Radical Cyclization of β-Alkoxymethacrylates: Expedient Synthesis of (+)-Methyl Nonactate

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Eun Lee* and Seung Jib Choi

Department of Chemistry, College of Natural Sciences, Seoul National University, Seoul 151-742, Korea

eunlee@snu.ac.kr

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ABSTRACT



Radical cyclization of the β -alkoxymethacrylate obtained from 5-benzyloxy-1-iodohexan-3-ol led to the stereoselective preparation of the benzyl ether of (+)-methyl nonactate, demonstrating "2,5-cis" selectivity in the radical cyclization step in forming a tetrahydrofuran ring system and "threo" selectivity in the hydrogen abstraction step.

Radical cyclization of β -alkoxyacrylates is a highly useful method for stereoselective preparation of cis-2,5-substituted tetrahydrofurans and cis-2,6-substituted tetrahydropyrans.¹ Radical cyclization reactions of different β -alkoxyacrylates were employed as key steps in the total synthesis of dactomelynes,² kumausyne,³ and kumausallene,⁴ demonstrating the generality of these reactions.⁵

One of the more difficult problems concerning these types of reactions would be the control of the stereoselectivity outside of the oxacycle when α -substituted β -alkoxyacrylates



are employed in the radical cyclization (Scheme 1). In this context, reported work⁶ by Guindon and co-workers on radical-mediated reduction of α -halo carboxylates is highly pertinent; it is reported that radical-mediated reduction of α -substituted β -alkoxy- α -halo carboxylates resulted in high threo selectivity. Theoretical studies^{6b} indicate that the stereoselectivity originates primarily from the preference for "outside alkoxy" conformation of the intermediate radical species. In this model, both allylic 1,3-strain and electrostatic repulsions are minimized, and an early transition state for hydrogen abstraction in which attack occurs from the least hindered face of the radical is apparently operative.

We were thus encouraged that the "2,5-cis" selectivity encountered in the β -alkoxyacrylate radical cyclization

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⁽⁵⁾ More recently, the scope of radical cyclization reactions of β -alkoxyacrylates expanded considerably; see the following references: (a) Use of acyl radicals: Evans, P. A.; Roseman, J. D.; Garber, L. T. J. Org. Chem. **1996**, 61, 4880 and references therein. (b) Formation of oxepanes in the presence of a Lewis acid: Yuasa, Y.; Sato, W.; Shibuya, S. Synth. Commun. **1997**, 27, 573. (c) Photosensitized electron-transfer cyclization of aldehydes: Pandey, G.; Hajra, S.; Ghorai, M. K.; Kumar, R. J. Org. Chem. **1997**, 62, 5966. (d) Sml₂-induced cyclization of aldehydes: Hori, N.; Matsukura, H.; Matsuo, G.; Nakata, T. Tetrahedron Lett. **1999**, 40, 2811. (e) O-Linked oxepane synthesis: Sasaki, M.; Noguchi, T.; Tachibana, K. Tetrahedron Lett. **1999**, 40, 1337.

^{(6) (}a) Guindon, Y.; Lavallée, J.-F.; Boisvert, L.; Chabot, C.; Delorme, D.; Yoakim, C.; Hall, D.; Lemieux, R.; Simoneau, B. *Tetrahedron Lett.* **1991**, *32*, 27. (b) Durkin, K.; Liotta, D.; Rancourt, J.; Lavallée, J.-F.; Boisvert, L.; Guindon, Y. J. Am. Chem. Soc. **1992**, *114*, 4912.

reactions in forming tetrahydrofuranyl ring systems may be coupled with the "threo" selectivity at the exocyclic α sites, which will offer easy access to a number of oxacyclic natural products on the condition that appropriately α -substituted β -alkoxyacrylates are prepared with relative ease. Herein, we wish to describe results of our recent efforts along these directions, which resulted in a short synthesis of (+)-methyl nonactate.⁷

(*R*)-3-Benzyloxybutanal(1)⁸ was treated with allyltrimethylsilane in the presence of titanium tetrachloride according to Reetz's procedure⁹ to give the alcohol **2**. It was converted into the tosylate **3** of 5-benzyloxyhexane-1,3-diol by ozonolysis, NaBH₄ reduction, and selective tosylation of the primary hydroxy group. When the tosylate **3** was reacted with excess methyl 3,3-dimethoxy-2-methylpropanoate(**4**)¹⁰ in benzene under reflux in the presence of pyridinium *p*-toluenesulfonate, conversion to the corresponding β -alkoxymethacrylate was reasonably efficient. The radical cyclization precursor **5** was then obtained via routine iodide substitution (Scheme 2).



Cyclization of **5** was studied under different reaction conditions. A chromatographically separable 9:1 mixture of

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the three product **6** and the erythro product **7** was obtained when the substrate **5** was allowed to react with tributylstannane in the presence of triethylborane and air in toluene at -20 °C. At -78 °C, the hydride abstraction became a little more selective, producing an 11:1 mixture of **6** and **7**. The best result was obtained when tris(trimethylsilyl)silane was employed as the hydride source as the reaction in toluene at -20 °C resulting in an almost exclusive formation of the product **6**. The reaction of **5** with tributylstannane in dichloromethane at -20 °C proceeded to yield a 4:1 mixture of **6** and **7**. Addition of magnesium bromide did not alter the ratio of the products.¹¹ Finally, hydrogenolysis of the benzyloxy group in **6** proceeded uneventfully to yield (+)methyl nonactate(**8**)¹² in high yield (Scheme 3).



The stereoselectivity observed in the key step may be rationalized by invoking the conformational preference of the intermediate radical as discussed above. Future investigations from these laboratories will focus on further developments in stereoselective radical reactions as applied in natural product synthesis.

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⁽⁷⁾ A large number of reports concern the synthesis of nonactic acid derivatives. Three of the more recent ones are as follows: (a) Lee, J. Y.; Kim, B. H. *Tetrahedron* **1996**, *52*, 571. (b) Mandville, G.; Girad, C.; Bloch, R. *Tetrahedron* **1997**, *53*, 17079. (c) Meiners, U.; Cramer, E.; Frölich, R.; Wibbeling, B.; Metz, P. *Eur. J. Org. Chem.* **1998**, 2073.

^{(8) (}a) Mahler, U.; Devant, R. M.; Braun, M. Chem. Ber. **1988**, 121, 2035. (b) Widmer, U. Synthesis **1987**, 568.

^{(11) &}quot;Erythro" selectivity was reported for chelation-controlled reductions of α -substituted β -alkoxy- α -iodo carboxylates in the presence of Lewis acids: Guindon, Y.; Lavallée, J.-F.; Llinas-Brunet, M.; Horner, G.; Rancourt, J. J. Am. Chem. Soc. **1991**, 113, 9701. This selectivity originates from reactions of chelated forms of the substrate α -iodo carboxylates. Obviously, the α -carbonyl radicals obtained from the cyclization step engage in hydrogen abstraction oblivious to the Lewis acid in our case.

⁽¹²⁾ The synthetic sample exhibited spectroscopic characteristics identical to those reported in the literature: $[\alpha]^{22}_{D} = +22.2$ (*c* 0.11, CHCl₃) (lit.^{7b} $[\alpha]^{20}_{D} = +21.8$ (*c* 1.04, CHCl₃)).