α-EWG-Substituted Enones: Suitable Substrates for Ring-Closing Metathesis

Julie Toueg,* Joëlle Prunet

Laboratoire de Synthèse Organique, UMR CNRS 7652, Ecole Polytechnique, DCSO, 91128 Palaiseau, France
Fax +33(1)69333851; E-mail: julie.toueg@polytechnique.org

Received 13 July 2006

Abstract: The A-ring of hexacyclinic acid has been synthesised, using a ring-closing metathesis involving an α-EWG-substituted enone as the key step. We have then explored the scope of this reaction, which gives access to various 5- and 6-membered rings.

Key words: metathesis, ring-closure, enones, natural products

Hexacyclinic acid (**1**) was isolated from *Streptomyces cellulosae* subsp. *griseorubiginosus* (strain S1013), and was shown to have some cytotoxic activity on three cell lines (HM02, HEPG2 and MCF7).[1] It reveals a unique hexacyclic carbon skeleton, whose structure is very close, and probably biosynthetically related to that of FR182877 (Figure 1), isolated from *Streptomyces* sp. No.9885 by Fujisawa Pharmaceutical Company in 1998.[2]

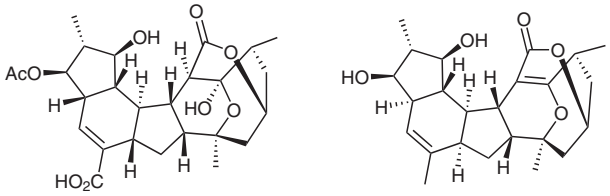
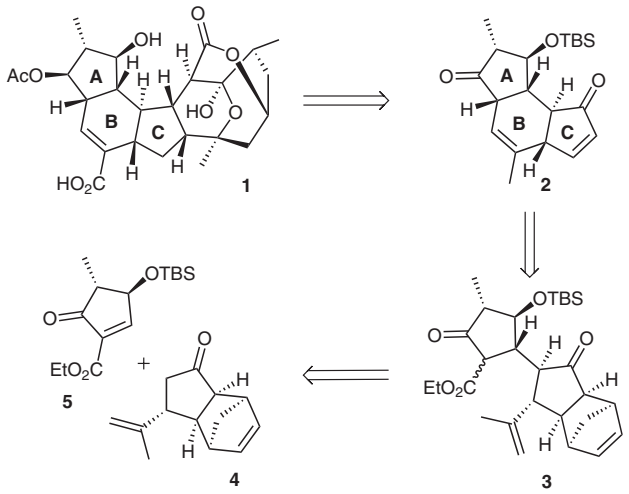


Figure 1 Structures of hexacyclinic acid and FR182877

The complex and challenging structure of these molecules has drawn interest among several groups, leading to diverse strategies towards the FR182877 ring system,[3] and two biomimetic total syntheses.[4] In spite of the similarities between FR182877 and hexacyclinic acid, the latter has not yet succumbed to total synthesis. However, Clarke[5] has reported the synthesis of the AB- and DEF-ring systems, while Landais[6] and Kalesse[7] recently published routes to ABC tricycles.

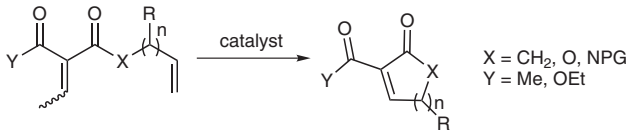
Our strategy for the synthesis of the ABC-ring system of hexacyclinic acid is shown in Scheme 1. Compound **2** would arise from compound **3** via a retro-Diels–Alder reaction, followed by a $Mn(OAc)_3$-mediated radical cyclisation, and decarboxylation of the ester group. Compound **3** would in turn result from a diastereoselective Michael addition of ketone **4** to enone **5**.



Scheme 1 Retrosynthetic analysis of the ABC-rings of **1**

We first focused on the synthesis of 5-membered ring enone **5**. Surprisingly, very few methods exist for the synthesis of cyclic α-carbalkoxyenones that do not require the use of selenium derivatives, even though such motives have proved to be valuable synthetic intermediates for total synthesis.[8] Noteworthy though is the work of Ikeda[9] that uses a rhodium-catalysed C–H insertion followed by spontaneous elimination on silica gel, intramolecular Knoevenagel condensations with titanium chloride leading to a variety of carbocycles,[10] and the study of Rodrigo[11] involving palladium carboxylation of the α-iodo enone. Unfortunately, these methods lack generality or require precursors, which are uneasy to handle.

We envisioned that these compounds could be formed by a ring-closing metathesis (RCM), in spite of the steric hindrance and electron deficiency of the α-carbalkoxyenone involved in this reaction (Equation 1), that could favour dimerisation of the terminal olefin over ring-closure. To the best of our knowledge, only examples of RCM with alkyl α-substituted enones have been reported so far.[12]



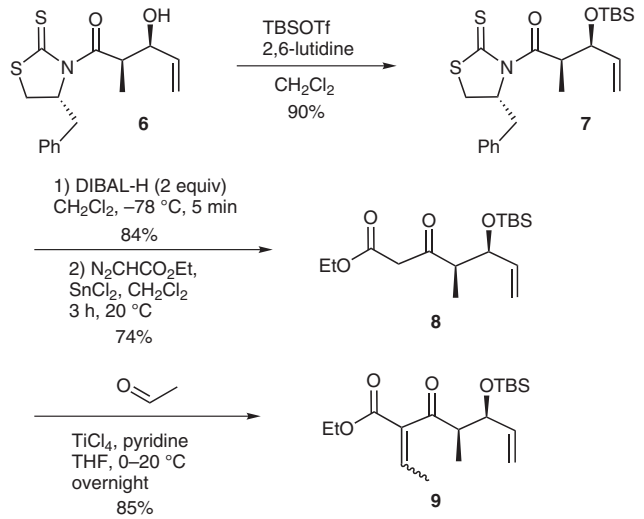
Equation 1

We thus prepared the precursor for this challenging ring-closing-metathesis reaction. Known aldol **6**[13] was protect-

SYNLETT 2006, No. 17, pp 2807–2811
Advanced online publication: 09.10.2006
DOI: 10.1055/s-2006-950274; Art ID: D20206ST
© Georg Thieme Verlag Stuttgart · New York

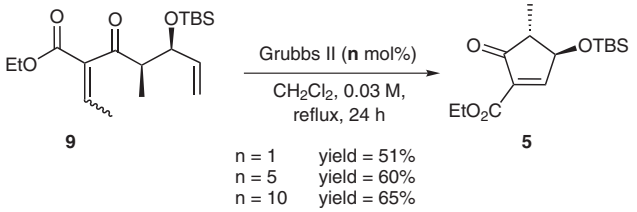
Downloaded by: Chinese University of Hong Kong. Copyrighted material.

ed as its TBS ether **7** (Scheme 2). Reduction of the thiazolidinethione auxiliary[13] furnished the corresponding aldehyde, which was directly transformed into β-keto ester **8**.[14] This compound underwent a Knoevenagel condensation with acetaldehyde to afford diene **9** as a 1:1 mixture of *E*/*Z* isomers.[15]



Scheme 2 Synthesis of diene **9**

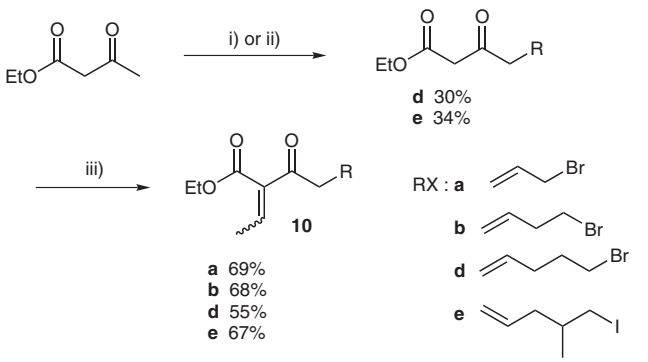
Diene **9** was engaged in the metathesis step. To our delight, the reaction proceeded smoothly in refluxing dichloromethane and furnished the desired cyclopentenone **5** after 24 hours in 51% yield with only 1 mol% of Grubbs' second-generation catalyst[16] (Equation 2). The yield improved to 65% with an increased amount of catalyst (10 mol%).



Equation 2 RCM leading to **5**

We then decided to explore the scope of this RCM, which is a new selenium-free access to cyclic α-carbalkoxyenones.

We first focused on the synthesis of carbocycles. Dienes **10a**,**b** were prepared in one step from ethyl 3-oxohept-6-enoate[17] and 3-oxooct-7-enoate,[17] respectively, and **10d**,**e** were prepared in two steps from ethyl acetoacetate, as shown in Scheme 3. Alkylation with the required halides furnished the β-keto esters **d** and **e** in modest yields, and Knoevenagel condensations[15] proved efficient to form the enones. Diene **10c** was prepared by a Baylis–Hillman reaction of methyl acrylate with *o*-allylbenzaldehyde followed by oxidation.[18]

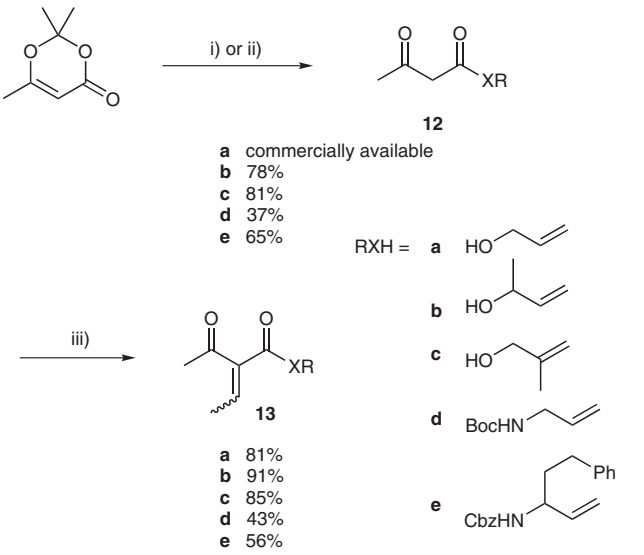


Scheme 3 Synthesis of precursors **10a**,**b** and **10c**,**d**. *Reagents and conditions*: i) LDA (2 equiv), 1 h, 0–20 °C, then **d** (1.3 equiv), THF; ii) NaH (1 equiv), 10 min, then *n*-BuLi (1 equiv), 10 min, 0–20 °C, then **e** (1.3 equiv), THF; iii) acetaldehyde (4.5 equiv), $TiCl_4$ (1.8 equiv), pyridine (3.5 equiv), THF, 0–20 °C, overnight.

Equation 3 RCM leading to carbocycles.

With compounds **10a–e** in hand, we tested the RCM step (Equation 3). The reaction proved very efficient for 5- and 6-membered ring formation (**11a–c**), with even a quantitative yield in the case of **11c** (Table 1). Unfortunately, we observed only dimers with compounds **10d** and even **10e**, where we had hoped the methyl substituent would favour the formation of the 7-membered ring.

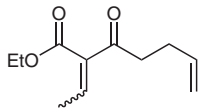
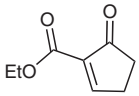
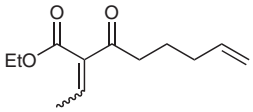
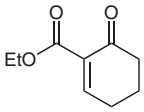
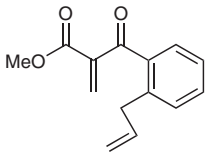
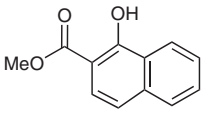
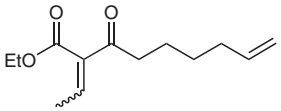
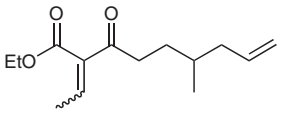
We then focused on the formation of lactones and lactams. The precursors were prepared in two steps from the corresponding alcohol or amine, as shown in Scheme 4.



Scheme 4 Synthesis of precursors **13a–e**. *Reagents and conditions*: i) **b–d** (1 equiv), xylene, 150 °C, 30 min; ii) **e** (0.6 equiv), toluene, reflux, overnight; iii) acetaldehyde (4.5 equiv), $TiCl_4$ (1.8 equiv), pyridine (3.5 equiv), THF, 0–20 °C, overnight.

Downloaded by: Chinese University of Hong Kong. Copyrighted material.

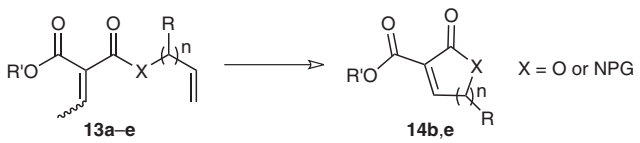
Table 1 Ring-Closing-Metathesis Step with Compounds **10a–e** Leading to Carbocycles[a]

Precursor	Product	Time (h)	Yield (%)
 **10a**	 **11a**	0.5	82
 **10b**	 **11b**	4	62
 **10c**	 **11c**	3	Quant.
 **10d**	Dimers only	24	–
 **10e**	Dimers only	24	–

[a] Reagents and conditions: 1 mol% Grubbs II, CH_2Cl_2, 0.03 M, reflux.

Reaction of alcohols on 2,2,6-trimethyl-1,3-dioxin-4-one proved very efficient, whereas the reaction with monoprotected amines was low-yielding.[19] Knoevenagel condensation occurred uneventfully with esters and amides, but only one diastereoisomer was obtained with the latter substrates. Considering the steric hindrance generated by the trisubstituted nitrogen in compounds **13d** and **13e**, it was assumed that the *E*-isomers were obtained in both cases.

Contrasting results were obtained when compounds **13a–e** were submitted to standard RCM conditions (Equation 4, Table 2).



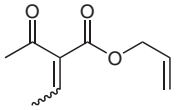
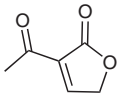
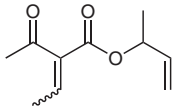
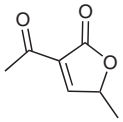
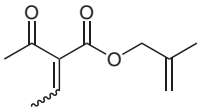
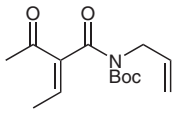
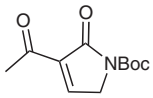
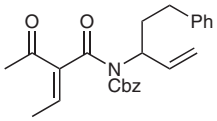
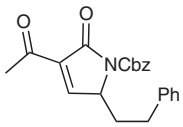
Equation 4 RCM leading to lactones and lactams

Reaction of dienes **13a** and **13d** only furnished traces of the desired 5-membered rings, the major products being dimers in both cases. Indeed, the terminal olefin here is much more reactive than in the case of carbocycles, so that dimerisation is much favoured. The only way to overcome this issue is to introduce a steric bias to form the γ-lactone and γ-lactam. Dienes **13b** and **13e**, which possess allylic substituents, led to lactone **14b** and lactam **14e** in 70% and 30% yields, respectively. However, example **13c** shows that formation of a tetrasubstituted olefin is not possible with such an α-carboxy-substituted enone.

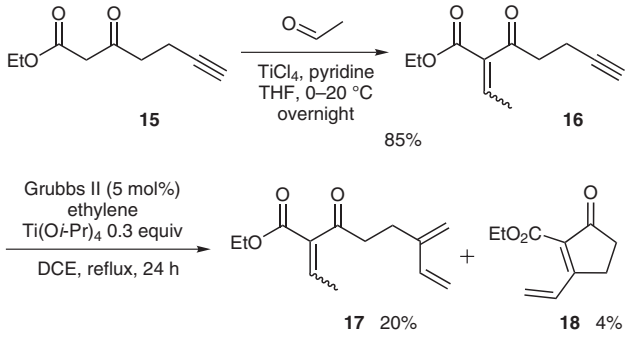
Finally, we tested the reactivity of an α-carbalkoxyenone in enyne RCM. We thus prepared precursor **16** from known β-keto ester **15**[20] (Scheme 5). No reaction occurred under our standard reaction conditions, or in refluxing 1,2-dichloroethane. Only when refluxed under an ethylene atmosphere in 1,2-dichloroethane with 5 mol% catalyst in the presence of Ti(O*i*-Pr)$_4$,[21] 4% of cyclised product could be isolated; the major compound **17** resulted from cross metathesis of **16** with ethylene, and no starting material was recovered. Ethylene atmosphere was required for any reaction to occur, but the same results were obtained when the reaction was run without Ti(O*i*-Pr)$_4$, except that the yield of the cyclised compound was even lower.

Downloaded by: Chinese University of Hong Kong. Copyrighted material.

Table 2 Ring-Closing Metathesis with Compounds **13a–e** Leading to Lactones and Lactams[a]

Precursor	Product	Time (h)	Yield (%)
 **13a**	 **14a**	24	Traces[b]
 **13b**	 **14b**	3	70[c]
 **13c**	No reaction	24	–
 **13d**	 **14d**	24	Traces[b]
 **13e**	 **14e**	19	30[c]

[a] Reagents and conditions: 1 mol% Grubbs II, CH_2Cl_2, 0.01 M, reflux.
[b] Dimers are the major products.
[c] Estimated from the NMR spectrum of the unpurified product as it decomposes on silica gel.



Scheme 5 Enyne ring-closing metathesis.

In conclusion, we have demonstrated that α-carbalkoxy-enones are suitable substrates for ring-closing metathesis under very mild conditions, leading to 5- and 6-membered carbocycles, naphthols, and γ-substituted γ-lactones and lactams. Enyne RCM is also possible with these precursors, but the yield of the desired diene is very low. This methodology has allowed us to synthesise the enantiopure A-ring of hexacyclinic acid.

Typical Procedure for RCM

Diene **10b** (88 mg, 0.42 mmol) was dissolved in 14 mL (0.03M) of dry CH_2Cl_2. Then Grubbs II catalyst was added (3.5 mg, 1 mol%) and the solution was refluxed for 4 h. The mixture was concentrated in vacuo. Purification on silica gel (PE–EtOAc, 7:3) afforded 44 mg (62%) of **11b** as a yellow oil.

IR (thin film): 1737, 1687, 1372, 1269, 1223, 1058, 551, 515, 486 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.32 (t, 3 H, *J* = 7.2 Hz, OCH_2CH_3), 2.01–2.10 (m, 2 H, H5), 2.48–2.57 (m, 4 H, H4 and H6), 4.27 (q, 2 H, *J* = 7.2 Hz, OCH_2CH_3), 7.66 (t, 1 H, *J* = 4.4 Hz, H3). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.3 (OCH_2CH_3), 22.3 (C5), 26.3 (C4), 38.9 (C6), 61.3 (OCH_2CH_3), 133.5 (C2), 155.8 (C3), 164.9 (CO_2Et), 194.6 (C1). MS (GC, CI NH_3): *m*/*z* = 186 [M + NH_4^+], 169 [M + H^+]. HRMS: *m*/*z* calcd for $C_9H_{12}O_3$: 168.0787; found: 168.0788.

Acknowledgment

We gratefully acknowledge the CNRS (UMR 7652) and the Ecole Polytechnique for financial support. J. T. thanks the Ecole Polytechnique for a fellowship, and Dr Gagosz and Dr Grimaud for helpful discussions.

Downloaded by: Chinese University of Hong Kong. Copyrighted material.

References

(1) Höfs, R.; Walker, M.; Zeeck, A. *Angew. Chem. Int. Ed.* **2000**, *39*, 3258.

(2) (a) Sato, B.; Muramatsu, H.; Miyauchi, M.; Hori, Y.; Hino, M.; Hashimoto, S.; Terano, H. *J. Antibiot.* **2000**, *53*, 123. (b) Sato, B.; Nakajima, H.; Miyauchi, M.; Hori, Y.; Hashimoto, S.; Terano, H. *J. Antibiot.* **2000**, *53*, 204. (c) Yoshimura, S.; Sato, B.; Miyauchi, M.; Kinoshita, T.; Takase, S.; Terano, H. *J. Antibiot.* **2000**, *53*, 615.

(3) (a) A-ring: Funel, J.-A.; Prunet, J. *J. Org. Chem.* **2004**, *69*, 4555. (b) AB-rings: Suzuki, T.; Nakada, M. *Tetrahedron Lett.* **2002**, *43*, 3263. ABC-rings: (c) Methot, J. L.; Roush, W. R. *Org. Lett.* **2003**, *5*, 4223. (d) Armstrong, A.; Goldberg, F. W.; Sandham, D. A. *Tetrahedron Lett.* **2001**, *42*, 4585. (e) Funel, J.-A.; Prunet, J. *Chem. Commun.* **2005**, 4833. DEF-rings: (f) Clarke, P.; Davie, R.; Peace, S. *Tetrahedron Lett.* **2004**, *45*, 927. (g) Clarke, P.; Davie, R.; Peace, S. *Tetrahedron* **2005**, *61*, 2335.

(4) (a) Starr, J. T.; Evans, D. A. *Angew. Chem. Int. Ed.* **2002**, *41*, 1787. (b) Evans, D. A.; Starr, J. T. *J. Am. Chem. Soc.* **2003**, *125*, 13531. (c) Vosburg, D. A.; Vanderwal, C. D.; Sorensen, E. J. *J. Am. Chem. Soc.* **2002**, *124*, 4552. (d) Vanderwal, C. D.; Vosburg, D. A.; Weiler, S.; Sorensen, E. J. *J. Am. Chem. Soc.* **2003**, *125*, 5393.

(5) AB-ring system: (a) Clarke, P.; Cridland, A. *Org. Lett.* **2005**, *7*, 4221. DEF-ring system: (b) Clarke, P.; Grist, M.; Ebden, M.; Wilson, C.; Blake, A. J. *Tetrahedron* **2005**, *61*, 353. (c) Clarke, P.; Grist, M.; Ebden, M.; Wilson, C. *Chem. Commun.* **2003**, 1560.

(6) James, P.; Felpin, F.-X.; Landais, Y. *J. Org. Chem.* **2005**, *70*, 7985.

(7) Stellfeld, T.; Bhatt, U.; Kalesse, M. *Org. Lett.* **2004**, *6*, 3889.

(8) For representative examples of use of α-carbalkoxycyclo-enones in total synthesis, see: (a) Liu, H.-J.; Shia, K.-S. *Tetrahedron* **1998**, *54*, 13449. (b) Liu, H.-J.; Tran, D. D.-P. *Tetrahedron Lett.* **1999**, *40*, 3827. (c) Zhu, J.-L.; Shia, K.-S.; Liu, H.-J. *Chem. Commun.* **2000**, 1599. For re-presentative examples of use of α-carboxylactones in total synthesis, see: (d) Hoye, T. R.; Caruso, A. J.; Magee, A. S. *J. Org. Chem.* **1982**, *47*, 4152. (e) Horne, D. A.; Fugmann, B.; Yakushijin, K.; Büchi, G. *J. Org. Chem.* **1993**, *58*, 62. (f) Ishihara, J.; Sugimoto, T.; Murai, A. *Tetrahedron* **1997**, *53*, 16029. For representative examples of use of α-carboxylactams in total synthesis, see: (g) Vedejs, E.; Campbell, J. B. Jr.; Gadwood, R. C.; Rodgers, J. D.; Spear, K. L.; Watanabe, Y. *J. Org. Chem.* **1982**, *47*, 1534. (h) Vedejs, E.; Reid, J. G.; Rodgers, J. D.; Wittenberger, S. J. *J. Am. Chem. Soc.* **1990**, *112*, 4351. (i) Vedejs, E.; Wittenberger, S. J. *J. Am. Chem. Soc.* **1990**, *112*, 4357. (j) Thomas, E. J.; Watts, J. P. *J. Chem. Soc., Chem. Commun.* **1990**, 464. (k) Thomas, E. J.; Watts, J. P. *J. Chem. Soc., Chem. Commun.* **1990**, 467. (l) Ackermann, J.; Matthes, M.; Tamm, C. *Helv. Chim. Acta* **1990**, *73*, 122. (m) Merifield, E.; Thomas, E. J. *J. Chem. Soc., Perkin Trans. 1* **1999**, 3269. (n) Vedejs, E.; Duncan, S. M. *J. Org. Chem.* **2000**, *65*, 6073.

(9) Rhodium carbene cyclisation: Yakura, T.; Ueki, A.; Kitamura, T.; Tarraka, K.; Nameki, M.; Ikeda, M. *Tetrahedron* **1999**, *55*, 7461.

(10) Intramolecular Knoevenagel condensation: (a) Kato, M.; Kamat, V. P.; Yoshikoshi, A. *Synthesis* **1988**, 699. (b) Funk, R. L.; Fitzgerald, J. F.; Olmstead, T. A.; Para, K. S.; Wos, J. A. *J. Am. Chem. Soc.* **1993**, *115*, 8849.

(11) Souza, F. E. S.; Sutherland, H. S.; Carlini, R.; Rodrigo, R. *J. Org. Chem.* **2002**, *67*, 6568.

(12) For representative examples of formation of rings bearing a conjugated *exo*-ester via RCM, see: (a) Kirkland, T. A.; Grubbs, R. H. *J. Org. Chem.* **1997**, *62*, 7310. (b) Chatterjee, A. K.; Morgan, J. P.; Scholl, M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2000**, *122*, 3783. (c) Hekking, K. F. W.; Van Deft, F. L.; Rutjes, F. P. J. T. *Tetrahedron* **2003**, *59*, 6751. (d) Thorstensson, F.; Kvarnström, I.; Musil, D.; Nilsson, I.; Samuelsson, B. *J. Med. Chem.* **2003**, *46*, 1165. (e) Grigg, R.; Hodgson, A.; Morris, J.; Sridharan, V. *Tetrahedron Lett.* **2003**, *44*, 1023. (f) Grigg, R.; Hodgson, A.; Morris, J.; Sridharan, V. *Tetrahedron Lett.* **2003**, *44*, 4899. (g) Kim, J. M.; Lee, K. Y.; Lee, S.; Kim, J. N. *Tetrahedron Lett.* **2004**, *45*, 2805. (h) Declerck, V.; Ribière, P.; Martinez, J.; Lamaty, F. *J. Org. Chem.* **2004**, *69*, 8372. (i) Lee, M. J.; Lee, K. Y.; Lee, J. Y.; Kim, J. N. *Org. Lett.* **2004**, *6*, 3313. (j) Krishna, P. R.; Narsingam, M.; Kannan, V. *Tetrahedron Lett.* **2004**, *45*, 4773. (k) Krafft, M. E.; Song, E.-H.; Davoile, R. J. *Tetrahedron Lett.* **2005**, *46*, 6359. (l) Lee, K. Y.; Gowrisankar, S.; Kim, J. N. *Bull. Korean Chem. Soc.* **2005**, *26*, 1481. For recent examples of butenolide formation, see: (m) Crimmins, M. T.; Zhang, Y.; Diaz, F. A. *Org. Lett.* **2006**, *8*, 2369. (n) Bassetti, M.; D'annibale, A.; Fanfoni, A.; Minissi, F. *Org. Lett.* **2005**, *7*, 1805.

(13) (a) Crimmins, M. T.; Chaudhary, K. *Org. Lett.* **2000**, *2*, 775. (b) Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. *J. Org. Chem.* **2001**, *66*, 894. (c) Crimmins, M. T.; Chaudhary, K. *J. Am. Chem. Soc.* **2005**, *127*, 13810.

(14) Holmquist, C. R.; Roskamp, E. J. *J. Org. Chem.* **1989**, *54*, 3258.

(15) Antonioletti, R.; Bovicelli, P.; Malancara, S. *Tetrahedron* **2002**, *58*, 589.

(16) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953.

(17) Langer, P.; Eckardt, T.; Stoll, M. *Org. Lett.* **2000**, *2*, 2991.

(18) Lawrence, N. J.; Crump, J. P.; McGown, A. T.; Hadfield, J. A. *Tetrahedron Lett.* **2001**, *42*, 3939.

(19) (a) Clemens, R. J.; Hyatt, J. A. *J. Org. Chem.* **1985**, *50*, 2431. (b) Skerry, P. S.; Swain, N. A.; Harrowven, D. C.; Smyth, D.; Bruton, G.; Brown, R. C. D. *Chem. Commun.* **2004**, 1772. (c) Cook, G. R.; Sun, L. *Org. Lett.* **2004**, *6*, 2481.

(20) Hayakawa, K.; Yodo, M.; Kanematsu, K. *J. Am. Chem. Soc.* **1984**, *106*, 6735.

(21) Ghosh, A. K.; Cappiello, J.; Shin, D. *Tetrahedron Lett.* **1998**, *39*, 4651.

Downloaded by: Chinese University of Hong Kong. Copyrighted material.