Stereochemistry of the Alkoxyselenation of Substituted 3,4-Dihydropyrans: a Useful Process for the Construction of 2-Alkoxy-5,6-dihydro-2*H*-pyrans

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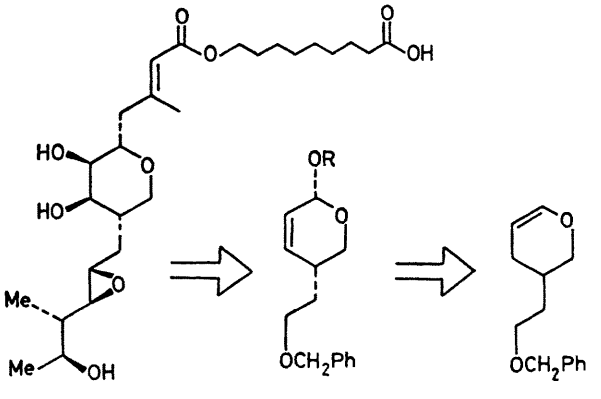
Summary The stereochemistry of the alkoxyselenation of 3,4-dihydro-2*H*-pyrans has been examined as part of a study to identify new routes to monosaccharide components.

IN our efforts to accomplish a total synthesis of the antibiotic substance, pseudomonic acid A (**1**),[1] we have been concerned with the conversion of substituted 3,4-dihydro-2*H*-pyrans into 2-alkoxy-5,6-dihydro-2*H*-pyrans [*e.g.*, the key transformation of (**3**) into (**2**)].



(1) (2) (3)

While such reactions have previously received considerable attention as a consequence of their importance in the construction of monosaccharide components found in antibiotics, this methodology generally calls for a tedious bromoalkoxylation reaction in liquid ammonia followed by dehydrobromination with sodium methoxide in refluxing methanol.[2] With the emergence of organoselenium chemistry,[3] this process can be reinvestigated by relying on the ease of selenoxide elimination for introduction of the carbon–carbon double bond. The stereochemistry of the initial alkoxyselenation reaction is also a matter of primary importance, for the strict definition of the stereochemistry of the substituents at C-2 and C-5 in (**2**) is, for example, crucial to achieving the desired stereocontrol in the subsequent functionalization of this molecule by vicinal hydroxylation (or by other reactions such as hydroboration/oxidation leading to deoxysugars).

The alkoxyselenation reactions were investigated with the dihydropyrans shown in the Table. A limited examination of the influence of solvent, temperature, and alcohol on the stereochemical course of the reaction was also made.[4] The standard reaction conditions consisted of adding the dihydropyran (1 equiv.) to a slight excess of phenylselenenyl chloride (1·1 equiv.) in tetrahydrofuran (THF) at room temperature, followed by the immediate addition of a mixture of the alcohol (1·7 equiv.) and triethylamine (1·5 equiv.) over 2–3 min. After 1 h, the reaction mixture was poured into 5% $NaHCO_3$ and extracted with ether. The organic layer was washed with brine and dried ($MgSO_4$). The crude isolated product was chromatographed on activity III neutral alumina with ether–hexanes as eluent.

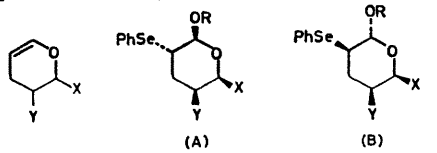
In all cases examined (except entry 1) a mixture of the two diastereomers was produced. With the benzyloxyethyl substituted dihydropyran (entry 2), a preference for formation of that product with the C-2 alkoxy *syn* to the C-5 appendage (ratio 2·5 : 1) resulted. This fact can be rationalized by assuming that the substituent exhibits a conformational anchoring effect leading to a preponderance of the dihydropyran isomer with the substituent at C-3 equatorial (ΔG *ca.* 0·6 kcal mol^{-1}).[5] Generation of that episelenonium ion which allows diaxial ring opening through a chair-like transition state then affords the major isomer (A, entry 2). No change in isomer distribution was observed when this reaction was conducted at −70 °C. Only when Bu^tOH was employed as the alcohol component was slightly more of the major isomer produced, but at the expense of the isolated yield.

The majority of the results found with the other dihydropyrans can be rationalized similarly, taking into account anomeric and reverse anomeric effects,[6] and the fact that the incoming phenylselenyl group may be directed in its addition through complexation with polar groups (*e.g.*, —OMe). In the case of 2-methoxy-3,4-dihydro-2*H*-pyran (entry 4), some

TABLE. Alkoxyselenation of 3,4-dihydro-2*H*-pyrans.

Entry	Dihydropyran[a]	Alcohol	Reaction solvent	% Products (A)[a]/(B)[b]	% Combined yield
1	X,Y = H	MeOH	THF	—	90
2	X = H; Y = $CH_2CH_2OCH_2Ph$	MeOH	THF	71/29	71
		$PhCH_2OH$	THF	71/29	76
		Bu^tOH	THF	83/17	44
3	X = CH_2OMe; Y = H	MeOH	THF	34/66[d]	62
		MeOH	C_6H_6	39/61[d]	72
		MeOH	CCl_4	70/30[d]	62
4	X = OMe; Y = H	MeOH	THF	43/47 + 10%C[e]	66
		MeOH	CH_2Cl_2	53/17 + 30%C[e]	66
		MeOH	CCl_4	33/55 + 12%C[d,e]	70
5	X = CO_2Me; Y = H	MeOH	THF	66/34[d]	62

a b c



(A) (B)

[d] Product ratios determined by ^1H n.m.r. integrations. [e] C = $(MeO)_2CH[CH_2]_2CH(SePh)CHO$.

of the novel ring-opened selenenylated 1,5-dialdehyde containing a masked carbonyl group was also produced.

With this stereochemical information, we have also now investigated the *syn* elimination reaction of these selenides. The stereoisomers A and B of entry 2 (R = Me), which were separated by chromatography, were each oxidized with sodium metaperiodate ($NaHCO_3$, $MeOH–H_2O$), and the selenoxides then refluxed in CCl_4 in the presence of $CaCO_3$ for 15 min to effect elimination. The isomeric 2-methoxy-5,6-dihydro-2*H*-pyrans formed in $> 95\%$ yield exhibited distinct chemical shift differences in their ^1H n.m.r. spectra thus providing further substantiation for the original stereochemical assignments. The other selenides could be converted into their respective alkoxydihydropyrans in a comparable fashion.

The overall yield (67%) for the conversion of (**3**)→(**2**) (R = Me) was quite satisfactory, thus emphasizing the importance of the alkoxyselenation reaction as an alternative to bromoalkoxylation in effecting this synthetic transformation.

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