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Diastereospecific Hydroxyselenation of Cyclohex-2-enyl Phenylglycinates

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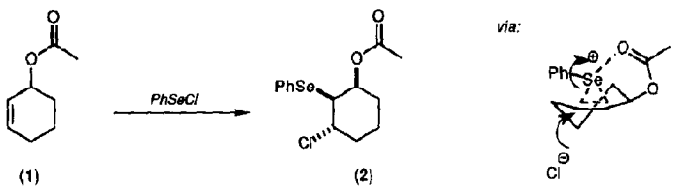
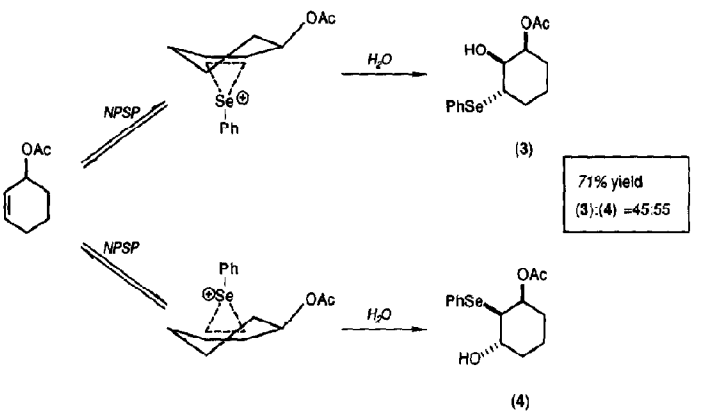
Abstract: *Cyclohex-2-enyl esters of homochiral (R)-2-phenylglycine undergo completely regio- and diastereospecific addition reactions with N-phenylselenophthalimide. The resulting selenoalcohols are separable by routine chromatography and may be converted into homochiral 1,3-cyclohexanediols in which the hydroxyl groups are differentiated.*

The reaction of 1-acetoxycyclohex-3-ene (1) with phenylselenenyl chloride has been studied and claimed to proceed *via* neighbouring group participation of one of the lone pairs of the carbonyl oxygen, leading to 1,2-*cis*-2,3-*trans*-3-chloro-1-hydroxy-2-selenenylcyclohexanes (2) (scheme 1).[1] Given this



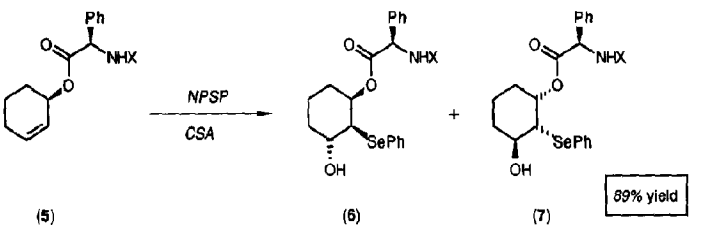
SCHEME 1

admirable specificity, we wished to extrapolate these observations and study a corresponding hydroxyselenenylation, using a suitable electrophilic selenenylating reagent in the presence of water. The reaction of (1) with N-phenylselenenylphthalimide[2] in the presence of water[3] did, indeed, give a good yield of products arising from 1,2-*trans*-hydroxyselenenylation of the alkene. However, the reaction proceeded to give a 1:1 mixture of regioisomeric hydroxyselenides (3) and (4), thereby indicating no preference in formation of selenonium ion intermediates (scheme 2).[4] This observation is in accord with the absence of face selectivity in other reactions of (1) and is in direct contradiction of the mechanism proposed to explain the diastereospecificity of chloroselenenylation.[1] The reaction of the phenylacetate of cyclohex-2-en-1-ol gave an identical yield of another 1:1 mixture of regioisomers, thus suggesting that the steric influences upon the stereochemical course of the reaction are minimal.



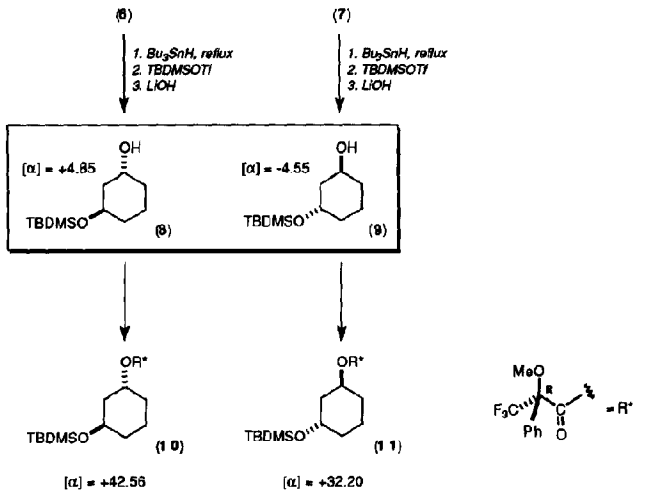
SCHEME 2

However, in a parallel study into the feasibility of intramolecular cyclization reactions, the reaction of the N-benzyloxycarbonyl phenyl glycine ester of cyclohex-2-en-1-ol (**5**) (prepared by reaction of the DBU salt of Z-phenylglycine with 1-bromocyclohex-2-ene in refluxing benzene) under the same conditions was regioselective. Hydroxyselenation of (**5**) using NPSP in the presence of camphor sulfonic acid monohydrate gave the diastereomeric hydroxyselenides (**6**) and (**7**) as the *only products* of the reaction (scheme 3). (**6**) and (**7**) were separable by chromatography.



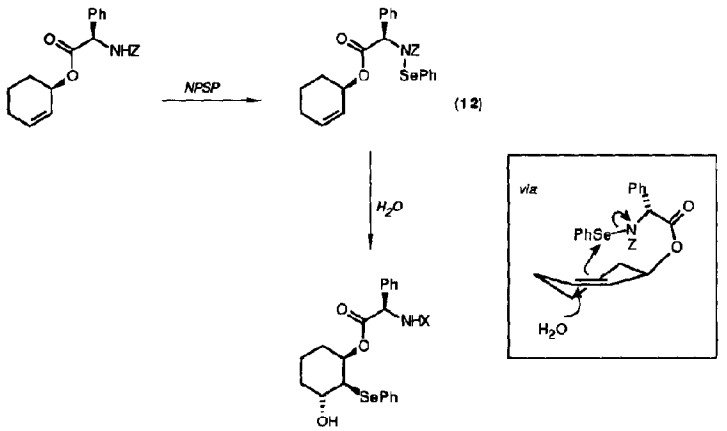
SCHEME 3

This assignment of regiochemistry was confirmed by chemical correlation: homolytic reductive deselenenylation followed by hydroxyl silylation and ester hydrolysis gave monosilylated 1,3-*trans*-dihydroxycyclohexanes (**8**) and (**9**) (scheme 4).[5] A racemic mixture of (**8**) and (**9**) possessed exactly identical analytical data to that previously reported for the racemic material.[6] These compounds could be obtained enantiomerically pure by chromatographic separation of the deselenenylated hydroxy esters. The enantiomeric purity of (**8**) and (**9**) was shown by analysis of their Mosher's esters (**10**) and (**11**) to be at least 95%. The tentative assignment of absolute stereochemistry indicated was determined by analysis of the ^{1}H nmr spectra of (**10**) and (**11**).[7,8] These reactions thus allow rapid preparation of differentially protected homochiral *trans*-cyclohexane 1,3-diols in an efficient manner: the combined yield of (**8**) and (**9**) from cyclohexene is 62%. The reaction is also easily adapted to multigram scale.



SCHEME 4

The reasons for the complete regiocontrol observed in these reactions are at present under investigation in our laboratories: one possible explanation is that there may be an equilibrium process which transfers a phenylselenenyl moiety between the phthalimide nitrogen and the amino ester nitrogen to give an N-selenenylurethane (**12**) which would then facilitate an intramolecular delivery of selenium to only one face of the cycloalkene, as shown in scheme 5. The independent preparation and reactivity of saturated analogues of (**12**) is a focus of our research at this time.



SCHEME 5

Acknowledgement

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References and notes

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2. Nicolaou, K.C.; Claremon, D.A.; Barnette, W.E.; S. P. Seitz, S.P.; *J. Am. Chem. Soc.*, **1979**, *101*, 3704.
3. Nicolaou, K.C.; *Tetrahedron*, **1981**, *37*, 4097.
4. Bange, J.; Haughan, A.F.; Sweeney, J.B.; *Tetrahedron Lett.*, **1993**, manuscript submitted for publication.
5. Data for (**8**):(Found: 230.1727; $C_{12}H_{26}O_2Si$ requires 230.1702); $[\alpha]_D^{24}$ -4.55 (C 1 in EtOAc); ν_{max} (CCl_4)/cm^{-1} 3623 (OH); δ_H (500MHz; $CDCl_3$) 0.02 (3H, s, MeSi), 0.03 (3H, s, MeSi), 0.87 (9H, s, tBu), 1.26-1.82 (8H, m, 4 x CH_2), 4.01-4.06 (1H, m, C<u>H</u>OSitBuMe$_2$), 4.07-4.11 (1H, m, C<u>H</u>OH); δ_C (125MHz; $CDCl_3$) 67.62 (CH), 67.12 (CH), 42.85 (CH_2), 34.63 (CH_2), 33.72 (CH_2), 25.81 (CH_3), 18.92 (CH_2), 18.06 (C), -4.83 (CH^3), -4.86 (CH_3); m/z 230 (M^+, 1.2%), 213 (2.4), 173 (31.1), 171 (43.7), 97 (100), 81 (45.3), 75 (51.4).
   Data for (**9**): Found: 230.1722; $C_{12}H_{26}O_2Si$ requires 230.1702); $[\alpha]_D^{24}$ +4.85 (C 1 in EtOAc); ν_{max} (CCl_4)/cm^{-1} 3623 (OH); δ_H (500MHz; $CDCl_3$) 0.02 (3H, s, MeSi), 0.03 (3H, s, MeSi), 0.87 (9H, s, tBu), 1.26-1.82 (8H, m, 4 x CH_2), 4.01-4.06 (1H, m, C<u>H</u>OSitBuMe$_2$), 4.07-4.11 (1H, m, C<u>H</u>OH); δ_C (125MHz; $CDCl_3$) 67.62 (CH), 67.12 (CH), 42.85 (CH_2), 34.63 (CH_2), 33.72 (CH_2), 25.81 (CH_3), 18.92 (CH_2), 18.06 (C), -4.83 (CH_3), 4.86 (CH_3); m/z 230 (M^+, 1.3%), 213 (2.7), 173 (32.2), 171 (29.9), 170 (22.6), 97 (100), 81 (66.9), 75 (66.6)
6. Evans, D.A.; Fu, G.C.; Hoveyda, A.H.; *J. Am. Chem. Soc.*, **1988**, *110*, 6917.
7. Data for (**10**):Found: 389.1403; $C_{18}H_{24}F_3O_4Si$ requires 389.1396); $[\alpha]_D^{23}$ +32.2 (C 1 in EtOAc); ν_{max} (CCl_4)/cm^{-1} 1754 (CO); δ_H (270MHz; $CDCl_3$) 0.02 (3H, s, MeSi), 0.03 (3H, s, MeSi), 0.87 (9H, s, tBu), 1.37-1.88 (8H, m, 4 x CH_2), 3.54 (3H, brs, OMe), 3.92-4.03 (1H, m, C<u>H</u>OSitBuMe$_2$), 5.36-5.45 (1H, m, C<u>H</u>OH), 7.37-7.45 (3H, m, Ph), 7.50-5.57 (2H, m, Ph); δ_C (67.5MHz; $CDCl_3$) 165.56 (C), 132.43 (C), 129.50 (CH), 128.35 (CH), 127.30 (CH), 123.38 (q, J 288, CF_3), 84.46 (q, J 28, <u>C</u>CF_3), 73.68 (CH), 67.21 (CH), 55.22 (CH_3), 39.36 (CH_2), 34.05 (CH_2), 29.97 (CH_2), 25.76 (CH_3), 18.89 (CH_2), 18.05 (C), -4.91 (CH_3); m/z 389 (M^+-57, 5.4%), 333 (2.5), 309 (3.9), 291 (100), 189 (80.6), 183 (42.8), 81 (66.2), 73 (29.0).
   Data for (**11**): Found: 389.1415; $C_{18}H_{24}F_3O_4Si$ requires 389.1396); $[\alpha]_D^{23}$ +42.6 (C 1 in EtOAc); ν_{max} (CCl_4)/cm^{-1} 1747 (CO); δ_H (270MHz; $CDCl_3$) 0.00 (3H, s, MeSi), 0.01 (3H, s, MeSi), 0.87 (9H, s, tBu), 1.37-1.86 (8H, m, 4 x CH_2), 3.54 (3H, brs, OMe), 3.87-3.98 (1H, m, C<u>H</u>OSitBuMe$_2$), 5.36-5.46 (1H, m, C<u>H</u>OH), 7.37-7.43 (3H, m, Ph), 7.48-7.55 (2H, m, Ph); δ_C (67.5MHz; $CDCl_3$) 165.61 (C), 129.51 (CH), 128.38 (CH), 127.32 (CH), 123.41 (q, J 287.9, CF_3), 84.46 (q, J 28, <u>C</u>CF_3), 73.64 (CH), 67.11 (CH), 55.22 (CH_3), 39.14 (CH_2), 34.06 (CH_2), 30.24 (CH_2), 25.78 (CH_3), 19.08 (CH_2), 18/05 (C), -4.93 (CH_3); m/z 389 (M^+-57, 1.9%), 333 (1.1), 309 (1.8), 291 (399.9), 189 (100), 105 (23.5), 81 (26.7).
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