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Communications

Synthetic and Mechanistic Studies of the Retro-Claisen Rearrangement. 2. A Facile Route to Medium-Ring Heterocycles via Rearrangement of Vinylcyclopropane- and Cyclobutanecarboxaldehydes

Robert K. Boeckman, Jr.,* Matthew D. Shair, J. Ramon Vargas, and Lesley A. Stolz

Department of Chemistry, University of Rochester, Rochester, New York 14627-0216

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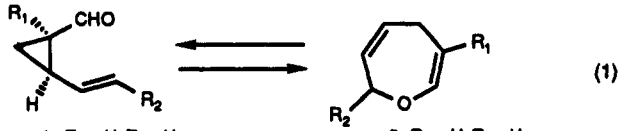
Summary: New methodology for the synthesis of medium-ring (7- or 8-membered ring) O and N heterocycles is described.

Considerable attention has been focused on the construction of medium-ring ethers as a consequence of the discovery of a number of biologically active natural substances containing these substructures (e.g., the brevitoxins and laurencin).[1] A number of ingenious routes to these ethers and related amines have been described; however, few constitute general methods amenable to the preparation of enantiomerically pure materials.[2-5]

We required access to such medium-ring vinyl ethers for metalation studies and as synthetic intermediates and were intrigued by the observation of Rhoads and that *cis*-vinylcyclopropanecarboxaldehyde (1) and dihydrooxepin 2 are in equilibrium via a retro-Claisen rearrangement (eq 1), a finding which has not been previously exploited since



(1)

1 R_1 = H; R_2 = H
3 R_1 = CHO; R_2 = alkyl, aryl

2 R_1 = H; R_2 = H
4 R_1 = CHO; R_2 = alkyl, aryl

the equilibrium favors the aldehyde isomer (K_{eq} = 0.05).[2,6,7] However, our studies of the retro-Claisen rearrangement suggested that the equilibrium could be manipulated to favor the medium-ring heterocycle using a suitably positioned π-conjugating stabilizing group.[8] Thus, vinylcyclopropanedicarboxaldehydes 3 and related systems were expected to undergo facile conversion to formyl dihydrooxepins 4 (eq 1). On the basis of this idea, we describe a flexible, efficient route to functionalized medium-ring heterocycles (enantiomerically pure if required).

Propenyl diester (±)-5 was obtained by dialkylation of ethyl malonate with (*E*)-1,4-dibromo-2-pentene (phase

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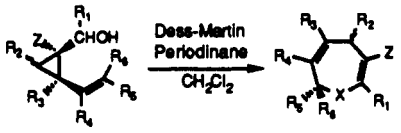
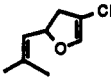
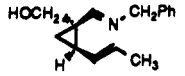
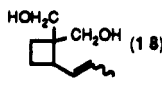
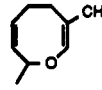
Table I



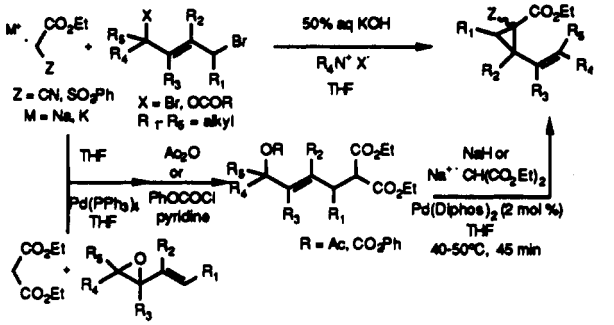
substrate[a,b]	prepn[c]	product[d]	yield[e] (%)
R_5 or $R_6 = CH_3$ (6)	A, B	R_5 or $R_6 = CH_3$ (8)	85
$R_4 = CH_3$	A	$R_4 = CH_3$	95
$R_3 = CH_3$	A	$R_3 = CH_3$	95
$R_2, R_5 = CH_3$	A	$R_2, R_5 = CH_3$	91
$R_4 = CH_3$; $R_5 = C_2H_5$[f]	B, C	$R_4 = CH_3$; $R_5 = C_2H_5$[g]	90
$R_5 = R_6 = CH_3$ (13)	D	 (14)	95
$R_4 = OAc$; $R_5(R_6) = CH_3C_2H_5$ (15,16)	D	$R_4 = OAc$; $R_5(R_6) = CH_3C_2H_5$ (17)	57
$Z = SO_2Ph$	A	$Z = SO_2Ph$	97
$Z = CN$[h]	A	$Z = CN$[i]	90[j]
$R_5 = CH_2Ph$	B	$R_5 = CH_2Ph$ (20)	68
$R_1 = CH_3$; $R_5 = CH_2Ph$ (23)	E	$R_1 = CH_3$; $R_5 = CH_2Ph$ (24)	83
$R_1 = CH_2$-2,4-$(CH_3O)_2Ph$; $R_5 = CH_3$	E	$R_1 = CH_2$-2,4-$(CH_3O)_2Ph$; $R_5 = CH_3$	70
	E	$R_5 = CH_3$; X = NCH_2Ph (27)	95
 (18)	F	 (19)	88

[a] R_n = H, Z = CH_2OH unless otherwise specified. [b] All reactions employed 2.5–3 equiv of oxidant and 9 equiv of pyridine at 25 °C for 30 min unless otherwise specified. [c] (A) alkylation of diethyl malonate with the appropriate dibromide; (B) Pd^0-catalyzed cyclization of monoalkylation product; (C) Pd^0-catalyzed alkylation of a vinyl epoxide then B; (D) reduction of formyl oxepin or oxacene then addition of an alkyllithium; (E) Pd^0-catalyzed alkylation of an allylic cyclic carbonate, then B; (F) 1,4 addition of vinyl Grignard reagent then acylation and reduction. [d] R_n = H, X = O, Z = CHO unless otherwise specified. [e] Yields of isolated chromatographically pure material. [f] A 2:1 mixture (*E*/*Z*) of diastereomers (95% ee) oxidized at 0 °C for 30 min. [g] oxepin exhibited 95% ee (determined by conversion to the SAMP hydrazone). [h] ~1:1 mixture of cyano alcohols rearranged. [i] Only *cis*-cyano aldehyde rearranged, trans was recovered unchanged. [j] Yield based on conversion of *cis*-cyano aldehyde.

transfer) in ~60% yield.[9] Reduction of the diester (±)-**5** with LAH in Et_2O provided the diol (±)-**6** (88%). *Unexpectedly, oxidation of* (±)-**6** *with Dess–Martin periodinane* (**7**)[10] (*2.5–3 equiv*) *buffered with pyridine* (*9 equiv*) *directly provided the formyl dihydrooxepin* (±)-**8** *in 80–90% yield.* Although alternative oxidants (e.g., PDC) were screened, **7** proved optimal (Table I); however, tetrapropylammonium perruthenate (TPAP) is also suitable in some cases.[11] Significantly, alkyl-substituted cyclopropanes lacking the π-conjugating stabilizing group or a cis relationship between the formyl group and olefin failed to undergo rearrangement upon oxidation (Table I), providing evidence that rearrangement is likely concerted.[6]

Two routes to the substrates have been employed (Scheme I): (1) dialkylation of malonate or equivalent anions with bifunctional electrophiles and (2) intramolecular Pd^0-catalyzed cyclization of malonyl allyl acetates or carbonates prepared by alkylation of malonate with differentiated bifunctional electrophiles or by Pd^0-catalyzed alkylation of vinyl epoxides, the latter useful for enantiomerically pure materials.[12,13] Allylic acetate **9** and carbonate **10** were obtained from *R*-(+)-lactic acid via standard methods or via vinyl epoxide **11** available by asymmetric epoxidation of crotyl alcohol.[14] Addition of **9** (95% ee) to a mixture of 2–10 mol % of $Pd(diphos)_2$, prepared in situ from $Pd(OAc)_2$,[12d,15] NaH, and diethyl malonate in THF at 40–50 °C afforded an ~7:1 (*E*/*Z*) mixture of enantiomercially enriched cyclopropanes **5** and **12** (both 85% ee determined by conversion of the related diols to the bis Mosher ester).[16] Diester **12** is also isomeric at the ring center as shown by rearrangement of the derived mixture of diols to the oxepin **8** (85% ee).[17] This stereochemical duality, arising by reaction of the two possible reactive rotamers of **9**, has not been clearly demonstrated for carbon nucleophiles, although it has been observed for heteroatom nucleophiles and follows logically from the postulated mechanistic model as does the potential for loss of enantiomeric purity via isomerization of the π-allyl palladium intermediate.[18,19] Phenyl carbonate **10** provided the best compromise of reactivity and enantioselectivity, affording **5** (95% ee) and **12** (93:7, *E*/*Z*) in 82% yield which were directly converted to dihydrooxepin **8** (95% ee) as above.

Scheme I



The rearrangement tolerates a variety of substitution patterns and stabilizing groups, such as CHO, CN, and SO_2Ph (the latter the least stabilizing group examined), in the substrate. The only limitation encountered involves diol **13** which affords dihydrofuran **14** via the dihydrooxepin (NMR) and, plausibly, the derived tertiary allylic cation since rearrangement of the related diols **15** and **16** to **17** occurs smoothly. In this case, dihydrofuran for-

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(17) Both elements of chirality undergo inversion in **12**, so both **5** and **12** afford the same enantiomer of **8** since rearrangement occurs exclusively via a boat transition state due to strain in the related chair transition state.
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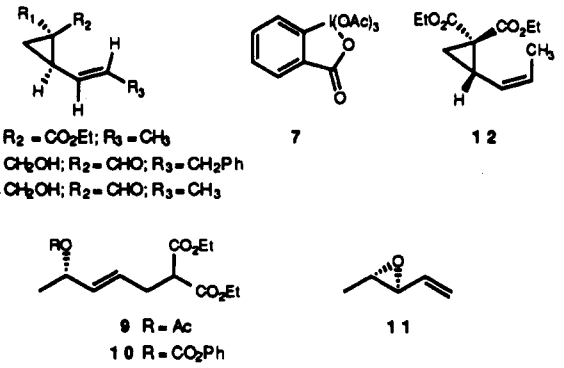
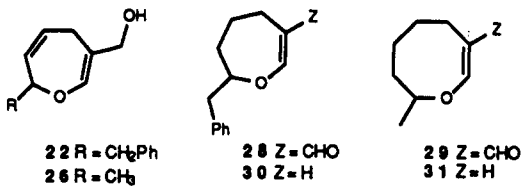


mation is retarded by destabilization of the equivalent allylic cation by the acetoxy group. The rearrangement was extended to the corresponding 4-membered ring systems. Cyclobutane diol **18**, prepared in three steps (57% overall) from methyl 1-cyclobutenecarboxylate,[20,21] upon oxidation afforded the formyl dihydrooxacene **19** (88%).



Selective reduction of the formyl group in **20** with DIBAL-H (or $NaBH_4$) affords an equilibrium mixture (~4:1) of **21** and **22** (94%), and this mixture was converted to **23** via silylation (TBSOTf), addition of CH_3Li/THF, and desilylation. Oxidation then afforded fully substituted vinyl ether **24** (83%). Nitrogen was also introduced by reaction of **25** and **26** (~4:1 from reduction of **8**) with excess benzylamine (THF, 25 °C) followed by oxidation of the unstable imine to afford dihydroazepine **27** (85% overall). Trihydrooxacene **19** and dihydrooxepin **20** are readily reduced with $(Ph_3P)_3RhCl/H_2$[22] (3 atm) to the stable tetrahydro and hexahydro derivatives **28** and **29** (80–90%) which undergo ready decarbonylation at 120 °C (stoichiometric $(Ph_3P)_3RhCl$ in CH_3CN containing MgO, sealed tube) to **30** and **31** (94% and 70%, respectively).[23,24]

Since the stereochemistry of this rearrangement had not been examined, we sought to establish a lower limit on the stereoselectivity. NMR methods cannot exclude as much as 4–5% of the product arising via a stepwise mechanism, so we exploited the reversibility of the rearrangement to enhance the sensitivity of our measurements. Thus, **8** (95% ee) was subjected to four cycles of reduction/reoxidation after which **8** was found to have 95% ee. Since no detectable loss in enantiomeric purity had occurred, ≤1% of the reaction is proceeding via a stepwise pathway.[25] Further studies of this rearrangement and applications to the construction of complex naturally occurring medium ring heterocycles are currently in progress.

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Supplementary Material Available: General experimental procedure for the Dess–Martin oxidation/retro-Claisen rearrangement and characterization data of all new dihydrooxepin, dihydroazepine, and dihydrooxacene compounds (6 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(21) **18**: (1) $CH_3CH{=}CHMgBr$, CuI (0.1 equiv), TMSCl (6 equiv), THF, −78 °C; (2) LDA (1.05 equiv), THF, addition over 1.5 h, −78 °C, then CH_3O_2CCN (2.1 equiv), −78 °C, 2 h; (3) LAH (2.3 equiv), Et_2O, then aqueous base (diol water soluble).

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(24) Catalytic decarbonylation is under study: O'Connor, J. M.; Ma, J. *J. Org. Chem.* **1992**, *57*, 5075.

(25) Calculations show that after four cycles the ee should have declined to ~87.5% if 1% (~80.7% if 2%) of the product arises via a biradical or other mechanism in which facial discrimination in the intermediate(s) is lost.