Pergamon

Tetrahedron Letters, Vol. 38, No. 31, pp. 5489-5492, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01228-8

Strigol and Sorgolactone Synthetic Studies
Use of Winterfeldt's Template to Control the C-2′ Configuration

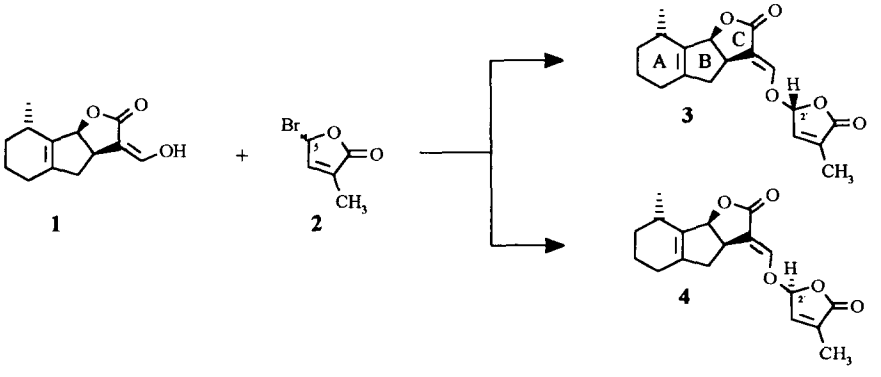
Susanne Röhrig, Lothar Hennig, Matthias Findeisen, Peter Welzel*
Fakultät für Chemie und Mineralogie der Universität Leipzig
Talstr. 35, D-04103 Leipzig (Germany)

Dietrich Müller
Fakultät für Chemie der Ruhr-Universität, D-44780 Bochum (Germany)

Abstract - A route comprising (i) a cycloaddition reaction of citraconic anhydride with the Winterfeldt auxiliary, (ii) hydride reduction of the cycloadduct, (iii) a (formal) ether formation, and (iv) a cycloreversion reaction allows efficient stereocontrol at C-2′ in the synthesis of strigol and its structural analogues.

Germination of seeds of root parasitic plants of the genera *Striga*, *Alectra* (Scrophulariaceae), and *Orobanche* (Orobanchaceae) is stimulated by root exsudates from their host plants. Prominent stimulants are strigol, its acetate, and sorgolactone (**3**).[1]

We and others have reported on a rather comprehensive set of structure-activity relations. There seem to exist very specific interactions between the stimulant and the binding site(s) at the seeds which are, in addition, species dependent. Both the absolute and the relative configuration at the butenolide C-2′ are of major importance as far as seed germination potency is concerned.[1]

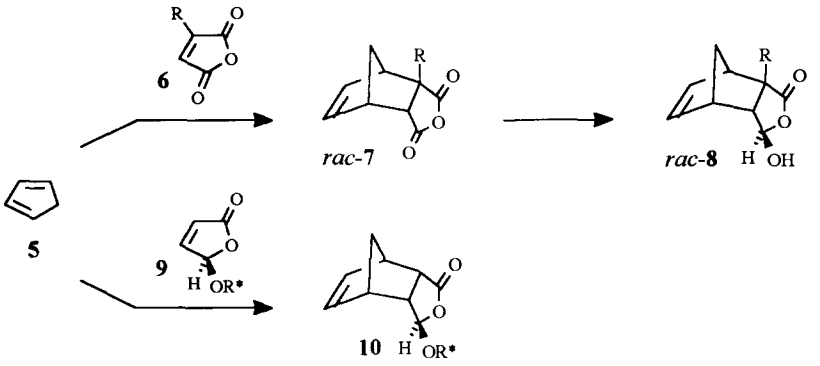


Scheme 1

Whereas a number of methods have been developed for the stereoselective synthesis of the A-B-C ring system of these compounds, the control of the C-2′ configuration has remained an unsolved problem until recently.

In all the classical syntheses an intermediate of type **1** was coupled to an electrophilic species such as *rac*-**2** or *rac*-**20** to give a 1:1 mixture of coupling products such as **3** and **4**.

The first attempt to solve this synthetic problem used a stereodirecting group at C-3′ (Michael addition/*retro*-Michael reaction sequence). However, this approach turned out to be synthetically unsatisfying.[2]



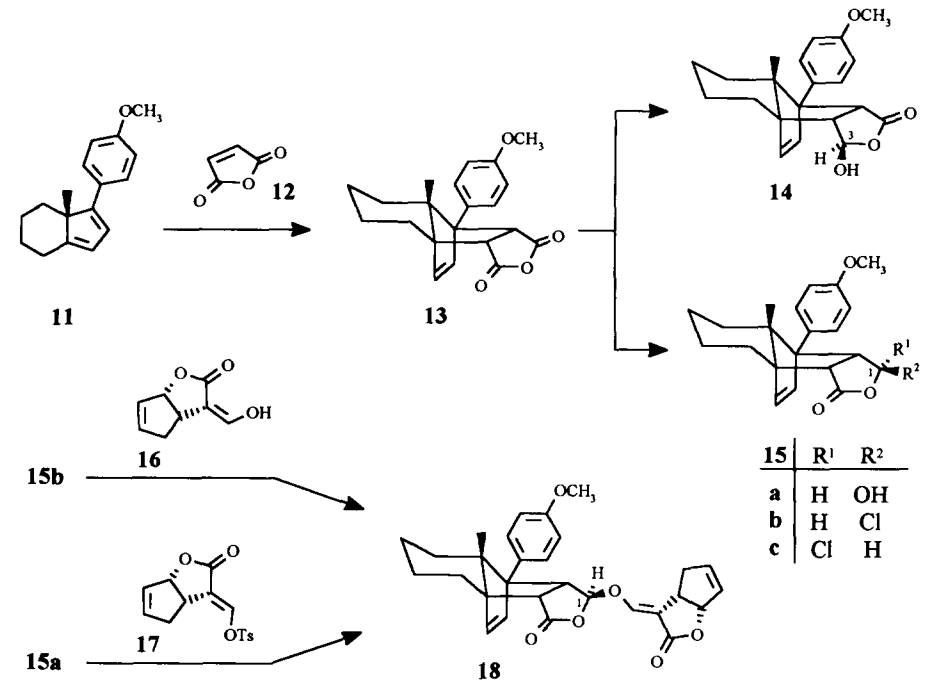
Scheme 2

Another method was used as indicated in Scheme 2. Cyclopentadiene on reaction with **6** furnished *rac*-**7**. After reduction *rac*-**8** was resolved by several methods.[3] In principle, one could also resolve the dienophile first and then perform the cycloaddition (**5** + **9** → **10**).[4] **8** has been coupled stereoselectively to a hydroxymethylene-lactone (of type **1**), and in the final step the desired compound was liberated by a *retro*-Diels-Alder reaction.[3] Although this process provides the desired stereocontrol it suffers from the fact that it involves a resolution step.

We describe here a new synthetic scheme in which an optically active butenolide equivalent is prepared by enantioselective synthesis. In particular, we made use of Winterfeldt's auxiliary which is easily available from the Hajos-Wiechert ketone.[5,6] We first tried to add *rac*-**2** and *rac*-**20**, respectively, to **11** to obtain the cycloadducts **22d** and **22b** by kinetic resolution and subsequent *in-situ* anomerization.[7] Unfortunately, even under high-pressure conditions (11 kbar) the desired cycloadducts were not formed. Recourse was then made to the cycloaddition of citraconic acid anhydride (**19**). In a model series **11** and maleic acid anhydride (**12**) reacted cleanly at 20°C as described by Winterfeldt[8] to provide endo-cycloadduct **13**. Reduction of **13** with $Li(OtBu)_3AlH$[9] provided **14** and **15a** in a 1:8 ratio. In both cases the OH-group was ß (trans to the etheno bridge) as shown by careful ^1H NMR analysis and NOE measurements. On reaction with $SOCl_2$ in pyridine **15a** furnished a mixture of **15b** and **15c** whereas in CH_2Cl_2 solution practically solely **15b** was formed (98:1 ratio). Reaction of **15b** with **16** (obtained from Helmchen's iodolactone[10] by elimination and formylation) provided the desired coupling product **18** in 96 % yield. The substitution reactions at C-1 of the furanone ring are obviously complex and do not follow a simple S_N reaction pathway. Hydroxylactone **15a** could also be coupled to **17** to give **18** (NaH as base in THF solution), albeit in lower yield (47 %).

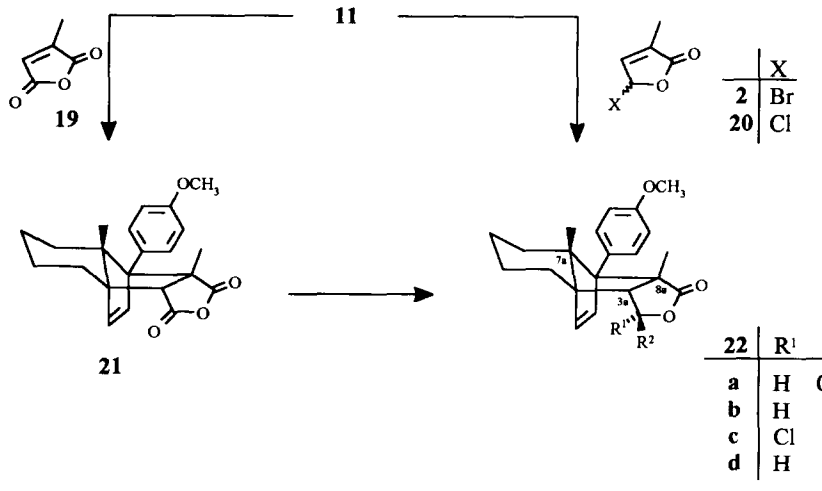
For the cycloaddition reaction between **11** and **19** high-pressure conditions were required as already found by Winterfeldt.[5] In this case the extra methyl group directed the hydride addition to the distant CO group giving exclusively **22a**. A careful NMR analysis of **22a** revealed that the cycloaddition had unexpectedly[5,6] occurred in the endo mode. In particular, NOE enhancements between the methyl groups at C-7a and C-8a and between the 7a-methyl group and 3a-H proved the endo configuration. Again, treatment of **22a** with $SOCl_2$ in pyridine

led to the formation of **22b** and **22c** whereas in CH_2Cl_2 the reaction was selective and provided **22b** almost exclusively.



15	R^1	R^2
a	H	OH
b	H	Cl
c	Cl	H

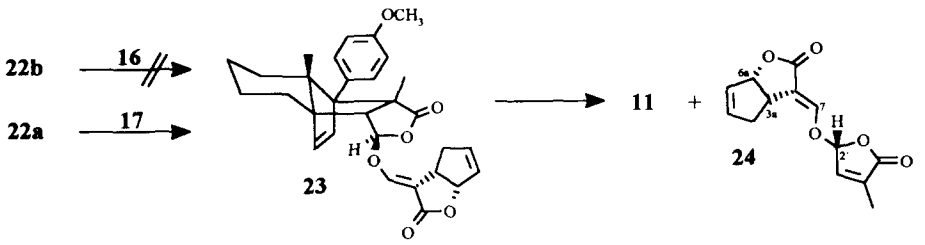
Scheme 3



	X
2	Br
20	Cl

22	R^1	R^2
a	H	OH
b	H	Cl
c	Cl	H
d	H	Br

Scheme 4



Scheme 5

In contrast to the model experiments reported above we were unable to achieve the coupling between **22b** and **16**. Fortunately, **22a** did react with **17** (conditions as above) to give **23** in 56 % yield. Finally, on flash vacuum pyrolysis (500°C, 10^{-6} bar) the *retro*-Diels-Alder cleavage occurred and provided the desired strigol and sorgolactone analogue **24** (*ent*-2′-*epi*-GR28)[11] in 59 % yield. **11** was recovered in 81 % yield. **24** is the enantiomer of a compound obtained previously.[2]

In conclusion, we have been able to develop a short and selective scheme which allows to control the configuration at C-2′ of strigol and sorgolactone analogues without the need of a resolution step.

Acknowledgements - The high-pressure experiments were performed in the laboratory of Prof. F.-G. Klärner (Essen). We wish to thank Prof. Klärner and V. Breitkopf for their support. Prof. W. Sander (Bochum) provided us with the opportunity to perform the flash vacuum pyrolysis experiments in his institute. We wish to thank Prof. Sander and C. Junker for their support. The iodolactone of optically active cyclopentenylacetic acid, the precursor of **16**, was generously provided by Prof. G. Helmchen (Heidelberg). Financial support by the Deutsche Forschungsgemeinschaft (We 595/25-1) and the Fonds der Chemischen Industrie is gratefully acknowledged.

REFERENCES AND NOTES

[1] For leading references, see: Kranz, A.; Samson-Schulz, E.; Hennig, L.; Welzel, P.; Müller, D.; Mayer-Figge, H.; Sheldrick, W.S. *Tetrahedron* **1996**, *47*, 14827-14840; Mori, K.; Matsui, J.; Bando, M.; Kido, M.; Takeuchi, Y. *Tetrahedron Lett.* **1997**, *38*, 2507-2510.

[2] Frischmuth, K.; Marx, A.; Petrowitsch, T.; Wagner, U.; Koerner, K.; Zimmermann, S.; Meuer, H.; Sheldrick, W.S.; Welzel, P. *Tetrahedron Lett.* **1994**, *35*, 4973-4976.

[3] Thuring, J.W.J.F.; Nefkens, G.H.L.; Schaafstra, R.; Zwanenburg, B. *Tetrahedron* **1995**, *51*, 5047-5056.

[4] Feringa, B.L.; de Jong, J.C. *J. Org. Chem.* **1988**, *53*, 1125-1127.

[5] Winterfeldt, E. *Chem. Rev.* **1993**, *93*, 827-843.

[6] Borm, C.; Meibom, D.; Winterfeldt, E. *J. Chem. Soc., Chem. Commun.* **1996**, 887-894.

[7] Lemieux, R.U.; Hendricks, K.B.; Stick, R.V.; James, K. *J. Am. Chem. Soc.* **1975**, *97*, 4056-4062.

[8] Beckmann, M.; Meyer, T.; Schulz, F.; Winterfeldt, E. *Chem. Ber.* **1994**, *127*, 2505-2509.

[9] Canonne, P.; Plamondon, J.; Akssira, M. *Tetrahedron* **1988**, *44*, 2903-2912.

[10] Sennhenn, P.; Gabler, B.; Helmchen, G. *Tetrahedron Lett.* **1994**, *35*, 8595-8598.

[11] FAB-MS: m/z = 271.0 $[M+Na]^+$, 249.0 $[M+H]^+$.- ^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.04 (4′-CH_3), 2.41 - 2.56 (4-H), 2.74 - 2.92 (4-H*), 3.63 - 3.75 (3a-H), 5.51 - 5.59 (6a-H), 5.83 - 5.90 (6-H), 6.02 - 6.09 (5-H), 6.13 - 6.17 (2′-H), 6.92 - 6.97 (3′-H), 7.45 (7-H), $J_{(4'\text{-}CH_3,3')}$ = 1.5 Hz, $J_{(4'\text{-}CH_3,2')}$ = 1.5 Hz, $J_{(4,4^*)}$ = 17.6 Hz, $J_{(4,3a)}$ = 2.6 Hz, $J_{(3a,4^*)}$ = 8.8 Hz, $J_{(6a,3a)}$ = 7.7 Hz, $J_{(6,5)}$ = 5.9 Hz, $J_{(2',3')}$ = 1.5 Hz, $J_{(7,3a)}$ = 2.6 Hz.- CD (CH_3CN, c = 40.29 μmol l^{-1}): λ_{max} (Δε) = 198 (16.9), 209 (8.3), 221 (14.6), 253 nm (-4.6).

(*Received in Germany* 23 *May* 1997; *accepted* 18 *June* 1997)