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Efficient Synthesis of Butenolide–Medium Ring Ether Hybrids by a [3 + 2] Cyclization-Ring-Closing Metathesis Strategy

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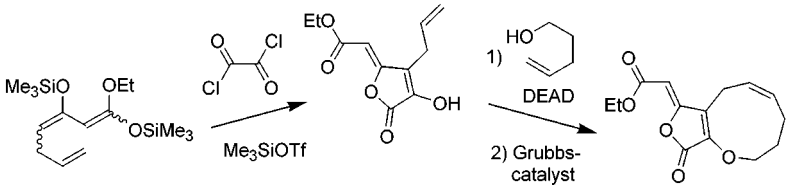
ABSTRACT



A new strategy for the synthesis of bicyclic γ-alkylidenebutenolides, butenolide–medium ring ether hybrids, is reported which involves Me_3-SiOTf-catalyzed cyclization of 1,3-bis(trimethylsilyloxy)-1,3-butadienes with oxalyl chloride, Mitsunobu reaction, and subsequent ring-closing metathesis.

The development of new synthetic methods for the efficient construction of biologically active compounds is an important field in organic chemistry. In this context, natural products are of particular importance as lead structures.[1] However, the isolation of new natural products is rather difficult and time-consuming. Therefore, the concept of the synthesis of natural product hybrids and analogues, containing two different pharmacophoric subunits, has been recently devised.[2] This concept has been also used by nature in the combined biosynthesis of vitamin E which is formed from a terpene and shikimic acid.[3] The hybrid vincristin is formed from aspido sperma and an iboga alkaloid and represents an important drug against blood cancer of children.[4]

Many natural products, including prominent compounds such as freelingyne, tetrenolin, dihydroxerulin, and patulin, belong to the pharmacologically important group of γ-alkylidenebutenolides.[5,6] Similarly, medium-ring ethers are found

(1) For the isolation of *strobilurines*, see: (a) Zapf, A.; Werle, A.; Anke, T.; Klostermeyer, D.; Steffan, B.; Steglich, W. *Angew. Chem.* **1995**, *107*, 255; *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 196. For the isolation of epothilones, see: (b) Höfle, G.; Bedorf, N.; Steinmetz, H.; Schomburg, P.; Gerth, K.; Reichenbach, H. *Angew. Chem.* **1996**, *108*, 1671; *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1567.

(2) (a) Hoppen, S.; Emde, U.; Friedrich, T.; Grubert, L.; Koert, U. *Angew. Chem.* **2000**, *112*, 2181; *Angew. Chem., Int. Ed.* **2000**, *39*, 2099. (b) Tietze, L. F.; Schneider, G.; Wölfling, J.; Nöbel, T.; Wulff, C.; Schubert, I.; Rübeling, A. *Angew. Chem.* **1998**, *110*, 2644; *Angew. Chem., Int. Ed.* **1998**, *37*, 2469. (c) Wang, J.; De Clerq, P. J. *Angew. Chem.* **1995**, *107*, 1698; *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1749. (d) Depew, K. M.; Zeman, M.; Boyer, S. H.; Denhart, D. J.; Ikemoto, N.; Crothers, D. M.; Danishefsky, S. J. *Angew. Chem.* **1996**, *108*, 2972; *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2797.

(3) (a) Netscher, T. *Chimia* **1996**, *50*, 563. (b) Furuya, T.; Yoshikawa, T.; Kimura, T.; Kaneko, H. *Phytochemistry* **1987**, *26*, 2741. (c) Stocker, A.; Fretz, H.; Frick, H.; Rüttimann, A.; Woggon, W.-D. *Bioorg. Med. Chem.* **1996**, *4*, 1129.

(4) (a) Magnus, P.; Mendoza, J. S.; Stamford, A.; Ladlow, M.; Willis, P. *J. Am. Chem. Soc.* **1992**, *114*, 10232. (b) Bornmann, W. G.; Kuehne, M. E. *J. Org. Chem.* **1992**, *57*, 1752.

(5) Reviews: (a) Rao, Y. S. *Chem. Rev.* **1976**, *76*, 625. (b) Pattenden, G. *Prog. Chem. Nat. Prod.* **1978**, *35*, 133. (c) Knight, D. W. *Contemp. Org. Synth.* **1994**, *1*, 287. (d) Negishi, E.-i.; Kotora, M. *Tetrahedron* **1997**, *53*, 6707.

(6) (a) Siegel, K.; Brückner, R. *Chem. Eur. J.* **1998**, *4*, 1116. (b) Goerth, F.; Umland, A.; Brückner, R. *Eur. J. Org. Chem.* **1998**, 1055. (c) Enders, D.; Dyker, H.; Leusink, F. R. *Chem. Eur. J.* **1998**, *4*, 311. (d) Görth, F. C.; Brückner, R. *Synthesis* **1999**, 1520. (e) Knight, D. W.; Pattenden, G. *J. Chem. Soc., Perkin Trans 1* **1979**, 62. (f) Ingham, C. F.; Massy-Westropp, R. A.; Reynolds, G. D.; Thorpe, W. D. *Aust. J. Chem.* **1975**, *28*, 2499. (g) Ohe, F. v. d.; Brückner, R. *Tetrahedron Lett.* **1998**, 1909. (h) Hanisch, I.; Brückner, R. *Synlett* **2000**, 374.

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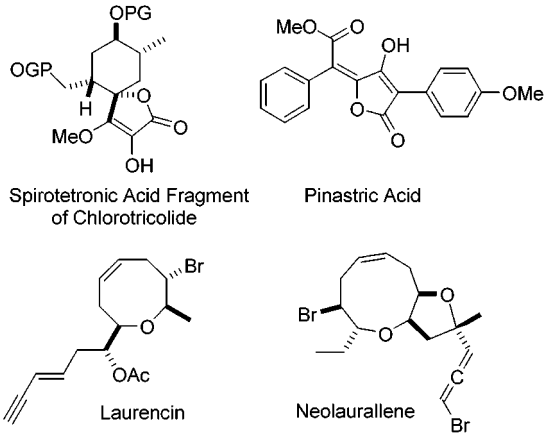
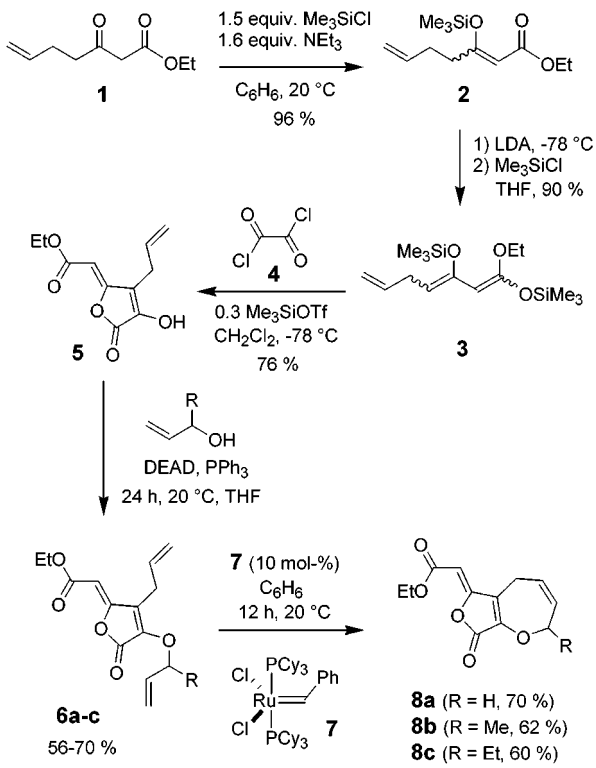
in a number of biologically active marine natural products, such as brevetoxins A and B, yessotoxin, ciguatoxin, laurencin, and maitotoxin.[7] We have recently reported[8] a new synthesis of α-hydroxy-γ-alkylidenebutenolides by the first regio- and stereoselective cyclizations of 1,3-dicarbonyl dianion equivalents with oxalic acid dielectrophiles. Herein, we wish to report an efficient synthesis of 5,*n* bicyclic butenolides ($n = 7-9$) which can be regarded as hybrids of the pharmacologically relevant subunits of γ-alkylidene-butenolides and medium-ring ethers.



Our starting point was the reaction of the dianion of ethyl acetoacetate with allyl bromide which afforded ethyl 3-oxo-hept-6-enoate **1** in 82% yield. Unfortunately, all attempts to directly prepare β-allyl-γ-alkylidenebutenolide **5** by using our dianion methodology[8a] failed: reaction of dilithiated ethyl 3-oxoheptenoate **1** with *N*,*N*′-dimethoxy-*N*,*N*′-dimethyl-ethanediamide resulted in a complex mixture. This can be explained by the lability of the dianion of **1**. Therefore, we have envisaged a Lewis acid-catalyzed synthesis of butenolide **5** via the 1,3-bis(trimethylsilyloxy)-1,3-butadiene **3** which represents an electroneutral dianion equivalent.[9] Bissilyl enol ether **3** was efficiently prepared by formation of the silyl enol ether **2** (using Me_3SiCl/NEt_3) in 96% yield (Scheme 1). Deprotonation of **2** with LDA at −78 °C and subsequent addition of Me_3SiCl afforded diene **3** in 90% yield. To our satisfaction, Me_3SiOTf-catalyzed cyclization of **3** with oxalyl chloride **4** afforded the γ-alkylidenebutenolide **5** in 76% yield with very good regioselectivity and *Z*-selectivity.

Scheme 1



The chemoselective alkylation of the α-hydroxy group proved problematic: reaction of **5** with allyl bromide in the presence of K_2CO_3 afforded the desired allylated butenolide **6a**, however, in only 22% yield. The low yield can be explained by the general base lability of the Michael position of γ-alkylidenebutenolides.[6f] The use of 2-bromo-3-butene resulted in formation of an inseparable mixture of products, presumably due to decomposition and competing S_N/S_N' reactions. The problem could be eventually solved by the use of the Mitsunobu reaction: treatment of **5** with allylic alcohol, 2-hydroxy-3-butene, and 3-hydroxy-1-pentene in the presence of PPh_3/DEAD afforded the corresponding allylated butenolides **6a**−**c** in good yields with very good chemoselectivities.[10] The chemoselective alkylation of γ-alkylidene-butenolides has to our knowledge not been reported so far.[11] To our satisfaction, the ring-closing metathesis (RCM)[12] of **6a**−**c** using the Grubbs catalyst **7** proceeded uneventfully

(7) For medium-ring ethers, see: (a) Altenbach, H.-J. In *Organic Synthesis Highlights*; Mulzer, J., Altenbach, H.-J., Braun, M., Krohn, K., Reissig, H.-U., Ed.; VCH: Weinheim, 1991. (b) Nicolaou, K. C.; Hwang, C.-K.; Marron, B. E.; DeFrees, S. A.; Couladouros, E. A.; Abe, Y.; Carroll, P. J.; Snyder, J. P. *J. Am. Chem. Soc.* **1990**, *112*, 3040 and cited literature. (c) Overman, L. E. *Acc. Chem. Res.* **1992**, *25*, 358. (d) Brandes, A.; Hoffmann, H. M. R. *Tetrahedron* **1995**, *51*, 145. (e) Alvarez, E.; Diaz, M. T.; Perez, R.; Ravelo, J. L.; Regueiro, A.; Vera, J. A.; Zurita, D.; Martin, J. D. *J. Org. Chem.* **1994**, *59*, 2848. (f) Robinson, R. A.; Clark, J. S.; Holmes, A. B. *J. Am. Chem. Soc.* **1993**, *115*, 10400. (g) Paquette, L. A.; Sweeney, T. J. *Tetrahedron* **1990**, *46*, 4487.

(8) Langer, P.; Stoll, M. *Angew. Chem.* **1999**, *111*, 1919; *Angew. Chem., Int. Ed.* **1999**, *38*, 1803. (b) Langer, P.; Krummel, T. *Chem. Commun.* **2000**, 967. (c) Langer, P.; Eckardt, T. *Synlett* **2000**, 844.

(9) (a) Krohn, K.; Ostermeyer, H.-H.; Tolkiehn, K. *Chem. Ber.* **1979**, *112*, 2640−2649. (b) Chan, T.-H.; Brownbridge, P. *J. Am. Chem. Soc.* **1980**, *102*, 3534. (c) Molander, G. A.; Cameron, K. O. *J. Am. Chem. Soc.* **1993**, *115*, 830.

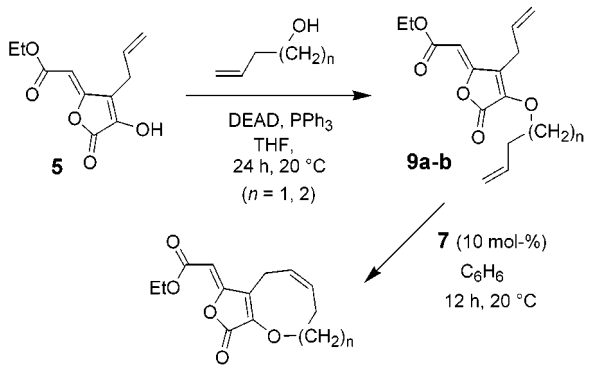
(10) **Representative experimental procedure:** To a degassed THF solution (6 mL) of **5** (240 mg, 1.1 mmol), 3-hydroxy-1-pentene (114 mg, 1.32 mmol), and PPh_3 (347 mg, 1.32 mmol) was added a THF solution (2 mL) of DEAD (0.205 mL, 1.32 mmol). The solution was stirred at 20 °C for 14 h. The solvent was removed in vacuo, and the residue was purified by chromatography (silica gel, ether: petroleum ether = 1:3) to give **6c** as a light yellow oil (180 mg, 56%). ^{1}H NMR ($CDCl_3$, 250 MHz): 0.95, 1.28 (2 × t, $J = 7$ Hz, 2 × 3 H, 2 × CH_3), 1.75 (m, 2 H, $CHCH_2$), 3.10 (m, 2 H, $CCH_2CH{=}CH$), 4.22 (q, $J = 7$ Hz, 2 H, OCH_2CH_3), 5.00−5.40 (m, 5 H, $CHC{=}O$, 2 × $CH{=}CH_2$), 5.60−5.90 (m, 2 H, $CH{=}CH_2$).^{13}C NMR ($CDCl_3$, 62.5 MHz): δ_C 9.15, 14.16, 26.50, 28.03, 60.69, 82.99, 96.86, 117.56, 119.05, 129.61, 132.18, 136.27, 144.60, 155.46, 162.49, 163.37. MS (70 eV, EI): 292 (20, M^+). Anal. Calcd for $C_{16}H_{20}O_5$: C 65.74, H 6.90. Found: C 65.56, H 7.10. All new compounds were characterized spectroscopically and gave correct elemental analyses and/or high-resolution mass spectra.

(11) For Mitsunobu reactions of tetronic acid derivatives, see: Bajwa, J. S.; Anderson, R. C. *Tetrahedron Lett.* **1990**, *48*, 6973.

and afforded the bicyclic γ-alkylidenebutenolides **8a**−**c** in good yields (Scheme 1).[13]

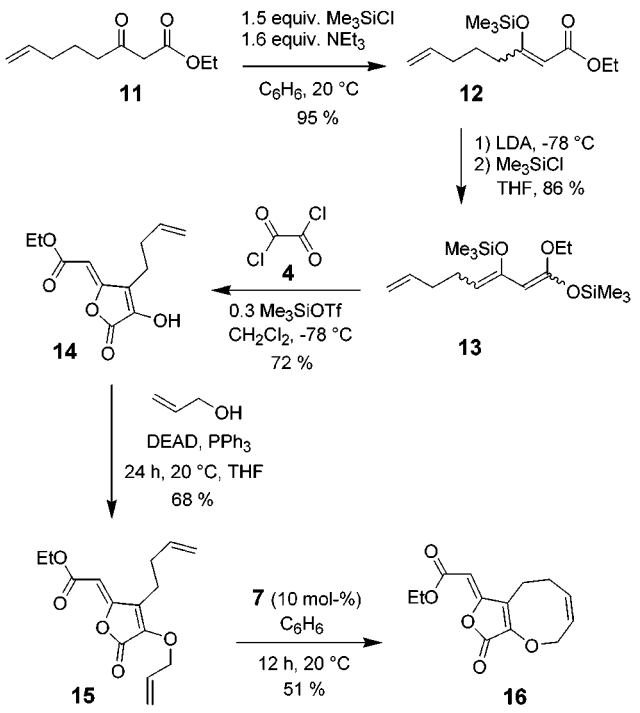
The application of the RCM reaction to the formation of medium-sized rings is of great current interest, and only a few examples have been reported so far.[14] Therefore, we have studied the synthesis of butenolide−ring ether hybrids containing medium-sized rings. Reaction of γ-alkylidenebutenolide **5** with 1-hydroxy-3-butene and 1-hydroxy-4-pentene afforded the cyclization precursors **9a** and **9b**, respectively, in good yields. Ring-closing metathesis of **9a**,**b** afforded the bicyclic butenolides **10a**,**b** containing an eight- and a nine-membered ring, respectively, in acceptable yields (Scheme 2).

Scheme 2



Reaction of the dianion of ethyl acetoacetate with 1-bromo-3-butene afforded ethyl 3-oxooct-7-enoate **11** in 88% yield (Scheme 3). Silylation of **11** afforded the silyl enol ether **12** (95%) which was transformed into the 1,3-bis(trimethylsilyloxy)-1,3-butadiene **13** in 86% yield. Cyclization of **13** with oxalyl chloride afforded the γ-alkylidenebutenolide **14** in 72% yield with very good regioselectivity and *Z*-selectivity. Mitsunobu reaction of **14** with allylic alcohol afforded the cyclization precursor **15**. Ring-closing metathesis of **15** using catalyst **7** afforded the medium-sized bicyclic butenolide **16** which represents a positional isomer of butenolide **10a**.

Scheme 3



In summary, we have developed a new and efficient synthesis of bicyclic butenolides containing a medium-sized ring ether moiety. In this context, the first chemoselective alkylation of γ-alkylidenebutenolides was developed. The medium-sized rings were prepared in acceptable to good yields by ring-closing metathesis. The bicyclic products prepared represent hybrids of γ-alkylidenebutenolides and medium-ring ethers. These substance classes are of pharmacological relevance and occur in a variety of natural products.

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(12) Reviews: (a) Schuster, M.; Blechert, S. *Angew. Chem.* **1997**, *109*, 2124; *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036. (b) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371. (c) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (d) Fürstner, A. *Synlett* **1999**, 1523.

(13) **Representative experimental procedure:** To a degassed benzene solution (8 mL) of butenolide **6c** (0.23 mmol, 66 mg) was added catalyst **7** (19 mg, 10 mol %). The solution was stirred for 12 h under argon and for 4 h at the air. The solvent was removed in vacuo, and the residue was purified by chromatography (silica gel, ether: petroleum ether = 1:1) to give **8c** as a light yellow oil (28 mg, 60%). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.05, 1.31 (2 × t, J = 7 Hz, 2 × 3 H, OCH_2CH_3), 1.85 (m, 2 H, CH_2), 2.93 (dd, J = 17 Hz, J = 7 Hz, 1 H, CCH_2CH=CH), 2.45 (dt, J = 17 Hz, J = 3 Hz, 1 H, CCH_2CH=CH), 4.22 (q, J = 7 Hz, 2 H, OCH_2CH_3), 5.25 (s, 1 H, C*H*C=O), 5.85, 6.10 (2 × m, 2 × 1 H, C*H*=C*H*). ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ_C 9.31, 14.21, 22.60, 27.62, 60.78, 80.14, 95.59, 120.57, 131.23, 131.86, 146.74, 156.30, 162.81, 163.44. MS (70 eV, EI): 264 (100, M^+). Anal. Calcd for $C_{14}H_{16}O_5$: C 63.63, H 6.10. Found: C 63.35, H 6.32.

(14) For an account of the synthesis of medium-sized rings by RCM, see: (a) Maier, M. E. *Angew. Chem.* **2000**, *112*, 2153; *Angew. Chem., Int. Ed.* **2000**, *39*, 2073. See also: (b) Crimmins, M. T.; Choy, A. L. *J. Am. Chem. Soc.* **1999**, *121*, 5653. (c) Miller, S. J.; Kim, S.-H.; Chen, Z.-R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 2108.