

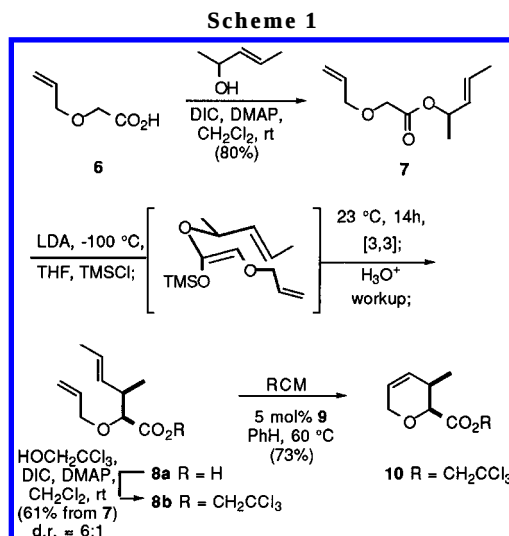
Tandem Glycolate Claisen Rearrangement/ Ring-Closing Metathesis: A Stereochemically General Synthesis of Substituted Dihydropyran-2-carboxylates

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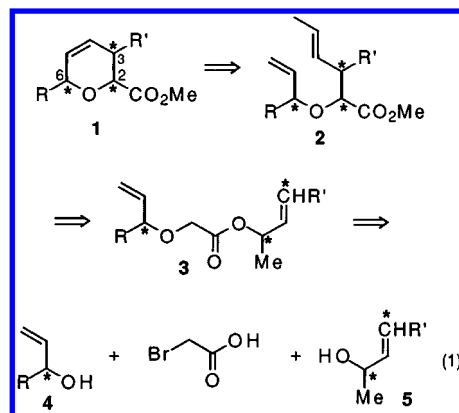
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Hydropyrans are important structural units found in synthetic and natural ionophores and polyether macrolides.^{1,2} Recent efforts directed at hydropyran synthesis include anionic cyclization,³ cationic cyclization,⁴ radical cyclization,⁵ hetero-Diels–Alder cycloaddition,⁶ dioxanone Claisen rearrangement,⁷ and ring-closing metathesis of enol ethers.⁸ To date, however, there has been no demonstration



of a *stereochemically general* method for the synthesis of dihydropyrans of general structure **1** (eq 1).



We envisioned the tandem sequence of glycolate Claisen rearrangement⁹/ring-closing metathesis¹⁰ as providing such a protocol. Diene metathesis substrate **2** contains an α -alkoxy- γ,δ -unsaturated ester, known to be available via a glycolate Claisen rearrangement⁹ of substrates such as **3**. Merger of two allylic alcohol subunits with a bromoacetic acid linchpin would afford this glycolate Claisen substrate. Stereogenicity at the indicated centers in **1** would follow in a predictable fashion from the indicated stereogenic centers in the allylic alcohol components **4** and **5**. This convergent and stereochemically general synthesis of substituted dihydropyrans is illustrated herein for *cis*- and *trans*-3-substituted dihydropyran-2-carboxylates and for all four diastereomeric permutations of 3,6-disubstituted dihydropyran-2-carboxylates.

A simple example in a racemic series is illustrated in Scheme 1. *O*-Alkylation of allyl alcohol with bromoacetic acid (2 equiv of NaH, THF, 66 °C) gave **6**, which afforded glycolate Claisen substrate **7** upon Steglich–Hassner¹¹ coupling with (*E*)-3-penten-2-ol. Subjection of the ester to standard Ireland–Claisen conditions¹² effected the [3,3]-

(13) (a) see ref 9a. (b) Typical procedure: A solution of glycolate ester in THF is added slowly to a solution of freshly prepared LDA at –100 °C. After the solution is stirred at –100 °C for 15 min, the supernatant of a centrifuged 1:1 (v/v) mixture of TMSCl and triethylamine is added. The mixture is allowed to warm to ambient temperature and stirred overnight. The silyl ester is hydrolyzed by treatment with either 1 M NaOH or 1 M HCl. The acid is isolated by acid/base extractions.

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Table 1. Tandem Glycolate Claisen Rearrangement/Ring-Closing Metathesis

Entry	Substrate	Claisen Product (yield, %; d.r. ^a)	RCM Product (yield, %)
1		 (61; 6:1)	 (73) ^b
2		 (84; 20:1)	 (69) ^b
3		 (82; 14:1)	 (69) ^b
4		 (56; 5:1)	 (48) ^c
5		 (52; 6:1)	 (51) ^c
6		 (53; 4:1)	 (68) ^c
7		 (47; >20:1)	 (85) ^c

^a Diastereomeric ratio; isomers separated by flash chromatography. ^b RCM conditions: PhH (0.01 M), 60–80 °C, 1–3 h, 5 mol % of **9**. ^c RCM conditions: CH₂Cl₂ (0.1 M), 23–60 °C, 4–5 days, 20 mol % of **9**.

sigmatropic shift via the bracketed silyl ketene acetal.¹³ Chelation control over enolate geometry and π -facial preferences dictated by the chairlike transition state produce, after esterification, the metathesis substrate **8b** with the relative stereochemistry shown for the major isomer (diastereoselectivity 6:1). Exposure of **8b** to [RuCl₂(=CHPh)(PCy₃)₂] (**9**)¹⁴ in benzene (60 °C, 0.5 h) or CH₂Cl₂, (23 °C, 3 h) gave *cis*-3-substituted dihydropyran-2-carboxylate **10** in 73% yield.

Further examples of metathesis substrate preparation via the glycolate Claisen rearrangement are summarized in Table 1. Combination of two enantiopure alcohols^{15,16} with bromoacetic acid to provide glycolate Claisen substrate **3** (as in Scheme 1) is represented in entries 4–7. Control of the relative stereochemistry at the nascent C2 and C3 centers (cf. Table 1, entries 4 and 5) is exerted by the choice of *Z*- or *E*-allylic alcohols in substrate ester syntheses. Absolute stereogenicity at those centers is transferred from

the substrate allylic stereocenter (*) via equatorial deployment of the methyl substituent on the pericyclic chairlike transition structure (see Scheme 1). Although good Claisen rearrangement diastereoselectivities were observed in entries 1–3 using standard conditions for silyl ketene acetal formation,¹² the more oxygenated substrates in entries 4–7 gave poor diastereoselectivities (~1:1) and substantial amounts of C-silylation byproducts with this protocol. Fortunately, adding 2 equiv of LDA to a solution of ester and TMSCl in 20% (v/v) HMPA/THF at –100 °C for 1 h and then warming to ambient temperature^{9k} afforded moderate to high (4:1 to >20:1) stereoselectivities and better rearrangement yields. The major isomer in each case was separated by flash chromatography for use as the substrate for the next step.

Table 1 also summarizes the ring-closing metathesis reactions of the glycolate Claisen rearrangement products. The substrates in entries 1–3 generally reacted under milder conditions (CH₂Cl₂, 23 °C, 1–3 h or benzene, 80 °C, 1 h) than those in entries 4–7. The latter substrates have allylic branching at both alkene termini, which is known to retard the metathesis reaction.¹⁷ Reaction times of several days at 23 °C in CH₂Cl₂ were required for entries 4–7 to provide moderate to good yields of the 2,3,6-trisubstituted dihydropyrans **25**–**28**. Conducting the reactions at higher concentrations, in CHCl₃, or in the presence of cuprous chloride^{14c} failed to promote acceleration.

The product **25** of entry 4 matches the absolute stereochemistry of the four asymmetric carbons in the hydropyran subunit of the ionophore antibiotic zincophorin.¹⁸ The entry 5 product **26** possesses the relative (but enantiomeric) stereochemistry present in the ionophore antibiotic indanomyacin.¹⁹ Dihydropyran-2-carboxylate products **25** and **26** were stereochemically correlated with known samples prepared by alternate methods. The relative ease by which enantiopure allylic alcohols can now be obtained²⁰ allows for their employment in this glycolate Claisen/ring-closing metathesis tandem sequence. Products **25**–**28** represent all four possible diastereomeric 2,3,6-trisubstituted dihydropyrans (*trans*, *trans*; *cis*, *trans*; *trans*, *cis*; *cis*, *cis*), thus demonstrating a stereochemically universal route to these heterocycles.²¹

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Supporting Information Available: Experimental procedures and characterization data (79 pages).

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