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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

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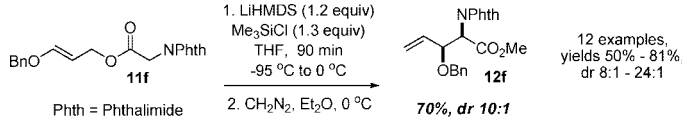
ABSTRACT



A diastereoselective Ireland−Claisen approach to β-alkoxy α-amino acid esters is reported. Amino acid esters of enol ethereal 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 neooxazolomycin[8] 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]

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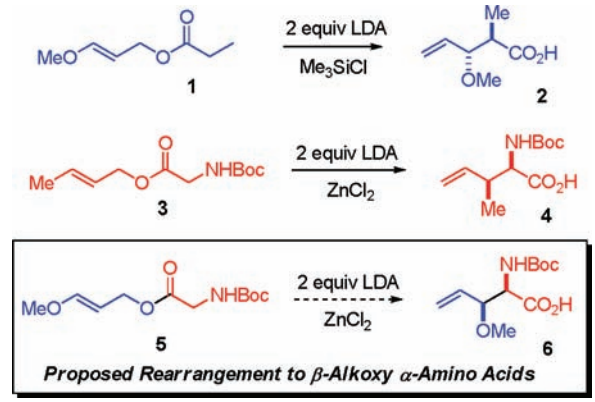
reduction of amino β-keto esters,[11] enantioselective dihydroxylation,[12] enantioselective aminohydroxylation,[13] asymmetric Strecker reaction,[14] intramolecular Pd(0)-catalyzed allylic alkylation,[15] photocycloadditions,[16] azomethine ylide cycloaddition,[17] dynamic kinetic resolution,[18] enantioselective 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 enamides[23] can be utilized as substrates for the preparation of $\beta^{2,3}$-amino acid systems through an Ireland−Claisen approach[24] 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 Me_3SiCl at −95 °C before warming to 0 °C (Table 1). The rearranged acid

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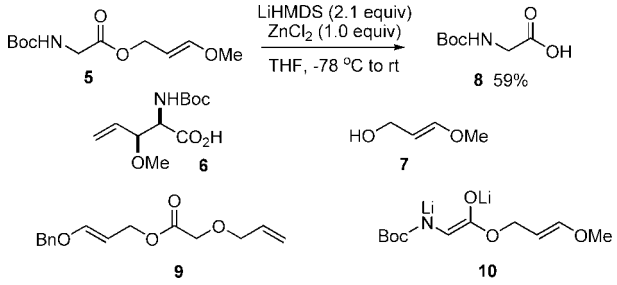
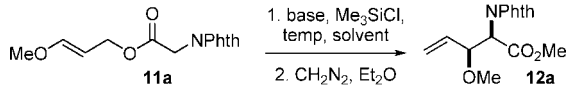
Scheme 2. Initial Rearrangement Attempts



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

Table 1. Initial Reaction Development



entry	base	solvent	temp (°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.

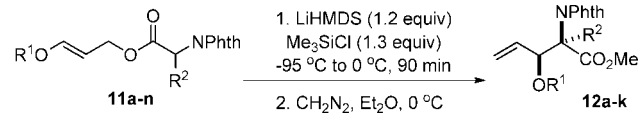
suggesting the formation of small amounts of desired rearranged product along with elimination, silylation products together with unconverted starting material. Using Na- or KHMDS at −95 °C leads to a drop in reaction quality, both in terms of yield and diastereoselectivity. Other Li−amide bases such 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 dr ≥ 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*-NO_2-Ph, *p*-CF_3-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_2i-Pr	H	**12c**	64[c]	18:1
11d	CH_2t-Bu	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	*o*-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	*p*-OMe-Ph	H	-	0[c]	-
11k	*p*-NO_2-Ph	H	-	0[c,f]	-
11l	*p*-CF_3-Ph	H	-	0[c,f]	-
11m	*o*-I-Ph	H	**12j**	50[c]	>25:1
11n	Me	Me	**12k**	71[c]	24:1

[a] Isolated yield. [b] Diastereomeric ratio measure by ^{1}H 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 (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 °C. In contrast, a faster addition of base over 1 min by hand, still at −95 °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]

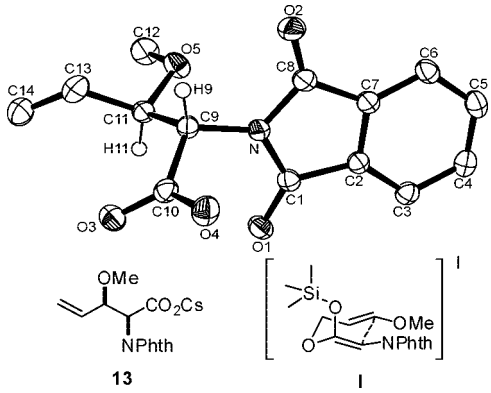


Figure 1. ORTEP plot of of cesium carboxylate **13** (ellipsoids shown at 30% probability) and chair transition state **I**.

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

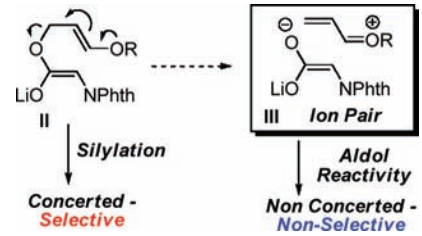
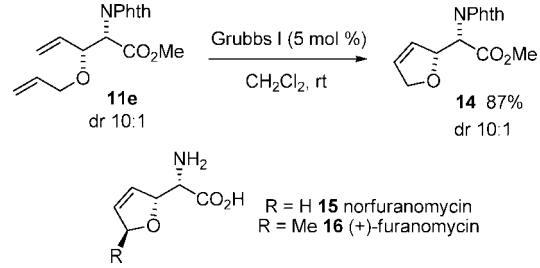


Figure 2. Possible selective and nonselective outcomes of enolate **II**.

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.

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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.

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