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An Enyne Metathesis/(4 + 2)-Dimerization Route to (±)-Differolide

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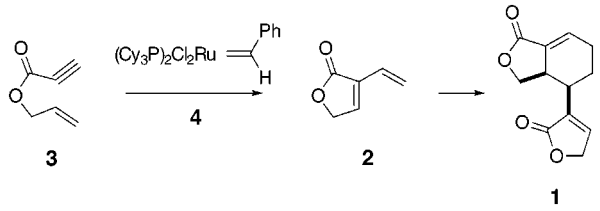
ABSTRACT

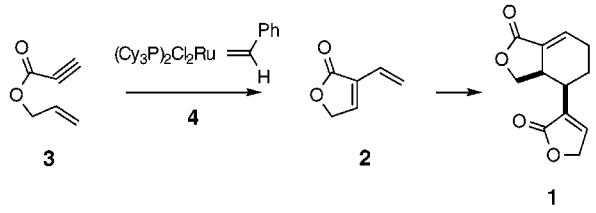


A concise total synthesis of (±)-differolide (1) has been achieved. 2-Vinylbutenolide (2) was prepared by enyne metathesis of allyl propynoate (3) using the Grubbs initiator 4. This reaction was examined by ^{1}H NMR spectroscopy, which led to the hypothesis that low concentration of ruthenium species and high concentration of enyne substrate would be advantageous. Accordingly, slow addition of 4 to solutions of enyne 3 was found to be beneficial. Spontaneous dimerization of 2 gave (±)-differolide (1) and an isomer.

(±)-Differolide (**1**) was isolated in 1986 from cultures of the actinomycete *Streptomyces aurantiogriseus*, strain *Tü 3149*.[1] The structure was determined by single-crystal X-ray analysis and is supported by the ^{1}H NMR spectroscopic data. That this compound is racemic suggested to us that a (perhaps spontaneous) Diels−Alder reaction of 2-vinylbutenolide (**2**) might be a key event in its formation. Indeed, this consideration raises the possibility that (±)-**1** is not naturally occurring but could have been first formed during isolation. We have now synthesized **2** by enyne metathesis of allyl propynoate (**3**)[2] using the Grubbs initiator carbene complex **4**.[3] In fact, 2-vinylbutenolide readily dimerizes to give (±)-differolide (**1**) as the major product (Scheme 1).[4]

Enyne metathesis[5] (one version of the larger class of enyne cycloisomerization reactions[6]) can be promoted by various metals and may or may not involve metal−carbene chemistry. The subset of carbene-mediated enyne metathesis reactions can proceed by either of two pathways (Scheme 2). Initial intermolecular reaction of the metal−carbene complex can occur either with the alkyne or the alkene. Subsequent intramolecular involvement of the alkene or alkyne, respectively, results in formation of the same conjugated diene product. These two possibilities are portrayed specifically for conversion of enyne **3** to 2-vinylbutenolide **2** in Scheme 2.

Scheme 1



We examined the reaction of **3** with **4** by ^{1}H NMR spectroscopy to look for one or more of the obligatory intermediates **5**−**7** and/or **8**−**10**. Thus, substrate **3** (0.025 M) and benzylidenecarbene **4** (~25 mol %; Ru=C*H*Ph at δ = 20.02 ppm) were combined in CD_2Cl_2 at room tempera-

(1) Keller-Schierlein, W.; Bahnmüller, U.; Dobler, M.; Bielecki, J.; Stümpfel, J.; Zähner, H. *Helv. Chim. Acta* **1986**, *69*, 1833−1836.
(2) Balas, L.; Jousseaume, B.; Langwost, B. *Tetrahedron Lett.* **1989**, *30*, 4525−4526.
(3) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 100−110.
(4) A stereoselective (21 step) synthesis of each enantiomer of differolide has been reported. Mori, K.; Tomioka, H.; Fukuyo, E.; Yanagi, K. *Liebigs Ann. Chem.* **1993**, 671−681.
(5) Mori, M. *J. Synth. Org. Chem. Jpn.* **1998**, *56*, 433−442.
(6) Trost, B. M.; Krische, M. J. *Synlett* **1998**, 1−16.

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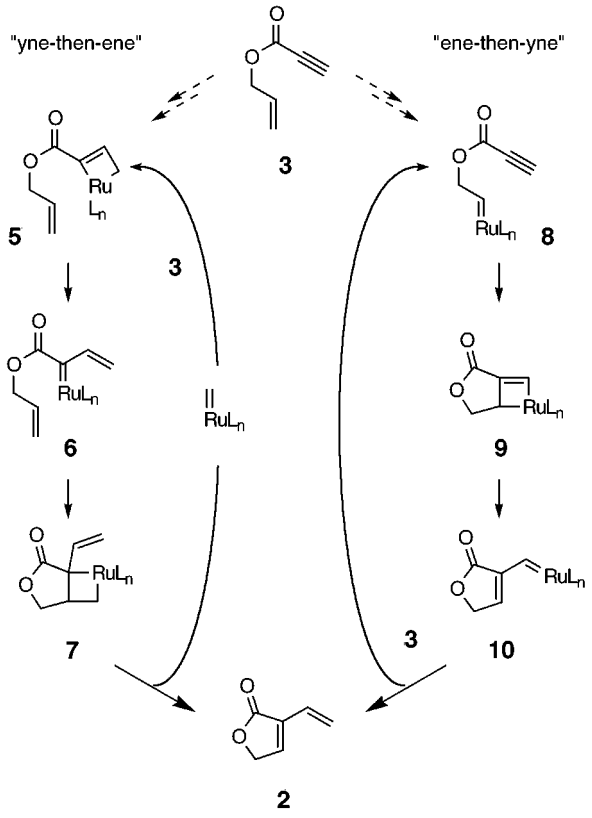
Scheme 2



ture. New carbene proton resonances at $\delta = 18.91$ (t, $J = 4$ Hz) and 20.24 (s) ppm, which we attribute to the alkylidene intermediate **8** and vinylcarbene **10**, respectively, quickly appeared. While these observations do not rule out the "yne-then-ene" pathway (intermediates **5**−**7** lack carbene alkylidene protons), they do provide direct evidence that the "ene-then-yne" pathway is viable. Styrene was also produced, which is further evidence for the initial generation of **8** from reaction of **3** with **4**.

An important ramification of the "ene-then-yne" pathway is that substrate concentration is critical; i.e., product **2** is not released until intermediate **10** encounters another molecule of enyne **3**. This suggests that higher substrate concentrations should be advantageous. However, we have elsewhere observed that the autodecomposition of starting benzylidene initiator **4** occurs faster at higher concentrations. Taken together, these observations prompted the series of experiments summarized in Table 1 in which the concentration of **3** was increased while the concentration of complex **4** was minimized. It is noteworthy that the progress of these reactions was conveniently monitored by ^{1}H NMR analysis of aliquots of the reaction mixtures even when *nondeuterated* CH_2Cl_2 was the reaction solvent. By using a straightforward suppression of the solvent resonance at δ 5.3 ppm in these unlocked samples, we were able to obtain high-quality spectra for identification of major and minor reaction components, even when starting substrate concentrations were as low as 0.01 M. The best overall reaction conditions we have found use a syringe pump to add slowly a solution of the initiator **4** to a solution of **3** at relatively high concentration. When the carbene **4** was added in a single portion (entry 1), reaction progress stopped at only ∼20% conversion (i.e., ∼two turnovers per Ru). The effective concentration of initiator **4** was then reduced by slow addition of just 5 mol % of the carbene to solutions of higher concentration of enyne **3** (entries 2 and 3), which resulted in higher turnover and conversion. Addition of a larger amount of carbene **4** over a longer time (entry 4) resulted in complete consumption of enyne **3**. On a preparative scale, these conditions provided 2-vinylbutenolide (**2**) in 40% isolated yield (MPLC).

Table 1. Reaction Conditions for Metathesis of Enyne **3**[a]

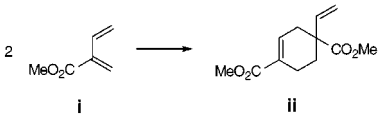
entry	[enyne **3**]	mol % Ru	addition time	[diene **2**]: [styrene][b]	% convn[c]
1	0.03 M	10	one portion	2:1	20
2	0.10 M	5[d]	5 h	8:1	50
3	1.0 M	5[d]	30 h	9:1	50
4	0.10 M	10[d]	37 h	9:1	100

[a] Methylene chloride solvent at ambient temperature. [b] Measured by integration of the ^{1}H NMR spectrum of an aliquot of the reaction mixture (using solvent suppression of the CH_2Cl_2 resonance at δ 5.3 ppm). [c] Measured[b] as the [diene **2**]/[enyne **3**]. [d] Added as an ∼0.04 M solution in CH_2Cl_2.

(7) 2-Vinylbutenolide (**2**) was initially prepared (Donaldson, S. M. Ph.D. Thesis, University of Minnesota, 1990) from (i) 2-bromo-2-butenolide (coupling of 3-bromo-2-TBSO-furan with various vinyl−metal species), (ii) trimethylsilyl vinyl acetate (aldol addition to 2-bromoacetaldehyde followed by lactonization and dehydration), or (iii) ethyl crotonate (aldol with $THPOCH_2CHO$, and various lactonization/dehydration sequences). These routes were far less efficient than the enyne metathesis described now. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (t, $J = 2.5$ Hz, 1H), 6.44 (dddd, $J = 17.5, 11.5, 1, 1$ Hz, 1H), 6.26 (dddd, $J = 17.7, 1, 1, 1$ Hz, 1H), 5.48 (dddd, $J = 10.8, 1, 1, 1$ Hz, 1H), and 4.82 (dddd, $J = 2, 1, 1, 1, 1$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 144.6, 130.2, 125.2, 121.2, and 69.6; IR (0.008 M in $CDCl_3$) 3010, 2930, 2860, 1755, 1620, 1580, 1440, 1400, 1340, 1310, 1300, 1210, 1200, 1100, 1060, 1030, and 990 cm^{-1}; MS (EI, 70 eV, *m/z*, rel int) 110 (M^+, 60), 82 (43), 81 (50), and 53 (100).

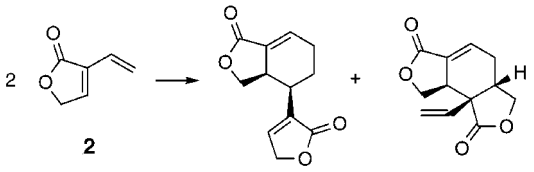
(8) (a) Sydnes, L. K.; Skattebøl, L.; Chapleo, C. B.; Leppard, D. G.; Svanholt, K. L.; Dreiding, A. S. *Helv. Chim. Acta* **1975**, *58*, 2061−2073. (b) Goldberg, O.; Dreiding, A. S. *Helv. Chim. Acta* **1976**, *59*, 1905−1910. (c) McIntosh, J. M.; Sieler, R. A. *J. Org. Chem.* **1978**, *43*, 4431−4433. (d) Hoffmann, H. M. R.; Rabe, J. *Angew. Chem., Int. Ed. Engl.* **1983**, *22*, 795−796. (e) Poly, W.; Schomburg, D.; Hoffmann, H. M. R. *J. Org. Chem.* **1988**, *53*, 3701−3710. (f) Alanine, A. I. D.; Fishwick, C. W. G.; Jones, A. D.; Mitchell, M. B. *Tetrahedron Lett.* **1989**, *30*, 5653−5654. (g) Nájera, C.; Mancheño, B.; Yus, M. *Tetrahedron Lett.* **1989**, *30*, 6085−6088. (h) Spino, C.; Crawford, J. *Can. J. Chem.* **1993**, *71*, 1094−1097. (i) Hoffmann, R.; Mattay, J.; Banning, A.; Rodewald, U.; Möller, M. M. *J. Prakt. Chem./Chem.-Ztg.* **1994**, *336*, 343−349. (j) Spino, C.; Pesant, M.; Dory, Y. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 3262−3265. (k) Spino, C.; Crawford, J.; Cui, Y.; Gugelchuk, M. *J. Chem. Soc., Perkin Trans. 2* **1998**, 1499−1506.

(9) For example, the parent 2-carbomethoxybutadiene (**i**) dimerizes at room temperature to give **ii** (mikanecic acid dimethyl ester), exclusively.[8] This adduct arises from reaction of the more electron deficient dienophilic π-bond in **i** [as does the minor adduct **11** in the dimerization of 2-vinylbutenolide (**2**)] and results in para-selectivity (in contrast to the meta-orientation of the carbonyl groups observed in the minor isomer **11**).



i ii

Scheme 3



The first sample of **2** we isolated[7] underwent spontaneous dimerization when stored neat at room temperature. (The dimerizations of related 2-carbonyl-substituted butadiene derivatives have been studied[8] and are also remarkably facile.[9]) Two adducts (from among eight possible racemic regio- and stereoisomeric 4 + 2 dimers) were observed in an ~9:1 ratio (Scheme 3). The major compound was (±)-differolide (**1**, mp 171−175 °C). The minor component was the isomeric dimer **11**[10] (colorless oil) in which the butenolide alkene rather than the vinyl group had participated as the dienophile.[11]

Table 2. Reaction Conditions for Dimerization of 2-Vinylbutenolide (**2**)

entry	solvent	temperature	time	additive	% **1**[a]	% **11**[a]	% **2**[a]
1	none	rt	3 days	none	9	1	27
2	none	0 °C	10 days	none	10	1	30
3	$CDCl_3$[b]	rt	10 days	none	5	0.6	35
4	$CDCl_3$[b]	rt	14 days	BHT[c]	31	4	18
5	$CDCl_3$[b]	rt	14 days	MB[d]	29	4	20
6	$CDCl_3$[b]	50 °C	1 day	none	(91)	(9)	(0)
7	$CDCl_3$[b]	50 °C	1 day	BHT[c]	(88)	(12)	(0)
8	C_6D_6[b]	75 °C	12 h	none	(89)	(11)	(0)
9	C_6D_6[b]	75 °C	12 h	MB[d]	(89)	(11)	(0)

[a] Isolated yields after MPLC on silica gel. Numbers in parentheses represent product ratios measured directly by ^{1}H NMR analysis. [b] Solution experiments were performed at a concentration of ~0.75 M. [c] 2,6-Di-*tert*-butyl-4-methylphenol. [d] Methylene blue.

The dimerization of **2** was studied under of a variety of conditions in order to gain insight into the mechanism of the reaction. These experiments are summarized in Table 2. All of the various conditions led to the formation of **1** and **11** in essentially the same ratio (7−10:1). In each case there was evidence of the generation of intractable, presumably polymeric material. This was minimized when the dimerization was performed in the presence of the radical inhibitors BHT or methylene blue. That these products arose from a Diels−Alder like event is supported by the facts that the rate of dimerization is insensitive to solvent polarity and is, qualitatively, second order in [**2**].

In summary, the metathesis of enyne **3**, which contains an electron-deficient alkyne, provides a rapid entry to the parent 2-vinylbutenolide (**2**) skeleton. Slow addition of the benzylidene ruthenium carbene **4** permitted maintenance of high substrate and low ruthenium carbene concentrations. Optimal reaction conditions were conveniently scouted using proton NMR analysis of aliquots of reactions run in non-deuterated solvent. Spontaneous dimerization of **2** to (±)-differolide (**1**) proceeds in a highly selective manner and suggests that **1** might be an artifact of isolation.

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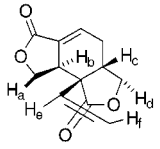
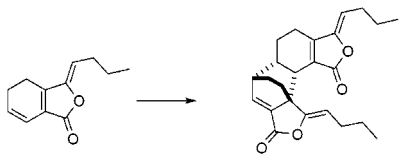
(10) The structure assignment of **11** rests principally on ^{1}H NMR studies. COSY analysis established the regiochemistry of the adduct. Key NOE interactions were observed between H_a/H_e, H_b/H_d, and H_c/H_f (see below). The proximity of protons H_b and H_d is consistent only with the relative configuration assigned to **11**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.05 (ddd, J = 5.5, 3.5, 3.5 Hz, 1H), 5.89 (dd, J = 17.5, 11.0 Hz, 1H), 5.40 (d, J = 11.0 Hz, 1H), 5.23 (d, J = 17.5 Hz, 1H), 4.59 (dd, J = 9.5, 9.5 Hz, 1H), 4.51 (dd, J = 9.0, 8.0 Hz, 1H), 4.31 (dd, J = 9.0, 8.0 Hz, 1H), 3.96 (dd, J = 9.0, 9.0 Hz, 1H), 3.21−3.25 (m, 1H), 2.82 (dddd, J = 9.5, 8.0, 8.0, 3.5 Hz, 1H) 2.76 (dddd, J = 19.5, 8.0, 5.5, 2.5 Hz, 1H), and 2.27 (dddd, J = 19.5, 3.5, 3.5, 3.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.0, 168.0, 134.4, 132.8, 126.9, 119.7, 70.0, 67.7, 52.8, 39.2, 37.6, and 25.5; IR (0.008 M in $CDCl_3$) 2925, 1770, 1695, 1640, 1430, 1370, 1350, 1310, 1265, 1230, 1210, 1110, 1090, 1060, and 1020 cm^{-1}. Anal. Calcd for $C_{12}H_{12}O_4$: C, 65.45; H, 5.45; Found: C, 65.62; H, 5.67.



11

(11) (a) The regioselectivity in the formation of (±)-differolide (**1**), in contrast to its regioisomer **11**, is the same as that observed in the dimerization of the 4-alkylidene-2-vinylbutenolide derivative **iii** (ligustilide).[11b] Thus, **iii** dimerized to (±)-levistolide A (**iv**). It is noteworthy that the naturally occurring form of **iv** is also racemic.[11c] (b) Ogawa, Y.; Mori, Y.; Maruno, M.; Wakamatsu, T. *Heterocycles* **1997**, *45*, 1869−1872. (c) Kaouadji, M.; Reutenauer, H.; Chulia, A. J.; Marsura, A. *Tetrahedron Lett.* **1983**, *24*, 4677−4678.



iii **iv**