

Selective Synthesis of (2Z,4E)-Dienyl Esters by Ene–Diene Cross Metathesis[†]

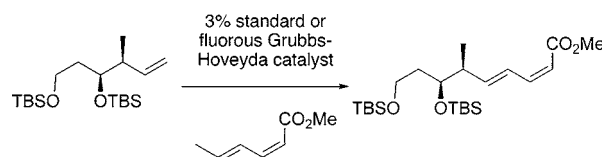
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ABSTRACT



Cross metathesis of terminal alkenes with methyl (2Z,4E)-hexadienoate and related dienyl esters provides substituted (2Z,4E)-dienyl esters in good yields. Small-scale reactions are effectively promoted by the standard second-generation Grubbs–Hoveyda catalyst (GH-II), while a new fluorous GH-II catalyst is used for separation and recovery in gram-scale reactions. The transformation is featured in a rapid synthesis of the bottom fragments of the potent anticancer agents (–)-dictyostatin and 6-*epi*-dictyostatin.

The presence of a (2Z,4E)-dienyl ester (in lactone form) is one of the key structural features that differentiates the potent dictyostatin family¹ of anticancer agents from its cousins in the discodermolide family.² Recent syntheses of dictyostatin and related molecules³ implement classical approaches to this functionality, typically involving stepwise olefinations with attendant oxidation/reduction, protection/deprotection, or

other refunctionalization steps. While reliable, these approaches are multistep. Toward the end of developing a short, efficient synthesis of (–)-dictyostatin, we engaged in experiments directed at a rapid, general approach to substituted (2Z,4E)-dienyl esters (*cis,trans*) by ene–diene cross metathesis.

Cross-metatheses reactions of two alkenes have seen increasing use in synthesis of late,⁴ and ene–diene cross-metathesis reactions are also known.^{4e} Our departure point was a recent report by Grubbs and co-workers on cross metathesis of alkenes with (2E,4E)-dienyl esters (*trans,trans*).⁵ This work showed how to use substituent effects on the diene to encourage regioselective cross metathesis and showed that formation of the new double bond at C4–C5 occurred with modest to good *E*-selectivity.

We previously developed a traditional cross-metathesis/Still–Gennari approach to the dictyostatin bottom fragment, and we wanted to telescope this to a single step by ene–diene cross metathesis (Figure 1).³ⁱ The key open question for intended use in dictyostatin synthesis and related applications was the fate of the “spectator” double bond at C2–C3 of the dienyl ester. Can a less stable (*Z*)-1,2-disubstituted

[†] Dedicated to Professor Steven M. Weinreb on the occasion of his 65th birthday.

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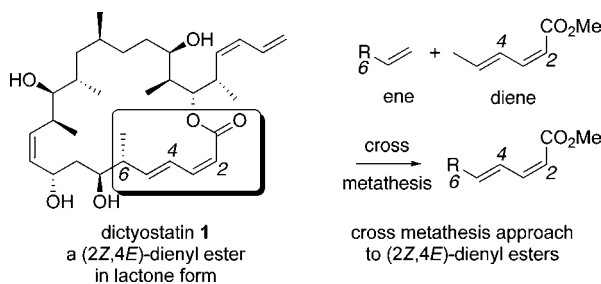


Figure 1. Structure of dictyostatin **1** and ene–diene cross-metathesis approach to the (2*E*,4*E*)-dienyl ester fragment.

alkene survive the cross metathesis without isomerization? We are pleased to report that the title cross-metathesis reaction of alkenes with (2*Z*,4*E*)-dienyl esters occurs in good yield, with high *E*-selectivity at the newly formed alkene (C4–C5) and with strict retention of the *Z* geometry at the spectator alkene (C2–C3). These features align perfectly with the needs of the dictyostatin synthesis, and a gram-scale preparation of the dienyl ester fragment of 6-*epi*-dictyostatin is reported.

The structures of the catalysts used in this work are shown in Figure 2. The second-generation Grubbs catalyst (G-II) **2**

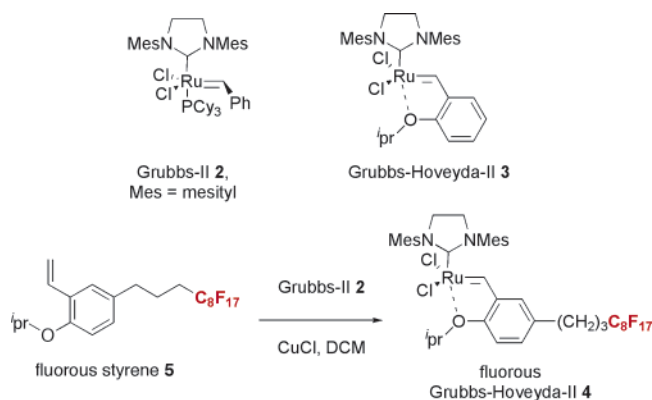


Figure 2. Structures of metathesis catalysts.

and the second-generation Grubbs–Hoveyda catalyst (GH-II) **3** are commercially available. The second-generation fluoros Grubbs–Hoveyda catalyst^{6a–c} (fGH-II) **4** is new, but it is closely related to an existing catalyst.^{6a} This was readily prepared by exchange of fluoros styrene **5** with **2** and was isolated as a bright green solid.⁷

Initially, we surveyed catalysts and solvents in the cross-metathesis reaction of readily available alkene (*R,S*)-**6**^{3f} (C5–

C9 of dictyostatin) and methyl (2*Z*,4*E*)-hexadienoate **7** (C1–C4). A mixture of 1 equiv of **6** (0.2 M), 1 equiv of **7**, and Grubbs second-generation catalyst **2** (5 mol %) was refluxed in dichloromethane for 8 h (Table 1). The solvent was

Table 1. Initial Solvent and Catalyst Survey^a

catalyst	solvent	T (°C)	conc of 6 and 7 (M)	yield ^b (%)
2	CH ₂ Cl ₂	40	0.2	47
2	CH ₂ Cl ₂	40	0.15	58
2	CH ₂ Cl ₂	40	0.1	43
2	toluene	110	0.1	23
2	toluene	110	0.2	25
3	CH ₂ Cl ₂	40	0.15	62
4	CH ₂ Cl ₂	40	0.15	64

^a Conditions: 1 equiv of alkene **6**, 1 equiv of diene **7**, 5 mol % of catalyst, 8 h. ^b Isolated yields.

removed, and the crude product was purified twice by silica gel chromatography to provide an encouraging 47% yield of **8**. Importantly, this cross-metathesis product was a single compound resulting from metathesis at C4 of **7**, and there was no evidence of metathesis products from the C2–C3 alkene.⁵ We also obtained a impure fraction containing unreacted starting material **6** (see below). Diluting the reaction mixture to 0.15 M increased the yield of **8** to 58%, but the yield dropped to 43% on further dilution to 0.1 M. Conducting reactions in toluene at 110 °C provided **8** in only 23% (0.1 M) and 25% (0.2 M) yields. Under the optimum solvent and concentration conditions (CH₂Cl₂, 0.15 M), the use of Hoveyda–Grubbs catalyst **3** provided **8** in 62% isolated yield, while f-GH catalyst **4** gave a comparable 64% isolated yield.

Table 2. Ene–Diene Stoichiometry Survey^a

equiv of ene 9	equiv of diene 6	yield of 10 ^b (%)
1	2	64
1	1.5	65
1	1.2	68
1	1	69
1.2	1	71
1.5	1	76
2	1	79

^a Conditions: 5 mol % of catalyst **2**, CH₂Cl₂, 40 °C, 8 h. ^b Isolated yields of **10**.

(6) (a) Light fluoros metathesis catalysts with SPE separation: Matsugi, M.; Curran, D. P. *J. Org. Chem.* **2005**, *70*, 1636–1642. (b) Heavy fluoros metathesis catalyst with liquid–liquid separation: Yao, Q. W.; Zhang, Y. L. *J. Am. Chem. Soc.* **2004**, *126*, 74–75. (c) Heavy fluoros catalyst with fluoros silica support: Michalek, F.; Bannwarth, W. *Helv. Chim. Acta.* **2006**, *89*, 1030–1037. (d) Catalyst with dissociatable fluoros phosphine: da Costa, R. C.; Gladysz, J. A. *Chem. Commun.* **2006**, 2619–2621.

Table 3. Scope of Cross Metathesis: Ene Component^a

entry	R ¹	R ²	yield ^b
1		H	58%
2		H	65%
3		H	62%
4		H	61%
5	CH ₂ C ₆ H ₄ - <i>p</i> -OMe	H	69%
6	CH ₂ Ph	H	76% ^c
7	CH ₂ OAc	CH ₂ OAc	68%
8	CH ₂ Cl	CH ₂ Cl	63%
9		H	76% ^d

^a Conditions: 1 equiv of ene, 1 equiv of **7**, 5 mol % of **2**, 0.15 M, CH₂Cl₂, 40 °C, 8 h. ^b Isolated yields as single isomer. ^c E/Z ratio = 10:1. ^d E/Z ratio = 8:1.

To optimize the stoichiometry of the reaction, we ran a series of individual reactions with excess *p*-allylanisole **9** (1.2, 1.5, and 2 equiv) and another series of reactions with excess diene **7** (1.2, 1.5, and 2 equiv). The results of these experiments are summarized in Table 2.

(*Z,E*)-Diene **10** was produced as a single stereoisomer, but the isolated yields of for the series of reactions did not vary dramatically. The starting point was equimolar stoichiometry, which produced a 69% yield of **10**. When ene **9** was used in excess (1.2–2 equiv), the yields of **10** increased slightly (71–79%), while when diene **6** was in excess (1.2–2 equiv), the yields of **10** decreased slightly (68–64%).

These results indicate that competing reactions⁸ cannot be completely suppressed by using a modest excess of one component and, therefore, that a 1/1 stoichiometry is satisfactory for most applications.

(7) Fluorous reagents and FluoroFlash silica products were purchased from Fluorous Technologies, Inc. D.P.C. holds an equity interest in this company.

The results of a series of experiments to show the scope of the reaction with respect to the alkene are summarized in Table 3. These reactions were run under the standard conditions with diene **7** and catalyst **2**. Changing the secondary alcohol protecting group on **6** from TBS to MOM or PMB as well as use of a free primary alcohol provided cross-metathesis products in comparable isolated yields (58–65%, entries 1–4). The metathesis yields improved with ene components that were not branched at the allylic carbon. *p*-Allylanisole and allylbenzene provided dienes in 69% and 76% yields (entries 5 and 6), although the allylbenzene product was contaminated with minor amounts of the (4*Z*) isomer (*E/Z* = 10/1). Reactions with a pair of symmetrical 1,2-disubstituted alkenes (entries 7 and 8) provided similar yields (68% and 63%). Ene–diene metathesis with the complex triene⁹ in entry 9 provided a single tetraene regioisomer in 76% yield as an 8/1 *E/Z* mixture at the C4 alkene. All products were exclusively *Z*-isomers at the spectator C2 alkene.

The scope with respect to the dienyl ester component was also briefly investigated with terminal alkenes, and these results are summarized in Table 4. Standard conditions were

Table 4. Scope of Cross Metathesis: Ene Component^a

entry	R	diene	product	yield ^b (%)
1	CH ₂ C ₆ H ₄ - <i>p</i> -OMe	11	13a	68
2	CH ₂ Ph	11	13b	63
3	CH ₂ C ₆ H ₄ - <i>p</i> -OMe	12	14a	71
4	CH ₂ Ph	12	14b	73
5	Ph	12	14c	73

^a Conditions: 1 equiv of ene, 1 equiv of **7**, 5 mol % of **2**, 0.25 M, CH₂Cl₂, 40 °C, 8 h. ^b Isolated yields as single isomer.

used, except that reactant concentrations were 0.25 M. Cross metathesis of allylbenzene and *p*-allylanisole with methyl (2*Z*,4*E*)-4-methylhexadienoate **11** (reacting alkene trisubstituted) provided the diene products **13a,b** in 68 and 63% yields, while cross metathesis of the same two alkenes and styrene with ethyl (2*Z*,4*E*)-3-methylhexadienoate **12** (spectator alkene trisubstituted) provided the corresponding products **14a–c** in 71–73% yields. All of these products were single stereoisomers at both the reacting (4*E*) and spectator (2*Z*) sites.

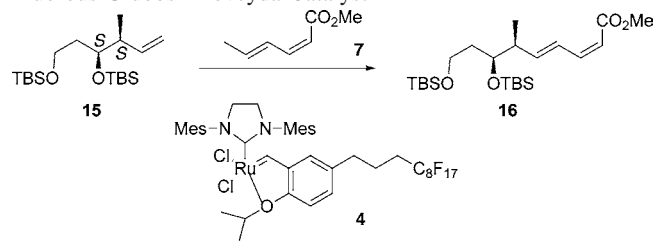
The final goal was to implement a gram-scale process with catalyst removal and recycle for potential use in the synthesis

(8) In addition to the target product **10**, these reaction mixtures exhibited a second, less polar spot on TLC. The spot contained a mixture of products resulting from metathesis of alkene **9** (no methyl ester or conjugated alkene protons in the ¹H NMR spectrum). A similar mixture (¹H NMR, TLC) was generated by self-metathesis of **9** in the absence of **7**.

(9) Brummond, K. M.; Mitasev, B. *Org. Lett.* **2004**, *6*, 2245–2248.

of (–)-dictyostatin and analogues. For this we used the fluororous GH-II catalyst **4** because related catalysts^{6a} have recently been shown to be readily and reliably separated from reaction products by fluororous solid-phase extraction.¹⁰ The diene component was **7** as usual, and the alkene component was (S,S)-**15**, which is readily available by Brown allylboration.^{3f} The study is directed toward the synthesis of 6-*epi*-dictyostatin, a highly potent isomer of the natural product,^{3f} and the results of a series of preparative metathesis runs are summarized in Table 5.

Table 5. Three Preparative Cross-Metathesis Cycles with Fluororous Grubbs–Hoveyda Catalyst **4**^a



cycle	scale (mmol)	weight of 15	weight of 4 (g)	yield of 16	recovered 4
1	42	15.0	1.3	10.9 g, 59%	1.0 g, 74%
2	31	11.0	1.0	8.1 g, 60%	0.7 g, 70%
3	21	7.5	0.7	5.2 g, 56%	0.4 g, 70% ^b

^a Conditions: 1 equiv of **15**, 1 equiv of **7**, 3 mol % of **4**, 0.15 M, CH₂Cl₂, 40 °C, 8 h, followed by fluororous SPE. ^b Recrystallized twice.

In the first cycle, alkene **15** (15 g, 42 mmol), diene **6** (42 mmol), and 3 mol % of fHG-II catalyst **4** were refluxed in CH₂Cl₂ for 8 h. After cooling and concentration, the crude product was loaded onto a 50 g fluororous SPE cartridge⁷ that was eluted in a first pass with 9/1 MeOH/H₂O followed by second pass elution with THF. The MeOH/H₂O fraction yielded 10.9 g (59%) of diene **16** after column chromatog-

raphy (to remove some **15** and other products¹¹), and the THF fraction yielded 74% of fHG-II catalyst **4** after recrystallization. (The crude catalyst recovery was nearly quantitative; however, NMR spectroscopic analysis showed small but significant impurities.) Cycles 2 and 3 were run the same way with the entire sample of recovered catalyst by scaling **15** accordingly, and yielded 60 and 56% of diene **16**. The recovered fHG-II catalyst **4** was returned in 70% yields after recrystallization from both experiments. In total, the initial lot of 1.3 g (1.3 mmol) of **4** was used to metathesize 33.5 g (94 mmol) of **15** into 24.2 g of purified **16** as a single stereoisomer (59% total overall yield). The recovered catalyst **4** from the last cycle was later used for other small scale experiments.

In summary, cross-metathesis reactions of monosubstituted or symmetrical 1,2-disubstituted alkenes with methyl (2Z,4E)-hexadienoate and related dienyl esters provides substituted (2Z,4E)-dienyl esters in good yields and stereoselectivities. The Z-geometry of the spectator alkene of the dienyl ester is strictly retained in the product, while the newly formed alkene is mainly or exclusively the E-isomer. Large scale reactions are conveniently conducted with 3% of the fluororous Grubbs–Hoveyda catalyst **4**, which can be recovered and recycled as illustrated by the rapid preparation of 24 g of a key intermediate for the synthesis of 6-*epi*-dictyostatin.

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Supporting Information Available: Complete experimental details and compound characterization data, as well as copies of ¹H and ¹³C NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(10) Reviews on fluororous SPE: (a) Curran, D. P. In *The Handbook of Fluorous Chemistry*; Gladysz, J. A., Curran, D. P., Horvath, I. T., Eds.; Wiley-VCH: Weinheim, 2004; pp 101–127. (b) Curran, D. P. *Aldrichim. Acta* **2006**, 39, 3–9. (c) Zhang, W.; Curran, D. P. *Tetrahedron* **2006**, in press.

(11) The less polar impurity fraction from the flash chromatography accounted for 37% of the mass balance and contained a substantial amount of **15** (~50%) along with other unidentified products (homodimers?) derived from **15**. (A product with a similar ¹H NMR spectrum was generated by metathesis of **15** in the absence of **7**.) The entire mixture fraction was directly reused in a cross metathesis with **7** to provide an additional 20% of pure **16** after fspe and flash chromatography. Including the reuse of the mixture fraction raises the overall yield of **16** based on **15** in cycle 1 to 79%.