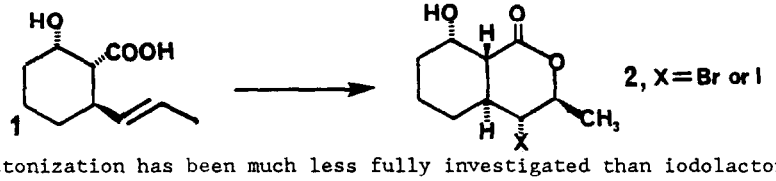
Tetrahedron Letters,Vol.26,No.45,pp 5497-5500,1985 0040-4039/85 $3.00 + .00
Printed in Great Britain

REGIOSELECTIVITY OF THE HALOLACTONIZATION OF γ,δ-UNSATURATED ACIDS

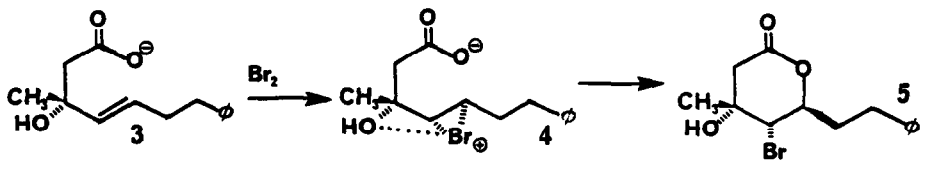
Barry B. Snider* and Madeline I. Johnston
Department of Chemistry, Brandeis University, Waltham, MA 02254

Abstract: Bromolactonization of 4-hexenoic acids gives a greater percentage of δ-lactones than does iodolactonization. Substituents in the 3-position favor the formation of δ-lactones while substituents in the 6-position favor the formation of γ-lactones.

During the course of a total synthesis of (±)-ramulosin, which was carried out as a model study for a projected synthesis of actinobolin, we needed to carry out a halolactonization of the γ,δ-unsaturated acid 1 to obtain the δ-lactone 2.[1] At the outset of our work we were uncertain of our ability to carry out such a transformation since either kinetic[2] or thermodynamic[3] iodolactonization of related γ,δ-unsaturated acids leads to the more stable γ-lactone as the major or exclusive product. As expected, iodolactonization of 1 gave a mixture containing from 0 to 14% of the desired lactone 2.



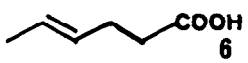
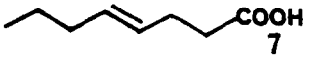
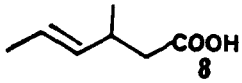
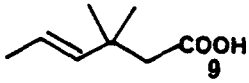
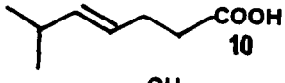
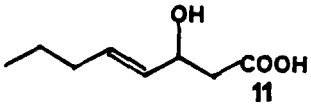
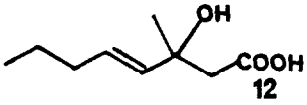
Bromolactonization has been much less fully investigated than iodolactonization, presumably because dibromination is a competing side reaction.[2] Barnett and co-workers have explored the halolactonization of β,γ-unsaturated acids. Originally it appeared that bromolactonization gave the β-lactone and iodolactonization gave the γ-lactone.[4] More recent work indicated that these variations result from differences in procedure, not differences in halogen.[5] Sato et al. reported the regio- and stereospecific bromolactonization of 3 with bromine and sodium bicarbonate in methanol at -78 °C to give 5 in 70% yield with only traces of the other three isomers.[6] They proposed that the stereoselectivity resulted from selective formation of 4, in which the bromonium ion is associated with the hydroxy group, and that the regioselectivity resulted from the inductive electron withdrawal by the hydroxy group which distorts the bromonium ion to favor attack by the nucleophile at the end distant from the hydroxy group because of steric and inductive effects. Fortunately, bromolactoni-



zation of 1 with bromine in methanol as described above gave an 88% yield of a mixture of bromolactones which contained 78% of the desired lactone 2.[1]

These results indicate that there is a substantial difference between iodo- and bromolactonization, and that Sato's rationalization for the selective formation of 5 is incomplete. We therefore embarked on a systematic study of the regioselectivity of the halolactonization of 4-alkenoic acids in which the double bond is trans-1,2-disubstituted so that halolactonization is inherently unbiased. The regioselectivity of the halolactonizations of acids 6-12 are shown in Table I. Iodolactonization was carried out in homogeneous media with I_2/KI and in two-phase media with I_2 in ether/THF.[7] Bromolactonization was carried out with NBS[8] to minimize formation of the dibromide and to prevent ring opening of the unstable δ-lactone.[9] The bromolactonizations of 6-8 were more reproducible in the presence of traces of acetic acid. The procedure of Sato et al.,[6] bromine in methanol, was also explored.

Table I. Halolactonization of γ,δ-Unsaturated Acids.

Acid	Ratio of γ:δ Lactones (% Yield)			
	I_2/KI $NaHCO_3$	I_2 ether/THF $NaHCO_3$	NBS THF AcOH	Br_2 MeOH $NaHCO_3$ -78°C
 6	>20:1 85%	24:1 71%	2.7:1 91%	1:1[a] 46%
 7	>15:1 91%	---	2.7:1 85%	2.7:1[a] 50%
 8	6.5:1 88%	1.5:1 83%	1:1.2 78%	1:1.2 66%
 9	1.1:1 86%	1:1 81%	1:2.4 86%	1:2.5 93%
 10	>9:1 70%	---	>9:1 76%	>9:1 38%
 11	5:1 70%	5:1 76%	2.3:1 92%	2:1 45%
 12	1:3.4 74%	1:3.5 85%	<1:9 93%	<1:9 89%

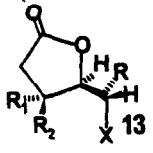
a. The methyl ester resulting from methanolysis of the δ-lactone was obtained.

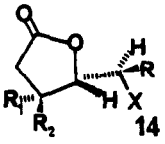
Both the substrate structure and the halolactonization method influence the regiochemistry. In all cases bromolactonization leads to more of the δ-lactone than does iodolactonization. A detailed examination of bromo- and iodoetherification reactions by Williams and

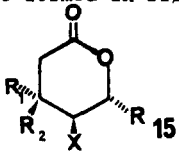
Dubois[10] is helpful in understanding this phenomenon. Second-order rate coefficients have been determined for the haloetherification of a series of alcohols, CH_2=CH-$(CH_2)_n$-OH for n = 1 to 4. For n = 3, in which a tetrahydrofuran is formed, neighboring group rate acceleration is 60 for iodination and 0.7-1.5 for bromination. For n = 4, in which a tetrahydropyran is formed, neighboring group rate acceleration is 8 for iodination and 0.2-0.4 for bromination. These results suggest that the rate determining step in bromoetherification is attack of bromine on the double bond to give a bromonium ion, while the rate determining step in iodoetherification is attack of the hydroxy group on the iodine-double bond complex. Similar differences, which may be operative in halolactonization,[2] could be responsible for the greater amount of δ-lactone in bromolactonization.

Steric effects play an important role in determining the product mixture. Substituents at C_3 hinder attack of the carboxylate at C_4 and favor formation of the δ-lactone, while substitutents at C_6 hinder attack at C_5 and favor formation of the γ-lactone. Contrary to a previous report,[11] 4-hexenoic acid (6) gives almost exclusively the γ-lactone under both iodolactonization conditions. Bromolactonization of 6 with NBS gives 27% of the δ-lactone. Use of bromine in methanol leads to a 1:1 mixture of the γ-lactone and methyl ester derived from ring opening of the unstable δ-lactone.[9] An equal amount of uncyclized addition products are formed under these conditions. Halolactonization of 7, in which an ethyl group has been added to C_6, gives virtually identical results. However, halolactonization of 10, in which two methyl groups have been added to C_6, gives only the γ-lactone. Halolactonization of 8, with a methyl substituent on C_3, gives a greater percentage of δ-lactone than 6 under all conditions, and 9, with two methyl substituents on C_3, gives an even greater percentage of δ-lactone than 8 under all conditions.

Chamberlin has shown that iodolactonization of 3-hydroxy-4-alkenoic acids in a neutral two-phase medium gives the cis-3-hydroxy-4-iodoalkyl-γ-lactone.[7] We therefore chose to examine the regio- and stereochemistry of the halolactonizations of 11 and 12. The γ-lactones were primarily or exclusively the cis-γ-lactones 13b and 13c as reported by Chamberlin.[7] (See Table II) The δ-lactones, which are formed in significant amounts from


13


14


15

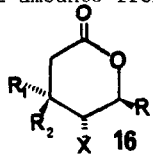

16

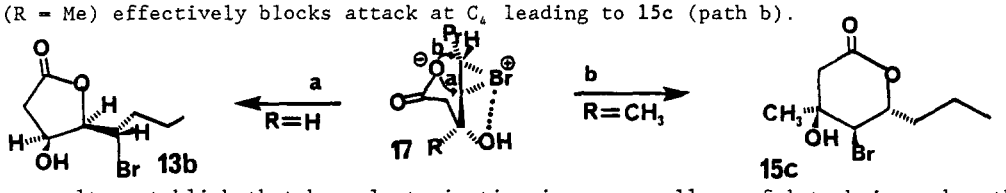
Table II. Stereochemistry of the Halolactonization of 8, 11 and 12.

Substrate	Reaction conditions	% yield of 13	14	15	16
a R = Me, R_1 = H, R_2 = Me	X = I, I_2 ether	36	14	4	29
(from 8)	X = Br, NBS	22	14	5	37
b R = Pr, R_1 = H, R_2 = OH	X = I, I_2 ether	60	4	8	4
(from 11)	X = Br, NBS	47	0	29	0
c R = Pr, R_1 = Me, R_2 = OH	X = I, I_2 ether	19	0	66	0
(from 12)	X = Br, NBS	9	0	84	0

iodolactonization of 12 and bromolactonization of 11 and 12, also have the hydroxy and halo groups in a cis relationship (15b or 15c) as previously reported for 3.[6] The γ-lactone obtained from 8, with a methyl group at C_3, is also predominantly the cis isomer 13a as

reported in a related system.[12] However, the predominant δ-lactone formed from 8 is the isomer 16a with a trans relationship between the methyl and halide groups.

The effect of substituents at C_3 is puzzling. Comparison of the halolactonizations of 8 and 9 leads one to believe that introduction of the second methyl group has only a modest directing effect favoring the δ-lactone. On the other hand, comparison of the halolactonization of 11 and 12 suggests that the methyl group plays a crucial role. Alternatively this can be expressed as follows: 8 gives more δ-lactone than 11, while the methyl homolog 9 gives less δ-lactone than the methyl homolog 12. It is possible that coordination of the hydroxy group to the halonium ion in the halolactonization of 11 and 12 gives the intermediate 17, which will lead to a lactone with the observed cis stereochemistry. If R = H, attack at C_4 (path a) is not hindered so that 13b is the major product. Introduction of a methyl group at C_3 in 17 (R = Me) effectively blocks attack at C_4 leading to 15c (path b).



These results establish that bromolactonization is a generally useful technique when the δ-lactone is desired. The studies with 6-12 delineate those features which control the ring size of the lactone.

Acknowledgment: The authors thank the National Institutes of Health for generous financial support.

References and Notes.

1. Cordova, R.; Snider, B. B. Tetrahedron Lett. 1984, 25, 2945.
2. For reviews see: Dowle, M. D.; Davies, D. I. Chem. Soc. Rev. 1979, 171. Staninets, V. I.; Shilov, E. A. Russ. Chem. Rev. (Engl. Transl.) 1971, 40, 272. Bartlett, P. A. in "Asymmetric Synthesis, Vol.3" Morrison, J. D., Ed.; Academic Press: Orlando, Florida, 1984; pp 416-430.
3. Bartlett, P. A.; Myerson, J. J. Am. Chem. Soc. 1978, 100, 3950.
4. Barnett, W. E.; McKenna, J. C. Tetrahedron Lett. 1971, 2595.
5. Barnett, W. E.; Sohn, W. H. Tetrahedron Lett. 1972, 1777.
6. Sato, A.; Ogiso, A.; Noguchi, H.; Mitsui, S.; Kaneko, I.; Shimada, Y. Chem. Pharm. Bull. 1980, 28, 1509.
7. Chamberlin, A. R.; Dezube, M.; Dussault, P.; McMills, M. C. J. Am. Chem. Soc. 1983, 105, 5819.
8. Jew, S-s.; Terashima, S.; Koga, K. Tetrahedron, 1979, 35, 2337and 2345.
9. The δ-lactone is thermodynamically less stable than the γ-lactone and hydrolyzed 22 times as rapidly in base and 170 times as rapidly in acid. See: Brown, H. C.; Brewster, J. H.; Shechter, H. J. Am. Chem. Soc. 1954, 76, 467 and references cited therein.
10. Williams, D. L. H.; Bienvenüe-Goetz, E.; Dubois, J. E. J. Chem. Soc.(B) 1969, 517.
11. Staninets, V. I.; Shilov, E. A.; Koryak, E. B. J. Org. Chem. USSR 1968, 4, 259.
12. Günther, H. J.; Guntrum, E.; Jäger, V. Justus Liebigs Ann. Chem. 1984, 15.

(Received in USA 2 August 1985)