Optically Active Allenes from β-Lactone Templates: Asymmetric Total Synthesis of (−)-Malyngolide

Zhonghui Wan and Scott G. Nelson*

Department of Chemistry
University of Pittsburgh
Pittsburgh, Pennsylvania 15260

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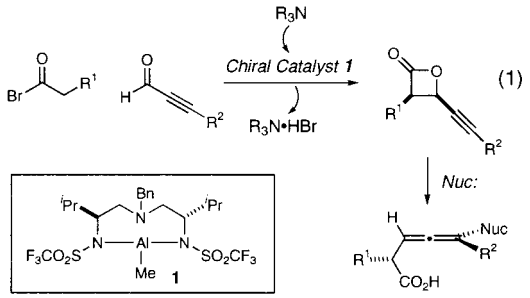
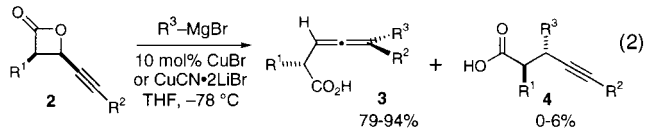
Allenes have emerged as increasingly popular intermediates for asymmetric organic synthesis due largely to the potential for relaying the associated axial chirality to ensuing bond constructions.[1,2] The S_N2' addition of nucleophiles to suitably derivatized, optically active propargylic ethers is among the most direct route to the enantiomerically enriched allenes required for asymmetric synthesis.[3,4] Alkyne-substituted β-lactones are subject to S_N2' nucleophilic addition analogous to that observed for activated propargylic alcohols, rendering these lactones as complimentary precursors to allene derivatives.[5] Our recent success in preparing optically active alkynyl-substituted β-lactones via catalytic asymmetric acyl halide−aldehyde cyclocondensation (AAC) reactions prompted us to explore the union of the asymmetric AAC reactions and ensuing S_N2' ring opening as a general strategy for preparing optically active allene derivatives (eq 1).[6] This report details the successful implementation of this strategy to the asymmetric synthesis of structurally diverse di- and trisubstituted allenes via an operationally simple two-step procedure from propargylic aldehydes. The utility of this reaction technology to asymmetric organic synthesis is demonstrated in a concise and efficient asymmetric synthesis of the naturally occurring antibiotic (−)-malyngolide.



(1)

Alkynyl-substituted β-lactones can be considered a subset of activated propargylic ethers in which ring strain imparts the necessary activation of the ether functional group to allow S_N2' nucleophilic addition. On the basis of this premise, we anticipated that nucleophilic addition to the β-lactone's remote alkyne terminus would be subject to the well-established stereoelectronic requirements for S_N2' addition and, therefore, proceed with rigorous translation of the lactone stereogenic center to the chiral allene reaction product.[7] To evaluate this hypothesis, a series of optically active alkynyl-substituted β-lactones were prepared from asymmetric AAC reactions catalyzed by the Al(III) catalyst **1** using either acetyl or propionyl bromide and the requisite propargylic aldehyde (eq 1).[6] The resulting enantiomerically enriched β-lactones **2** participated in efficient S_N2' ring opening using alkyl Grignard reagents and a Cu(I) reaction catalyst (10 mol %), providing access to a variety of structurally diverse optically active allenes **3** (eq 2).[8]



(2)

Copper-catalyzed additions of various organometallic nucleophiles to the β-lactone electrophiles uniformly proceed in high yields and with consistent chirality transfer from the β-lactones **2** to the derived β-allenic acids **3** (Table 1). Nucleophilic addition appears insensitive to the steric environment about the nucleophilic carbon atom; straight-chain, branched, and aryl Grignard reagents promote equally efficient ring opening to the optically active allenic acids **3** (entries a−g). Addition of unbranched nucleophiles can be accompanied by variable amounts (0−6%) of S_N2 lactone ring opening leading to β-disubstituted carboxylic acids **4** (entries c, i, j).[9] Using CuCN·2LiBr as the reaction catalyst (10 mol %) affords substantially improved regioselectivity in these examples relative to CuBr·DMS. Ring opening of sterically hindered alkynyl lactones is also possible with MeMgBr addition to the trimethylsilyl-substituted alkynyl lactone **2** (R^1 = Bn, R^2 = $SiMe_3$) providing the optically active trisubstituted allene **3h** in 80% yield (entry h). Variation in the electronic properties of the requisite nucleophiles is also tolerated in this allene synthesis with zinc ester enolates (entry i) and the magnesium anion of acetonitrile (entry j) affording the optically active trisubstituted allenes. The attenuated reactivity of zinc enolates relative to alkyl Grignard reagents necessitated higher reaction temperatures (22 °C) for complete reaction; this temperature requirement is believed to be responsible for the modest erosion of allene enantiomeric purity relative to the lactone precursor that is observed in this one example.[10] The stereochemical outcome of these reactions pro-

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(8) Either CuCN·2LiBr or CuBr·DMS were used as reaction catalysts. Stoichiometric Gilman cuprates were considerably less reactive toward S_N2' ring opening relative to the Cu(I)-catalyzed alkyl Grignard additions.

(9) For the competing modes of nucleophilic ring opening available to β-lactone electrophiles, see: Pommier, A.; Pons, J.-M. *Synthesis* **1993**, 441−459.

(10) Enantiomeric purity of the allene derivatives **3** was assayed by Ag(I)-catalyzed cyclization of the carboxylic acid or allenic alcohol (obtained from the LAH reduction of the carboxylic acid) and separation of the δ-lactone or dihydropyran enantiomers, respectively, by chiral GC or HPLC. See Supporting Information for details.

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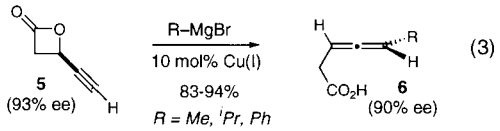
Table 1. S_N2' Ring Opening of Alkynyl-Substituted β-Lactones **2**

	lactone **2** (% ee)		allene (**3**) (% ee)	% yield **3**
	R^1	R^2	R^3	(% ee)[a]
a	H	CH_2OBn (93)	$CHMe_2$ (**3a**)	92 (92)
b	H	CH_2OBn (93)	$CH_2CH_2CHCH_2$ (**3b**)	94 (93)[b]
c	H	CH_2OBn (93)	$(CH_2)_{10}CH_3$ (**3c**)	90 (92)[c]
d	H	CH_2OBn (93)	C_6H_5 (**3d**)	93 (nd)[d]
e	H	CH_2OBn (93)	CH_3 (**3e**)	92 (93)[b]
f	H	CH_2OBn (93)	CMe_3 (**3f**)	93 (nd)[d]
g	CH_3	$(CH_2)_2OPMB$ (90)	CH_3 (**3g**)	88 (90)[e]
h	Bn	$SiMe_3$ (93)	CH_3 (**3h**)	80 (nd)[d]
i	H	CH_2OBn (93)	$CH_2CO_2CMe_3$ (**3i**)	84 (83)[b,f]
j	H	CH_2OBn (93)	CH_2CN (**3j**)	79 (90)[g]

[a] See ref 10 for determination of stereoisomer ratios. [b] CuCN·2LiBr was used as the reaction catalyst. Unless otherwise noted, CuBr·DMS was used as the reaction catalyst. [c] Isolated with 2.8% of regioisomer **4**. [d] Not determined. All related examples provided complete translation of lactone chirality. [e] Value represents diastereomeric excess. [f] Isolated with 6% of regioisomer **4**. [g] Isolated with 1.6% of regioisomer **4**.

vides the first evidence that 4-alkynyl-2-oxetanones belong to the class of propargylic ethers that undergo stereospecific *anti*-1,3-substitution reactions.[11]

Optically active 1,3-disubstituted allenes are also conveniently obtained from the β-lactone templates. 4-Ethynyl-2-oxetanone **5**, obtained in 93% ee from cyclocondensation of 3-trimethylsilylpropynal and subsequent silyl group cleavage, provides a common platform for preparing a variety of disubstituted allenic acids (eq 3). Copper-catalyzed Grignard addition to **5** affords the 1,3-disubstituted allenes **6** bearing straight chain, branched, or aryl substituents as the exclusive reaction products in high yields and with consistent chirality transfer.



The β-allenic acids emerging from the AAC-S_N2' ring opening sequence provide versatile precursors to optically active oxygen heterocycles by exploiting the annulative addition of the carboxylate terminus onto the allene unit.[12] To highlight this utility, β-lactones and the derived allenic acids were examined as conduits for a concise, fully stereocontrolled synthesis of the naturally occurring antibiotic (−)-malyngolide (**7**).[13,14] The synthesis was predicated on establishing the δ-lactone core of malyngolide by the cyclization of the trisusbstituted allenic acid **8** that would be, in turn, obtained from β-lactone **9** (Figure 1). Following this synthesis strategy, both stereogenic centers present in malyngolide would be established in the initial asymmetric AAC reaction with the lactone β-stereocenter ultimately being relayed to the requisite tertiary carbinol stereocenter via the intermediacy of the chiral allene **8**.

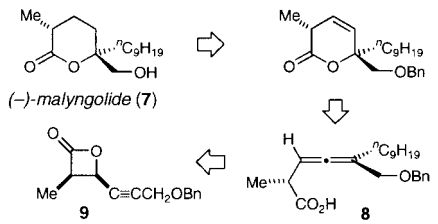
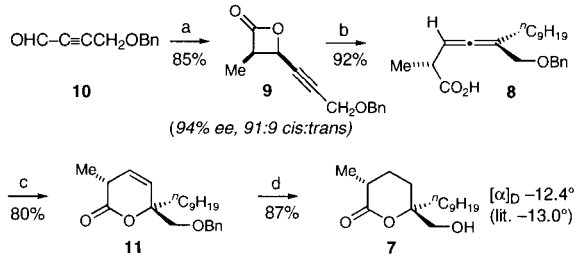


Figure 1. Malyngolide retrosynthesis.

Scheme 1[a]



[a] (a) 10 mol % **1**, EtCOBr, $^iPr_2NEt$, CH_2Cl_2, −50 °C. (b) $^nC_9H_{19}MgBr$, 10 mol % CuBr, THF, −78 °C. (c) 10 mol%, $AgNO_3$, 5 mol % $^iPr_2NEt$, 80 °C, CH_3CN. (d) H_2, Pd−C.

The malyngolide synthesis was initiated with the asymmetric AAC reaction of propionyl bromide and 4-benzyloxybuynal (**10**)[15] catalyzed by the Al(triamine) complex **1** (10 mol %) to provide the *cis*-3,4-disubstituted-2-oxetanone **9** in 85% yield (94% ee, 91:9 *cis:trans*) (Scheme 1).[6b] Copper-catalyzed ring opening of **9** with nonyl Grignard delivered the optically active trisubstituted allene **8** (92%). Electrophilic activation of the trisubstituted allene was expected to engage the carboxylic acid in a 6-*endo-trig* cyclization in preference to the competitive 5-*exo-dig* pathway owing to the enhanced stabilization provided to the developing positive charge at the disubstituted allene terminus in the transition state leading to the δ-lactone.[16] Consistent with this expectation, Ag(I)-catalyzed cyclization of allenic acid **8**, accelerated by a substoichiometric quantity of soluble amine base (5 mol % $^iPr_2$-NEt), resulted in rapid formation of the δ-lactone **11** (80%), thereby establishing the requisite tertiary carbinol stereocenter. Ensuing Pd(0)-catalyzed alkene dihydrogenation proceeded with concomitant hydrogenolysis of the benzyl ether to afford synthetic (−)-malyngolide (**7**) in 87% yield (94% ee, 100% de) in four steps and 54% overall yield from the aldehyde **10**.[17,18]

The asymmetric AAC-S_N2' ring opening sequence provides an efficient and operationally simple enantioselective synthesis di- and trisubstituted allene derivatives. The optically active allenes provided the cornerstone for a highly efficient enantioselective synthesis of the naturally occurring antibiotic malyngolide, an investigation that highlights the utility of these allene derivatives in asymmetric organic synthesis.

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Supporting Information Available: Experimental procedures and representative ^1H and ^{13}C spectra (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) Stereoselection in S_N2' nucleophilic additions to activated propargylic electrophiles can vary depending on leaving group structure. See ref 7.

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(17) The minor diastereomer introduced during the initial AAC reaction was removed at this stage by column chromatography.

(18) The structure of (+)-tanikolide, a close structural relative to malyngolide, has recently been reported, see: Singh, I. P.; Milligan, K. E.; Gerwick, W. H. *J. Nat. Prod.* **1999**, *62*, 1333−1335. An asymmetric synthesis of (−)-tanikolide from allenic acid **3c** was completed via a two-step procedure analogous to that used in preparing (−)-malyngolide. See Supporting Information for full procedural details.