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REGIOSELECTIVE NUCLEOPHILIC RING OPENING OF OXABICYCLIC COMPOUNDS

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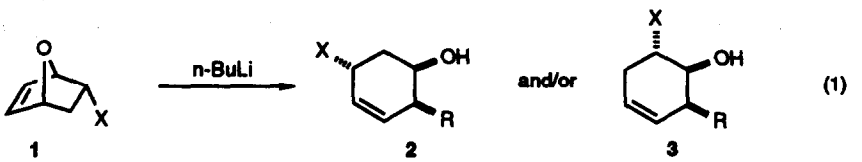
Summary: The ring opening of unsymmetrical oxabicyclic compounds was found to be highly regioselective, giving rise to products from the attack of the nucleophile distal to the bridgehead substituent. Ozonolysis furnished acyclic chains with up to five stereocenters and differentiated ends.

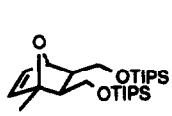
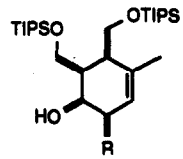
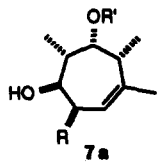
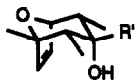
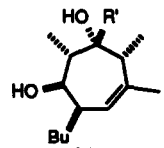
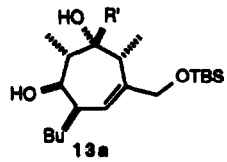
The development of methodology to synthesize compounds with known relative stereochemistry is a continuing challenge in synthetic organic chemistry. Both our group and the group of Arjona have reported one such strategy which utilizes the nucleophilic ring opening of meso oxabicyclic [2.2.1] and [3.2.1] compounds and subsequent ozonolysis to generate acyclic fragments with up to 5 contiguous stereocenters.[2-6] We now extend our investigation of this reaction from symmetrical, meso oxabicyclic substrates to unsymmetrical oxabicyclic compounds.[7]

Ring opening of unsymmetrical substrates with a substituent at the bridgehead could conceivably give rise to two regioisomers.[8] At the outset of this study, there was conflicting data on the structural requirements for regioselective ring opening in oxabicyclic [2.2.1] systems. We had established that the ring opening reaction of unsymmetrical [2.2.1] oxabicyclic compounds **1** (X=CH_2OBn) by organocuprates was not regioselective.[3a] However, compound **1** (X=OH) gave only **2** when treated with n-BuLi, although both **2** and **3** were obtained when the hydroxyl group was protected (X=OBn).[2a] This selectivity was not only a function of the protection of the hydroxyl group, but was also a proximity effect, for we observed little regioselectivity when **1** (X=CH_2OH) was treated with n-BuLi.[3b,9] No data was available for unsymmetrical [3.2.1] compounds.



1 **2** **3** (1)

Table 1. Regioselective Ring Opening of Oxabicyclic Compounds

Entry	Substrate	Adduct[1]		Yield
1				
	4	**5a**	R = Et	97%
		5b	n-Bu	96%
		5c	s-Bu	100%
		5d	t-Bu	96%
2				
	6 R = H	**7a**	R = Et	59%
		7b	n-Bu	81%
	8 R = TBDMS	**9**	R = t-Bu	100%
3				
	10a R' = Me	**11a**		72%
	10b R' = $TMSCH_2$	**11b**		76%
4				
	12a R' = H	**13a**		69%
	12b R' = Me	**13b**		64%
	12c R' = $TMSCH_2$	**13c**		63%

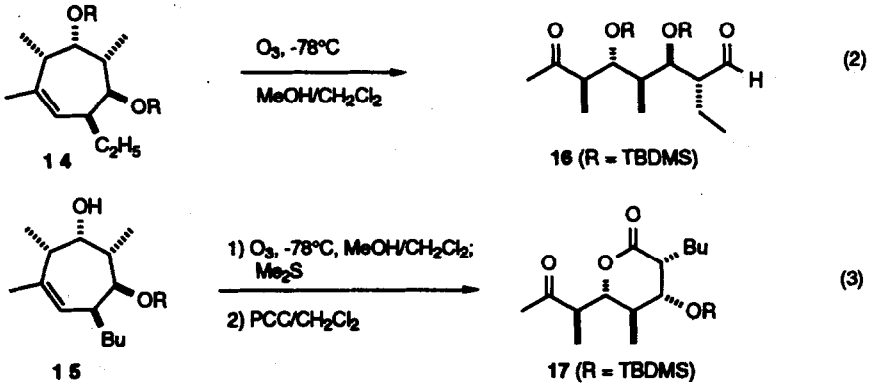
1. 5 equiv of R-Li in ether at 0°C.

Table 1 shows the results of our study of the ring opening reaction of unsymmetrical substrates.[10] The unsymmetrical oxabicyclo[2.2.1] compound **4** undergoes regioselective opening with primary, secondary, and tertiary alkyllithium reagents, the facility of the reaction increasing with increasing substitution of the nucleophile (entry 1).[11] Excellent yields of cyclohexenols **5a-5d** have been obtained. Similarly, unsymmetrical [3.2.1] oxabicyclic compounds also undergo regioselective ring opening to give cycloheptenols with 5 contiguous stereocenters in good yields (entries 2-4).[12] When the hydroxyl group at C_3 is protected (entry 2), regioselective

ring opening gives the same major regioisomer, albeit under more vigorous conditions.[13]

The high regioselectivity of the ring opening takes on additional significance in the next step of the overall strategy: oxidative cleavage of the ring. Starting from a symmetrical substrate, ring opening and ozonolysis yields a dialdehyde or diol[2b] which requires several additional steps to differentiate the termini. Methodology to achieve this differentiation has been developed and successfully applied to the syntheses of stereochemically complex fragments of rifamycin S[13] and ionomycin. Although this strategy is successful, oxidative cleavage of substrates prepared from the ring opening of unsymmetrical substrates would be more efficient, giving ketoaldehydes or ketoacids which do not require further functional group manipulations to differentiate the ends.

Ozonolyses of **14** and **15** were performed to illustrate the concept. Ketoaldehyde **16** (R=TBDMS) was isolated in 70% yield following treatment of **14** with ozone (CH_2Cl_2:MeOH 1:2, -78°C, then Me_2S). Reaction of the monoprotected compound **15**, followed by PCC oxidation gave **17** in 59% yield for the two steps.



In summary, we have established that bridgehead substituents control the site of attack of nucleophilic ring opening in oxabicyclic [3.2.1] and [2.2.1] compounds. Subsequent ozonolysis under oxidative conditions provides acyclic compounds with differentiated termini. Studies to exploit these results in the synthesis of natural products are in progress.

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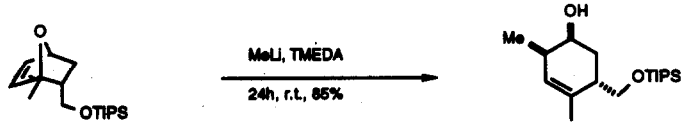
References and Notes

1. a) A. P. Sloan Foundation Fellow, 1991-93; Lilly Grantee, 1992-1994; BioMega Young Investigator 1990-1993; NSERC(Canada) University Research Fellow 1987-1992. b) NSERC(Canada) Postgraduate Scholar 1989-1992, Ontario Graduate Scholar 1992-1993.
2. For [2.2.1] compounds, see: a) Arjona, O.; Fernandez de la Pradilla, R.; Garcia, E.; Martin-Domenech, A.; Plumet, J. *Tetrahedron Lett.* **1989**, *30*, 6437, and Acena, J.L.; Arjona, O.; Fernandez de la Pradilla, R.; Plumet, J.; Viso, A. *J. Org. Chem.* **1992**, *57*, 1945. For [3.2.1] compounds, see: b) Lautens, M.;

Abd-El-Aziz, A.S.; Lough, A. *J. Org. Chem.* **1990**, *55*, 5305.

3. a) Lautens, M.; Smith, A.C.; Abd-El-Aziz, A.S.; Huboux, A.H. *Tetrahedron Lett.* **1990**, *31*, 3253. b) Unpublished results of Dr. R. K. Belter.
4. Lautens, M; DiFelice, C.; Huboux, A. *Tetrahedron Lett.*, **1989**, *30*, 6817.
5. Lautens, M.; Chiu, P. *Tetrahedron Lett.* **1991**, *32*, 4827.
6. Lautens, M.; Ma, S.; Belter, R.K.; Chiu, P.; Leschziner, A. *J. Org. Chem.* **1992**, *57*, 4065.
7. The regioselective ring opening results were first presented at the 74th Canadian Chemical Conference and Exhibition, June 2-6, 1991, Hamilton, Ontario, Canada. Abstract # 428, IO A1.
8. Crystallographic analysis of the products from ring opening of symmetrical oxabicyclo[3.2.1] compounds by organolithium reagents have shown that the nucleophile and the newly generated hydroxyl group bear a *syn* relationship, see ref. 2b. The stereochemistry of the substituted cyclohexenes from opening of [2.2.1] compounds was determined by ^{1}H NMR. Thus, only the two regioisomers with a *syn* relationship between the alkyl and hydroxyl substituents were regarded as possible products. This stereochemical relationship has been confirmed by a crystallographic analysis of a derivative of **7b**.
9. Nucleophilic ring-opening of an unsymmetrical oxabicyclic compound using thiophenol and BF_3•Et_2O was not regioselective, see: a) Rigby, J.H.; Wilson, J.A.Z. *J. Org. Chem.* **1987**, *52*, 34. Following completion of our work (ref. 7), regioselective ring opening of unsymmetrical oxabicyclo[2.2.1] substrates derived from IMDAF was reported: b) Woo, S.; Keay, B.A. *Tetrahedron Lett.* **1992**, *33*, 2661.
10. The oxabicyclo[2.2.1] substrate was synthesized from the Diels-Alder reaction of maleic anhydride with 2-methylfuran, reduction with $LiAlH_4$, and protection using TIPSCl. The [3.2.1] oxabicyclic precursors were prepared using literature methods, see: Sato, T.; Noyori, R. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 2745.
11. No ring opening was observed when unsymmetrical [3.2.1] compounds were reacted with MeLi. Among the reaction conditions examined were: MeLi in ether, MeLi in ether/TMEDA at 0°-75°C, MeLi/^{t}BuOK, MeLi/12-crown-4. Methyl equivalents $MeSCH_2Li$ and $PhSCH_2Li$ also failed. In contrast to the results of Keay (ref. 9b), we find that the ring opening of a [2.2.1] compound occurs using MeLi/TMEDA, results of Dr. Carmel Cregg.



12. A typical experimental procedure follows: To 47.0 mg (0.280 mmol) of **6** in 1.0 mL of dry ether was added 0.48 mL n-BuLi (2.5M in hexanes, 1.2 mmol) at 0°C. The reaction mixture was stirred at 0°C for 3 hours, then diluted with ether and quenched with a saturated aqueous solution of NH_4Cl. The organic layer was separated and combined with ethereal extracts of the aqueous layer. After drying over anhydrous $MgSO_4$, the solvent was removed *in vacuo*, and the residue was purified by column chromatography on silica gel (15% EtOAc/hexanes) to afford 51.4 mg of **7b** (81%). The ^{1}H and ^{13}C NMR spectra of the cycloheptenols showed broad signals at room temperature which sharpened at 65°C, indicating that a single stereoisomer was produced.
13. Lautens, M.; Belter, R. K. *Tetrahedron Lett.* **1992**, *33*, 2617.

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