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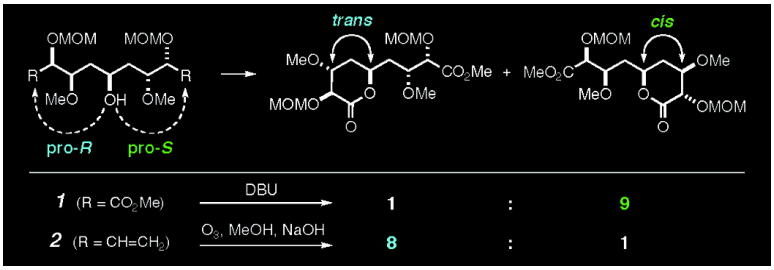
J. Am. Chem. Soc., **2005**, 127 (23), 8256-8257• DOI: 10.1021/ja051604b • Publication Date (Web): 18 May 2005



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Divergent Kinetic Control of Classical versus Ozonolytic Lactonization: Mechanism-Based Diastereoselection

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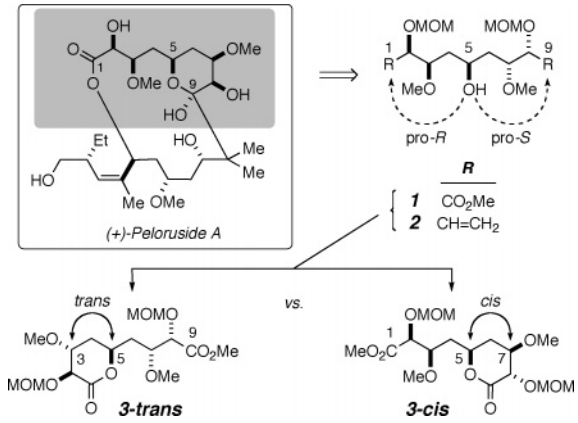
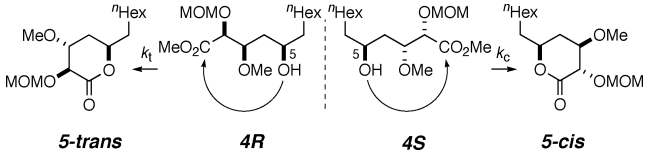
As part of a program with the ultimate goal of a synthesis of peloruside A,[1] we have developed selective and complementary lactonization reactions of substrates **1** and **2** (Scheme 1). Each contains diastereotopic terminal R groups that can be differentiated by engaging the hydroxy group on the chirotopic but nonstereogenic[2] C5 (peloruside numbering, throughout). This would lead to the 3,5-trans-monolactone ester **3-*trans*** [from cyclization to pro-*R* C1] or to the 5,7-cis-monolactone ester **3-*cis*** [to pro-*S* C9]. As we report below, diester **1** gives lactone **3-*cis***; diene **2** gives **3-*trans***. This unexpected complementarity originates from the mechanistically orthogonal pathways that govern the classical (acid- or base-catalyzed) cyclization of **1** versus the ozonolytic lactonization of **2**.

Scheme 1



The pair of C5-epimeric model monoesters **4***R* and **4***S* (*R* and *S* denote the configuration at C5 in **4**, Scheme 2) was studied first. Results of classical lactonizations of a ca. 1:1 mixture of these C5-epimers are presented in Table 1 (entries 1 and 2). Because these are half-models of **1**, it was necessary to monitor the competitive, initial rate ratio (k_{rel}).[3] At full conversion, the **5-*trans***:**5-*cis*** ratio is, of course, 1:1. Acid catalysis (entry 1) gave a moderate level of stereoselectivity. Base-catalyzed cyclization significantly enhanced the preference (ca. 1:18, entry 2) for formation of **5-*cis***.

Scheme 2



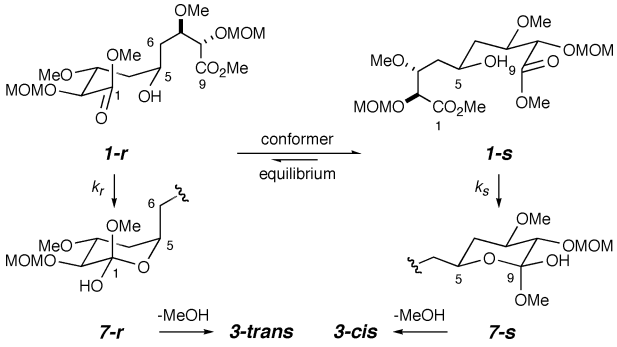
The more complex, peloruside-relevant diester **1** was studied next. Results from models **4***R*/**4***S* proved to be excellent indicators of outcomes with **1**. The level of discrimination of the diastereotopic esters by the C5−OH in **1** is now revealed simply by the product ratio, **3-*trans***:**3-*cis***. Treatment of **1** with TFA was, again, slightly selective for **3-*cis*** (entry 3). Catalysis with DBU gave, again, a greater preponderance of **3-*cis*** (entry 4).[4]

Table 1. Kinetic Lactonization Data for Substrates **4** and **1**

entry	substrate[a]	catalyst[b]	k_{rel} 5-*trans*:5-*cis*[c]	k_{rel} 3-*trans*:3-*cis*[c]
1	**4*R*/4*S***	TFA	1:4[d]	
2	**4*R*/4*S***	DBU	1:18[e]	
3	**1**	TFA[f]		1:2[g]
4	**1**	DBU[f]		1:9[h]

[a] With ca. 8 mM substrate, ambient temp, $CDCl_3$. [b] With ca. 30 mol % catalyst loading. [c] Ratios from ^1H NMR spectra. [d] Breakthrough ratio (ref 3) at ca. 10% conversion (NMR). [e] Breakthrough ratio (ref 3) at ca. 60% conversion (NMR). [f] In the absence of added catalyst, the lactonization rate was negligible. [g] 89% yield (SiO_2 purified). [h] 91% yield (SiO_2 purified).

Scheme 3

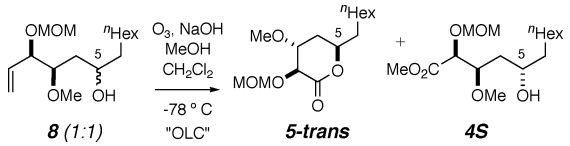


A rationale for these diastereoselectivities is presented in Scheme 3. Two different preclosure *conformations* of **1** are shown as structures **1-*r*** and **1-*s*** (*r* and *s* denote the configuration at the prostereogenic C5 that would result from lactonization). These can lactonize to **3-*trans*** and **3-*cis***, respectively. We focus only on chairlike conformers in which the α-MOM ether groups are equatorial since the carbonyl group in these should be stereoelectronically activated toward nucleophilic attack (cf., α-hetero/Felkin−Ahn considerations)[5] by the C5-hydroxyl.[6] Conformer **1-*s*** should be more highly populated than **1-*r*** since the latter has a quasi-1,3-diaxial interaction between C6 and the ester methoxy group. Under the reasonable assumption that the rate constants k_s and k_r are identical, cyclization to form the tetrahedral intermediate (TI) **7-*s*** will occur more frequently because of the larger population of **1-*s***.[2a,7] Furthermore, the reaction of an ester and a neutral alcohol is known to be governed by general base catalysis.[8] The rate-determining step is, therefore, likely to be *formation* of the TI. If so here, the observed preference for formation of **3-*cis*** over **3-*trans*** (Table 1, entries 3 and 4) reflects the conformational equilibrium between **1-*r*** and **1-*s***. Even if *breakdown* of hemiortho ester TI **7** to give **3** is rate-limiting, a greater pre-equilibrium population of **7-*s*** would account for the observed diastereoselectivity. As they should,

10.1021/ja051604b CCC: $30.25

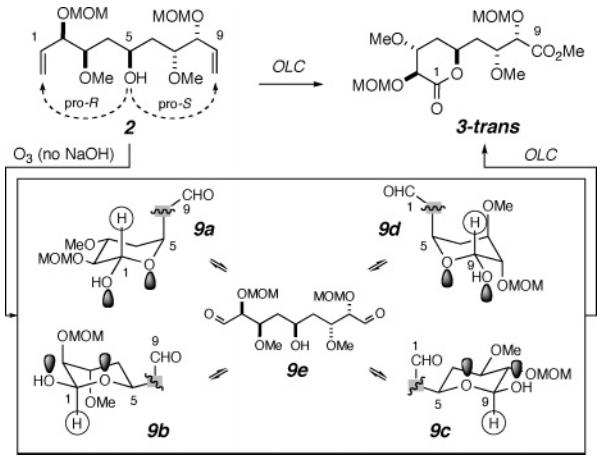
these arguments also explain the results for the mixture of epimeric half-model esters **4*R*** and **4*S*** (Table 1, entries 1 and 2).

We then examined the mechanistically distinct and unorthodox Marshall *ozonolytic esterification* ($R^1CH{=}CH_2 + R^2OH + NaOH + O_3$ to $R^1CO_2R^2$) of the dienol substrate **2**.[9] During this process, a hydrogen is oxidatively removed from a hemiacetal intermediate en route to the ester. When the alkene and hydroxyl group are present in the same substrate, lactonization can occur. We first examined this ozonolytic cleavage using the epimeric mixture of model half-ester alkenols **8**. Treatment of **8** with ozone in a 1.2 M solution of NaOH (10 equiv) in $MeOH/CH_2Cl_2$ (1:1) at −78 °C [hereafter termed the ozonolytic lactonization conditions (OLC)] gave as the major initial products (NMR analysis) lactone **5-*trans*** (from **8*R***) and methyl ester **4*S*** (from **8*S***) (71% combined yield).[10]



On the basis of this surprising selectivity, ozonolytic lactonization of diene **2** was examined. The outcome was complementary to that of the acid- and base-induced lactonizations of the diester **1**. Namely, whereas cyclization of **1** favors **3-*cis***, oxidative lactonization of **2** gave the diastereomeric lactone **3-*trans*** (**3-*trans*:3-*cis*** = 8:1, 65%, combined yield after MPLC, Scheme 4). This reversal of stereoselectivity, in which the pro-*S* alkene in **2** was preferentially converted to the C9-methyl ester and the pro-*R* alkene to the C1-lactone, is intriguing.

Scheme 4



The mechanistic landscape of this reaction is undoubtedly complex. Two control experiments provided considerable insight. When dimethyl ester **1** was subjected to OLC, it was *not* converted to **3**. Therefore, **1** is not an intermediate in the reaction. When diene **2** was subjected to modified OLC in which the NaOH was omitted, the manifold of isolable hemiacetal−aldehydes **9a**−**e** (and no observable **3**) was generated (Scheme 4). Moreover, when that mixture was resubjected to OLC, a similar ratio of **3-*trans*:3-*cis*** was cleanly produced. This indicates that diene **2** is rapidly converted to the dialdehyde equivalent **9**[11] and that the stereodiscriminating event lies during the subsequent conversion of **9** to **3**.

We can only speculate as to the full mechanistic origin of the selective formation of **3-*trans***. Assuming that the critical oxidation[12] of the hemiacetal C−H bond proceeds through one of the four stereoelectronically activated[9c] species **9a**−**d**, likely via the conjugate bases[13] of these hemiacetals, one is faced with the dilemma of explaining why one of **9a** or **9b** (the precursors to **3-*trans***) is oxidized faster than either **9c** or **9d**. A possibility is that species having an adjacent axial C−O bond oriented anti to the hemiacetal C−H (i.e., **9b** or **9d**) may be particularly reactive because of a hyperconjugative captodative effect that would serve to weaken the C−H bond. If so, the reaction would siphon through **9b** since it is certainly more highly populated than **9d**.[7b]

To summarize, complementary, stereoselective, kinetic lactonizations of peloruside A-relevant substrates **1** and **2** (and models **4** and **8**) have been achieved. The inherent versatility provided by the use of mechanistically divergent reaction classes is notable.

Acknowledgment. This investigation was supported by a grant awarded by the DHHS (GM-65597). T.D.R. was partially supported by a predoctoral traineeship from an NIH Chemistry Biology Interface Training Grant (T32-GM-08700).

Supporting Information Available: Spectroscopic characterization data for new compounds and ^1H NMR spectra typically used for determining ratios. This material is available free of charge via the Internet at http://pubs.acs.org.

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(3) This "breakthrough ratio" of **5-*trans*:5-*cis*** was measured at the earliest time, where the less rapidly formed diastereomer could be quantified.

(4) Additional bases and solvents were screened. Weak bases (TEA, ImH, and $^iPr_2NH$) were ineffective. Stronger bases [DBN, DMAP, 1,1,3,3-tetramethylguanidine, and phosphazine base $P_1{-}^t$Bu (Schwesinger, R.; Willaredt, J.; Schlemper, H.; Keller, M.; Schmitt, D.; Fritz. H. *Chem. Ber.* **127**, 2435−2454)] all gave ratios of **3-*trans*:3-*cis*** comparable to that of DBU (in $CDCl_3$, CD_2Cl_2, C_6D_6, or d_8-THF). Substantial differences in reaction rates were observed. For example, DBU is the fastest, but products **3** begin to deteriorate at longer reaction times, probably via α-deprotonation events. Thus, an equilibrium value for **3-*trans*:3-*cis*** has not been observed under basic (or acidic, MOM ether cleavage) conditions.

(5) It is interesting to consider the possibility that Felkin−Ahn factors might be controlling the stereochemical outcome of an addition reaction to a *carboxyl* functional group rather than the usual aldehyde or ketone carbonyl. Ahn, N. T.; Eisenstein, O. *Nouv. J. Chim.* **1977**, *1*, 61−70.

(6) Stereoelectronic factors also dictate that the departing methoxy group occupies an axial site for the collapse of hemiortho esters to lactones, as is the case in **7-*r*** and **7-*s***. See: Deslongchamps, P. In *Stereoelectronic Effects in Organic Chemistry*; Baldwin, J. E., Ed.; Organic Chemistry Series; Pergamon Press: Elmsford, NY, 1983; Vol. 1, pp 54−90.

(7) (a) The following fundamental tenet, surprisingly often overlooked, is always operative: a rate is a rate constant times a concentration (i.e., rate = $k \times$ [A]). (b) The analysis of Curtin−Hammett controlled processes often benefits from breakdown of the competing events into these individual components of rate constant and concentration.

(8) (a) Kilpatrick, M. *J. Am. Chem. Soc.* **1928**, *50*, 2891−2902. (b) Jencks, W. P.; Carriuolo, J. *J. Am. Chem. Soc.* **1961**, *83*, 1743−1750.

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(10) Since **4*S*** rapidly lactonizes upon handling (interestingly, considerably faster than **1**), the yield of purified (and coeluting) **5-*cis*** and **5-*trans*** was determined after complete lactonization of **4*S***.

(11) It is relevant that primary ozonides derived from terminal alkenes bearing allylic ethers cleave regioselectively to α-alkoxy aldehydes and the formaldehyde carbonyl oxide: Kawamura, S.; Yamakoshi, H.; Nojima, M. *J. Org. Chem.* **1996**, *61*, 5953−5958.

(12) The oxidant could be ozone itself or one of the reactive species (such as $O_3^{\bullet-}$, $HO^{\bullet}$, $O^{\bullet-}$) formed by reaction between ozone and hydroxide. Forni, L.; Bahnemann, D.; Hart, E. J. *J. Phys. Chem.* **1982**, *86*, 255−259.

(13) The pK_a of acetaldehyde hydrate in water is 13.5. Bell, R. P.; McTigue, P. T. *J. Chem. Soc.* **1960**, 2983−2994.

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