Tetrahedron Letters, Vol. 34, No. 49, pp. 7899-7902, 1993
Printed in Great Britain

0040-4039/93 $6.00 + .0
Pergamon Press Ltd

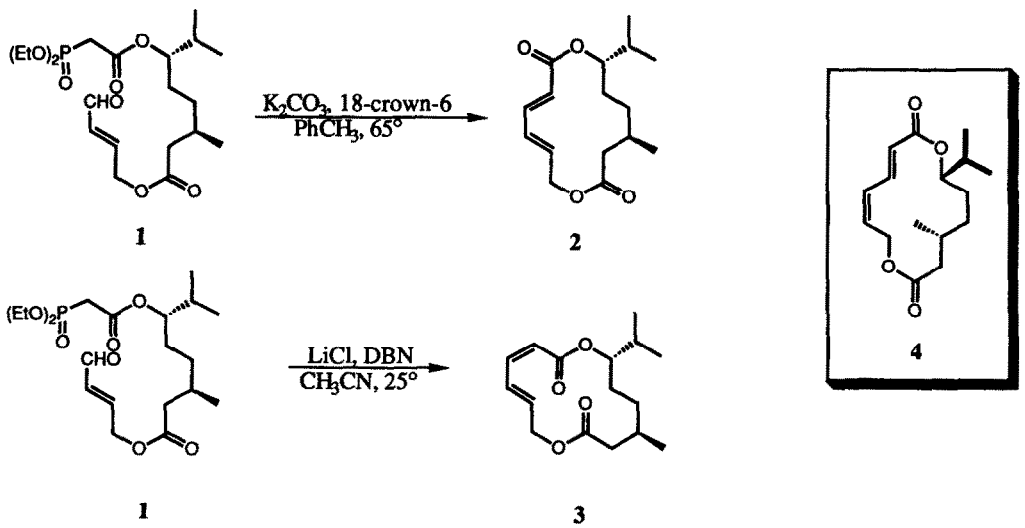
Stereodivergence in An Intramolecular Horner-Emmons Macrocyclization. Effect of Reaction Conditions on Product Distribution

Michelle L. Morin-Fox and Mark A. Lipton*

Department of Chemistry, Purdue University, West Lafayette, IN 47907-1393

Abstract: In a macrocyclization by intramolecular Horner-Emmons reaction, it has been shown that employment of K_2CO_3/18-crown-6 leads to formation of an *E*-disubstituted olefin as the major isomer whereas the use of LiCl/DBN affords the *Z*-isomer as the major product. Changes were made to the base, solvent and reaction temperature in an attempt to identify the factors which influence the stereochemical outcome of the cyclization. The results of this study suggest that the sterodivergence arises from a change in the rate-determining step of the reaction, posssibly attributable to the strength of the base employed. Such an effect has been previously invoked in the intermolecular Horner-Emmons reaction to account for *Z*-selective conditions.

Since its introduction in 1978, the intramolecular Horner-Emmons olefination has become an increasingly popular method for macrocyclization.[1-6] Since these cyclizations are typically carried out on highly functionalized acyclic precursors, increasingly mild conditions have been sought to minimize side-reactions, leading to the development of a number of different conditions.[3,4] Recently, during a synthesis of the strained macrocyclic diene **2**, we had occasion to employ such a cyclization. While our first attempt (Table 1, entry 1) led to the desired (*E,E*) isomer **2** as the major product, the use of conditions developed by Masamune and Roush[4] (LiCl,DBN,CH_3CN) resulted in formation of the (*Z,E*) isomer **3** as the major product (entry 6).[7] In both cases, small amounts of the (*E,Z*) isomer **4** were also observed, most likely arising from isomerization of **1** to the *Z*-enal prior to cyclization.



1 **2** **1** **3** **4**

In retrospect, the formation of the (*Z,E*) isomer should not have been surprising. While it has been observed previously that intramolecular Horner-Emmons reactions afford a kinetic product distribution,[5] the macrocycles obtained have typically been relatively unstrained. In the present study, molecular mechanics calculations predict the desired (*E,E*) isomer **2** to be considerably more strained (>10 kcal/mol) than the (*Z,E*) isomer **3** despite the strain inherent to a *cis*-disubstituted olefin; consequently one would expect **3** to predominate under conditions leading to a thermodynamic product distribution. Indeed, the more surprising result is that one can obtain the more strained isomer **2** as the major product using relatively mild reaction conditions. This discovery led to further exploration of the effects of solvent, temperature and counterion on product distribution (Table 1).

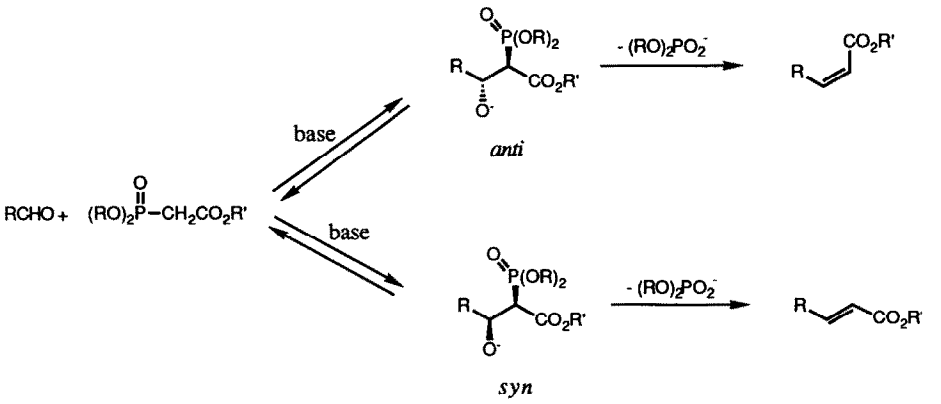
Table 1. Conditions employed for the macrocyclization of **1**[a]

Entry	Base (equivalents)	Solvent	Temp	Isolated yield (%)	
				2	**3**
1	K_2CO_3 (6) / 18-crown-6 (12)	toluene	65°	62	12
2	K_2CO_3 (6) / 18-crown-6 (12)	toluene	80°	[b]	[b]
3	K_2CO_3 (6) / 18-crown-6 (12)	THF	65°	0	0
4	KHMDS(1.1) / 18-crown-6 (3)	toluene	25°	49	3
5	KHMDS(1.1) / 18-crown-6 (3)	CH_3CN	25°	22	8
6	DBN (10) / LiCl (10)	CH_3CN	25°	<3	53
7	NaH (1)	THF	35°	51	10

[a] All reactions run for 12 hours and resulted in consumption of starting material
[b] Roughly equal amounts of **2**, **3** and the (*E,Z*) isomer **4** were obtained

When potassium carbonate/18-crown-6 was used as the base (entries 1-3) the reaction proved quite sensitive to changes in temperature and solvent. Temperatures below 60° resulted in slower reaction rates, but above 70° an erosion in stereoselectivity was seen, possibly due to isomerization of the initially formed (*E,E*) diene. Even more dramatically, when the solvent was changed from toluene to THF (entry 3) the reaction failed to afford any macrocyclic products. Changing the base from carbonate to hexamethyldisilazide (entries 4-5) gave qualitatively similar results, even when the solvent was changed from toluene to the relatively polar acetonitrile; likewise, changing the base to sodium hydride and eliminating the 18-crown-6 (entry 6) still gave results quite close to those obtained with K_2CO_3/18-crown-6. All of these results contrast sharply with those obtained using DBN/LiCl in acetonitrile (entry 6). Although the role of solvent cannot be eliminated altogether, it is presumed that the change in stereoselectivity is due to the weaker basicity of the reagents employed in entry 6.

Intermolecular examples of the reversal of stereoselectivity in Horner-Emmons olefinations are well-known,[8,9,10] and have been attributed to changes in the rate of decomposition of the intermediate alkoxide.[11] *Z*-Selective Horner-Emmons olefinations typically result from the use of a potassium counterion in conjunction with 18-crown-6 to enhance the nucleophilicity of the intermediate alkoxide.[8] It is presumed that a more nucleophilic alkoxide results in the acceleration of phosphate elimination, thus making the initial aldol step rate-determining (Scheme I). This interpretation is based on a presumed product-like transition state in the second step and tacitly assumes an *anti*-selective aldol step.[10]



Scheme I

Application of this reasoning to the intramolecular Horner-Emmons reaction of **1** leads to the conclusion that employment of K_2CO_3/18-crown-6 results in a rate-determining first step. This conclusion is in accord with the assumption of a high entropic barrier to macrocyclization as well as the knowledge that the product-like transition state of the second step should be lower in energy for the *anti* aldol adduct. Intriguingly, the kinetic aldol product in the cyclization of **1** would appear to be a *syn* isomer. While interpretations of this observation are tenuous at best, it seems most likely that the added constraint of macrocyclization changes the energies (and possibly the structures) of the aldol transition states. It appears from examination of the data in Table 1 that, in contrast to the intermolecular case, most conditions result in a relatively fast phosphate elimination and only the use of the weakly basic conditions of DBN/LiCl leads to the more stable alkene.

One remaining question is why only those conditions developed by Masamune and Roush lead to the thermodynamic product. The most likely answer invokes an increased lifetime of the intermediate adducts, perhaps arising from the protonation of the alkoxides by the conjugate acid of DBN, allowing the comparatively slow retro-aldol equilibration step to occur. While the generality of these findings to other macrocyclic systems is unclear at present, it is worthy of note that considerable ring strain can be introduced via an intramolecular Horner-Emmons cyclization and that drastic changes in the product distribution can be effected by relatively modest changes in reaction conditions.

Acknowledgements. Acknowledgement is made to the Donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research. Professors Philip Fuchs and Scott Rychnovsky are thanked for helpful discussions and advice.

REFERENCES AND NOTES

1. Burri, K.F.; Cardone, R.A.; Chen, W.Y.; Rosen, P. *J. Am. Chem. Soc* **1978**, *100*, 7069-7071.
2. (a)Stork, G.; Nakamura, E. *J. Org. Chem* **1979**, *44*, 4010-4011. (b)Nicolaou, K.C.; Seitz, S.P.; Pavia, M.R.; Petasis, N.A. *J. Org. Chem* **1979**, *44*, 4011-4013.
3. Nicolaou, K.C.; Seitz, S.P.; Pavia, M.R. *J. Am Chem Soc.* **1982**, *104*, 2030-2031.

4. (a)Blanchette, M.A.; Choy, W.; Davis, J.T.; Essenfeld, A.P.; Masamune, S.; Roush, W.R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183-2186. (b)Tius, M.A.; Fauq, A.H. *J. Am. Chem. Soc.* **1986**, *108*, 1035-1039.

5. (a)Marshall, J.A.; DeHoff, B.S. *Tetrahedron Lett.* **1986**, *27*, 4873-4876. (b)Marhsall, J.A.; DeHoff, B.S *Tetrahedron* **1987**, *43*, 4849-4860.

6. (a)Meyers, A.I.; Comins, D.L.; Roland, D.M.; Henning, R.; Shimizu, K. *J. Am. Chem. Soc.* **1979**, *101*, 7104-7105. (b)Still, W.C.; Gennari, C.; Noguez, J.A.; Pearson, D.A. *J. Am. Chem. Soc.* **1984**, *106*, 260-262. (c)Novack, V.J.; Still, W.C. *J. Am. Chem. Soc.* **1984**, *106*, 1148-1149. (d)Nicolaou, K.C.; Chakraborty, T.K.; Daines, R.A.; Simpkins, N. S.; *J. Chem . Soc. Chem. Commun.* **1986**, 413-416. (e)Kodama, M. Shibara, Y.; Sumitomo, H.; Fukuzumi, K.; Minami, H.; Miyamoto, Y. *Tetrahedron Lett.* **1986**, *27*, 2157-2160. (f)Somers, P.K; Wandless, T. J.; Schreiber, S.L. *J. Am. Chem. Soc.* **1991**, *113*, 8045-8056. (g)Smith, III, A.B.; Rano, A.T.; Chida, N.; Sulikowski, G.A.; Wood, J.L. *J. Am. Chem. Soc.* **1992**, *114*, 8008-8022. (h) Nakajima, N. and Yonemitsu, O. Conformational Control in Macrolide Synthesis. In *Studies in Natural Products Chemistry, Vol. 11*, Atta-ur-Rahman Ed. Elsevier: Amsterdam, 1992; pp. 151-180 and references therein.

7. Macrocycles **2-4** were characterized by ^{1}H- and ^{13}C-NMR and mass spectrometry

1 - ^{1}H (300 MHz, $CDCl_3$): δ9.58 (d, 1H, J=7.8), 6.82 (dt, 1H, J=15.8, 0.8), 6.25 (ddt, 1H, J=15.8, 7.7, 1.1), 4.85 (dd, 2H, J=4.3, 1.9), 4.76 (m, 1H), 4.16 (m, 4H), 2.95 (d, 2H, J=21.7), 2.40 (dd,1H, J=15.0, 5.7), 2.18 (dd, 1H), 1.95 (m, 1H), 1.84 (m, 1H), 1.53 (m, 2H), 1.33 (t, 6H, J=7.1), 1.18 (m, 2H), 0.85 (d, 3H, J=6.6), 0.81 (d, 6H, J=6.8); ^{13}C (75 MHz, $CDCl_3$) 192..8, 172.1, 165.6, 149.7, 132.1, 80.0, 76.8, 62.55, 62.47, 62.2, 41.2, 33.5, 32.3, 31.2, 30.3, 28.4, 18.5, 17.3, 16.4, 16.3

2 - ^{1}H (300 MHz, $CDCl_3$) δ6.87 (dd, 1H, J=15.7, 9.9), 6.58 (dd, 1H, J=15.5, 9.9), 6.30 (d, 1H, J=15.8), 6.08 (m, 1H), 5.08 (dd, 1H, J=10.4, 9.2), 4.22 (dd, 1H, J=10.6, 6.1), 3.90 (m, 1H), 2.29 (dd, 1H, J=2.6, 2.0), 1.87 (m, 2H), 1.53 (m, 2H), 1.26 (m, 1H), 1.13 (m, 1H), 0.94 (d, 3H, J=6.5), 0.91 (d, 6H, J=6.6), 0.84 (m, 1H); ^{13}C (75 MHz, $CDCl_3$) δ172.8, 156.6, 140.9, 136.6, 131.7, 123.8, 85.6, 76.7, 62.6, 43.4, 33.9, 33.5, 33.2, 32.6, 18.8, 18.1

3 - ^{1}H (300 MHz, $CDCl_3$) δ7.1 (br. dd, 1H, J=17.2, 9.6), 6.55 (t, 1H, J=11.4), 6.01 (dt, 1H, J=15.4, 2.5), 5.67 (d, 1H, J=11.4), 5.0 (br. dd, 1H, J=17.2, 4.6), 4.74 (m, 1H), 4.6 (br. dd, J=16.7, 6.2), 2.59 (dd, 1H, J=14.6, 3.4), 2.32 (d, 1H, J=9.2), 1.2-2.2 (m, 8H), 1.11 (d, 3H, J=6.8), 0.8-1.0 (m, 6H); ^{13}C (50 MHz, $CDCl_3$) δ 173.9, 166.8, 143.9, 142.3, 127.0, 118.8, 63.4, 62.9, 42.4, 32.9, 31.8, 30.9, 29.1, 20.3, 19.0, 18.1; CIMS (isobutane) *m/z* 281 (MH^+), 171 (MH^+-$C_6H_6O_2$)

4 - ^{1}H (200 MHz, $CDCl_3$) δ7.68 (dd, 1H, J=15.6, 11.8), 6.35 (dt, 1H, J=2.4, 11.2), 5.95 (m, 1H), 5.80 (d, 1H, J=15.6), 5.11 (m, 1H), 4.66 (m, 1H), 4.51 (dd, 1H, J=14.8, 6.2), 2.12-2.32 (m, 3H), 1.94 (m, 1H), 1.49-1.66 (m, 3H), 1.28 (m, 1H), 0.97 (d, 3H, J=6.3), 0.92 (d, 3H, J=2.3), 0.89 (d, 3H, J=2.1); ^{13}C (50 MHz, $CDCl_3$) δ 173.5, 167.0, 139.1, 133.6, 126.7, 123.1, 78.7, 62.6, 42.1, 32.7, 31.6, 30.7, 20.1, 19.4, 19.0, 17.8; CIMS (isobutane) *m/z* 281 (MH^+), 171 (MH^+-$C_6H_6O_2$)

8. Still, W.C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405-4408.

9. Marshall, J.A.; DeHoff, B.S.; Cleary, D.G. *J. Org. Chem.* **1986**, *51*, 1735-41.

10. Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873-3888.

11. Redjal, A.; Seyden-Penne, J. *Tetrahedron Lett.* **1974**, *15*, 1733-1736.

(Received in USA 27 July 1993; accepted 1 October 1993)