

An Ireland–Claisen Approach to
 β -Alkoxy α -Amino Acids

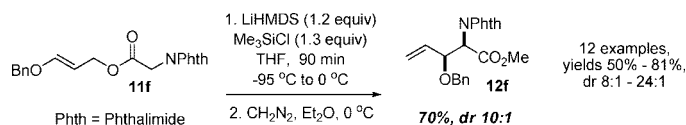
James P. Tellam, Gabriele Kociok-Köhn, and David R. Carbery*

Department of Chemistry, University of Bath, Bath, BA2 7AY, U.K.

d.carbery@bath.ac.uk

Received September 17, 2008

ABSTRACT



A diastereoselective Ireland–Claisen approach to β -alkoxy α -amino acid esters is reported. Amino acid esters of enol ether allylic alcohols undergo facile *syn*-selective [3,3]-sigmatropic rearrangement via silyl ketene acetals. Substrate synthesis, rearrangement development, stereoselectivity, and product elaboration are discussed.

β -Hydroxy- α -amino acids are biologically important molecules with two key examples, serine and threonine, taken together representing 10% of nature's proteinogenic amino acids. The β -hydroxy α -amino acid unit is featured prominently in a number of important natural products.¹ For example, kaitocephalin,² sphingofungins E + F,³ altemicidin,⁴ and the acyl derivatives, lactacystin,⁵ salinosporamide

A,⁶ oxazolomycin,⁷ and neooxazolomycin⁸ have represented significant synthetic challenges in recent years. The importance of these molecules is reflected in the large number of reported synthetic routes to β -hydroxy- α -amino acids. Strategies include aldol reactions,⁹ enzymatic aldol reactions,¹⁰

(1) (a) Kang, S. H.; Kang, S. Y.; Lee, H. S.; Buglass, A. J. *Chem. Rev.* **2005**, *105*, 4537. (b) Ohfuné, Y.; Shinada, T. *Eur. J. Org. Chem.* **2005**, 5127.

(2) For recent synthetic work, see: (a) Kawasaki, M.; Shinada, T.; Hamada, M.; Ohfuné, Y. *Org. Lett.* **2005**, *7*, 4165. (b) Takahashi, K.; Haraguchi, N.; Ishihara, J.; Hatakeyama, S. *Synlett* **2008**, 671. (c) Vaswani, R. G.; Chamberlin, A. R. *J. Org. Chem.* **2008**, *73*, 1661.

(3) For recent synthetic work, see: (a) Horn, W. S.; Smith, J. L.; Bills, G. F.; Raghoobar, S. L.; Helms, G. L.; Kurtz, M. B.; Marrinan, J. A.; Frommer, B. R.; Thornton, R. A.; Mandala, S. M. *J. Antibiot.* **1992**, *45*, 1692. (b) Kobayashi, S.; Furuta, T.; Hayashi, T.; Nishijima, M.; Hanada, K. *J. Am. Chem. Soc.* **1998**, *120*, 908. (c) Kobayashi, S.; Matsumura, M.; Furuta, T.; Hayashi, T.; Iwamoto, S. *Synlett* **1997**, 301. (d) Lee, K. Y.; Oh, C. Y.; Ham, W. H. *Org. Lett.* **2002**, *4*, 4403. (e) Li, M.; Wu, A. M. *Synlett* **2006**, 2985. (f) Liu, D. G.; Wang, B.; Lin, G. Q. *J. Org. Chem.* **2000**, *65*, 9114. (g) Trost, B. M.; Lee, C. B. *J. Am. Chem. Soc.* **1998**, *120*, 6818.

(4) (a) Kan, T.; Kawamoto, Y.; Asakawa, T.; Furuta, T.; Fukuyama, T. *Org. Lett.* **2008**, *10*, 169. (b) Kende, A. S.; Liu, K.; Brands, K. M. J. *J. Am. Chem. Soc.* **1995**, *117*, 10597.

(5) For selected recent synthetic approaches, see: (a) Balskus, E. P.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2006**, *128*, 6810. (b) Brennan, C. J.; Pattenden, G.; Rescouri, G. *Tetrahedron Lett.* **2003**, *44*, 8757. (c) Donohoe, T. J.; Sintim, H.; Sisangia, L.; Harling, J. D. *Angew. Chem., Int. Ed.* **2004**, *43*, 2293. (d) Fukuda, N.; Sasaki, K.; Sastry, T.; Kanai, M.; Shibasaki, M. *J. Org. Chem.* **2006**, *71*, 1220. (e) Page, P. C. B.; Hamzah, A. S.; Leach, D. C.; Allin, S. M.; Andrews, D. M.; Rassias, G. A. *Org. Lett.* **2003**, *5*, 353. (f) Panek, J. S.; Masse, C. E. *Angew. Chem., Int. Ed.* **1999**, *38*, 1093. (g) Wardrop, D. J.; Bowen, E. G. *Chem. Commun.* **2005**, 5106.

(6) For selected recent synthetic approaches, see: (a) Caubert, V.; Masse, J.; Retailliau, P.; Langlois, N. *Tetrahedron Lett.* **2007**, *48*, 381. (b) Endo, A.; Danishefsky, S. J. *J. Am. Chem. Soc.* **2005**, *127*, 8298. (c) Ling, T. T.; Macherla, V. R.; Manam, R. R.; McArthur, K. A.; Potts, B. C. M. *Org. Lett.* **2007**, *9*, 2289. (d) Ma, G.; Nguyen, H.; Romo, D. *Org. Lett.* **2007**, *9*, 2143. (e) Margalef, I. V.; Rupnicki, L.; Lam, H. W. *Tetrahedron* **2008**, *64*, 7896. (f) Reddy, L. R.; Saravanan, P.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 6230. (g) Takahashi, K.; Midori, M.; Kawano, K.; Ishihara, J.; Hatakeyama, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 6244.

(7) For recent work, see: (a) Bulger, P. G.; Moloney, M. G.; Trippier, P. C. *Org. Biomol. Chem.* **2003**, *1*, 3726. (b) Mohapatra, D. K.; Mondal, D.; Gonnade, R. G.; Chorghade, M. S.; Gurjar, M. K. *Tetrahedron Lett.* **2006**, *47*, 6031. (c) Papillon, J. P. B.; Taylor, R. J. K. *Org. Lett.* **2000**, *2*, 1987. (d) Wang, Z. Y.; Moloney, M. G. *Tetrahedron Lett.* **2002**, *43*, 9629.

(8) (a) Bennett, N. J.; Prodder, J. C.; Pattenden, G. *Tetrahedron* **2007**, *63*, 6216. (b) Kende, A. S.; Kawamura, K.; Devita, R. J. *J. Am. Chem. Soc.* **1990**, *112*, 4070. (c) Onyango, E. O.; Tsurumoto, J.; Imai, N.; Takahashi, K.; Ishihara, J.; Hatakeyama, S. *Angew. Chem., Int. Ed.* **2007**, *46*, 6703.

(9) For recent aldol approaches to β -hydroxy α -amino acids, see: (a) Ma, B.; Parkinson, J. L.; Castle, S. L. *Tetrahedron Lett.* **2007**, *48*, 2083. (b) Willis, M. C.; Cutting, G. A.; Piccio, V. J.-D.; Durbin, M. J.; John, M. P. *Angew. Chem., Int. Ed.* **2005**, *44*, 1543. (c) Thayumanavan, R.; Tanaka, F.; Barbas, C. F. *Org. Lett.* **2004**, *6*, 3541. (d) Kobayashi, J.; Nakamura, M.; Mori, Y.; Yamashita, Y.; Kobayashi, S. *J. Am. Chem. Soc.* **2004**, *126*, 9192. (e) MacMillan, J. B.; Molinski, T. F. *Org. Lett.* **2002**, *4*, 1883.

(10) (a) Sagui, F.; Conti, P.; Roda, G.; Contestabile, R.; Riva, S. *Tetrahedron* **2008**, *64*, 5079. (b) Steinreiber, J.; Fesko, K.; Mayer, C.; Reisinger, C.; Schürmann, M.; Griengl, H. *Tetrahedron* **2007**, *63*, 8088. (c) Steinreiber, J.; Fesko, K.; Reisinger, C.; Schürmann, M.; van Assema, F.; Wolberg, M.; Mink, D.; Griengl, H. *Tetrahedron* **2007**, *63*, 918.

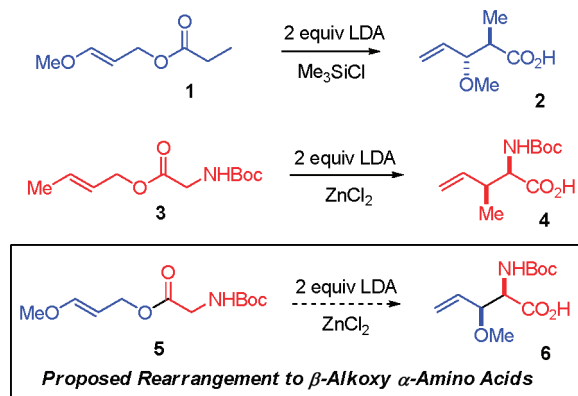
reduction of amino β -keto esters,¹¹ enantioselective dihydroxylation,¹² enantioselective aminohydroxylation,¹³ asymmetric Strecker reaction,¹⁴ intramolecular Pd(0)-catalyzed allylic alkylation,¹⁵ photocycloadditions,¹⁶ azomethine ylide cycloaddition,¹⁷ dynamic kinetic resolution,¹⁸ enantioselective hydrogenation,¹⁹ and oxy-Michael reaction.²⁰ However, few sigmatropic approaches have been reported, an exception being Sutherland's Pd-catalyzed [3,3]-sigmatropic Overman rearrangement route.²¹

The Ireland–Claisen rearrangement reaction has developed into a powerful C–C bond-forming reaction.²² This [3,3]-sigmatropic process benefits from predictable diastereocontrol, enantiospecific chirality transfer via chair transition states, and the ability to form controlled congested quaternary stereocenters. Recently, we have shown that enamides²³ can be utilized as substrates for the preparation of $\beta^{2,3}$ -amino acid systems through an Ireland–Claisen approach²⁴ and believed a similar synthetic analysis may offer a route to β -hydroxy α -amino acids.

Prior to commencing this program of research, two rearrangements were pertinent in our thinking (Scheme 1). First, Ireland's allylic enol ether **1** has been shown to rearrange to *anti*- β -alkoxy acid **2** with the formation of a new secondary ether stereocenter.²⁵ Second, the work of Kazmaier has shown that allylic amino ester **3** undergoes a highly diastereoselective rearrangement to new *syn*-allylic amino acid **4** via a chelated Zn-enolate.²⁶ We felt a combination of **1** and **3** would offer substrate **5**, capable of forming *syn*- β -alkoxy α -amino acid **6** after [3,3]-sigmatropic rearrangement (Scheme 1).

The use of suitable alkoxy groups, such as benzyloxy, would offer options for subsequent deprotection to β -hydroxy

Scheme 1. Proposed Ireland–Claisen Synthesis of β -Alkoxy α -Amino Acids



α -amino acids. Furthermore, the Kazmaier protocol has been shown to be effective for the formation of α -quaternary amino acids.²⁷ This aspect is particularly appealing as suitable substrates would allow access to the α -substituted β -hydroxy- α -amino acid substitution patterns seen in a number of the important natural products such as salinosporamide-A, lactacystin, altemicidin, and sphingosines already mentioned.

Ester **5** was synthesized through carbodiimide coupling of the known alcohol **7**²⁵ and *N*-Bocglycine **8**. This ester was observed to be thermally sensitive and unstable to silica gel during attempted purification. With ester **5** in hand, the feasibility of the proposed [3,3]-sigmatropic reaction could be examined. Application of Kazmaier's standard reaction conditions dissapointingly did not form the desired amino acid **6**, with the parent *N*-Bocglycine **8** isolated in 59% yield (Scheme 2).^{28,29}

This observation was unexpected as glycolate ester **9**, which also possesses an α -carbonyl heteroatom, has been rearranged efficiently without incident.³⁰ We suspected the presence of the second anionic center upon the formed enolate **10** was causing particular instability (Scheme 2), leading to enolate decomposition. Accordingly, the phthalimide protecting group was chosen to offer increased electron-withdrawing capacity and to remove the acidic N–H moiety.³¹ Therefore, EDCI coupling of alcohol **7** and *N*-phthaloylglycine offered access to ester **11a**, in 84% yield.

After considerable investigation, ester **11a** was observed to rearrange efficiently when LiHMDS is added via a syringe pump over 15 min to a solution of **11a** and Me₃SiCl at –95 °C before warming to 0 °C (Table 1). The rearranged acid

(27) (a) Kazmaier, U. *Amino Acids* **1996**, *11*, 283. (b) Kazmaier, U. *Tetrahedron Lett.* **1996**, *37*, 5351. (c) Kazmaier, U. *J. Org. Chem.* **1996**, *61*, 3694. (d) Kazmaier, U.; Gorbitz, C. H. *Synthesis* **1996**, 1489.

(28) In our hands, Kazmaier's crotyl ester **3** rearranges efficiently under the Zn-enolate promotion, completely in accord with Kazmaier's report.

(29) A number of variables (solvent, base, temperature, and additive) were examined during this period of the project with no rearranged product observed.

(30) Fujiwara, K.; Goto, A.; Sato, D.; Kawai, H.; Suzuki, T. *Tetrahedron Lett.* **2005**, *46*, 3465.

(31) Bartlett, P. A.; Barstow, J. F. *J. Org. Chem.* **1982**, *47*, 3933.

(11) Lei, A.; Wu, S.; He, M.; Zhang, X. *J. Am. Chem. Soc.* **2004**, *126*, 1626.

(12) Alonso, M.; Riera, A. *Tetrahedron: Asymmetry* **2005**, *16*, 3908.

(13) (a) Zhang, H.; Xia, P.; Zhou, W. *Tetrahedron: Asymmetry* **2000**, *11*, 3439. (b) Morgan, A. J.; Masse, C. E.; Panek, J. S. *Org. Lett.* **1999**, *1*, 1949.

(14) Davis, F. A.; Srirajan, V.; Fanelli, D. L.; Portonovo, P. *J. Org. Chem.* **2000**, *65*, 7663.

(15) Amador, M.; Ariza, X.; Garcia, J.; Sevilla, S. *Org. Lett.* **2002**, *4*, 4511.

(16) Griesbeck, A. G.; Bondock, S.; Lex, J. *J. Org. Chem.* **2003**, *68*, 9899.

(17) Alker, D.; Hamblett, G.; Harwood, L. M.; Robertson, S. M.; Watkin, D. J.; Eleri Williams, C. *Tetrahedron* **1998**, *54*, 6089.

(18) Kazuishi, M.; Goto, T.; Hiroki, Y.; Hamada, Y. *Angew. Chem., Int. Ed.* **2004**, *43*, 882.

(19) Kuwano, R.; Okuda, S.; Ito, Y. *J. Org. Chem.* **1998**, *63*, 3499.

(20) Hernandez-Juan, F.; Richardson, R.; Dixon, D. *Synlett* **2006**, 2673.

(21) (a) Fanning, K. N.; Jamieson, A. G.; Sutherland, A. *Org. Biomol. Chem.* **2005**, *3*, 3749. (b) Swift, M. D.; Sutherland, A. *Tetrahedron Lett.* **2007**, *48*, 3771.

(22) For reviews, see: (a) Castro, A. M. M. *Chem. Rev.* **2004**, *104*, 2939. (b) Chai, Y. H.; Hong, S. P.; Lindsay, H. A.; McFarland, C.; McIntosh, M. C. *Tetrahedron* **2002**, *58*, 2905. (c) McFarland, C. M.; McIntosh, M. C. In *The Claisen Rearrangement* Hiersemann; Udo, M. N., Ed.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2007; p 117.

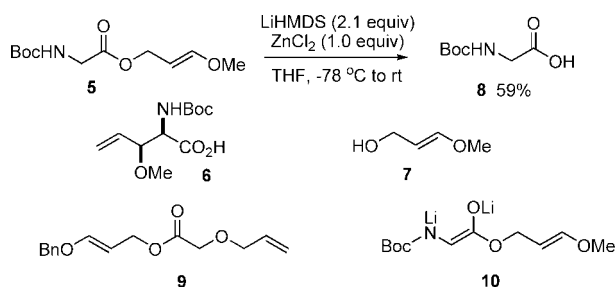
(23) For a recent review concerning synthetic transformations of enamides, see: Carbery, D. R. *Org. Biomol. Chem.* **2008**, *6*, 3455.

(24) Ylioja, P. M.; Mosley, A. D.; Charlot, C. E.; Carbery, D. R. *Tetrahedron Lett.* **2008**, *49*, 1111.

(25) (a) Ireland, R. E.; Thaisrivongs, S.; Vanier, N.; Wilcox, C. S. *J. Org. Chem.* **1980**, *45*, 48. (b) Ireland, R. E.; Wilcox, C. S. *Tetrahedron Lett.* **1977**, *18*, 2839. (c) Ireland, R. E.; Wipf, P.; Xiang, J. N. *J. Org. Chem.* **1991**, *56*, 3572.

(26) Kazmaier, U.; Pähler, S.; Endermann, R.; Häbich, D.; Kroll, H.-P.; Riedl, B. *Bioorg. Med. Chem.* **2002**, *10*, 3905.

Scheme 2. Initial Rearrangement Attempts



was derivatized as the methyl ester to aid isolation and purification. When the reaction is initiated at higher temperatures ($-78\text{ }^{\circ}\text{C}$) or when nonethereal solvents (PhMe) are used, the reaction provides an intractable reaction product mixture with ^1H NMR analysis of crude reaction mixtures

Table 1. Initial Reaction Development

entry	base	solvent	temp ($^{\circ}\text{C}$)	yield (%)	dr
1	LiHMDS	THF	-78	0 ^a	-
2	NaHMDS	THF	-78	0 ^a	-
3	KHMDS	THF	-78	0 ^a	-
4	LiHMDS	THF	-95	74	11:1
5	LiHMDS	Ether	-95	65	9:1
6	LiHMDS	PhMe	-95	0 ^a	-
7	NaHMDS	THF	-95	45	7:1
8	KHMDS	THF	-95	34	6:1
9	LDA	THF	-95	0 ^a	-
10	LiHMDS	THF	-95	0 ^b	-

^a Intractable reaction mixture. ^b TIPSOTf used as a silylation additive.

suggesting the formation of small amounts of desired rearranged product along with elimination, silylation products together with unconverted starting material. Using Na- or KHMDS at $-95\text{ }^{\circ}\text{C}$ leads to a drop in reaction quality, both in terms of yield and diastereoselectivity. Other Li-amide bases such as LDA (entry 9) are not suitable for this Ireland–Claisen protocol.

With the optimal reaction conditions identified, a range of substrates were synthesized so the generality of this Ireland–Claisen approach to β -alkoxy α -amino acid systems could be investigated (Table 2).

The reaction is seen to be general, offering yields of 50–81% and $\text{dr} \geq 8:1$. A range of O-functionality has been investigated including simple alkyl (Me, Et, CH_2iPr , and CH_2tBu), a number of protecting groups (allyl, Bn, and PMB), phenoxy groups (Ph, *p*-OMe-Ph, *p*-NO₂-Ph, *p*-CF₃-Ph, and *o*-I-Ph), and synthetic handles (allyl, *o*-I-Bn, *o*-I-Ph).

The phenoxy substrates (**11i**–**11m**) offered interesting chemoselectivity. Substrates **11k** and **11l** which feature

electron-withdrawing groups were observed to not undergo rearrangement with complete recovery of starting material. In contrast, the methoxy-substituted substrate **11j** was completely consumed but furnished a complex reaction mixture and is believed to undergo facile elimination of the β -phenoxy α -amino acid product. However, substrates **11i** and **11m** do rearrange with high diastereoselectivity.

Table 2. Rearrangement of *N*-Phthaloyl Amino Esters

ester	R ¹	R ²	product	yield (%) ^a	dr ^b
11a	Me	H	12a	74 ^c	11:1
11b	Et	H	12b	79 ^c	9:1
11c	CH_2iPr	H	12c	64 ^c	18:1
11d	CH_2tBu	H	12d	78 ^c	13:1
11e	Allyl	H	12e	70 ^c	10:1
11f	Bn	H	12f	70 ^c	10:1
11f	Bn	H	12f	64 ^d	2:1
11g	<i>o</i> -I-Bn	H	12g	50 ^c	14:1
11h	PMB	H	12h	63 ^c	8:1
11i	Ph	H	12i	81 ^c	14:1
11j	<i>p</i> -OMe-Ph	H	-	0 ^c	-
11k	<i>p</i> -NO ₂ -Ph	H	-	0 ^{c,f}	-
11l	<i>p</i> -CF ₃ -Ph	H	-	0 ^{c,f}	-
11m	<i>o</i> -I-Ph	H	12j	50 ^c	>25:1
11n	Me	Me	12k	71 ^c	24:1

^a Isolated yield. ^b Diastereomeric ratio measure by ^1H NMR analysis of crude reaction mixtures. ^c LiHMDS solution added by hand over 15 min via syringe pump. ^d LiHMDS solution added by hand over 1 min. ^e Intractable mixture. ^f Starting ester was recovered in >95%.

Importantly, (rac)-alanine-derived ester **11n** is found to rearrange efficiently and with excellent *syn* selectivity ($\text{dr} = 24:1$). This now offers a general route to the functionalized serine/alanine hybrid amino acid fragments seen in the sphingosine natural products.

The relative stereochemistry of the rearrangement was confirmed through X-ray crystallographic analysis of Cs-carboxylate **13**. The observed diastereoselection suggests the intermediacy of a *Z*-silyl ketene acetal which rearranges through a chair transition state **I** (Figure 1).

The diastereoselectivity of this rearrangement reaction appears to be particularly sensitive to temperature variations caused by exotherms created during reactant mixing; for example, the reaction of benzyloxy substrate **11f** was seen to provide a representative dr of 10:1 when the addition of base was completed over 15 min via syringe pump at $-95\text{ }^{\circ}\text{C}$. In contrast, a faster addition of base over 1 min by hand, still at $-95\text{ }^{\circ}\text{C}$, led to an observed dr of 2:1. This observation may be consistent with nonconcertedness during this transformation. A possible scenario is the scission of intermediate enolate (**II**, Figure 2) with formation of ion pair **III**.

This situation may now lead to a nonconcerted, nonselective C–C bond-forming event on recombination of the Li-

glycinate nucleophile and the acrolein oxonium electrophile.³² Such a scenario would mirror the polar transition states described by Curran for methoxy-substituted allyl vinyl ethers in Claisen rearrangements.³³

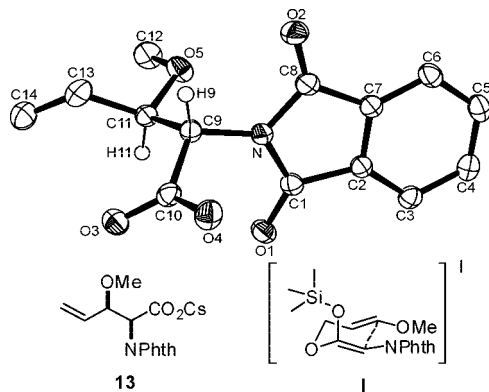


Figure 1. ORTEP plot of cesium carboxylate **13** (ellipsoids shown at 30% probability) and chair transition state **I**.

A key motivation for developing this new Ireland–Claisen transformation was the synthetic handle offered by the alkene moiety formed from the rearrangement. To demonstrate the synthetic utility, **11e** was subjected to a ring-closing metathesis reaction. Diene **11e** was observed to undergo efficient ring closure when promoted by the first-generation Grubbs catalyst to form dihydrofuran **14** in excellent yield (Scheme 3). This structure is a protected norfuranomycin **15**³⁴ which has been shown to possess similar levels of biological activity as the parent antibiotic, (+)-furanomycin **16**.³⁵

In conclusion, a new Ireland–Claisen approach to β -alkoxy α -amino acid systems has been developed. The reaction

(32) (a) Dikshit, D. K.; Singh, S. *Tetrahedron Lett.* **1988**, 29, 3109. (b) Hong, B.-C.; Chen, Z.-Y.; Nagarajan, A.; Kottani, R.; Chavan, V.; Chen, W.-H.; Jiang, Y.-F.; Zhang, S.-C.; Liao, J.-H.; Sarshar, S. *Carbohydr. Res.* **2005**, 340, 2457.

(33) Coates, R. M.; Rogers, B. D.; Hobbs, S. J.; Curran, D. P.; Peck, D. R. *J. Am. Chem. Soc.* **1987**, 109, 1160.

(34) Kazmaier, U.; Pähler, S.; Endermann, R.; Häbich, D.; Kroll, H.-P.; Riedl, B. *Bioorg. Med. Chem.* **2002**, 10, 3905.

(35) Katagiri, K.; Tori, K.; Kimura, Y.; Yoshida, T.; Nagasaki, T.; Minato, H. *J. Med. Chem.* **1967**, 10, 1149.

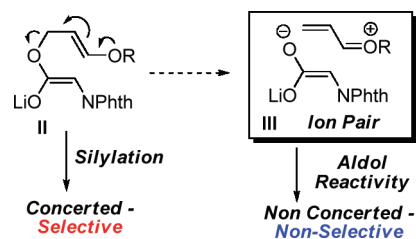
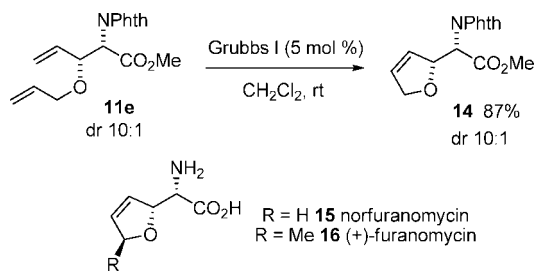


Figure 2. Possible selective and nonselective outcomes of enolate **II**.

offers good to excellent levels of *syn*-diastereoselectivity. The reaction is particularly sensitive to reaction conditions.

Scheme 3. Ring-Closing Metathesis Reaction of **11e**



Further investigations concerning mechanism and substrate scope are currently ongoing in our laboratories.

Acknowledgment. We gratefully acknowledge EPSRC and the University of Bath (JPT) for funding. AstraZeneca and Pfizer are thanked for unrestricted funding.

Supporting Information Available: Experimental procedures, compound characterization data, and CIF file for structure **13**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

OL802169J