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Group Selective Radical Cyclizations with Oppolzer's Camphor Sultam

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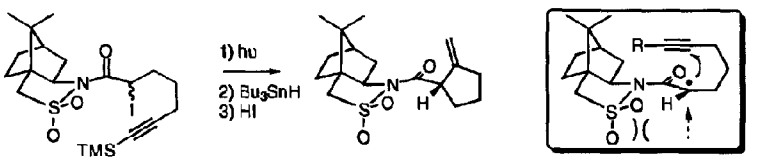
Summary: Acyl derivatives of Oppolzer's camphor sultam provide moderate levels of group selectivity (~85/15) in representative radical cyclizations of dienes and diynes.

Prior efforts to control stereochemistry in radical addition and cyclization reactions have focused on face selectivity. Stereoselective radical reactions can operate under either substrate control or chiral auxiliary control, and the two faces of either a chiral radical or a chiral alkene can now be reliably differentiated.[1] Herein we report the first examples of diastereotopic group selective[2] radical cyclizations of a diene and a diyne under chiral auxiliary control.[3] Examples of substrate-controlled[4] group selective radical cyclizations will be reported separately.

We selected substrates for group selective cyclizations based on our experience with using Oppolzer's camphor sultam in asymmetric radical additions and cyclizations.[5] In the representative example shown in eq 1, cyclization of the iodosultam **1** by the atom transfer method,[6] followed by deiodination and reductive desilylation, provided (methylene)cyclopentane **2** and its diastereomer (not shown) in a ratio of 91/9. According to our stereochemical model[5c] (see **3**), Oppolzer's sultam is a "dialkylpyrrolidine in disguise", and a cis-1,4-interaction between one of the sultam oxygens and an approaching reagent partially shields the α-face of these molecules. Our results suggest that Oppolzer's camphor sultam should be useful for related group selective radical reactions, and that the outcome of such reactions can be anticipated by applying the model.[7]

eq 1



D-camphor sultam **1** **2** **3**

As a first test of this notion, we selected the diyne **6b** (see eq 2). Cyclization of the derived radical could produce four products,[8] whose ratios can be anticipated by combining Beckwith's model for radical cyclizations[9] with the results and model in eq 1. Beckwith's model predicts that the acyl sultam and the butynyl side chain will be trans in the product, and substantial literature precedent[10] in related substrates suggests that the trans selectivity will be very high. The results and model in eq 1 predict which of the diastereotopic butynyl side-chains will prefer to react. Combining the two models (see model in box eq 2), the major product from the D-sultam should be **8**.

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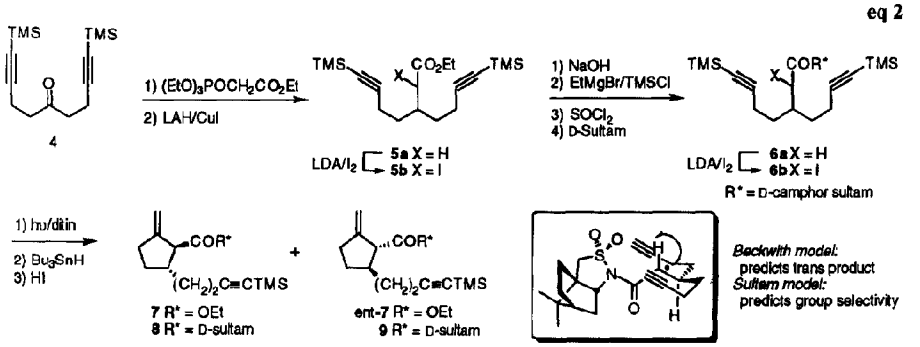
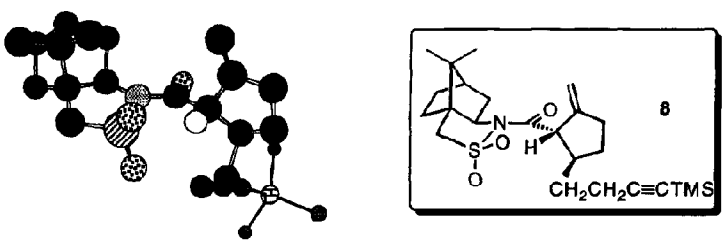
The synthesis of the iodide **6b** and its cyclization are summarized in eq. 2. Olefination of the symmetrical ketodiyne **4** followed by LAH/CuI reduction[11] provided the ester **5a**. This was hydrolyzed, and the resulting acid was coupled to the D-camphor sultam through the acid chloride. Iodination of the enolate derived from **6a** by the standard procedure[5b] was only partially successful, and consistently produced a mixture of iodide **6b** and starting material **6a**. Careful HPLC separation provided relatively pure iodide **6b** as a single diastereomer. Atom transfer cyclization was accomplished by the standard procedure;[5b] irradiation of an 80°C benzene solution of **6b** with a sunlamp in the presence of 10% hexamethylditin provided a mixture of vinyl iodide/silanes. This mixture was first reductively deiodinated with tin hydride, and then the resulting mixture of vinyl silanes was briefly exposed to aqueous HI. Under these conditions, protodesilylation of the vinyl silane occurred, but the alkynyl silane remained intact. After this three step sequence, we obtained a 60% yield of a mixture of two products, **8** and **9** in a ratio of 71/29.[12] We conducted a similar experiment at 7° C and we obtained a similar yield of **8** and **9** in an improved ratio of 83/17.

eq 2



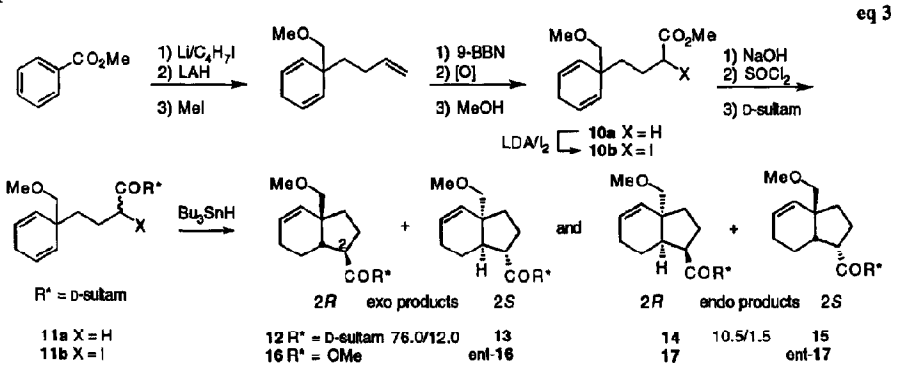
The structures of **8** and **9** were assigned by a combination of chemistry and crystallography. Ester **5a** was first iodinated, and cyclization of this iodide as before then provided one major[13] racemic product. According to the strong precedent, this must be the trans isomer **7**/ent-**7**.[10] This result suggests that **8** and **9** must both be trans isomers of different group selectivity (as opposed to cis/trans isomers of the same group selectivity). Finally, the full structure of the major product **8** was secured by x-ray crystallography. As shown in Figure 1, this structure is that predicted by the combined models. As with all of these sultams,[5c] the crystal structure of the product bears a close resemblance to what we imagine that the transition state might look like.

Figure 1. X-ray Crystal Structure of 8



To explore group selective reactions of alkenes, we selected diene **11b**. This was readily prepared as shown in eq 3. Coupling of the acid chloride derived from **10a** to the D-sultam and iodination as usual provided the requisite precursor **11b** (one major diastereomer), which was cyclized by a standard reduction with tributyltin hydride. Separation of the products from the tin residue provided a mixture of the four cyclized products **12-15** along with a trace (1-2%) of the directly reduced product **11a**. After preparation of authentic samples (see below), we were able to determine by a combination of GC and NMR analysis that the ratio of these cyclic products was 76.0/12.0/10.5/1.5. Careful HPLC separation of this mixture provided the recovered **11a** along with one fraction containing a mixture of "2*R*" exo and endo products **12** and **14** and another fraction containing the "2*S*" exo and endo products **13** and **15**. Further separation was not possible.

eq 3



Exo/endo configurations were assigned by cyclizing iodoester **10b** to provide an inseparable 80/20 mixture of racemic isomers **16**/ent-**16** and **17**/ent-**17**. Prolonged treatment of this mixture with DBU resulted in a 91/9 mixture of racemic **16**/**17**. We believe that this is the equilibrium ratio, and we assigned the exo stereochemistry to the more stable product. Hydrolysis of the racemic 80/20 mixture of products **16**/**17** and coupling to the D-sultam then provided an authentic mixture of all four products **12-15** from which the two exo (**12** and **13** major) and the two endo (**14** and **15** products) could be identified. Despite our best efforts, we were not able to secure a crystalline product or derivative for x-ray analysis, and we currently assign the group selectivity based only on the model. However, we now know that the face selectivity in these reactions is very reliable,[7] so we are confident that this assignment is correct. The ratios in eq 3 can be viewed in a number of ways. The combined exo/endo ratio from **11b** is 88/12—marginally higher than that from the ester **10b** (80/20). Within both the exo and endo manifolds, the group selectivity is about 87/13 (within the endo manifold, this ratio is less reliable due to the very small amount of **15**).

These results clearly show that group selective radical reactions are possible, and they also suggest that such reactions can be predictably designed based on existing results in face selective systems. In both examples (eqs 2, 3), relative stereochemistry (cis/trans, exo/endo) was well anticipated by choosing related achiral models. Group selection ratios were modestly overestimated by the face selective models: in each case we were expecting ratios on the order of 92/8, but the observed ratios (83/17 and 87/13) were somewhat lower. These ratios could probably be improved by using better chiral auxiliaries.[1,3] Recently, we have observed very high group selectivities in substrate controlled reactions, and we will report these results separately.

Acknowledgement: We thank the National Institutes of Health for funding of this work.

References and Notes

1. Review: Porter, N. A.; Giese, B.; Curran, D. P. *Acc. Chem. Res.* **1991**, *24*, 296.
2. a) For a recent leading reference to diastereotopic group selective reactions, see Wipf, P.; Kim, Y. *Tetrahedron Lett.* **1992**, *33*, 5477. b) For a group selective radical hydrogen transfer, see: Sugimura, T.; Goto, S.; Koguro, K.; Futagawa, T.; Misaki, S.; Morimoto, Y.; Yasuoka, N.; Tai, A. *Tetrahedron Lett.* **1993**, *34*, 505.
3. Recent uses of chiral auxiliaries in radical reactions: a) Stack, J. G.; Curran, D. P.; Rebek, J.; Ballester, P. *J. Am. Chem. Soc.* **1991**, *113*, 5918. b) Porter, N. A.; Bruhnke, J. D.; Wu, W. X.; Rosenstein, I. J.; Breyer, R. A. *J. Am. Chem. Soc.* **1991**, *113*, 7788. c) Chen, M.-Y.; Fang, J.-M.; Tsai, Y.-M.; Yeh, R.-L. *J. Chem. Soc., Chem. Commun.* **1991**, 1603. d) Zoretic, P. A.; Weng, X. Y.; Biggers, C. K.; Biggers, M. S.; Caspar, M. L.; Davis, D. G. *Tetrahedron Lett.* **1992**, *33*, 2637. e) Stack, J. G.; Curran, D. P.; Geib, S. V.; Rebek, J.; Ballester, P. *J. Am. Chem. Soc.* **1992**, *114*, 7007. f) Porter, N. A.; Allen, T. R.; Breyer, R. A. *J. Am. Chem. Soc.* **1992**, *114*, 7676. g) Snider, B. B.; Zhang, Q. W. *Tetrahedron Lett* **1992**, *33*, 5921. h) Kneer, G.; Mattay, J. *Tetrahedron Lett.* **1992**, *33*, 8051. i) Veit, A.; Lenz, R.; Seiler, M. E.; Neuburger, M.; Zehnder, M.; Giese, B. *Helv Chim Acta* **1993**, *76*, 441. j) Yamamoto, T.; Ishibuchi, S.; Ishizuka, T.; Haratake, M.; Kunieda, T. *J. Org. Chem.* **1993**, *58*, 1997. k) Giese, B.; Hoffmann, U.; Roth, M.; Velt, A.; Wyss, C.; Zehnder, M.; Zipse, H. *Tetrahedron Lett.* **1993**, *34*, 2445. l) Hamon, D. P. G.; Massy-Westropp, R. A.; Razzino, P. *Tetrahedron* **1993**, *49*, 6419.
4. We are aware of one example of a substrated controlled group selectivity, though the level of selectivity is very low. See compound **17** in Beckwith, A. L. J.; Roberts, D. H. *J. Am. Chem. Soc.* **1986**, *108*, 5893.
5. a) Curran, D. P.; Shen, W.; Zhang, J.; Heffner, T. A. *J. Am. Chem. Soc.*, **1990**, *112*, 6738. b) Curran, D. P.; Shen, W.; Zhang, L.; Geib, S. V.; Lin, C.-H. *Heterocycles*, submitted for publication. c) Kim, B. H.; Curran, D. P. *Tetrahedron* **1993**, *49*, 293. d) The experiment summarized in eq 1 was actually conducted in the L-enantiomeric series (see ref. 5a), but the D-enantiomers are shown for consistency with this work.
6. Curran, D. P.; Chang, C.-T. *J. Org. Chem.* **1989**, *54*, 3140.
7. While we believe that our model is useful, we caution that it is not essential for making stereochemical predictions. It is more the stereochemical reliability of the sultam than the "correctness" of any given model that allows accurate prediction of the outcome of these reactions (see reference 5c).
8. The role of the trimethylsilyl group is to prevent small amounts of 6-endo cyclization observed with terminal alkynes. This group is lost during the hydrolysis of **5a**, necessitating a resilylation prior to formation of **6a**.
9. a) Beckwith, A. J. J.; Schiesser, C. H. *Tetrahedron* **1985**, *41*, 3925. b) Spellmeyer, D. C.; Houk, K. N. *J. Org. Chem.* **1987**, *52*, 959.
10. Leading reference: Curran, D. P.; Seong, C. M. *Tetrahedron* **1992**, *48*, 2157.
11. Tsuda, T.; Fujii, T.; Kawasaki, K.; Saegusa, T.; *J. Chem. Soc., Chem. Commun.* **1980**, 1013.
12. Selected spectral data. Compound **8**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.03 (d, J = 1.9 Hz, 1 H), 4.95 (d, J = 1.9 Hz, 1 H), 3.89 (t, J = 6.3 Hz, 1 H), 3.62 (d, J = 7.4 Hz, 1 H), 3.53 (d, J = 14.4 Hz, 1 H), 3.44 (d, J = 14.4 Hz, 1 H), 2.65-2.50 (m, 1 H), 2.45-2.34 (m, 2 H), 2.20 (t, J = 7.4 Hz, 2 H), 2.10-1.25 (m, 10 H), 1.17 (s, 3 H), 0.95 (s, 3 H), 0.10 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.2, 151.2, 108.5, 107.3, 84.2, 65.5, 55.5, 53.4, 48.0, 47.7, 44.6, 43.6, 33.3 (2C), 31.1, 26.5, 20.9, 19.9, 18.6, 0.2. Compound **12** (mixed with **14**): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.82-5.72 (m, 1 H) (ratio 7.1/1.0), 3.91 (t, J = 6.7 Hz, 1 H), 3.51 (d, J = 13.4 Hz, 1 H), 3.42 (d, J = 13.4 Hz, 1 H), 3.32 (s, 3 H), 3.48-3.18 (m, 2 H), 2.62-1.25 (m, 16 H), 1.18 (s, 3 H), 0.98 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.5, 132.4, 127.2, 80.1, 65.5, 59.5, 53.4, 48.2, 47.8, 47.4, 46.7, 46.5, 44.9, 38.9, 35.6, 33.0, 28.4, 26.5, 21.8, 21.0, 20.4, 20.0; IR (neat) 2923, 1692, 1454, 1395, 1331, 1267, 1213, 1165, 1132, 1067, 991, 785, 766, 739; MS (*m/e*) 407, 375, 362, 343, 328, 311, 298, 280, 270, 242, 216, 192, 165, 147, 133, 119, 107, 91, 79, 67, 55.
13. A minor isomeric product (cis?) was detected in the crude GCMS (ratio 16/1), but we could not isolate this minor product.

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