution of the ABC chromophor is cancelled out and twice the CD of the ring D chromophore remains.[33]

A comparison of the CD spectra of **21** and *ent*-**21** with those of **22a** and *ent*-**22a** revealed that the CD band around 250 nm of **22a**/**22b** extends to a longer wavelength than that of **21a** and *ent*-**21**. This means that in the region of about 270 nm of strigolactones only the contribution of the ring D chromophor determines the spectra. Therefore, in strigolactones the configuration at C-2′ can directly be correlated with the sign of the CD around 270 nm. 2′*R* compounds have a negative CD around 270 nm whereas the CD of 2′*S* compounds is positive at this wavelength. This rule has proven its value in several series of strigolactones, in particular in the GR 28,[22] demethylsorgolactone[13] and sorgolactone series.[14]

Stereoselective synthesis

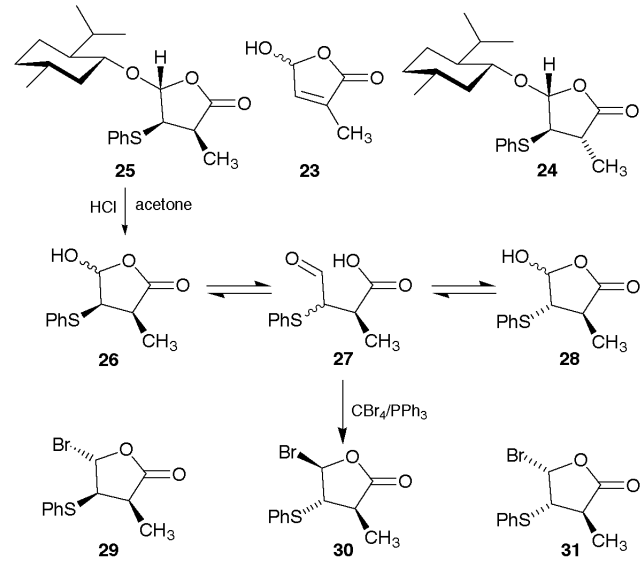
More effective than any of the procedures summarized above are, of course, synthetic methods that allow installation of the correct configuration at C-2′ predictably. This will be the topic of the following paragraph.

Synthetic approaches that allow control of the C-2′ configuration of strigol-type compounds

A general introduction to the problem has been given by Frischmuth *et al.*[34] We shall review here only sequences that lead to stereohomogeneous strigolactones. In addition only sequences will be summarized leading to compounds that contain the methyl group in unit D since it has been found that this methyl group is essential for the bioactivity.[8]

The Michael addition–nucleophilic substitution–elimination approach[22,35]

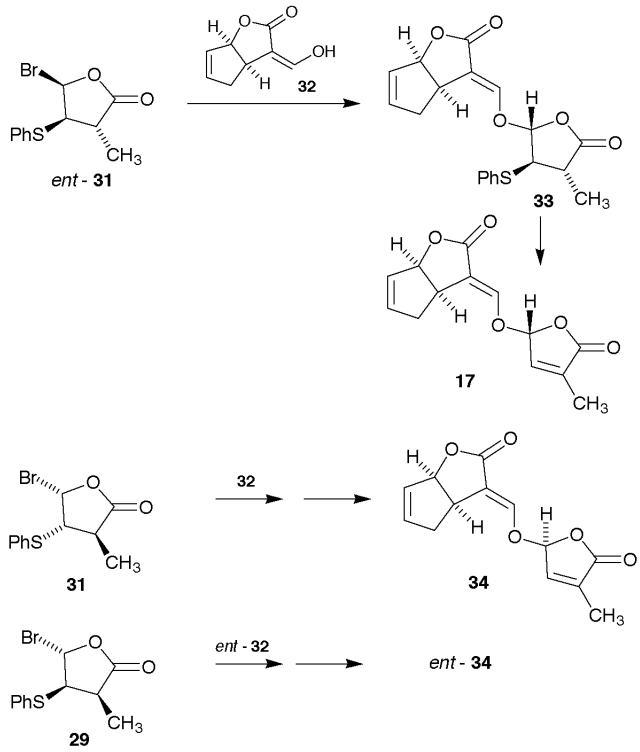
Following Feringa's work, from *rac*-**23** and (−)-menthol the two diastereoisomers **22a** and **22b** were prepared and separated by crystallization at low temperatures.[32] On addition of thiophenol in the presence of triethylamine **22a** formed adducts **24** and **25** with the phenylthio group *trans* to the menthyloxy substituent (Scheme 4). Similar reactions were performed with



Scheme 4

22b. The phenylthio group was introduced with the aim of stereodirecting the coupling of the butenolide moiety to the ABC part of strigolactones. On acid-catalyzed removal of the auxiliary menthyl group from **25** a mixture of compounds was formed which contained more components than expected. When the hydrolysis products of **26** were treated with CBr_4 and PPh_3 three bromo derivatives were obtained which could be separated and shown by careful spectral analysis to have structures **29**–**31**. The formation of **30** and **31** can be explained assuming the hemiacetal hydrolysis products of **25** to be in equilibrium with the ring-opened aldehyde, the α-position of which is, of course, stereolabile.

Coupling of **31**, *ent*-**31** (obtained analogously) and **29** was performed with racemic **32** and with homochiral **32** and its enantiomer (accessible *via* resolution[22,35] and the elegant Pd-mediated enantioselective syntheses of cyclopent-2-en-1-ylacetic acid that have been developed in the laboratories of Trost[36] and Helmchen[37]) using silver carbonate and silver silicate, respectively, as promotors (Scheme 5). The conditions resemble the classical Königs–Knorr glycosylation with the phenylthio substituent as the stereodirecting neighbouring group. Silver silicate turned out to be a more suitable promotor. The results indicate that the phenylthio substituent does indeed force the nucleophilic attack at C-2′ to the opposite face of the ring. The sequence Michael addition–nucleophilic substitution–elimination is, thus, appropriate to control the configuration at C-2′ of strigolactones and to prepare **17**, **34** and *ent*-**34** [on routes (iii) and (iv), *vide supra*]. The problematic point is the stereolability

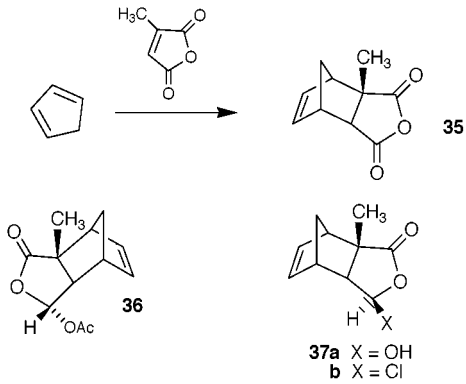


Scheme 5

of **27**, which makes the method unsuitable for practical applications.

The Zwanenburg approach[38]

Stereocontrol at C-2′ has been achieved by Zwanenburg by a sequence involving a Diels–Alder and a retro-Diels–Alder reaction. Compounds **37b** and *ent*-**37b** in which the *endo* face is sterically blocked have been used as synthetic equivalents of **14**. Diels–Alder reaction of cyclopentadiene with citraconic anhydride (Scheme 6), followed by $Li(OBu^t)_3AlH$ reduction of *rac*-

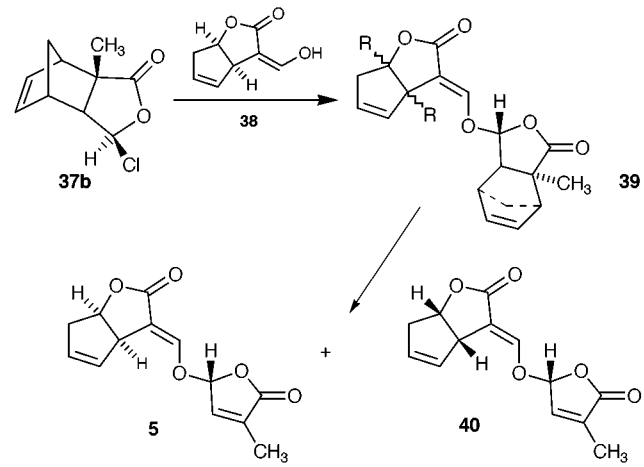


Scheme 6

35 provided *rac*-**37a** which was resolved either classically *via* the (+)- and (−)-menthyl acetals[21] or by making use of an enzymic kinetic resolution yielding *endo*-acetate **36** and the *exo*-alcohol **37a**, both in enantioenriched form.[39] Compounds **37a** and **36** were converted to chlorides **37** and *ent*-**37b**, respectively.

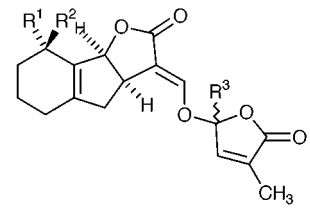
Coupling of **37b** to *rac*-**38** provided a 1 : 1 mixture of **39** (R = β-H) and **39** (R = α-H) (Scheme 7). Cycloreversion then led to diastereoisomers **5** and **40** with known configuration at C-2′. The enantiomers of **5** and **40** were prepared accordingly, making use of *ent*-**37b**.[21]

In a completely analogous fashion the follwing compounds were synthesized GR24 (**4**), its 2′-epimer, and their enantiomers;[12] demethylsorgolactone (**6**), the 2′-epimer and their



Scheme 7

enantiomers;[13] the sorgolactone stereoisomers **41a**–**d** and their enantiomers;[14] Nijmegen 1 and its enantiomer (**7**).[15]



41a R^1 = Me, R^2 = H, R^3 = β-H
b R^1 = Me, R^2 = H, R^3 = α-H
c R^1 = H, R^2 = Me, R^3 = β-H
d R^1 = H, R^2 = Me, R^3 = α-H

The Zwanenburg method, which has proven its merits, involves a resolution step. The advantage of the procedure when excuted as described until now [route (iii) *vide supra*] is that all stereoisomers of a given stimulant are available, a fact that is useful in the context of structure–activity work.

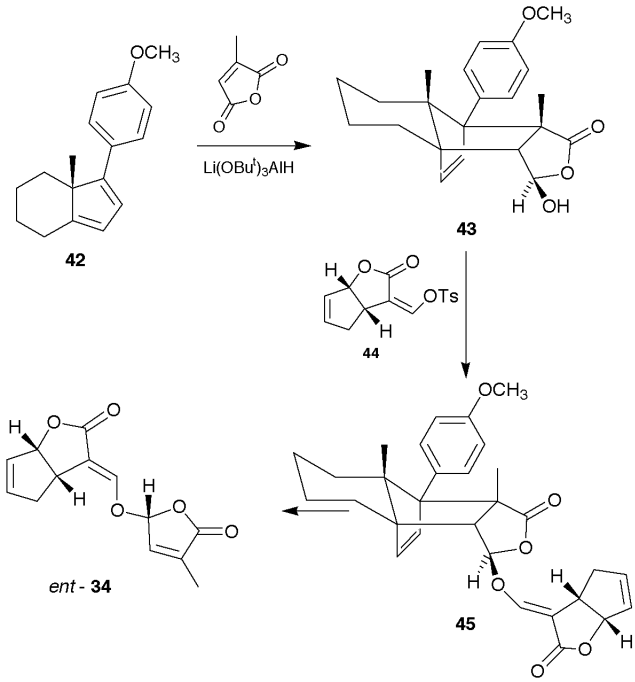
Use of the Winterfeldt template[23,40]

A highly selective route has been developed in Leipzig, which also involves the cycloaddition–cycloreversion strategy but replaces the resolution step, characteristic of the Zwanenburg approach, by an enantioselective synthesis. More specifically, the Winterfeldt diene **42**[41] which is available from the Hajos–Wiechert ketone was employed in the Diels–Alder reaction. Cycloaddition of **42** with citraconic anhydride to yield *endo*-adduct requires high-pressure conditions.[42] Reduction of the adduct with $Li(OBu^t)_3AlH$ furnished **43** as the main product. The coupling of **44** to the other half of the strigolactones posed problems and only the sequence **43** + **44** → **45** was successful (Scheme 8). On flash vacuum pyrolysis (500 °C, 10^{-6} bar), retro-Diels–Alder cleavage occurred and provided strigolactone *ent*-**34** as a single stereoisomer.

The synthesis of *ent*-**34** represents an example of route (iv) (*vide supra*). The important chiral materials used in the synthesis, Winterfeldtś template and **44** (obtained from Helmchenś iodo lactone[37]) are available *via* enantioselective reactions under the control of chiral catalysts.

Epilogue

It appears that many of the problems involved in the chemistry of strigol-type compounds have been solved in the past few years. One may wish to see application of these results in investigations aimed at understanding the mode of action of the strigolactones.



Scheme 8

Acknowledgements

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