Stereoselective Synthesis of Functionalized Carbocycles and Heterocycles via an Ester Enolate Claisen/Ring-Closing Metathesis Manifold†,‡

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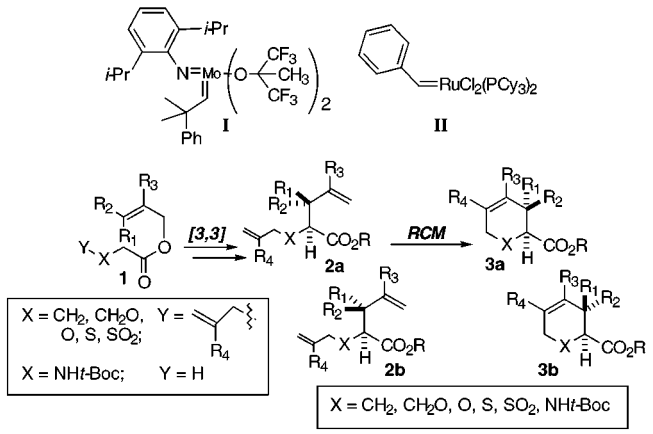
The Ireland ester enolate Claisen rearrangement[1] and variants thereof[2] are well-established protocol for stereoselective carbon−carbon bond formation. A more contemporary but equally powerful carbon−carbon bond-forming process involves ring-closing metathesis of α,ω dienes[3] as catalyzed by the transition-metal carbene complexes **I**[4] and **II**.[5−7] Our interest in obtaining diverse carbocyclic and heterocyclic scaffolds for solid-phase combinatorial synthesis prompted us to explore the possibility of utilizing these reactions as consecutive key steps according to Scheme 1.[8]

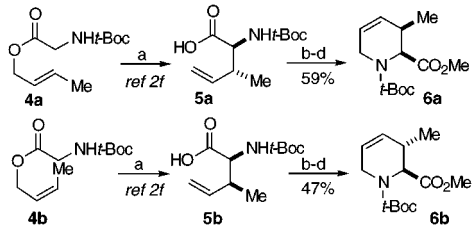
For the purpose of this study, all of the starting esters were derived from primary allylic alcohols and ω-unsaturated carboxylic acids.[9] Rearrangements were carried out using one of several silyl ketene acetal-forming conditions depending on the nature of the starting ester (Table 1). As anticipated, with glycolate-derived substrates (entries 1−8), chelation-assisted enolate formation provided a high degree of stereochemical control.[2a−e] Thus, relative stereochemical preferences were altered by adjusting the olefin geometry of the starting allylic alcohols. With esters derived from 5-hexenoic acid (entries 13 and 14), stereochemical toggling was conveniently achieved through manipulation of enolate geometry.[10,11] With the exception of entry 15, ring-closing metathesis substrates bearing geminal olefin substitution required the use of the more reactive molybdenum catalyst **I** (entries 6−10). In fact, substrates bearing relatively large alkene substituents (Ph or Me_3Si; entries 9 and 10, respectively) required more than the usual amount of catalyst to obtain useful quantities of desired products. Catalyst **I** was also required for the efficient cyclization of allytin-[12] and sulfur-containing[13,14] substrates (entries 4 and 11, respectively). It is notable that, in addition to fused bicyclic systems (entry 15), spirocyclic olefins are easily prepared *via* this method (entry 16).

As shown in Scheme 2, 3-substituted pipecolinic acids were accessed using a slightly modified sequence. Thus,

Scheme 1



Scheme 2[a]



[a] Key: (a) LDA (2 equiv), $ZnCl_2$ (1 equiv), THF, −78 °C to rt. See ref 2f. (b) KHMDS (2 equiv), allyl iodide, THF−DMF, −78 °C; (c) Me_3SiCHN_2, MeOH, rt; (d) catalyst **I** (2 mol%), CH_2Cl_2, rt, 12 h.

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(12) Catalyst **II** gave small amounts of cyclization product.

(13) No product was oberved using catalyst **II**.

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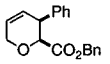
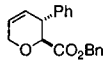
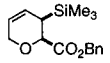
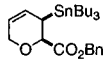
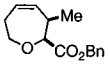
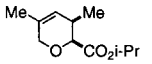
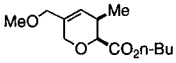
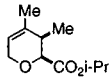
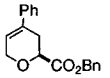
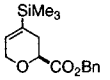
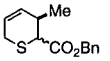
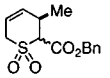
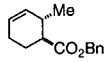
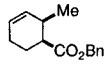
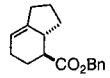
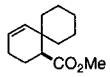
Table 1

Entry	1 R_1	R_2	R_3	R_4	X	[3,3] conditions[a,b]	2a:2b[c]	% yield[d]	RCM conditions[e]	3[f,g]	% yield[h]
1.	H	Ph	H	H	O	A	21:1	65	E		90
2.	Ph	H	H	H	O	A	1:8	87	E		81
3.	H	$SiMe_3$	H	H	O	A	8:1	78	E		83
4.	H	$SnBu_3$	H	H	O	A	10:1	98	G		91
5.	H	Me	H	H	CH_2O	A	7:1	90	F		74
6.	H	Me	H	Me	O	A	5:1	71	G		79
7.	H	Me	H	CH_2OMe	O	A	7:1	68	G		92
8.	H	Me	Me	H	O	A	9:1	69	G		83
9.	H	H	Ph	H	O	A	-----	85	I		56[i]
10.	H	H	$SiMe_3$	H	O	A	-----	93	H		70[i]
11.	H	Me	H	H	S	D	1:1	76	G		85[l]
12.	H	Me	H	H	S	D	1:1	76[j]	E		97[l]
13.	H	Me	H	H	CH_2	B	1:11	68	E		87[l]
14.	H	Me	H	H	CH_2	C	3:1	78	E		96[l]
15.	H	$-(CH_2)_3-$		H	CH_2	B	1:3	65	E		86[l]
16.	$-(CH_2)_4-$		H	H	CH_2	D[k]	-----	76	E		97

[a] (A) LiHMDS, TMSCl (in situ), THF, −95 °C to rt; (B) LDA, TMSCl, THF, −78 °C to rt; (C) LDA, TMSCl, THF−DMPU, −78 °C to rt; (D) TBDMSCl, Et_3N, CH_2Cl_2, 0 °C to rt. [b] Esterification conditions: ROH, EDCI, DMAP (cat.), CH_2Cl_2, rt or Me_3SiCHN_2, MeOH, rt. [c] Ratios were determined through integration of characteristic resonances using ^1H NMR at 400 MHz. [d] Refers to combined diastereomer mass following esterification. [e] (E) 2.5 mol % **II**, CH_2Cl_2, rt, 1−16 h. (F) 2.5 mol % **II**, 1,2-dichloroethane, 80 °C, 16 h. (G) 5 mol % **I**, benzene, rt, 1 h. (H) 50 mol % **I**, benzene, rt, 6 h. (I) 100 mol % **I**, benzene, rt, 6 h. [f] Major diastereomer from [3,3]. [g] Stereochemical assignments were made based on diagnostic ^1H NMR coupling constants and through comparison with known compounds. [h] Refers to combined diastereomer mass. [i] Product contained small amounts of catalyst derived impurity (2,6-diisopropylaniline) following chromatography. [j] Oxidized to the corresponding sulfone (PhSeSePh, H_2O_2, CH_2Cl_2, Et_2O, rt) prior to cyclization. [k] The silyl ketene acetal was heated at 65 °C for 2 h. [l] Isolated and characterized as a mixture of diastereomers after chromatography.

diastereoselective Kazmier−Claisen rearrangement[2f,g] of **4a** and **4b** gave acids **5a** and **5b**, respectively, again as a result of a chelation-controlled enolization process. *N*-Allylation[15] followed by esterification and ring-closing metathesis gave the desired pipecolinates **6a** and **6b** in good overall yields.

In conclusion, we have demonstrated that the ester enolate Claisen/ring-closing metathesis manifold is a powerful reaction tandem for the stereoselective synthesis of functionalized carbocycles and heterocycles. Additional work in this area, including application to the synthesis of natural products, will be reported in due course.

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Supporting Information Available: Experimental procedures and copies of spectra are included (22 pages).

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(15) No detectable epimerization was observed.