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Concise Synthesis of (*S*,*S*)-(+)-Dehydrohomoancepsenolide

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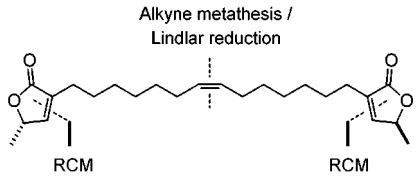
ABSTRACT



A concise total synthesis of the bis-butenolide 3 in optically active form is reported. Key steps are a zinc-mediated "three-component coupling" with formation of dienyne 9 which undergoes ring closing metathesis (RCM) on treatment with $(PCy_3)_2Cl_2Ru{=}CHPh$. Dimerization of the resulting butenolide 11 is then achieved via alkyne metathesis using $(tBuO)_3W{\equiv}CCMe_3$ as the catalyst. A Lindlar reduction completes this synthesis which delivers product 3 in only five steps with an overall yield of 25%.

It is believed that gorgonians flourishing in a marine environment inhabited by numerous potential predators defend themselves by chemical means. Many studies have been devoted to the isolation and characterization of secondary metabolites responsible for this defense mechanism because they may serve as potential lead structures for medicinal chemistry.[1] This led inter alia to the discovery of structurally diverse acetogenins such as the bis-butenolide derivative ancepsenolide (**1**) and congeners thereof (Figure 1).[2,3]

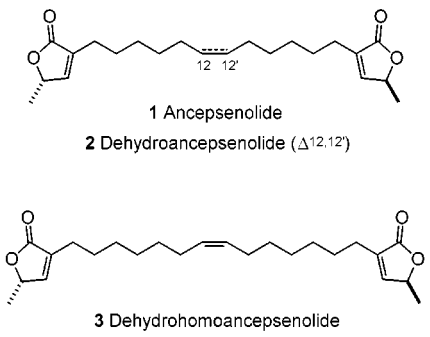


Figure 1. Structures of bis-butenolide acetogenins from marine sources.

Although compound **1** exhibits only moderate cytotoxic and antibiotic activity, it has been repeatedly targeted in recent years.[4,5] The most elegant approach was described by Trost et al. using a ruthenium-catalyzed Alder−ene reaction as the key step. This route did not only deliver ancepsenolide **1** in excellent yield but also allowed for the assignment of its absolute configuration as (*S*,*S*).[5a]

The Alder−ene approach, however, is less appropriate for the synthesis of those members of this class of natural

(1) For selected reviews discussing the importance of marine habitats for lead discovery, see the following references and literature cited therein: (a) *Drug Discovery from Nature*; Grabley, S., Thiericke, R., Eds.; Springer: Berlin, 1999. (b) Rinehart, K. L. *Pure Appl. Chem.* **1989**, *61*, 525. (c) Cragg, G. M.; Newman, D. J.; Weiss, R. B. *Sem. Oncol.* **1997**, *24*, 156. (d) Bewley, C. A.; Faulkner, D. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 2162. (e) Scheuer, P. J. *Science* **1990**, *248*, 173. (f) Faulkner, D. J. *Nat. Prod. Rep.* **1994**, *11*, 355.

(2) (a) Schmitz, F. J.; Kraus, K. W.; Ciereszko, L. S.; Sifford, D. H.; Weinheimer, A. J. *Tetrahedron Lett.* **1966**, *7*, 97. (b) Schmitz, F. J.; Lorance, E. D.; Ciereszko, L. S. *J. Org. Chem.* **1969**, *34*, 1989. (c) Schmitz, F. J.; Lorance, E. D. *J. Org. Chem.* **1971**, *36*, 719. (d) Guo, Y.-W.; Gavagnin, M.; Mollo, E.; Trivellone, E.; Cimino, G. *J. Nat. Prod.* **1999**, *62*, 1194.

(3) Review on acetogenins: Cave, A.; Figadère, B.; Laurens, A.; Cortes, D. *Prog. Chem. Org. Nat. Prod.* **1997**, *70*, 81.

(4) Syntheses of the racemate: (a) Podraza, K. F.; Sneden, A. T. *J. Nat. Prod.* **1985**, *48*, 792. (b) Larson, G. L.; Betancourt de Perez, R. M. *J. Org. Chem.* **1985**, *50*, 5257.

(5) Syntheses of enantiomerically pure **1**: (a) Trost, B. M.; Müller, T. J. J. *Am. Chem. Soc.* **1994**, *116*, 4985. (b) Yao, Z.-J.; Yu, Q.; Wu, Y.-L. *Synth. Commun.* **1996**, *26*, 3613

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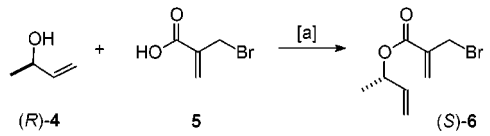
products containing a pre-exisiting double bond in their backbone.[6] Therefore, we were prompted to develop an alternative but equally efficient route that brings these compounds into reach.

Our synthesis of dehydrohomoancepsenolide **3**, a secondary metabolite isolated from the gorgonian octocoral *Pterogorgia citrina* collected off the west coast of Puerto Rico,[7] starts with an esterification of 1-buten-3-ol **4** with (bromomethyl)acrylic acid **5** (Scheme 1). Since model studies had

Scheme 1[a]

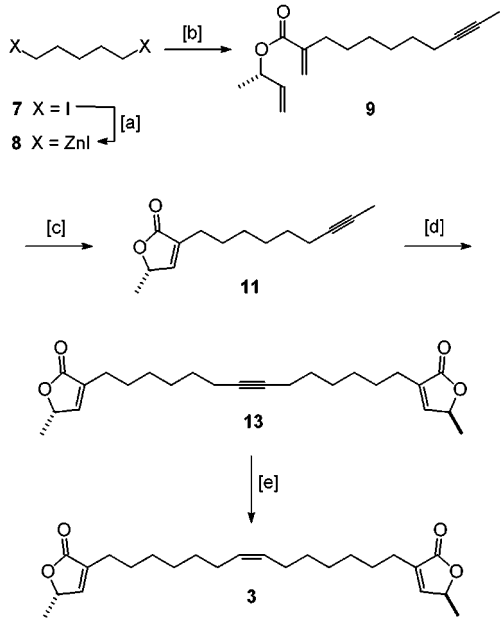


[a] [a] DEAD, PPh_3, Et_2O, 16 h, 71%.

shown that this reaction is best achieved under Mitsunobu conditions,[8] we used commercially available (*R*)-**4** (er ≥ 97:3) for the preparation of the required (*S*)-configurated ester **6**.

This compound was then subjected to a zinc-induced, copper-mediated "three-component coupling" reaction as described by Knochel et al. (Scheme 2).[9] Insertion of activated zinc[10] into both C−I bonds of 1,5-diiodopentane **7** followed by addition of CuCN (1 equiv) and LiCl to the bis-organozinc compound **8** thus formed afforded a 1,5-*hetero*bimetallic intermediate, which can be consecutively reacted with two different electrophiles. Specifically, addition of 1-iodo-1-propyne[11] and stirring of the resulting mixture

Scheme 2[a]



[a] [a] Zn, THF, 40 °C, 24 h; [b] (i) CuCN, 2 LiCl, THF, 0 °C, 15 min; (ii) 1-iodo-1-propyne (0.7 equiv), hexane, −60 → −35 °C, 15 h; (iii) (*S*)-**6** (1.5 equiv), 1 h, −78 °C → rt, 70%; [c] $(PCy_3)_2Cl_2Ru{=}CHPh$ **10** (16 mol %), CH_2Cl_2, reflux, 24 h, 70%; [d] $(tBuO)_3W{\equiv}CCMe_3$ **12** (10 mol %), toluene, 100 °C, 10 h, 75%; [e] Lindlar catalyst, quinoline cat., hexane/EtOH (1/1), H_2 (1 atm), rt, 30 min, 96%.

at −35 °C for 15 h followed by addition of (*S*)-**6** (−78 °C → rt, 1 h) provided compound **9** in 70% yield.

Having secured good access to this key intermediate, we attempted the cyclization of the butenolide entity by a ring closing olefin metathesis (RCM) reaction.[12] Although electron-deficient alkenes in general and acrylates in particular are known to be problematic substrates for this kind of transformation,[13] we were pleased to see that the envisaged cyclization **9** → **11** proceeds readily in 70% yield provided that it is carried out under high dilution conditions. A noteworthy aspect of this transformation is its chemoselective course: despite the fact that metathesis catalysts are fairly reactive toward alkynes, no enyne metathesis was interfering with the desired butenolide formation if the "standard" Grubbs carbene $(PCy_3)_2Cl_2Ru{=}CHPh$ **10**[14] is used as the catalyst. Interestingly enough, "second-generation" ruthenium carbene complexes containing N-heterocyclic carbene ligands, which were recently shown to be particularly powerful catalysts for metathesis reactions of acrylates,[15] turned out to be too reactive in this case as they did not rigorously distinguish between the alkyne and the alkene moieties of substrate **9**.

(6) The Alder−ene reaction produces two alkenes in the tether between the butenolide headgroups which must be hydrogenated en route to **1**.

(7) Rodriguez, A. D.; Ramirez, C. *J. Nat. Prod*. **1994**, *57*, 339.

(8) Mitsunobu, O. *Synthesis* **1981**, 1.

(9) (a) AchyuthaRao, S.; Knochel, P. *J. Org. Chem*. **1991**, *56*, 4591. (b) Knochel, P. In *Active Metals. Preparation, Characterization, Applications*; Fürstner, A., Ed.; VCH: Weinheim, 1995; p 191.

(10) Review: Fürstner, A. *Angew. Chem*. **1993**, *105*, 171; *Angew. Chem., Int. Ed. Engl*. **1993**, *32*, 164.

(11) Diner, U. E.; Lown, J. W. *Can. J. Chem*. **1971**, *49*, 403.

(12) Reviews: (a) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413. (b) Fürstner, A. *Top. Catal*. **1997**, *4*, 285. (c) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl*. **1997**, *36*, 2036. (d) Fürstner, A. *Top. Organomet. Chem*. **1998**, *1*, 37. (e) Ivin, K. J.; Mol, J. C. *Olefin Metathesis and Methathesis Polymerization*, 2nd ed.; Academic Press: New York, 1997.

(13) For successful RCM reactions of acrylates, see the following for leading references; note, however, that in most cases the reactions are only productive if catalyst **10** is used in combination with $Ti(OiPr)_4$: (a) Nicolaou, K. C.; Rodriguez, R. M.; Mitchell, H. J.; van Delft, F. L. *Angew. Chem., Int. Ed*. . **1998**, *37*, 1874. (b) Rutjes, F. P. J. T.; Schoemaker, H. E. *Tetrahedron Lett*. **1997**, *38*, 677. (c) Dirat, O.; Kouklovsky, C.; Langlois, Y.; Lesot, P.; Courtieu, J. *Tetrahedron: Asymmetry* **1999**, *10*, 3197. (d) Grossmith, C. E.; Senia, F.; Wagner, J. *Synlett* **1999**, 1660. (e) Ghosh, A. K.; Liu, C. *Chem. Commun*. **1999**, 1743. (f) Cossy, J.; Bauer, D.; Bellosta, V. *Tetrahedron Lett*. **1999**, *40*, 4187. (g) Ghosh, A. K.; Cappiello, J.; Shin, D. *Tetrahedron Lett*. **1998**, *39*, 4651. (h) The beneficial effect of $Ti(OiPr)_4$ on RCM was originally described in: Fürstner, A.; Langemann, K. *J. Am. Chem. Soc*. **1997**, *119*, 9130.

(14) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc*. **1996**, *118*, 100.

(15) (a) Fürstner, A.; Thiel, O. R.; Ackermann, L.; Schanz, H.-J.; Nolan, S. *J. Org. Chem*. **2000**, *65*, 2204. (b) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc*. **2000**, *122*, 3783.

(16) (a) Schrock, R. R.; Clark, D. N.; Sancho, J.; Wengrovius, J. H.; Rocklage, S. M.; Pedersen, S. F. *Organometallics* **1982**, *1*, 1645. (b) Freudenberger, J. H.; Schrock, R. R.; Churchill, M. R.; Rheingold, A. L.; Ziller, J. W. *Organometallics* **1984**, *3*, 1563. (c) Listemann, M. L.; Schrock, R. R. *Organometallics* **1985**, *4*, 74. (d) Schrock, R. R. *Polyhedron* **1995**, *14*, 3177.

Compound **11** was then dimerized via alkyne metathesis. Thus, treatment with catalytic amounts of the easily accessible Schrock alkylidyne complex $(tBuO)_3W{\equiv}CCMe_3$ **12**[16] in toluene at 100 °C affords the C_2-symmetrical product **13** in 75% yield. This example adds to the rapidly increasing list of successful applications of this emerging technology[17,18] and attests to the excellent application profile of the tungsten catalyst employed. Note that the chemoselectivity is now inversed since complex **12** selects exclusively for the alkyne over the alkene group of substrate **11**. Therefore, the sequence depicted in Scheme 2 demonstrates that modern metathesis catalysts allow one to selectively address alkenes in the presence of alkynes or vice versa. This rigorous distinction between different π-systems is important form the conceptual standpoint and further upgrades the impact of metathesis in general on the logic of retrosynthetic planning.

The total synthesis of dehydrohomoancepsenolide **3** was completed by a Lindlar hydrogenation of product **13** under standard conditions. Our route provides this bola-form butenolide of marine origin in optically active form in only five steps with 25% overall yield starting from commercially available substrates.[19,20] Moreover, it is obvious that the reaction sequence can be easily adapted to the preparation of other members of this family of natural products.

Further syntheses of bioactive targets that are economical in the total number of steps[21] due to a strategic use of metathetic conversions are in progress and will be reported in the near future.

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Supporting Information Available: Full experimental details as well as analytical and spectroscopic data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(17) Alkyne metathesis is a fairly old reaction but has found hardly any applications to advanced synthesis for a long period of time. Only recently, this situation is rapidly changing, cf. ref 18. For early examples of scrambling or dimerization of simple alkynes by structurally undefined catalyst systems see: (a) Mortreux, A.; Blanchard, M. *J. Chem. Soc., Chem. Commun.* **1974**, 786. (b) Villemin, D.; Cadiot, P. *Tetrahedron Lett.* **1982**, *23*, 5139. (c) Kaneta, N.; Hirai, T.; Mori, M. *Chem. Lett.* **1995**, 627. (d) Kaneta, N.; Hikichi, K.; Asaka, S.-I.; Uemura, M.; Mori, M. *Chem. Lett.* **1995**, 1055. (e) Pschirer, N. G.; Bunz, U. H. F. *Tetrahedron Lett.* **1999**, *40*, 2481. (f) For detailed mechanistic investigations of alkyne metathesis catalyzed by metal alkylidyne complexes see ref 16 and literature cited therein.

(18) (a) Fürstner, A.; Seidel, G. *Angew. Chem.* **1998**, *110*, 1758; *Angew. Chem., Int. Ed.* **1998**, *37*, 1734. (b) Fürstner, A.; Mathes, C.; Lehmann, C. W. *J. Am. Chem. Soc.* **1999**, *121*, 9453. (c) Fürstner, A.; Guth, O.; Rumbo, A.; Seidel, G. *J. Am. Chem. Soc.* **1999**, *121*, 11108. (d) Fürstner, A.; Grela, K. *Angew. Chem.* **2000**, *112*, 1292; *Angew. Chem., Int. Ed.* **2000**, *39*, 1234. (e) Fürstner, A.; Rumbo, A. *J. Org. Chem.* **2000**, *65*, 2608.

(19) The synthetic material was obtained as a solid (mp = 99−100 °C), whereas the natural product is described to be a colorless oil. All other analytical and spectroscopic data, however, are identical to those reported in ref 7, cf. Supporting Information.

(20) For syntheses of bioactive bola-form resorcinol derivatives, see: Fürstner, A.; Seidel, G. *J. Org. Chem.* **1997**, *62*, 2332.

(21) For a discussion, see: Fürstner, A. *Synlett* **1999**, 1523.