Diastereoselectivity in the Osmium Tetraoxide Promoted Dihydroxylation of Chiral (*E*)-Crotylsilanes: Asymmetric Synthesis of Silyl-Functionalized γ-Lactones

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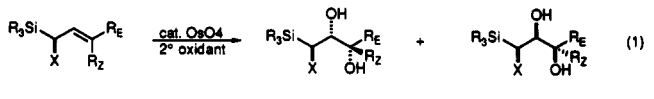
Summary: The catalytic osmylation of enantiomerically enriched (*E*)-crotylsilanes (2*S*,3*R*)-**1** and (2*R*,3*R*)-**2** containing a homoallylic, nitrogen-bearing stereocenter proceeds with good to high levels of diastereoselection generating silyl-functionalized trans-4,5 substituted γ-lactones **3** and **5** as the major diastereomers.

Current efforts in our laboratory are focusing on the development of functionalized (*E*)-crotylsilane reagents for their use as carbon nucleophiles in asymmetric addition reactions.[1,2] In studies designed to further explore the utility of these chiral silanes in the asymmetric synthesis of 6-deoxy hexopyranosides we examined the behavior of these reagents in diastereoselective vicinal dihydroxylation reactions promoted by osmium tetraoxide. Recent reports have appeared documenting the fact that the osmylation reaction of chiral (*E*)- and (*Z*)-crotylsilanes affords vicinal diols with predictable stereochemical outcome and useful levels of selectivity. Those studies are summarized in eq 1.[3] However, the osmylation reaction of chiral allylsilanes



[3a] Fleming et. al.: X = ^{i}Pr, Phenyl	major diastereomer	minor diastereomer
[3b] Vedejs & McClure: X = Me,	minor	major
[3c] Panek & Cirillo: X = OAc, OH	major	minor

possessing a second homoallylic stereocenter has been limited to a single report.[4] In that study essentially no diastereoselection was observed and only moderate levels of double asymmetric induction were reached using the Sharpless osmium-promoted asymmetric dihydroxylation system with dihydroquinidine and dihydroquinine-4-chlorobenzoate catalysts.[5]

The purpose of this paper is to disclose the results of our experiments concerning the utility of chiral (*E*)-crotylsilanes (2*S*,3*R*)-**1** and (2*R*,3*R*)-**2** in diastereoselective vicinal dihydroxylation reactions promoted by osmium tetraoxide affording silyl-functionalized γ-lactones **3** and **5** (eqs 2 and 3). The present study illustrates the utility of these chiral crotylsilane reagents in the development of an effective method for the asymmetric synthesis of 2-azido-2,6-dideoxy-D-*galacto*-hexopyranoside D-**11** and 2-azido-2,6-dideoxy-L-*talo*-hexopyranoside L-**13**. The D-azido hexose **11** is envisioned to act as a precursor to methyl *N*-methyl-2-amino-2,6-dideoxy-α-D-*galacto*-hexopyranoside, the carbohydrate component of the anti tumor agent neocarzinostatin.[6]

In this study a series of α-nitrogen substituted (*E*)-crotylsilanes were surveyed to examine the extent of π-facial selectivity in catalytic osmylation reactions. The choice of nitrogen substituent was based on its chemical stability under the osmylation conditions and to determine if there is evidence of a directed reaction.[7] These include an azide, acetamide, carbamate, and *N*,*N*-dimethylamino functional groups. The results obtained for the osmylations of diastereomerically pure (*E*)-crotylsilanes (2*S*,3*R*)-**1** and (2*R*,3*R*)-**2** are summarized in Tables I and II. Under the prescribed reaction conditions[8] [(i) 5 mol % OsO_4, TMNO (2.2 equiv), acetone/water (20:1), rt; (ii) 5% HCl and extractive isolation] generally high yields and useful levels of diastereoselection were obtained in the formation of the trans-4,5-substituted γ-lactones **3** and **5**. This trend is consistent with the notion that the diastereomer-determining step in these osmylation reactions takes place by addition of the osmium reagent anti to the silyl group.[9] The magnitude of diastereoselectivity was shown to be dependent upon two factors: (i) the type of nitrogen-bearing functional group and (ii) the relative stereochemistry (syn or anti) of the silane reagent.[10] In general, slightly higher levels of selectivity were observed for the syn diastereomers (compare entry 3 in Table I and entry 3 in Table II).

Preparation of α-Nitrogen-Bearing (*E*)-Crotylsilanes. The anti and syn diastereomers of the α-acetamido silanes **1b** and **2b**, α-carbamate substrates **1c**, **1d**, and **2c**, and the dimethylamino derivative **1e**[11] were prepared from the parent α-azido (*E*)-crotylsilanes (2*S*,3*R*)-**1a** and

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(3) (a) Fleming, I.; Sarkar, A. K.; Thomas, A. P. *J. Chem. Soc., Chem. Commun.* **1987**, 157–159. (b) Vedejs, E.; McClure, C. K. *J. Am. Chem. Soc.* **1986**, *108*, 1094–1096. (c) Panek, J. S.; Cirillo, P. F. *J. Am. Chem. Soc.* **1990**, *112*, 4873–4878.

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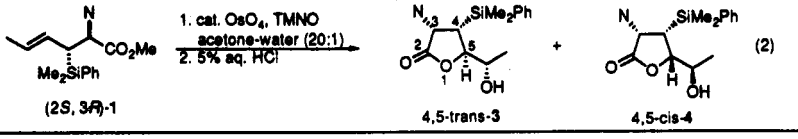
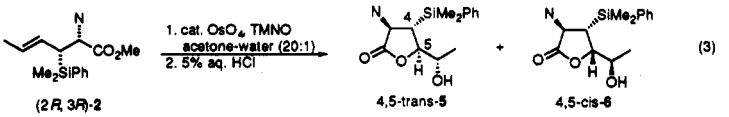
Table I. Diastereoselective Vicinal Dihydroxylation of *anti*-(*E*)-Crotylsilanes 1



entry	silane 1	N	rctn condns,[a] temp (°C) (time (h))	rctn diastereoselect.[b] 4,5-*trans*-3:4,5-*cis*-4	% yield[c]
1	(2*S*,3*R*)-1a	N_3	rt (20)	5:1	95
2	(2*S*,3*R*)-1a	N_3	0 → rt (25)	15:1	89
3	(2*S*,3*R*)-1b	NHAc	rt (21)	11:1	95
4	(2*S*,3*R*)-1c	$NHCO_2Me$	rt (24)	20:1	95
5	(2*S*,3*R*)-1d	$NHCO_2{}^tBu$	rt (24)	40:1	94
6	(2*S*,3*R*)-1e	$N(Me)_2$	rt (21)	14:1	54[d]
7	(2*S*,3*R*)-1e	$N(Me)_2$	0 → rt (24)	23:1	54[d]

[a] All osmylation reactions were run in acetone/H_2O [20:1; with 5 mol % OsO_4 and Me_3N → O (2.2 equiv)], 0.2–0.5 M in substrate. [b] Ratios were determined by ^1H-NMR (at 400 MHz, 93.94 kg) of the crude reaction mixture. [c] All yields were based on a mixture of diastereomeric γ-lactones isolated by chromatography on SiO_2. [d] Yield based on recovered starting material.

Table II. Diastereoselective Vicinal Dihydroxylation of *syn*-(*E*)-Crotylsilanes 2



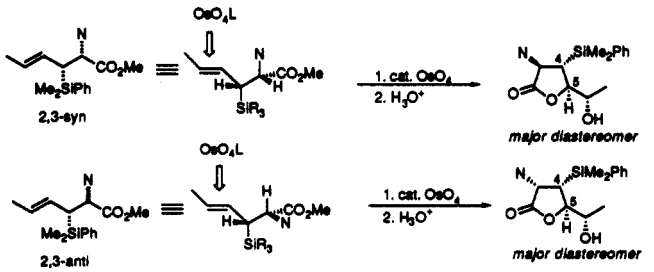
entry	silane 2	N	rxn condns,[a] temp (°C) (time (h))	rctn diastereoselect.[b] 4,5-*trans*-5:4,5-*cis*-6	% yield[c]
1	(2*R*,3*R*)-2a	N_3	rt (20)	7:1	95
2	(2*R*,3*R*)-2a	N_3	0 → rt (21)	26:1	98
3	(2*R*,3*R*)-2b	NHAc	rt (24)	35:1	87
4	(2*R*,3*R*)-2c	$NHCO_2Me$	rt (24)	>50:1	98

[a] All osmylation reactions were run in acetone/H_2O [20:1; with 5 mol % OsO_4 and Me_3N → O, (2.2 equiv)], 0.2–0.5 M in substrate. [b] Ratios were determined by ^1H-NMR (at 400 MHz, 93.94 kg) of the crude reaction mixture. [c] All yields were based on a mixture of diastereomeric γ-lactones isolated by chromatography on SiO_2.

(2*R*,3*R*)-**2a** which were obtained from an electrophilic azidation[12] of the derived β-silyl enolate from (3*S*)-(*E*)-methyl 3-(dimethylphenyl)silylhex-4-enoate and an Ireland–Claisen rearrangement[13] of (3*S*)-(*E*)-1-(dimethylphenylsilyl)buten-3-yl azidoacetate, respectively.

We began this study with the osmylation of (2*S*,3*R*)-methyl 2-azido-3-(dimethylphenylsilyl)-(*E*)-hex-4-enoate (**1a**, entry 1, Table I) which gave a 5:1 ratio (trans/cis) of diastereomeric γ-lactones **3a** and **4a**.[14] Interestingly, both **1a** and the corresponding syn diastereomer (2*R*,3*R*)-**2a**, exhibited higher selectivity when the osmylation reaction was started at 0 °C and allowed to warm to room temperature over 2 h, producing the diastereomeric γ-lactones **3a** and **5a** in a 15:1 and 26:1 ratios, respectively (trans/cis) (entry 2, Tables I and II). The reaction of (2*S*,3*R*)-methyl-2-acetamido-3-(dimethylphenylsilyl)-(*E*)-hex-4-enoate (**1b**, entry 3, Table I) under the standard conditions produced the expected γ-lactone products (**3b** and **4b**) in a combined yield of 95% as a 11:1 mixture of diastereomers. An examination of crotylsilanes possessing two different carbamate groups revealed that the preference for the formation of the trans lactone (osmylation occurs anti to the DMPS group) improved as the size of the carbamate group increased [$NHCO_2Me$ → $NHCO_2{}^t$Bu] (entries 4 and 5, Table I). Finally, the α-*N*,*N*-dimethylamino silane (2*S*,3*R*)-**1e** was also shown to be an effective substrate in the osmylation reaction and exhibited high selectivity in the formation of the trans-4,5-substituted lactone **3e**, but in lower yield (entries 6, 7). Consistent with the osmylation of the α-azido silanes **1a** and **2a** is the fact that the syn diastereomer (2*R*,3*R*)-**2c** exhibited higher selectivity (>50:1) than the anti diaste-

(9) The lack of kinetic evidence concerning these catalytic osmylation reactions invalidates the presumption that the product determining-step is based on the difference in the relative rates (k_{anti}/k_{syn}) of an irreversible addition of the osmium reagent to either face of the diastereotopic allyl silane. Although we have depicted the diastereomer determining-step below with the osmium reagent [OsO_4L] approaching anti to the silyl group, it is necessarily not an accurate representation and should not be considered a valid argument by which to formulate the basis of a mechanistic rationale.



(10) The catalytic osmylation reaction of anti and syn α-methoxy (*E*)-crotylsilanes under the prescribed reaction conditions showed low to modest levels of selectivity (anti/syn 1.5–2.5:1); Ph.D. thesis of M. A. Sparks, Boston University, 1992, unpublished results.

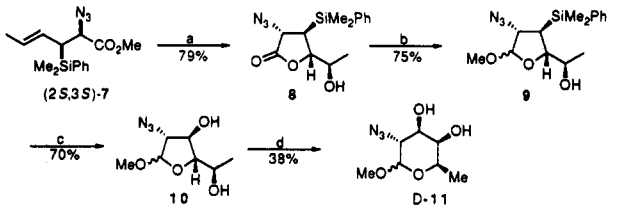
(11) The synthesis of the α-acetamido substrates **1b** and **2b** and α-carbamate substrates **1c,d** and **2c** NaOH/H_2O/^{t}BuOH, 25 °C, 30 min, 75% [cf. Keller, O.; Keller, W. E.; Look, G. Z.; Wersin, G. *Org. Synth.* **1985**, *63*, 160–170], respectively, on the corresponding α-amino esters which were prepared from the parent α-azido-(*E*)-crotylsilanes (2*R*,3*R*)-**1a** and (2*S*,3*R*)-**2a** by mild acid hydrolysis of the intermediate triphenylphosphine imine [(i) $(Ph)_3P$ (1.1 equiv), Et_2O, 0 °C → rt; (ii) 5% HCl]. The α-*N*,*N*-dimethylamino substrate (2*R*,3*R*)-**1e** was prepared in 65% yield by reductive amination of the primary amine [formaldehyde, $NaCNBH_3$ (3.0 equiv), CH_3CN [cf. Borch, R. F.; Hassid, A. I. *J. Org. Chem.* **1972**, *37*, 1673–1674].

(12) Panek, J. S.; Beresis, R.; Xu, F.; Yang, M. *J. Org. Chem.* **1991**, *56*, 7341–7344.

(13) Sparks, M. A.; Panek, J. S. *J. Org. Chem.* **1991**, *56*, 3438–3431.

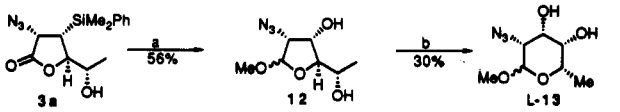
(14) All new compounds were isolated as chromatographically pure materials and exhibited acceptable ^1H NMR, ^{13}C NMR, IR, MS, and HRMS spectral data.

Scheme I[a]



[a] Legend: (a) (i) 5 mol % OsO_4, TMNO (2.2 equiv), acetone–water (20:1); (ii) 5% HCl; (b) (i) DIBAL (3.0 equiv), CH_2Cl_2, −78 °C, (ii) cat. AcCl, MeOH, rt; (c) $Hg(OAc)_2$ (1.5 equiv), CH_3CO_3H/CH_3CO_2H, cat. H_2SO_4; (d) cat. AcCl, MeOH, reflux 24 h (86% based on recovered starting material).

Scheme II[a]



[a] Legend: (a) (i) DIBAL (3.0 equiv), CH_2Cl_2, −78 °C, (ii) cat. AcCl, MeOH, rt, (iii) $Hg(OAc)_2$ (1.5 equiv), CH_3CO_3H/CH_3CO_2H, cat. H_2SO_4; (b) cat. AcCl, MeOH, reflux 24 h (86% yield based on recovered starting material.

reomer (2*S*,3*R*)-**1c** (20:1, compare entry 4, Table I and entry 5, Table II).[15]

Synthesis of D- and L-2-Azido-2,6-dideoxyhexopyranosides. The utility of this process is demonstrated with short syntheses of methyl 2-azido-D-*galacto*-hexopyranoside D-**11** and methyl 2-azido-L-*talo*-hexopyranoside L-**13** (Schemes I and II). The preparation of the D-hexopyranoside **11** began with the catalytic osmylation of diastereomerically pure (2*S*,3*S*)-**7**[12] [(i) 5 mol % OsO_4, TMNO (2.0 equiv) acetone–water (20:1), 0 °C → rt; (ii) 5% HCl] which afforded the γ-lactone **8** ($[\alpha]^{23}_D$ = +82.62, *c* = 0.61, CH_2Cl_2) in 79% yield as a single diastereomer after extractive isolation and chromatography on SiO_2. Reduction with diisobutylaluminum hydride (DIBAL) produced the lactol which was converted to the methyl hexofuranoside **9** in 75% yield after chromatography on SiO_2. Oxidation of the dimethylphenylsilyl (DMPS) group produced the secondary alcohol **10** with complete retention of configuration.[16] Finally, an acid-catalyzed equilibration of the methyl furanoside [AcCl/MeOH, reflux 24 h] provided the desired dideoxyhexopyranoside D-**11** as a 3:1 mixture of α,β-anomers.

The synthesis of the L-*talo*-hexopyranoside **13** is summarized in Scheme II. Lactone **3a** ($[\alpha]^{23}_D$ = +71.8, *c* = 0.1, CH_2Cl_2) was converted to the methyl furanoside and the DMPS group oxidized to the secondary alcohol with retention of configuration producing the (L)-dideoxyhexofuranoside **12**. The final step involved the acid-catalyzed equilibration of **12** affording methyl 2-azido-2,6-dideoxy-L-talopyranoside L-**13** as a 3.6:1 mixture of β/α-anomers.

In conclusion, the use of nearly enantiomerically pure (*E*)-crotylsilanes **1**, **2**, and **7** in catalytic osmylation reactions represents an effective method by which to produce highly functionalized γ-lactones with useful levels of diastereoselectivity. The selectivity exhibited by the silane reagents together with the high degree of functionalization contained in the derived γ-lactones suggest that they may be useful intermediates in asymmetric synthesis. Since the mechanism of the osmylation is not completely understood, the construction of an accurate working model for diastereoface selection in these reactions is not possible and any evidence for a directed reaction is not supported experimentally with kinetic evidence. Further exploration of these reagents and applications are underway in our laboratories and will be reported in due course.

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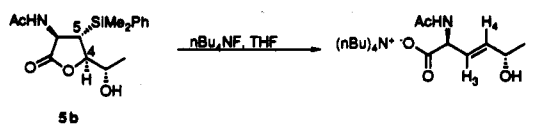
Supplementary Material Available: General experimental procedures for the catalytic osmylation reactions and relative stereochemical assignment as well as spectral data for all reaction products (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(15) Assignment of stereochemistry of the major diastereomer as the trans-4,5 substituted γ-lactones (osmylation anti to silicon) was determined by measurement of the coupling constants for trans olefinic protons ($J_{H3,H4}$) after a fluoride ion promoted opening the γ-lactone **5b** [(i) *n*-Bu_4NF (1.0 equiv)/THF/reflux] afforded a trans-β,γ-unsaturated ester which exhibited a vicinal coupling constant of $^3J_{H3,H4}$ = 15.4 Hz indicating an antiosmylation product (with respect to the DMPS group). Further support of our stereochemical assignment was obtained from the $^3J_{H3,H4}$ values for the product lactones **3** and **5** and the careful ^{1}H-NMR analysis of the derived hexopyranosides D-**11** and L-**13** (vide infra), see supplementary material for details.



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