Synthesis of Spirocyclic Butenolides by Ring Closing Metathesis

Peter Langer,* Uwe Albrecht

Institut für Chemie und Biochemie der Ernst-Moritz-Arndt-Universität Greifswald, Soldmannstr. 16, 17487 Greifswald, Germany
Fax +40(3834)864373; E-mail: planger@gwdg.de

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Abstract: Spirocyclic butenolides were efficiently prepared by a ring closing metathesis strategy.

Key words: butenolides, catalysis, metathesis, ruthenium, spirocompounds

Spirocyclic butenolides are of biological relevance and are present in a variety of pharmacologically relevant natural products, such as chlorotricolide[1a,b] and hydnuferruginine.[1c] Although a number of methods for the preparation of spirocyclic butenolides have been reported, more efficient syntheses need to be developed. The ring closing metathesis (RCM) reaction has been applied to the synthesis of oxygen and nitrogen heterocycles.[2] In the oxygen series most work has been focussed on the synthesis of dihydropyrans.[3] In contrast, the synthesis of butenolides has not been greatly explored so far.[4] Herein, we wish to report the synthesis of *spirocyclic* butenolides by RCM.[5] This method is of preparative usefulness, due to its simplicity and efficiency (Figure 1).

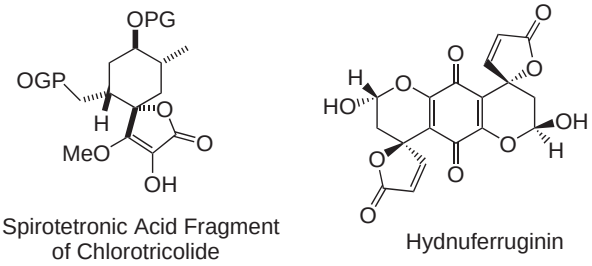
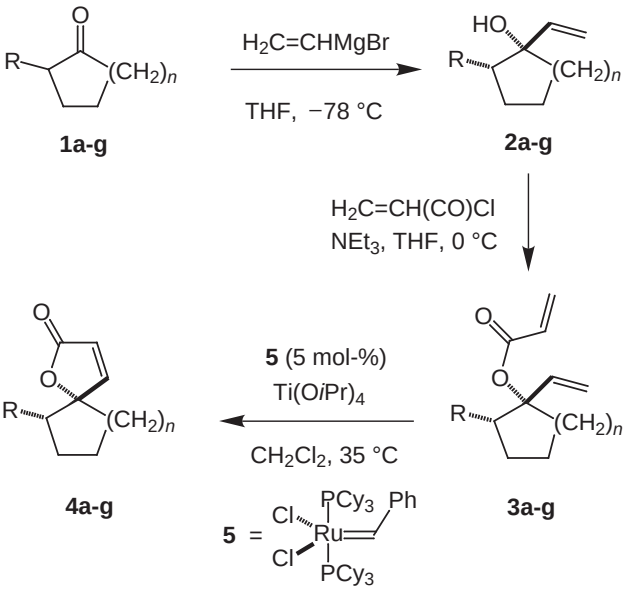


Figure 1

The reaction of cyclohexanone (**1a**) with vinyl magnesium bromide afforded the known alcohol **2a** which was transformed into the ester **3a** by treatment with acrylic chloride (Scheme 1, Table 1).[6] Ring closing metathesis using Grubbs' catalyst (**5**) afforded the desired spirocyclic butenolide **4a**, however, in only low yield. Optimal yields were eventually obtained when the reaction was carried out at 35 °C in CH_2Cl_2 in the presence of catalytic amounts of Ti(*i*PrO)$_4$.[7] Following the work of Fürstner et al. the Lewis acid was used to avoid interuption of the catalytic cycle by chelation of the substrate carbonyl to the metal.[8]



Scheme 1 Synthesis of butenolides **4a**–**g** by RCM

Table 1 Products and Yields from RCM

2,**3**,**4**	*n*	R	% (**2**)[a]	% (**3**)[a]	% (**4**)[a]
a	2	H	83	43	57
b	1	H	58	48	66
c	3	H	66	58	76
d	4	H	74	45	78
e	6	H	59	42	63
f	8	H	80	71	70
g	2	Me	49	30	80
g	2	Me	–	80[b]	80

[a] Isolated yields: for **2g**, **3g** and **4g**: *syn*/*anti* > 98:2.
[b] Prepared directly from **1g** at 0 °C without isolation of **2g**.

To study the preparative scope of the methodology, the ring size and the substituents of the cycloalkanone were systematically varied (Scheme 1, Table 1). Starting with cyclohexanone, cyclopentanone, cycloheptanone, cyclooctanone, cyclodecanone and cyclododecanone, the esters **3a**–**f** were prepared in two steps. The RCM of **3a**–**f** proceeded uneventfully and afforded the spirocyclic butenolides **4a**–**f** in good yields. The synthesis of butenolides containing two stereogenic centers was next studied. The reaction of vinylmagnesiumbromide with 2-methyl-

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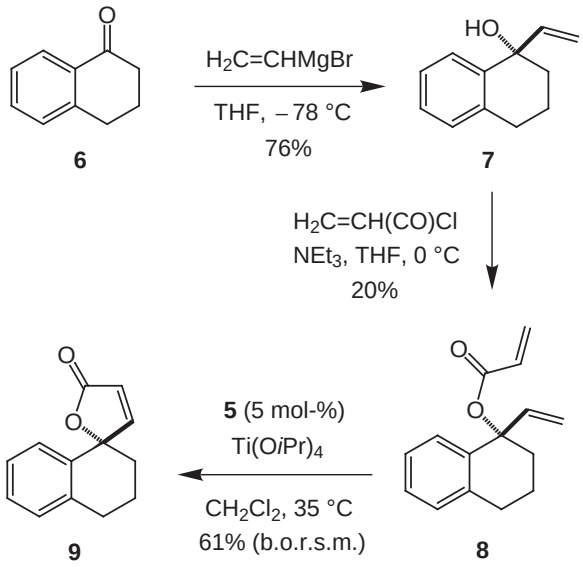
cyclohexanone proceeded with very good diastereoselectivity to give the known alcohol **2g**.[9] This compound was successfully transformed into the diastereomerically pure butenolide **4g** via the ester **3g**. The overall yield of **3g** could be significantly improved by direct synthesis from **1g** (without isolation of **2g**). The use of α-tetralone (**6**) as the starting material was next studied. Grignard reaction of **6** gave the alcohol **7**, which was transformed into the ester **8**. Ring closing metathesis of **8** afforded the known butenolide **9** (Scheme 2).[10]



Scheme 2 Synthesis of butenolide **9** (b.o.r.s.m. = based on recovered starting material)

In summary, we have developed a novel synthesis of pharmacologically relevant spirocyclic butenolides using RCM. Our strategy is currently applied to the synthesis of enantiomerically pure butenolides and natural products.

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(7) **Representative Experimental Procedure:** To a CH_2Cl_2-solution (30 mL) of **3f** (264 mg, 1 mmol) was added $Ti(iPrO)_4$ (42 mg, 0.15 mmol) and the solution was stirred for 1 h at 35 °C. A CH_2Cl_2-solution (10 mL) of **5** (82 mg, 0.1 mmol) was subsequently added and the reaction mixture was stirred at 35 °C for 48 h. The solvent was removed in vacuo and the residue was purified by column chromatography (silica gel, petroleum ether/ether = 3:1) to give **4f** as a white solid (165 mg, 0.70 mmol, 70%). Spectroscopic data of **4f**: ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.23–1.40 (m, 13 H, CH_2), 1.41–1.60 (m, 7 H, CH_2), 1.70–1.82 (m, 2 H, CH_2), 5.95 (d, *J* = 6 Hz, 1 H, CH), 7.48 (d, *J* = 6 Hz, 1 H, CH). ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 19.94, 21.79, 22.32, 25.68, 25.96 31.86, 91.87, 119.81, 160.79, 172.43. IR (KBr): ν = 3088 (w), 2957 (s), 2937 (s), 2864 (m), 2847 (m), 1743 (s), 1472 (s), 1444 (m)cm^{-1}. MS (70 eV): *m/z* (%) = 236 (100) [M$^+$], 208 (16), 179 (12), 165 (28), 151 (28); the exact molecular mass for $C_{15}H_{24}O_2$ *m/z* = 236.1776 ± 2 mD [M$^+$] was confirmed by HRMS (EI, 70 eV). Anal. Calcd for $C_{15}H_{24}O_2$: C, 76.23; H, 10.24. Found: C, 76.10; H, 10.76. All new compounds gave satisfactory spectroscopic data and correct elemental analyses and/or high resolution mass data.

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