Tetrahedron Letters, Vol.31, No.32, pp 4565-4568, 1990
Printed in Great Britain

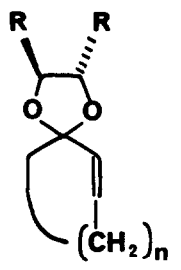
0040-4039/90 $3.00 + .00
Pergamon Press plc

DIASTEREOSELECTIVE MANIPULATIONS OF CONFORMATIONALLY RESTRICTED ENANTIOMERICALLY PURE BICYCLO[m.1.0]ALKANES. 1. NUCLEOPHILIC ADDITIONS TO THE CARBONYL CARBONS OF BICYCLO[m.1.0]ALKAN-2-ONES

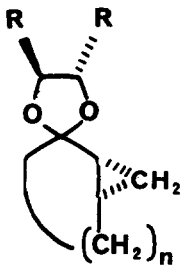
Eugene A. Mash*, Michelle A. Kaczynski, and Daniel P. Dolata
Department of Chemistry, The University of Arizona, Tucson, Arizona 85721

Abstract. Additions of nucleophiles to the carbonyls of several enantiomerically pure bicyclo[m.1.0]alkan-2-ones were found to be highly diastereoselective.

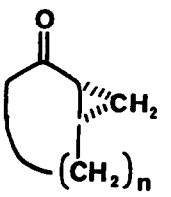
Recently there has been much interest in the diastereoselective manipulation of medium and large ring systems.[1] We have described the first, and to date only, general method for direct asymmetric introduction of stereogenic centers onto achiral medium and large carbocyclic rings via diastereoselective cyclopropanations of 2-cycloalken-1-one 1,4-di-O-benzyl-L-threitol ketals **1**.[2] Thus, bicyclo[m.1.0]alkan-2-ones **3** possessing cis ring fusion for m = 3-14 or trans ring fusion for m = 7-14 are now available in either enantiomeric form[3] from hydrolysis of the corresponding cyclopropane ketals **2**.[4]



1 R = CH_2OCH_2Ph



2



3

The usefulness of this cyclopropanation methodology in the asymmetric synthesis of natural products[5] which possess medium or large rings will depend in part upon the diastereoselectivity obtained during synthetic manipulations of enantiomerically pure cyclopropyl ketones **3**. We have therefore begun to examine the chemistry of these conformationally restricted bicyclic systems and report herein *uniformly high diastereoselectivities for nucleophilic additions to the carbonyl carbons* of representative enantiomerically pure medium and large ring bicyclo[m.1.0]alkan-2-ones.

Previously Winstein and coworkers had reported that LAH reductions of racemic cis- bicyclo[6.1.0]nonan-2-one (±)-8 and racemic cis-bicyclo[7.1.0]decan-2-one (±)-15 were highly diastereoselective.[6] We have confirmed these observations and have found that a wide range of carbon nucleophiles also will add in excellent yields and with high diastereoselectivity[7] to ketone 8 (Table 1, entries 3-8). While this high degree of diastereoselectivity was not exhibited by the smaller bicyclo[4.1.0]heptan-2-one and bicyclo[5.1.0]octan-2-one systems (entries 1 and 2), remarkably high diastereoselectivities resulted when methyl lithium was added to the carbonyls of larger enantiomerically pure bicyclic ketones (entries 9-13). Diastereoselectivity was uniformly high (>20:1) for cis cyclopropyl ketones 15 and 17, as well as for trans cyclopropyl ketones 19, 21, and 23. The observed diastereoselectivity may be the result of conformationally controlled exposure of one face of the carbonyl to the ring exterior (Figure 1).[1,6,8] Further explorations of the chemistry of the bicyclo[m.1.0]alkan-2-ones and related systems are currently underway in our laboratory.[9]

Figure 1. Nucleophilic Attack at Carbonyl of the Lowest Energy Conformations of Bicyclo[6.1.0]nonan-2-one (8).[8]

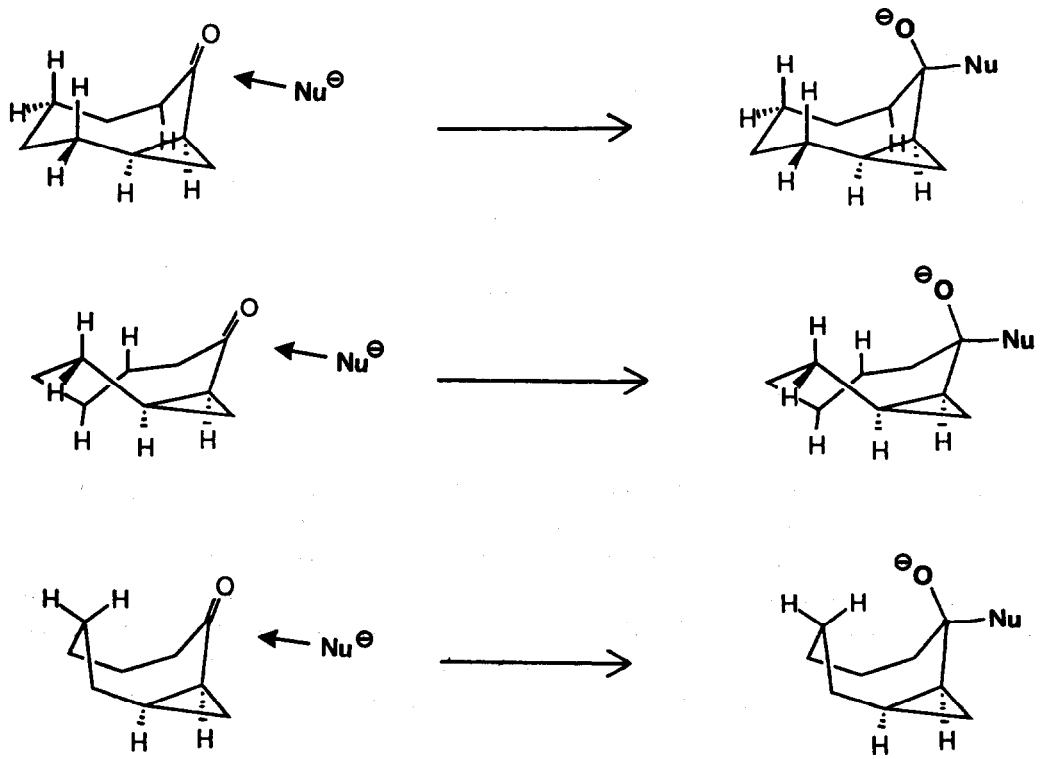
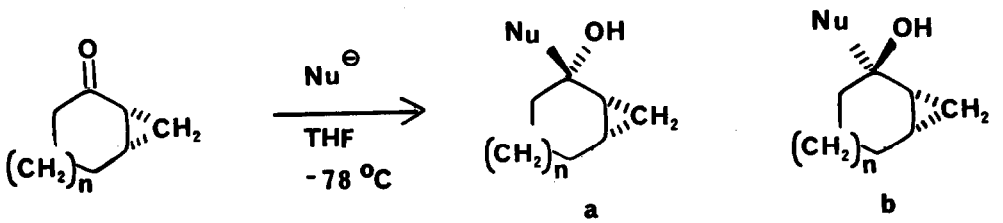
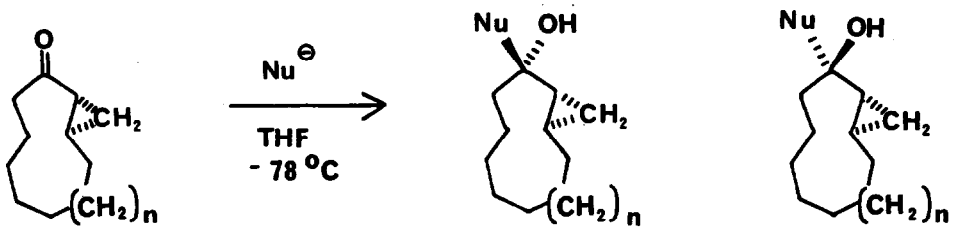


Table 1. Additions of Nucleophiles to Enantiomerically Pure Bicyclo[m.1.0]alkan-2-ones



Entry	Cyclopropyl Ketone	n	Nu:	Cyclopropyl Carbinol	Yield,%	Diastereomer Ratio[a]	$[\alpha]_D$,deg.[b]
1	4	1	MeLi	5	Ca.50[c]	2:1	---
2	6	2	MeLi	7	88	5:2	---
3	8	3	LAH	9	99	>20:1[d]	-21.7
4	8	3	MeLi	10	99	>20:1	-26.1
5	8	3	nBuLi	11	92	>20:1	-31.6
6	8	3	PhMgBr	12	99	>20:1	-73.1
7	8	3	CH_2=CHMgBr	13	99	>20:1	-43.9
8	8	3	nBuC≡CLi	14	98	>20:1	-62.4
9	15	4	MeLi	16	68	>20:1	-28.1
10	17	11	MeLi	18	94	>20:1	-12.2



Entry	Cyclopropyl Ketone	n	Nu:	Cyclopropyl Carbinol	Yield,%	Diastereomer Ratio[a]	$[\alpha]_D$,deg.[b]
11	19	2	MeLi	20	97	>20:1	+25.0
12	21	4	MeLi	22	90	>20:1	+85.2
13	23	6	MeLi	24	70	>20:1	-32.4

[a]Determined by 62.9-MHz ^{13}C NMR spectroscopy (see Ref.7).
[b]In $CHCl_3$.
[c]Ketone 4 and carbinols 5 chromatographically inseparable.
[d]Ratio of diastereomers a:b (see Ref. 6).

References and Footnotes

1. (a) Still, W.C.; MacPherson, L.J.; Harada, T.; Callahan, J.F.; Rheingold, A.L. Tetrahedron 1984, 40, 2275. (b) Still, W.C.; Galynker, I. Tetrahedron 1981, 37, 3981. (c) Still, W.C.; Galynker, I. J. Am. Chem. Soc. 1982, 104, 1774. (d) Still, W.C.; Novak, V. J. Am. Chem. Soc. 1984, 106, 1148. (e) Cameron, A.; Knight, D. J. Chem. Soc., Perkin Trans. I 1986, 161. (f) Neeland, E.; Ounsworth, J.; Sims, R.; Weiler, L. Tetrahedron Lett. 1987, 35. (g) Funk R.L.; Abelman, M.M.; Munger, J.D. Tetrahedron 1986, 42, 2831. (h) Schreiber, S.L.; Hulin, B.; Liew, W. Tetrahedron 1986, 42, 2945. (i) Mehta, G.; Rao, K. J. Am. Chem. Soc. 1986, 108, 8015. (j) Still, W.C.; Murata, S.; Revial, G.; Yoshihara, K. J. Am. Chem. Soc. 1983, 105, 625. (k) Schreiber, S.L.; Santini, C. J. Am. Chem. Soc. 1984, 106, 4038. (l) Vedejs, E.; Gapinski, D. J. Am. Chem. Soc. 1983, 105, 5058. (m) Corey, E.J.; Nicolaou, K.C.; Melvin, L. J. Am. Chem. Soc. 1975, 97, 654. (n) Doskotch, R.; Keely, S.; Hufford, C. J. Chem. Soc., Chem. Commun. 1972, 1137. (o) Takahashi, T.; Kanda, Y.; Nemoto, H.; Kitamura, K.; Tsuji, J.; Fukazawa, Y. J. Org. Chem. 1986, 51, 3393. (p) Takahashi, T.; Nemoto, H. Kanda, Y.; Tsuji, J.; Fujise, Y. J. Org. Chem. 1986, 51, 4315. (q) Maryanoff, B.; Almond, H. J. Org. Chem. 1986, 51, 3295. (r) Marshall, J.A.; Henson, T.; DeHoff, B. J. Org. Chem. 1986, 51, 4316. (s) Raucher, S.; Chi, K.; Hwang, K.; Burks, J. J. Org. Chem. 1986, 51, 5503. (t) Paquette, L.; Lin, H.; Belmont, D.; Springer, J. J. Org. Chem. 1986, 51, 4807. (u) Coates, R.; Muskopf, J.; Senter, P. J. Org. Chem. 1985, 50, 3541. (v) Quinkert, G.; Neim, M.; Glenneberg, J.; Billhardt, V.; Autze, V.; Bats, J.; Dunner, G. Angew. Chem. 1987, 26, 362. (w) Vedejs, E.; Dent, W.; Gapinski, D.; McClure, C. J. Am. Chem. Soc. 1987, 109, 5437. (x) Winkler, J.; Sridar, V. J. Am. Chem. Soc. 1986, 108, 1708. (y) Winkler, J.; Sridar, V. Tetrahedron Lett. 1988, 29, 6219-6222. (z) Keller, T.H.; Neeland, E.G.; Weiler, L. J. Org. Chem. 1987, 52, 1870-1872.

2. Mash, E.A.; Math, S.K.; Arterburn, J.B. J. Org. Chem. 1989, 54, 4951-4953.

3. From 1,4-di-O-benzyl-L-threitol and 1,4-di-O-benzyl-D-threitol prepared from L-tartaric acid and D-tartaric acid, respectively; see: Mash, E.A.; Nelson, K.A.; Van Deusen, S.; Hemperly, S.B. Org. Syn. 1989, 68, 92-103.

4. Cyclopropane ketals **2** were prepared as previously described[2] and subjected to acid-catalyzed hydrolysis (10% aqueous HCl, methanol, room temperature) to give in 88-99% yields the cyclopropyl ketones used in this study.

5. For previous uses of this methodology in natural products synthesis, see: (a) Nelson, K.A.; Mash, E.A. J. Org. Chem. 1986, 51, 2721-2724. (b) Mash, E.A.; Fryling, J.A. J. Org. Chem. 1987, 52, 3000-3003. (c) Mash, E.A. J. Org. Chem. 1987, 52, 4142-4143. (d) Mash, E.A.; Math, S.K.; Flann, C.J. Tetrahedron 1989, 45, 4945-4950.

6. (a) Poulter, C.D.; Friedrich, E.C.; Winstein, S. J. Am. Chem. Soc. 1970, 92, 4274-4281; (b) Poulter, C.D.; Winstein, S. J. Am. Chem. Soc. 1970, 92, 4282-4288.

7. Diastereomer ratios were determined by 62.9-MHz ^{13}C NMR spectroscopy (limit of detection ca. 20:1). See: Hiemstra, H.; Wynberg, H. Tetrahedron Lett. 1977, 18, 2183-2186.

8. From preliminary molecular mechanics studies of the preferred conformations of medium and large ring cyclopropyl ketones by Professor D. P. Dolata; manuscript in preparation.

9. Partial support of this research by the Howard Hughes Medical Institute and by the University of Arizona Foundation and the Office of the Vice President for Research is gratefully acknowledged.

(Received in USA 24 April 1990)