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An Intramolecular Hydrosilation Approach to Hexahydrooxonins Related to Obtusenyne. Effect of Catalyst and Conditions on Stereoselectivity

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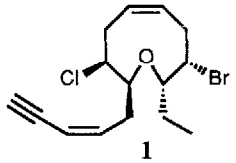
Key Words: Medium ring; Intramolecular hydrosilation; α-Hydroxy enol ether; Hexahydrooxonin; Stereoselectivity

Abstract: The intramolecular hydrosilation of the α-dialkylsilyloxy enol ethers **3** and **5** followed by oxidative work-up resulted in the diastereoselective synthesis of either the hexahydrooxonin diol **7** or **8** according to the catalyst and conditions employed.

Our strategy for the synthesis of the *Laurencia* natural product obtusenyne **1**, and related metabolites, involved preparation of the differentially protected hexahydrooxonin triol **2** (Figure 1).[1] A key transformation in the synthetic sequence to the racemic hexahydrooxonin **2** was intramolecular hydrosilation of the α-dimethylsilyloxy enol ether **3**.[1] This *Letter* describes the stereochemical outcome of the hydrosilation reaction using a variety of catalysts and conditions.



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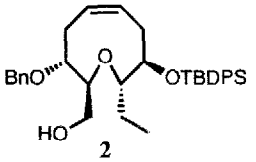

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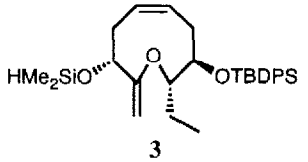


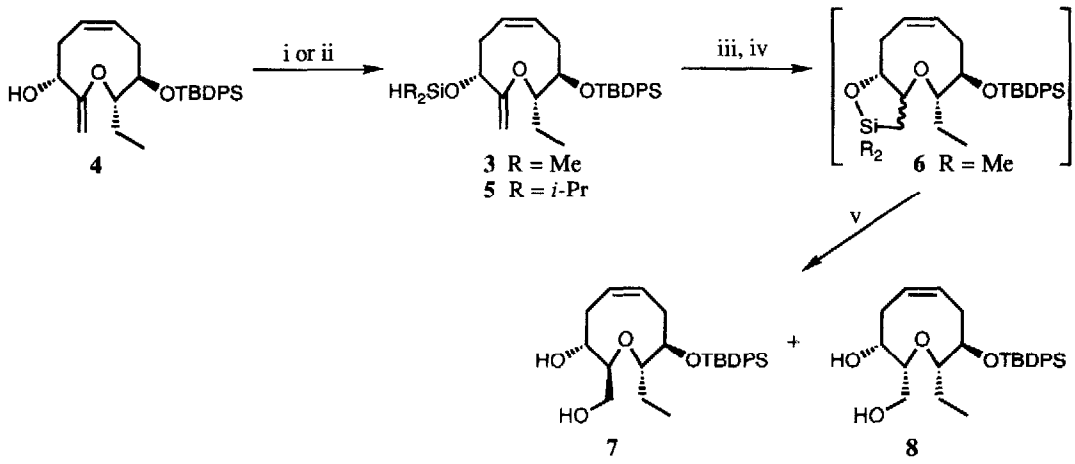
3

Figure 1

Recently, Tamao and Ito described the intramolecular hydrosilation of acyclic α-hydroxy enol ethers as a highly selective route to polyhydroxylated molecules,[2] a development of methodology previously applied to reactions of allyl and homoallyl alcohols.[3,4] Anwar and Davis have also reported the diastereoselective intramolecular hydrosilation of an allylic alcohol derivative, although they utilised somewhat different reagents and conditions.[5] Tamao and Ito observed the selective formation of *syn*-products from the intramolecular hydrosilation of acyclic α-hydroxy enol ethers;[2] the analogous reaction of the enol ether **3** would be predicted to favour the epimeric C-2 relative stereochemistry compared with the isomer **2** required for elaboration to obtusenyne **1**. However, it was far from clear at the outset of this study whether the cyclic compound **3** would give the same sense of stereocontrol as the acyclic examples reported. We describe in this *Letter* the results of such a study, and show that the diastereocontrol depends significantly on the conditions of the reaction.

The unstable α-dimethylsilyloxy enol ether **3** was prepared by heating the hydroxy compound **4**[1] with an excess of 1,1,3,3-tetramethyldisilazane, in the presence of a catalytic quantity of ammonium chloride,[2] and was used without purification (Scheme). The intramolecular hydrosilation experiments were carried out by treatment

of the enol ether **3** with a platinum or rhodium catalyst, under the conditions detailed in Table 1, followed by removal of the catalyst by stirring with ethylenediaminetetraacetic acid (EDTA) in hexane to afford the presumed silacycle intermediate **6**.[6,7] This was oxidatively cleaved,[2,8] without purification, to give a mixture of the hexahydrooxonin diols **7** and **8** (Scheme).



Scheme

Reagents and conditions: i, $(HMe_2Si)_2NH$ (excess), cat. NH_4Cl, 60 °C (quantitative); ii, *i*-Pr_2HSiCl, Et_3N, THF (92%); iii, conditions A, B or C (see Tables); iv, EDTA.2Na.$2H_2O$; v, H_2O_2, KOH, THF, MeOH.

The relative stereochemistry of the diols was assigned by spectroscopic analysis of the corresponding acetonides **9** and **10** (Figure 2). The observed ^1H NMR coupling constants between the protons attached to C-2 and C-3 enabled the assignment of relative stereochemistry, assuming that the six-membered rings adopted chair conformations.[9] In addition, a strong nOe between H_2 and H_9 (18%) of the acetonide **10**, indicated the *cis*-relationship of the C-2 and C-9 substituents.

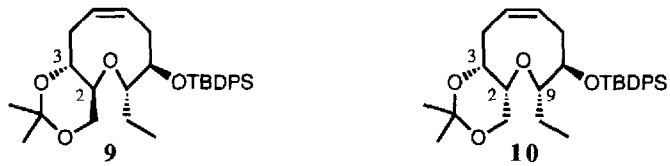


Figure 2

Intramolecular hydrosilation of the α-dimethylsilyloxy enol ether **3** with bis(1,3-divinyl-1,1,3,3-tetramethyldisiloxane)platinum(0),[11,12,13] the catalyst found most effective by Tamao,[2] gave the *cis*-oxonin diol **8** predominantly (Table 1, entry 1). Initial experiments had given variable ratios of the diols **7** and **8**, under apparently identical conditions. The inconsistent results were attributed to the presence of trace amounts of 1,1,3,3-tetramethyldisilazane, since exhaustive drying *in vacuo* of the enol ether **3** gave reproducible *cis*-selectivity. Indeed, addition of 10 mol% of 1,1,3,3-tetramethyldisilazane reversed the product selectivity (entry 2), giving the *trans*-diol **8** predominantly. The exess disilazane presumably modified the catalyst in some way, although the exact nature of this modification is not presently clear. Anwar and Davis have used Wilkinson's catalyst [tris(triphenylphosphine)rhodium(I) chloride] in refluxing THF for the *syn*-selective intramolecular hydrosilation of 2-methyl-3-diisopropylsilyloxyhept-1-ene.[5] Reaction of the enol ether **3** under these conditions

gave the *trans*-diol **7** with good selectivity (entry 3). The yield was moderate owing to partial cleavage of the dimethylsilyl group under the reaction conditions. Excellent selectivity for the required diol **7** (for obtusenyne **1**) was observed when (acetylacetonato)(norbornadiene)rhodium(I) was used as the catalyst (entry 4).[1,14] Use of the platinum(0)/vinylsiloxane catalyst in refluxing THF (optimum reaction conditions employed with the rhodium(I) catalysts) (entry 5) again gave predominantly the *cis*-diol **8** (*cf.* entry 1). Finally, use of the rhodium catalyst in toluene resulted in poor selectivity and incomplete reaction (entry 6).

Table 1. Intramolecular Hydrosilation of α-Dimethylsilyloxy Enol Ether **3**

Entry	Catalyst	Conditions	7 : 8	Yield (7+8)
1	$Pt\{[(CH_2{=}CH)Me_2Si]_2O\}_2$	**A**	16 : 84	72%
2	$Pt\{[(CH_2{=}CH)Me_2Si]_2O\}_2$ + $(HMe_2Si)_2NH$ (10 mol%)	**A**	83 : 17	84%
3	$Rh(PPh_3)_3Cl$	**B***	83 : 17	59%
4	$Rh(acac)(C_7H_8)$	**B**	≥ 95 : ≤ 5†	61%
5	$Pt\{[(CH_2{=}CH)Me_2Si]_2O\}_2$	**B**	12 : 88	57%
6	$Rh(acac)(C_7H_8)$	**A**	58 : 42	32%¶

Conditions: **A**, 2 mol% catalyst (0.1M in toluene), RT, 3h; **B**, 2 mol% catalyst, THF, reflux, 16h.
* No reaction at RT. ¶ Reaction had not gone to completion in 3h. † Ratio determined by ^1H NMR, otherwise the ratio shown refers to isolated compounds.

The intramolecular hydrosilation of the α-dimethylsilyloxy enol ether **3** using either rhodium(I) catalyst (Table 1, entries 3,4), followed by oxidative cleavage, gave the *trans*-oxonin diol **7** selectively, but in moderate yield due to competitive loss of the silyl group. Anwar and Davis had found that diisopropylsilyl derivatives were far more stable than the corresponding dimethylsilyl compounds.[5] The α-diisopropylsilyloxy enol ether **5**, prepared from the hydroxy compound **4** (Scheme), was indeed found to be stable on silica gel, and hydrosilation studies were performed. The ratios of the oxonin diols **7** and **8** obtained *via* intramolecular hydrosilation of the enol ether **5** (Table 2) were comparable to those found with the enol ether **3** (Table 1). Unfortunately, the expected increase in yield was not realised. It appeared that the intramolecular hydrosilation of the α-diisopropylsilyloxy enol ether **5** favoured formation of the *cis*-diol **8** to a greater extent than the corresponding hydrosilation of the α-dimethylsilyloxy enol ether **3**, although catalyst selectivity seemed to override substrate control.

Table 2. Intramolecular Hydrosilation of α-Diisopropylsilyloxy Enol Ether **5**

Entry	Catalyst	Conditions	7 : 8	Yield (7+8)
1	$Rh(PPh_3)_3Cl$	**B**	64 : 36	73%
2	$Rh(acac)(C_7H_8)$	**B**	92 : 8†	57%
3	$Pt\{[(CH_2{=}CH)Me_2Si]_2O\}_2$	**C***	9 : 91†	56%

Conditions: **B**, 2 mol% catalyst, THF, reflux, 16h; **C**, 2 mol% catalyst (0.1M in toluene), 60 °C, 16h;
* No reaction at RT. † Ratio determined by ^1H NMR, otherwise the ratio shown refers to isolated compounds.

The stereochemical outcome of the intramolecular hydrosilation of the enol ethers **3** and **5** depended on the catalyst and conditions employed. The 2,3-*syn* product, the *cis*-diol **8**, predominated in the presence of the platinum(0)/vinylsiloxane catalyst, although addition of 1,1,3,3-tetramethyldisilazane reversed the selectivity. Rhodium(I) catalysts in refluxing THF favoured the 2,3-*anti* product, *i.e.* *trans*-diol **7**. Tamao and Ito proposed a preferred cyclic transition state resulting from allylic strain effects to account for their observation of *syn*-selectivity.[2] The reasoning concentrated on the steric and electronic requirements of the enol ether substituents and did not consider interactions with the metal ligands. A lack of information about the likely preferred conformations of the enol ethers **3** and **5**, and therefore the possible effects that any metal ligands may exert on the transition state structure, precludes any confident explanation of the intramolecular hydrosilation results reported here. However, it appeared that the nature of the catalyst exerted the dominant influence on the reaction.

In summary, the intramolecular hydrosilation-oxidation sequence afforded selective access to either the *trans*-diol **7**, required for our route to obtusenyne **1**,[1] or the *cis*-diol **8**, depending on the choice of conditions. Application of this methodology to the synthesis of other medium-ring cyclic ethers is an attractive possibility.

Acknowledgements

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