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

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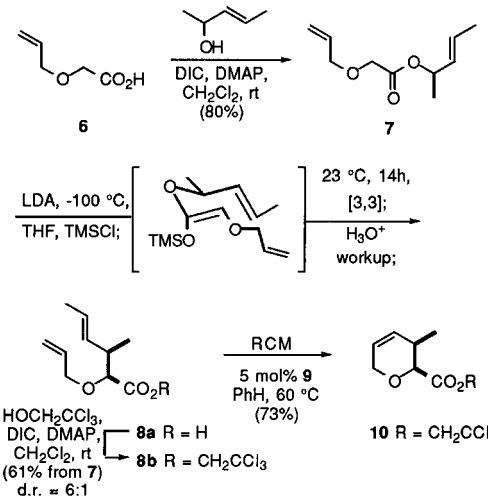
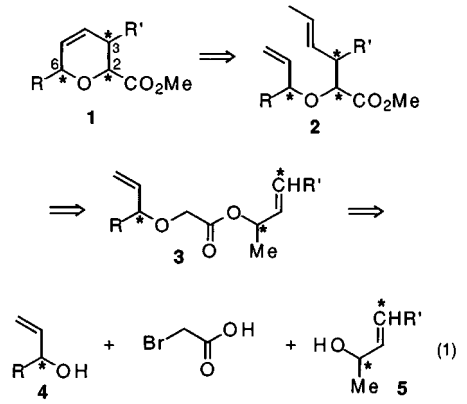
Hydropyrans are important structural units found in synthetic and natural ionophores and polyether macrolides.[1,2] Recent efforts directed at hydropyran synthesis include anionic cyclization,[3] cationic cyclization,[4] radical cyclization,[5] hetero-Diels−Alder cycloaddition,[6] dioxanone Claisen rearrangement,[7] 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).

Scheme 1





We envisioned the tandem sequence of glycolate Claisen rearrangement[9]/ring-closing metathesis[10] 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 rearrangement[9] 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 hydropyrans 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−Hassner[11] coupling with (*E*)-3-penten-2-ol. Subjection of the ester to standard Ireland−Claisen conditions[12] effected the [3,3]-

(1) (a) Burke, S. D.; Porter, W. J.; Rancourt, J.; Kaltenbach, R. F. *Tetrahedron Lett.* **1990**, *31*, 5285. (b) Burke, S. D.; O'Donnell, C. J.; Porter, W. J.; Song, Y. *J. Am. Chem. Soc.* **1995**, *117*, 12649. (c) Burke, S. D.; O'Donnell, C. J.; Hans, J. J.; Moon, C. W.; Ng, R. A.; Adkins, T. W.; Packard, G. K. *Tetrahedron Lett.* **1997**, *38*, 2593.

(2) (a) *Polyether Antibiotics*; Westley, J. W., Ed.; Marcel Dekker: New York, 1983; Vols. I and II. (b) Dobler, M. *Ionophores and Their Structures*; Wiley-Interscience: New York, 1981. (c) Robinson, J. A. *Prog. Chem. Org. Nat. Prod.* **1991**, *58*, 1−81.

(3) (a) Martín, V. S.; Nuñez, M. T.; Ramirez, M. A.; Soler, M. A. *Tetrahedron Lett.* **1990**, *31*, 763. (b) Mandai, T.; Ueda, M.; Kashiwagi, K.; Kawada, M.; Tsuji, J. *Tetrahedron Lett.* **1993**, *34*, 111. (c) Burke, S. D.; Jung, K. W.; Phillips, J. R.; Perri, R. E. *Tetrahedron Lett.* **1994**, *35*, 703. (d) Aicher, T. D.; Kishi, Y. *Tetrahedron Lett.* **1987**, *28*, 3463. (e) Duan, J. J.-W.; Kishi, Y. *Tetrahedron Lett.* **1993**, *34*, 7541. (f) Stamos, D. P.; Kishi, Y. *Tetrahedron Lett.* **1996**, *37*, 8643. (g) Cooper, A. J.; Salomon, R. G. *Tetrahedron Lett.* **1990**, *31*, 3813.

(4) (a) Bartlett, P. A. In *Asymmetric Synthesis*; Morrison, J. D., Ed.; Academic Press: New York, 1984; Vol. 3, p 411. (b) Boivin, T. L. B. *Tetrahedron* **1987**, *43*, 3309. (c) Hashimoto, M.; Kan, T.; Yanagiya, M.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1987**, *28*, 5665. (d) Faivre, V.; Lila, C.; Saroli, A.; Doutheau, A. *Tetrahedron* **1989**, *45*, 7765. (e) Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5330. (f) Nicolaou, K. C.; Prasad, C. V. C.; Somers, P. K.; Hwang, C.-K. *J. Am. Chem. Soc.* **1989**, *111*, 5335. (g) Semeyn, C.; Blaauw, R. H.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1997**, *62*, 3426.

(5) (a) Munt, S. P.; Thomas, E. J. *J. Chem. Soc., Chem. Commun.* **1989**, 480. (b) Kim, S.; Fuchs, P. L. *J. Am. Chem. Soc.* **1991**, *113*, 9864. (c) Burke, S. D.; Rancourt, J. *J. Am. Chem. Soc.* **1991**, *113*, 2335. (d) Esch, P. M.; Hiemstra, H.; de Boer, R. F.; Speckamp, W. N. *Tetrahedron* **1992**, *48*, 4659.

(6) (a) Danishefsky, S. J.; DeNinno, M. P. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 15. (b) Danishefsky, S. J.; Selnick, H. G.; Zelle, R. E.; DeNinno, M. P. *J. Am. Chem. Soc.* **1988**, *110*, 4368. (c) Lubineau, A.; Augé, J.; Lubin, N. *Tetrahedron* **1993**, *49*, 4639.

(7) (a) Burke, S. D.; Armistead, D. M.; Schoenen, F. J. *J. Org. Chem.* **1984**, *49*, 4320. (b) Burke, S. D.; Armistead, D. M.; Schoenen, F. J.; Fevig, J. M. *Tetrahedron* **1986**, *42*, 2787.

(8) Nicolaou, K. C.; Postema, M. H. D.; Claiborne, C. F. *J. Am. Chem. Soc.* **1996**, *118*, 1565.

(9) (a) Burke, S. D.; Fobare, W. F.; Pacofsky, G. J. *J. Org. Chem.* **1983**, *48*, 5221. (b) Bartlett, P. A.; Barstow, J. F. *Tetrahedron Lett.* **1982**, *23*, 623. (c) Bartlett, P. A.; Tanzella, D. J.; Barstow, J. F. *Tetrahedron Lett.* **1982**, *23*, 619. (d) Ager, D. J.; Cookson, R. C. *Tetrahedron Lett.* **1982**, *23*, 3419. (e) Sato, T.; Tajima, K.; Fujisawa, T. *Tetrahedron Lett.* **1983**, *24*, 729. (f) Kallmerten, J.; Gould, T. J. *Tetrahedron Lett.* **1983**, *24*, 5177. (g) Fujisawa, T.; Tajima, K.; Sato, T. *Chem. Lett.* **1984**, 1669. (h) Sato, T.; Tsunekawa, H.; Kohama, H.; Fujisawa, T. *Chem. Lett.* **1986**, 1553. (i) Barrish, J. C.; Lee, H. L.; Baggiolini, E. G.; Uskokovic, M. R. *J. Org. Chem.* **1987**, *52*, 1372. (j) Ireland, R. E.; Wipf, P.; Armstrong, J. D., III. *J. Org. Chem.* **1991**, *56*, 650. (k) Ireland, R. E.; Meissner, R. S.; Rizzacasa, M. A. *J. Am. Chem. Soc.* **1993**, *115*, 7166. (l) Hattori, K.; Yamamoto, H. *Tetrahedron* **1994**, *50*, 3099.

(10) (a) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res.* **1995**, *28*, 446. (b) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036.

(11) (a) Neises, B.; Steglich, W. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 522. (b) Hassner, A.; Alexanian, V. *Tetrahedron Lett.* **1978**, 4475.

(12) (a) Ireland, R. E.; Mueller, R. H. *J. Am. Chem. Soc.* **1972**, *94*, 5897. (b) Ireland, R. E.; Willard, A. K. *Tetrahedron Lett.* **1975**, 3975. (c) Ireland, R. E.; Mueller, R. H.; Willard, A. K. *J. Am. Chem. Soc.* **1976**, *98*, 2868. For recent reviews, see: (d) Blechert, S. *Synthesis* **1989,** 71. (e) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423.

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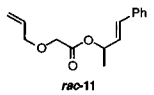
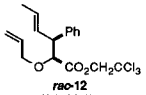
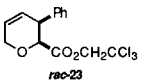
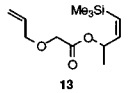
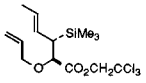
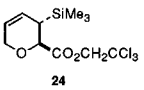
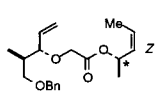
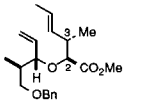
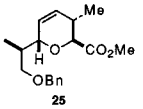
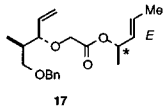
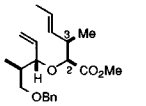
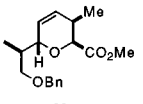
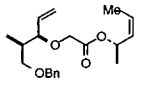
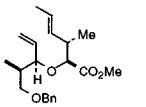
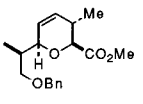
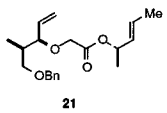
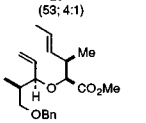
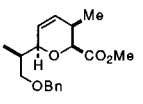
Table 1. Tandem Glycolate Claisen Rearrangement/ Ring-Closing Metathesis

Entry	Substrate	Claisen Product (yield, %; d.r.[a])	RCM Product (yield, %)
1	*rac*-**7**	*rac*-**8b** (61; 6:1)	*rac*-**10** (79)[b]
2	 *rac*-**11**	 *rac*-**12** (84; 20:1)	 *rac*-**23** (69)[b]
3	 **13**	 **14** (82; 14:1)	 **24** (68)[b]
4	 **15**	 **16** (56; 5:1)	 **25** (48)[c]
5	 **17**	 **18** (52; 6:1)	 **26** (51)[c]
6	 **19**	 **20** (53; 4:1)	 **27** (68)[c]
7	 **21**	 **22** (47; >20:1)	 **28** (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: CH_2Cl_2 (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 $[RuCl_2(=CHPh)(PCy_3)_2]$ (**9**)[14] in benzene (60 °C, 0.5 h) or CH_2Cl_2, (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 (CH_2Cl_2, 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 CH_2Cl_2 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 $CHCl_3$, 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 indanomycin.[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 obtained[20] 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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(14) (a) Fu, G. C.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1993**, *115*, 9856. (b) Schwab, P.; France, M. B.; Ziller, J. W.; Grubbs, R. H. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2039. (c) Dias, E. L.; Nguyen, S. T.; Grubbs, R. H. *J. Am. Chem. Soc.* **1997**, *119*, 3887.

(15) (3*S*,4*R*)- and (3*R*,4*R*)-4-Methyl-5-(phenylmethoxy)-1-penten-3-ol (used in entries 4−7) were prepared from (*S*)-(+)-methyl 3-hydroxy-2-methylpropionate. See: Burke, S. D.; Piscopio, A. D.; Marron, B. E.; Matulenko, M. A.; Pan, G. *Tetrahedron Lett.* **1991**, *32*, 857.

(16) (*S*)-(*Z*)- and (*S*)-(*E*)-3-penten-2-ol (used in entries 4−7) were prepared from (*S*)-ethyl lactate by the method of Kurth: (a) McKew, J. C.; Kurth, M. J. *Org. Prep. Proced. Int.* **1993**, *25*, 125. (b) McKew, J. C.; Kurth, M. J. *J. Org. Chem.* **1993**, *58*, 4589.

(17) (a) Fürstner, A.; Langemann, K. *J. Org. Chem.* **1996**, *61*, 3942. (b) Fürstner, A.; Langemann, K. *Synthesis* **1997**, 792.

(18) (a) Gräfe, U.; Schade, W.; Roth, M.; Radics, L.; Incze, M.; Ujszászy, K. *J. Antibiot.* **1984**, *37*, 836. (b) Brooks, H. A.; Gardner, D.; Poyser, J. P.; King, T. J. *J. Antibiot.* **1984**, *37*, 1501.

(19) Westley, J. W.; Evans, R. H., Jr.; Liu, C.-M.; Hermann, T.; Blount, J. F. *J. Am. Chem. Soc.* **1978**, *100*, 6784.

(20) (a) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765. (b) Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551. (c) Corey, E. J.; Bakshi, R. K.; Shibata, S.; Chen, C.-P.; Singh, V. K. *J. Am. Chem. Soc.* **1987**, *109*, 7925. (d) Midland, M. M.; McDowell, D. C.; Hatch, R. L.; Tramontano, A. *J. Am. Chem. Soc.* **1980**, *102*, 867. (e) Midland, M. M.; Tramontano, A.; Kazubski, A.; Graham, R. S.; Tsai, D. J. S.; Cardin, D. B. *Tetrahedron* **1984**, *40*, 1371.

(21) (a) This work has been reported in part. See: Ng, R. A.; Morrison, J. A.; Burke, S. D. *Abstracts of the 213th National Meeting of the American Chemical Society*, April 13−17, 1997, San Francisco, CA; American Chemical Society: Washington, DC, 1997; Abstract #ORGN 431. (b) For related independent work, see: Miller, J. F.; Termin, A.; Koch, K.; Piscopio, A. D. *J. Org. Chem.* **1998**, *63*, 3158−3159.