Regio- and Diastereoselective Synthesis of Lissoclinolide Analogues by Lewis Acid Catalyzed Cyclization of the First 1,5-Bis(trimethylsilyloxy)-1,3,5-hexatrienes with Oxalyl Chloride

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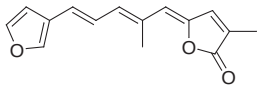
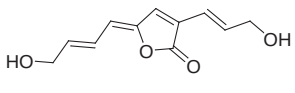
Abstract: The Lewis acid catalyzed cyclization of 1,5-bis(trimethylsilyloxy)-1,3,5-hexatrienes with oxalyl chloride resulted in formation of polyunsaturated butenolides.

Key words: butenolides, cyclizations, oxalic acid, regioselectivity, silyl enol ethers

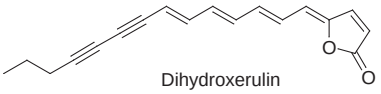
Polyunsaturated γ-alkylidenebutenolides, including prominent natural products such as freelingyne, dihydrofreelingyne, lissoclinolide, and dihydroxerulin, are of high pharmacological relevance.[1] Lissoclinolide, for instance, exhibits antibiotic activity against Gram-positive bacteria[2] and dihydroxerulin has proven to be an important nontoxic inhibitor in the biosynthesis of cholesterol.[3] γ-Alkylidenebutenolides have been prepared so far by Wittig reactions,[4] stereospecific β-eliminations,[5] or lactonizations of 2-en-4-ynoic acids and related methods.[6] We have recently reported[7] a new approach to γ-alkylidenebutenolides based on cyclizations of 1,3-dicarbonyl dianions and 1,3-bis(trimethylsilyloxy)-1,3-butadienes, electroneutral dianion equivalents,[8] with oxalic acid dielectrophiles. Herein, we wish to report an extension of this methodology to the synthesis of polyunsaturated γ-alkylidenebutenolides which relies on the first cyclizations of 1,5-bis(trimethylsilyloxy)-1,3,5-hexatrienes, a previously unknown substance class, with oxalyl chloride. The butenolides prepared represent important analogues and synthetic precursors to pharmacologically relevant natural products such as lissoclinolide.



Dihydrofreelingyne

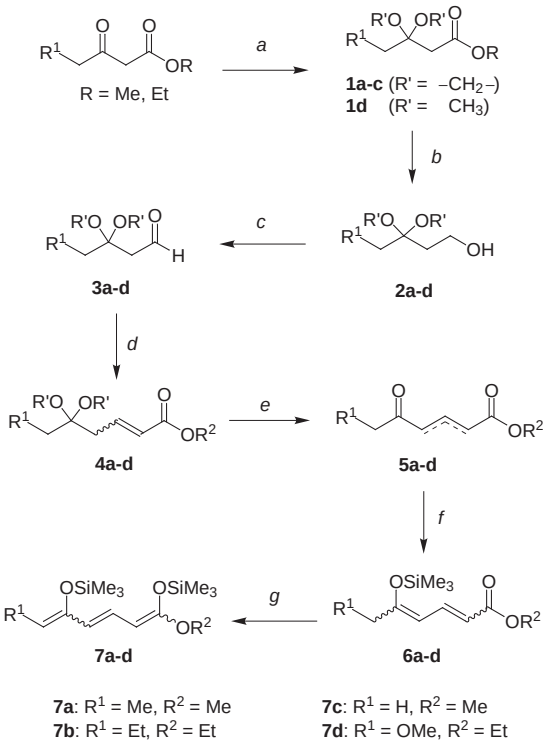


Lissoclinolide



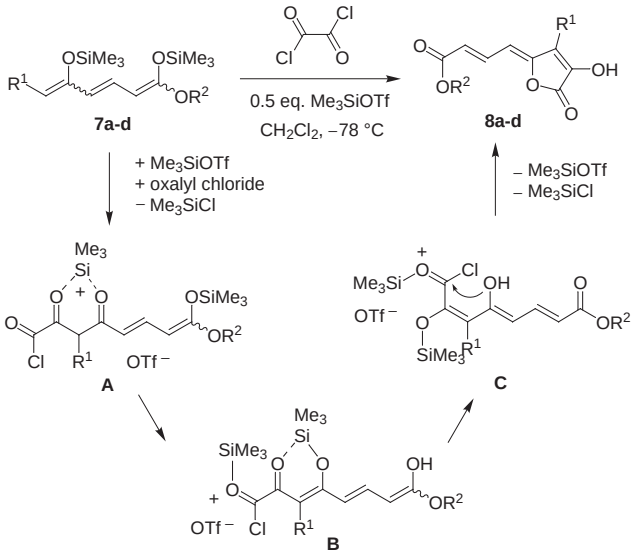
Dihydroxerulin

Despite many potential applications, 1,5-bis(trimethylsilyloxy)-1,3,5-hexatrienes have to our knowledge not been previously prepared. These new synthetic building blocks were prepared as follows (Scheme 1): acetalization of the corresponding β-ketoesters afforded the acetals **1a-d**; reduction of the ester group and subsequent Swern oxidation of the resulting alcohols afforded the aldehydes **3a-d** in good yields. Wittig reaction afforded the protected 1,5-ketoesters **4a-d**[9] which were deprotected and transformed into the novel silyl dienol ethers **6a-d** in high yields. Deprotonation of **6a-d** with LDA/HMPTA at −78 °C and subsequent addition of Me_3SiCl resulted in formation of the desired 1,5-bis(trimethylsilyloxy)-1,3,5-hexatrienes **7a-d** in good yields. For the synthesis of **7a-c** a spirocyclic acetal was used as the protecting group. In case of the synthesis of **7d**, this group could not be chemoselectively removed without destruction of the molecule. This problem was eventually solved by the use of the dimethylacetal protecting group.



Scheme 1 Synthesis of 1,5-Bis(trimethylsilyloxy)-1,3,5-hexatrienes **7a-d**. *a*: **1a-c**: $(CH_2OH)_2$, *p*-TosOH, toluene, Dean-Stark-trap, reflux, 12 h, 77−80%; **1d**: $(MeO)_3CH$, Amberlite IR-120$^+$, 20 °C, 62%; *b*: HAl(Bu-*i*)$_2$, CH_2Cl_2, −78 °C, 1 h, 60−92%; *c*: oxalyl chloride, DMSO, NEt_3, −78 °C, 78−95%; *d*: $Ph_3P{=}CHCO_2R^2$, THF, 20 °C, 1 h, 42−72%; *e*: **5a-c**: *p*-TosOH, acetone, reflux, 12 h, 65−84%; **5d**: TFA, CH_2Cl_2, 95%; *f*: Me_3SiCl, NEt_3, C_6H_6, 20 °C, 24 h, 77−98%; *g*: 1) 1.5 equiv. LDA, HMPTA, THF, −78 °C, 1 h, 2) Me_3SiCl, −78→20 °C, 4 h, 70−93%.

Reaction of triene **7a** with oxalyl chloride in the presence of 0.5 equiv. of trimethylsilyl-trifluoromethanesulfonate (Me_3SiOTf)[7c, 10] resulted in formation of the desired γ-alkylidenebutenolide **8a**.[11] Likewise, cyclization of trienes **7b-d** with oxalyl chloride afforded the butenolides **8b-d**. Complex mixtures were obtained when no Lewis acid was added or when stoichiometric amounts of $TiCl_4$ were used. The formation of butenolides **8a-d** proceeded with very good regioselectivity and (except for **8c**) with very good diastereoselectivity in favor of the products containing a *Z*-configured exocyclic double bond.



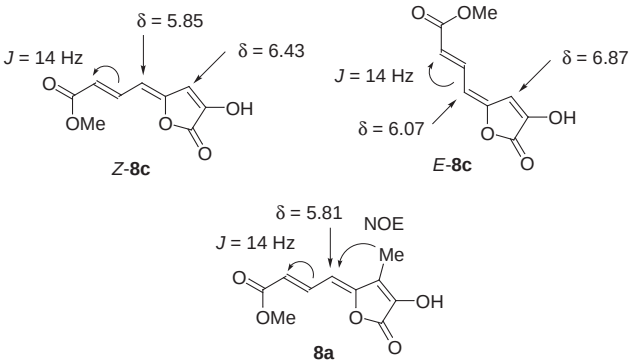
Scheme 2 Synthesis of polyunsaturated γ-alkylidenebutenolides **8a-d**

Table Synthesis of butenolides **8a-d**

8	R^1	R^2	*Z*:*E* [a]	Yield [%] [b]
a	Me	Me	> 98:2	55
b	Et	Et	> 98:2	41
c	H	Me	2:1	50
d	OMe	Et	10:1	32

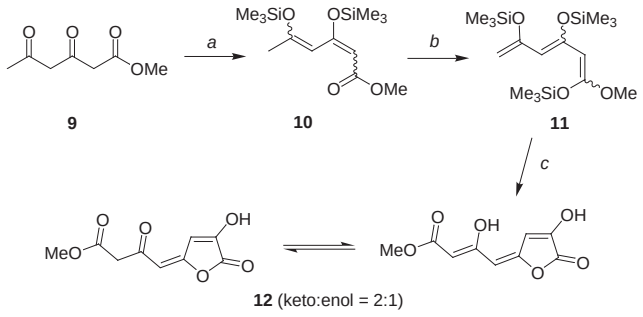
[a] By ^1H NMR of the products. [b] Isolated yield

The configuration of the products was determined as follows: For all butenolides, the ^3J = 14 Hz coupling between the hydrogen atoms 2′-H and 3′-H suggests that the corresponding double bond exhibits *E*-configuration. Similar coupling constants have been previously observed for related butenolides.[4] The geometry of the exocyclic double bond C-5−C-1′ was determined by NOESY measurements and by analysis of the chemical shifts (^1H NMR) of the hydrogen atoms 1′-H (for **8a-d**) and 4-H (for **8c**) following the general rule that the signals of *E*-configured γ-alkylidenebutenolides are shifted downfield relative to the signals of the respective *Z*-configured isomers.[4]



The formation of butenolides **8a-d** can be explained by the following working hypothesis (Scheme 2): oxalyl chloride is activated by Me_3SiOTf and subsequently attacked by the terminal carbon atom of the 1,5-bis(trimethylsilyloxy)-1,3,5-hexatriene to give intermediate **A**. Intramolecular silyl-migration resulted in formation of intermediate **B** and generation of an ester function (intermediate **C**). The product is formed by attack of the oxygen atom onto the activated carboxylic chloride, expulsion of Me_3SiCl and regeneration of the catalyst.

The high regioselectivity for the first condensation step suggests that for trienes **7a-d** the highest electron density is present at the terminal carbon atom. The regioselectivity of the cyclization step can be explained based on stereoelectronic considerations:[12] the formation of a five-membered ring by acylation of the carbon of an enol requires approach of the electrophile perpendicular to the plane of the double bond; in contrast, acylation of the oxygen requires approach in the plane of the enol. In case of five-membered rings, approach of the electrophile to the carbon atom of the enol is, thus, sterically difficult compared to its approach in the plane to the oxygen. The *Z*-selectivity of the formation of butenolides **8a-b** and **8d** can be explained by the steric influence of the substituent R^1.



Scheme 3 Synthesis of butenolide **12**. *a*: Me_3SiCl, NEt_3, $ZnCl_2$, CH_2Cl_2, 20 °C, 90%; *b*: 1) LDA, THF, −78 °C, 1 h, 2) Me_3SiCl, −78→20 °C, 4 h, 84%; *c*: oxalyl chloride, 0.3 eq. Me_3SiOTf, CH_2Cl_2, −78→20 °C, 12 h, 55%.

The use of 1,3,5-tris(trimethylsilyloxy)-1,3-5-hexatrienes in our cyclization reaction was next studied (Scheme 3). Triene **11** was prepared by conversion of methyl

3,5-dioxohexanoate **9** into the 1,3-bis(trimethylsilyloxy)-1,3-butadiene **10** which was subsequently transformed into **11**.[13] The Me_3SiOTf-catalyzed cyclization of triene **11** with oxalyl chloride afforded the γ-alkylidenebutenolide **12** with very good regio- and *E*-diastereoselectivity. The product resides as a 2:1-mixture of keto-enol-tautomers (in acetone-d_6). It is important to note that butenolides **12** and **8c** both contain a hydrogen atom at the β-position of the ring (4-H). However, only butenolide **12** (containing an additional carbonyl group) was formed with high *E*-diastereoselectivity, whereas **8c** was obtained as a mixture of isomers. The selectivity observed for the formation of **12** can be explained by the dipol-dipol repulsion between the oxygen atoms[14] or alternatively by the formation of a stabilizing intramolecular hydrogen bond C−H(4)···O in the product.

In summary, we have reported the first synthesis of 1,5-bis(trimethylsilyloxy)-1,3,5-hexatrienes. The cyclization of these compounds with oxalyl chloride allows for a direct, regio- and diastereoselective synthesis of polyunsaturated γ-alkylidenebutenolides under mild conditions. The efficiency of this process is remarkable, if one considers that the oxalic acid unit is prone to several drawbacks in reactions with nucleophiles.[15] The butenolides prepared represent important analogues and synthetic precursors to pharmacologically relevant natural products such as lissoclinolide.

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(11) *Typical experimental procedure for the preparation of butenolides* **8**: To a CH_2Cl_2 solution (10 mL) of oxalyl chloride (0.62 mmol, 80 mg) and of 1,5-bis(trimethylsilyloxy)-1,3,5-hexatriene **7a** (0.52 mmol, 156 mg) was added a CH_2Cl_2 solution (1 mL) of Me_3SiOTf (0.31 mmol, 70 mg) at −78 °C. The temperature of the reaction mixture was allowed to rise to 20 °C during 12 h. After stirring for 2 h at 20 °C the reaction mixture was extracted with a saturated aqueous solution of NaCl (20 mL) and with a solution of HCl (10%, 20 mL). The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were dried ($MgSO_4$), filtered and the solvent of the filtrate was removed in vacuo. The residue was purified by column chromatography (silica gel, ether/petroleum ether = 1:2→2:1) to give butenolide **8a** as a yellow solid (60 mg, 55%). ^{1}H NMR ($CDCl_3$, 250 MHz): δ 2.03 (s, 3 H, CH_3), 3.78 (s, 3 H, OCH_3), 5.81 (d, *J* = 12 Hz, 1 H, 1′-H), 6.00 (d, *J* = 14 Hz, 1 H, 3′-H), 7.76 (dd, *J* = 14 Hz, *J* = 12 Hz, 1 H, 2′-H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ 7.21 (CH_3), 52.78 (OCH_3), 105.53 (CH, C-1′), 120.93 (C), 122.16 (CH, C-3′), 136.17 (CH, C-2′), 141.86, 152.58, 164.45, 166.94 (C). MS (EI, 70 eV): 210 (M^+, 66), 179 (43), 95 (100), 83 (43), 57 (40). The exact molecular mass m/z = 210.0528 ±2 mDa (M^+) was confirmed by HRMS (70 eV, EI). All compounds were characterized by spectroscopic methods and gave correct elemental analyses and/ or high resolution mass spectra.

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