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The Influence of Substituents at Prochiral Centers on the Stereoselectivity of Enolate Radicals

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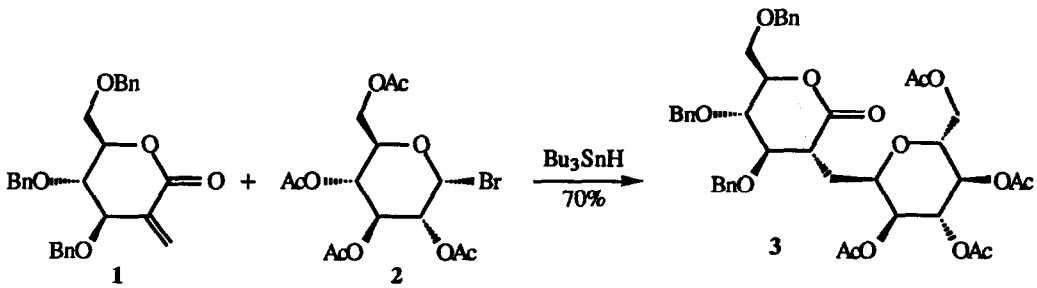
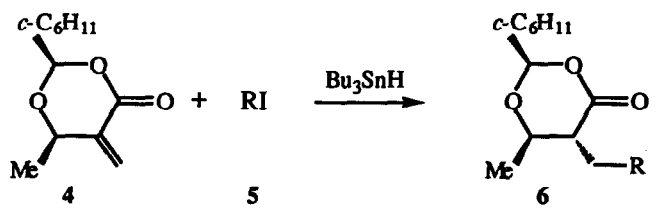
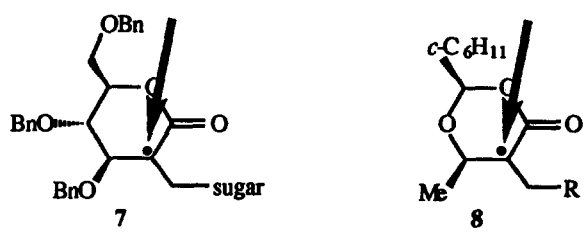
Abstract: *Increasing bulk of substituent R at the prochiral center of radicals* **10** *and* **13** *reverses the stereochemistry of the reaction. This effect is caused by the interaction between the groups at the stereogenic and the prochiral center.*

Our studies on the synthesis of C-disaccharides have shown that the radical reaction between carbohydrates **1** and **2** leads exclusively to lactone **3**.[1] Analogous radical reactions with radical trap **4** and radical precursor **5** gave lactone **6** stereoselectively.[2]



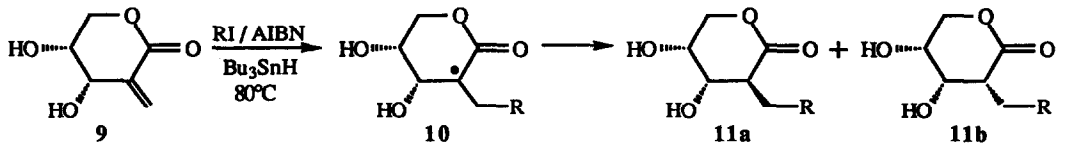


R = C_8H_{17} (49%); *c*-C_6H_{11} (71%); *t*-C_4H_9 (97%)

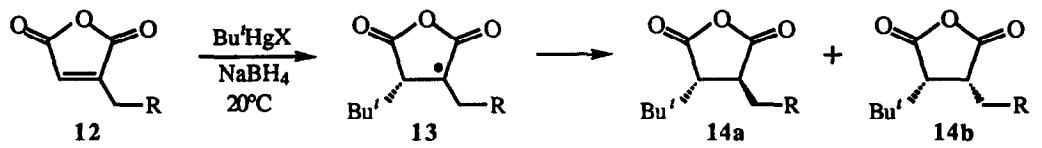


These results are surprising, because the intermediate enolate radicals **7** and **8** are attacked by Bu_3SnH *cis* to the adjacent BnO- and Me-group, respectively. We assumed[2] that in analogy to cyclic enolate anions[3] the prochiral center at the cyclic enolate radical could influence the

stereochemistry because of A-strain[4] effects. According to this suggestion the shielding effect of the groups at the prochiral center in **7** and **8** is more efficient than that of BnO- and Me-substituents at the stereogenic center. In order to prove this model, we have carried out experiments with radicals **10** and **13** where product mixtures arise and varied the bulk of substituents R at the exocyclic methylene group. The radicals were generated *via* addition reactions to alkenes **9** and **12**. Subsequent H-abstraction yielded products **11a+11b** and **14a+14b**, respectively.[5]

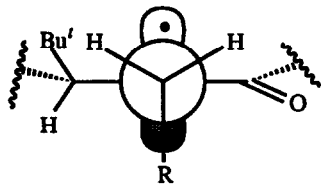


R	*n*-C_6H_{13}	*c*-C_6H_{11}	*t*-C_4H_9
11a : 11b (yield)	40 : 60 (65%)	60 : 40 (80%)	85 : 15 (50%)



R	H	CH_3	*c*-C_6H_{11}
14a : 14b (yield)	8 : 92 (87%)	15 : 85 (71%)	70 : 30 (90%)

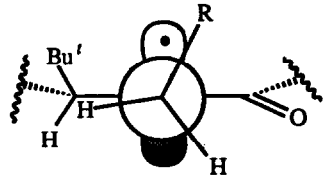
With small substituents (R=H, CH_3, *n*-C_6H_{13}) at the methylene group of radicals **10** and **13**, respectively, H-abstraction occurs *trans* to the OH or *t*-C_4H_9 substituent at the stereogenic center. But with larger groups at the prochiral center (R=*c*-C_6H_{11}, *t*-C_4H_9) the *cis*-reaction dominates. In order to understand this inversion of the stereoselectivity with increase of the bulk of the substituent R, we carried out calculations of radical **13** (R=CH_3, *t*-C_4H_9).[6] For R=CH_3 the two lowest energy conformers **13a** and **13b** have the same energy. But with R=*t*-C_4H_9 conformer **13a**, where the substituents at the chiral and prochiral centers are *anti* to each other is 5 kcal/mol more stable than the *syn*-conformer **13b**. Thus, increase of the bulk of the substituents favors the *anti*-conformer **13a** in which the shielding effect of group R is so efficient that H-abstraction *cis* to the *t*-C_4H_9 group at the stereogenic center can result (**13** → **14a**). In fact, *ab initio* and AM1 calculations demonstrate that transition structure **15** is by more than 4 kcal/mol the lowest transition state.[7]



13a

R : CH_3 = 0.2 kcal/mol

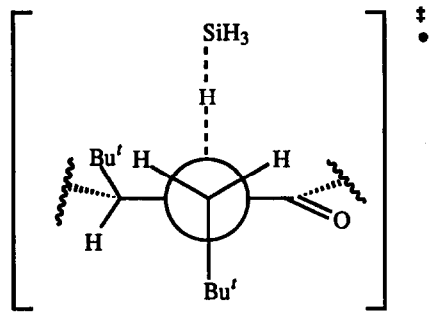
R : *t*-C_4H_9 ≡ 0.0 kcal/mol



13b

R : CH_3 ≡ 0.0 kcal/mol

R : *t*-C_4H_9 = 5.3 kcal/mol



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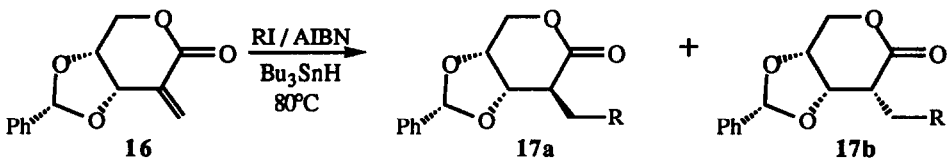
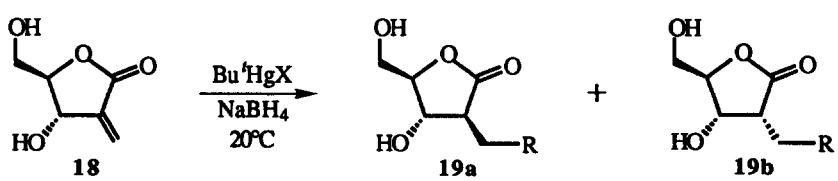
This influence of bulky substituents at the prochiral center can play a role even in cases where the shielding effect of the chiral center controls the stereoselectivity. Thus, addition reaction at alkene **16** gives mainly *cis*-product **17b**, whereas alkene **18** yields predominantly *trans*-product **19a**.[5] But in both cases *cis*-abstraction of H-atoms (formation of *trans*-products) increases with growing bulk of the alkyl group R.



16 **17a** **17b**

R: *n*-C_6H_{13} (**17a**:**17b** = 30:70; 85%) R: *t*-C_4H_9 (**17a**:**17b** = 35:65; 50%)



18 **19a** **19b**

R: *n*-C_6H_{13} (**19a**:**19b** = 85:15; 94%) R: *t*-C_4H_9 (**19a**:**19b** = 95:5; 82%)

Conclusion: Substituents R at the prochiral center exert important effects on the stereoselectivity of cyclic enolate radicals. With bulky groups *anti*-conformations are adopted preferentially. They promote radical attack *cis* to the shielding substituent at the stereogenic center.

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References and Notes

1. B. Giese, T. Witzel, *Angew.Chem.* **1986**, *98*, 459; *Angew.Chem.Int.Ed.Engl.* **1986**, *25*, 450. B. Giese, M. Hock, C. Lamberth, R.R. Schmidt, *Tetrahedron Lett.* **1988**, *29*, 1375.
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5. For the reaction conditions and the product analysis see ref.1 and B. Giese, G. Kretzschmar, *Chem.Ber.* **1984**, *117*, 3175.
6. All energy differences are given from ab initio single point calculations at UHF/6-31G*//UAM1 which were done using the program package Gaussian92, Revision C, M. J. Frisch, G. W. Trucks, M. Head-Gordon, P. M. W. Gill, M. W. Wong, J. B. Foresman, B. G. Johnson, H. B. Schlegel, M. A. Robb, E. S. Replogle, R. Gomperts, J. L. Andres, K. Raghavachari, J. S. Binkley, C. Gonzalez, R. L. Martin, D. J. Fox, D. J. Defrees, J. Baker, J. J. P. Stewart, and J. A. Pople, Gaussian, Inc., Pittsburgh PA, 1992.
   The geometries of the radicals were obtained from the calculation of a reaction path (stepsize 10°) for the rotation around the central bond shown in the Newman projection of **13**. This was done with the SCAMP 4.3 program (Dr. T. Clark, University Erlangen, Germany) using the keywords EF HESS=1 PRECISE UHF AM1.
7. The conformation analysis of the transition states was done with the calculation of the six possible staggered transition state conformations which were tested via frequency calculation. The calculations were carried out with the MOPAC6.0 program using the AM1 method with UHF wavefunctions.

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