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DIASTEREOSELECTIVE CYCLOPROPANATION VIA HOMOCHIRAL KETALS. DIOXOLANE STRUCTURAL EFFECTS

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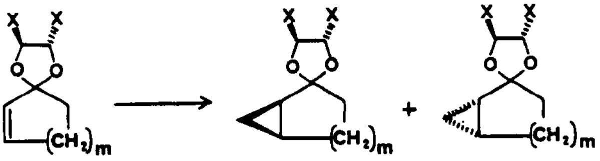
Abstract. A series of 2-cyclohexen-1-one ketals related to 2-cyclohexen-1-one 1,4-di-*O*-benzyl-L-threitol ketal but possessing different dioxolane appendages was prepared and subjected to Simmons-Smith cyclopropanation. The observed diastereoselectivity *decreased* when oxygen was present in the appendages. In the absence of appendage oxygen, the sense of the observed diastereoselectivity was found to depend upon dioxolane chirality. The amount of diastereoselectivity observed was remarkably independent of the nature of the appendages.

Not long ago we described a novel diastereoselective Simmons-Smith cyclopropanation reaction involving 2-cycloalken-1-one 1,4-di-*O*-benzyl-L-threitol ketals (Figure 1).[1] The observed diastereoselection was attributed to topological biasing of the faces of the alkene by the dissymmetrically positioned dioxolane appendages, and was presumed to result from chelation-controlled delivery of the Simmons-Smith reagent by appendage and/or dioxolane oxygen atoms.[2] However, experimental evidence pertaining to this assumed mechanism was not available. Since an understanding of the factors responsible for diastereoselection in the case at hand could prove helpful in attempts to extend and to generalize topologically controlled reagent delivery, we have undertaken studies to determine the structural features required for diastereoselective cyclopropanation. This letter describes our surprising results with a series of compounds related to 2-cyclohexen-1-one 1,4-di-*O*-benzyl-L-threitol **1** but possessing structural alterations in the dioxolane appendages (Table I).[3]

Figure 1. Diastereoselective Cyclopropanation



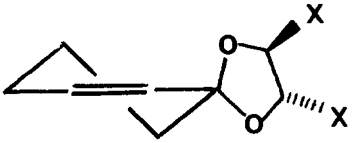
X = $CH_2OCH_2C_6H_5$ m = 1,2,3

Compounds 1,3,5,7,9,11, and 13 were prepared from 3-bromo-2-methoxycyclohexene and the corresponding diols[4] as previously described.[1,5] Yields appear in Table I.[6]

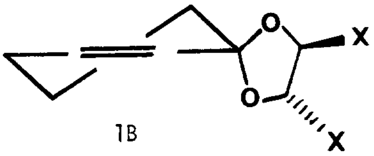
Simmons-Smith cyclopropanation[2,7] of these ene ketals provided in fair to excellent chemical yields mixtures of diastereomeric cyclopropanes (Table I). Where possible, the diastereomer ratio, measured by 62.9-MHz ^{13}C NMR spectroscopy,[8] and the identity of the major cyclopropane diastereoisomer were confirmed by hydrolysis[9] of the product cyclopropane ketals to optically active norcaranone.[2c,2d]

From the results presented in Table I a deeper understanding of this diastereoselective reaction begins to emerge. *Unexpectedly, appendage oxygen was unnecessary for efficient diastereoselection and even reduced the diastereoselectivity observed.* This reduction may be the result of competition between appendage and dioxolane oxygens for chelation controlled delivery of the Simmons-Smith reagent to *opposite faces* of the alkene. Thus, in second-generation diols designed for this diastereoselective process, the chelatory effects of appendage oxygen should be masked or otherwise eliminated. In the absence of appendage oxygen, facial selectivity was dependent upon dioxolane chirality. The amount of diastereoselectivity observed was remarkably independent of the nature of the appendages.

Assuming that reagent delivery is mediated by a dioxolane oxygen atom positioned pseudo-equitorially,[10] then cyclohexene ring conformer 1A must be more reactive and/or present in a higher concentration than cyclohexene ring conformer 1B. This difference in reactivity and/or the shift in equilibrium between 1A and 1B must be due to steric biasing and/or conformational anchoring by the dioxolane appendages. Studies to determine whether or not chelation control by dioxolane oxygen is involved in this process and the equilibrium distribution between the possible cyclohexene ring conformers are currently underway.[11]



1A



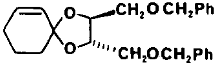
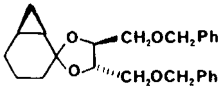
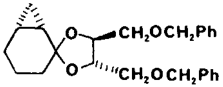
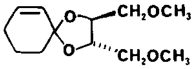
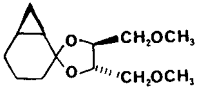
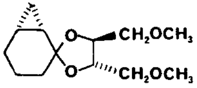
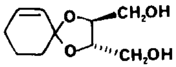
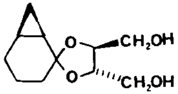
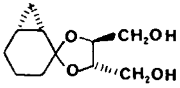
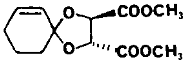
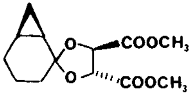
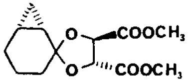
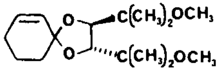
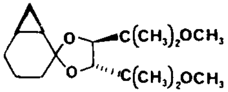
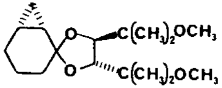
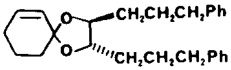
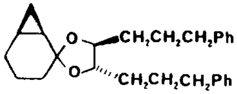
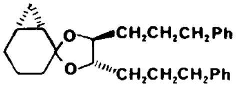
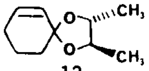
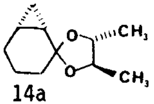
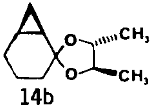
1B

X = $CH_2OCH_2C_6H_5$

Legend for Table I

[a] Reaction conditions: 400-700 mg of couple/mmol of ene ketal, 3 equiv. of CH_2I_2, 0.5M in refluxing diethyl ether, 1-24 h. [b] All yields refer to isolated and purified compounds. Satisfactory IR, NMR, and HRMS data were obtained for all compounds. [c] Determined by 62.9 MHz ^{13}C NMR spectroscopy. [d] Using Zn(Ag) couple. [e] A dl mixture was employed.

Table I. Diastereoselective Cyclopropanation of Dioxolane-modified Ene Ketals.[a]

Entry	Alkene	Yield, %[b]	Cyclopropanes		Yield, %[b]	Diastereomer Ratio[c]
1	 **1**	93	 **2a**	 **2b**	90-98	9:1
2	 **3**	63	 **4a**	 **4b**	86	5:1
3	 **5**	70	 **6a**	 **6b**	50(40)[d]	1:2(1:1.5)[d]
4	 **7**	83	 **8a**	 **8b**	37(42)[d]	1.5:1(3:1)[d]
5	 **9**	73	 **10a**	 **10b**	91	4:1
6[e]	 **11**	51	 **12a**	 **12b**	92	> 9:1
7	 **13**	84	 **14a**	 **14b**	86	9:1

References and Notes

1. Mash, E.A.; Nelson, K.A. *J. Am. Chem. Soc.*, 1985, **107**, 8256-8258.

2. The activating and directing effects of allylic and homoallylic oxygen atoms with regard to the Simmons-Smith reaction are well-documented. See: (a) Furukawa, J.; Kawabata, N. In *Advances in Organometallic Chemistry*; Stone, F.G.A.; West, R., Ed.; Academic Press: New York, 1974; Vol. 12, Chapter 3. (b) Simmons, H.E.; Cairns, T.L.; Vladuchick, S.A.; Hoiness, C.M. *Org. React.*, 1972, **20**, 1-131. (c) Johnson, C.R.; Barbacyn, M.R. *J. Am. Chem. Soc.*, 1982, **104**, 4290-4291. (d) Hill, R.K.; Morgan, J.W. *J. Org. Chem.*, 1968, **33**, 927-028. (e) Poulter, C.D.; Friedrich, E.C.; Winstein, S.J., *J. Am. Chem. Soc.*, 1969, **91**, 6892-6894.

3. For papers describing the effects of varying the enone portion of the ketal see: (a) Mash, E.A.; Nelson, K.A. *Tetrahedron Lett.*, 1986, 1441-1444. (b) Nelson, K.A.; Mash, E.A. *J. Org. Chem.*, 1986, **51**, 2721-2724. (c) Mash, E.A.; Nelson, K.A. *Tetrahedron*, submitted.

4. Preparative details will appear in a subsequent paper.

5. Garbisch, E.W., Jr. *J. Org. Chem.*, 1965, **30**, 2109-2120.

6. All yields refer to isolated and purified compounds. Satisfactory NMR, IR, and HRMS data were obtained for all compounds.

7. Shank, R.S.; Schechter, H. *J. Org. Chem.*, 1959, **24**, 1825-1826.

8. For previous examples of the use of ^{13}C NMR in determining diastereomer ratios, see: Hiemstra, H.; Wynberg, H. *Tetrahedron Lett.*, 1977, 2173-2186.

9. Conditions for hydrolysis: 10% aqueous hydrochloric acid, MeOH, room temperature, 1-4 hr. The recovered norcaranones were spectroscopically and chromatographically identical with racemic material prepared by cyclopropanation of 2-cyclohexen-1-one (ref. 2b, p. 85). Chemical yields and rotations of the product norcaranones follow:

from **2**: 83%, $[\alpha]_D^{25}$ +12.7° (*c* 3.4, $CHCl_3$)
from **4**: 86%, $[\alpha]_D^{25}$ +11.2° (*c* 2.1, $CHCl_3$)
from **6**: 89%, $[\alpha]_D^{25}$ -6.5° (*c* 0.42, $CDCl_3$) for Zn(Cu) couple
from **6**: 88%, $[\alpha]_D^{25}$ -4.3° (*c* 1.0, $CHCl_3$) for Zn(Ag) couple
from **8**: 44%, $[\alpha]_D^{25}$ +1.8° (*c* 0.4, $CDCl_3$) for Zn(Cu) couple
from **8**: 80%, $[\alpha]_D^{25}$ +6.6° (*c* 1.2, $CHCl_3$) for Zn(Ag) couple
from **10**: 65%, $[\alpha]_D^{25}$ +10.4° (*c*, 0.24, $CDCl_3$)
from **14**: 99%, $[\alpha]_D^{25}$ -15.5° (*c* 0.65, $CDCl_3$)

The largest rotation reported for (1*R*,6*S*)-norcaranone is $[\alpha]_D^{25}$ +15.3° (*c* 1.28, $CHCl_3$).[2c,2d]

10. Chan, J.H.-H.; Rickborn, B. *J. Am. Chem. Soc.*, 1968, **90**, 6406-6411.

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