

Proceedings

Intramolecular Cyclization of Alkenyl Alcohols: Towards the Synthesis of Oxacycles †

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Abstract: The presence of tetrahydropyrans, and other sized oxacycles, in natural products with interesting pharmacological properties has prompted researchers to try to develop new strategies for their selective synthesis. Moreover, these methodologies enable the introduction of structural modifications in the molecule for the synthesis of analogues with potential biological activity. An attractive atom economy process for the synthesis of these scaffolds is the intramolecular hydroalkoxylation of alkenes. However, this method has several drawbacks (such as the lack of generality and the presence of multiple side reactions) which have diminished its development. For many years our research group has been devoted to develop different strategies for the regio- and stereoselective synthesis of oxygen and nitrogen heterocycles. Herein we present our results on the effective acid catalyzed cyclization of alkenyl alcohols which bear a silyl group in their structure. As we will show, the presence of the silicon group is necessary for the cyclization to take place. Moreover, the cyclization towards tetrahydropyrans occurs with high stereoselectivity.

Keywords:

1. Introduction

Tetrahydropyrans are very important organic molecules which occur in a variety of bioactive natural products. An example of natural compound containing tetrahydropyrans is erythromycin, an antibiotic macrolide that decreases bacteria protein production [1]. This antibiotic was collected from bacteria *Saccharopolyspora erythraea* and is used to treat skin and respiratory infections produced by bacteria such as *Streptococcus* and *Staphylococcus*. The importance of these natural products is based on their interesting properties. However, due to their low availability in nature, many research groups have developed synthetic routes to access this type of heterocycles. In addition, synthesising a molecule has the great advantage of introducing different substituents that modify the main structural core in order to create analogues with potential biological activity.

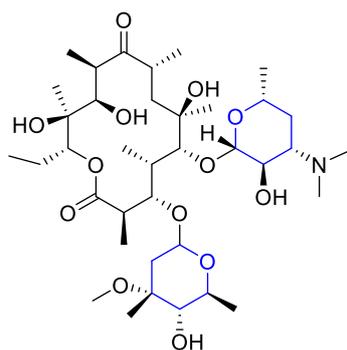


Figure 1. Erythromycin.

Different routes have been proposed for the stereoselective synthesis of tetrahydropyrans, some of them based on ring formation by nucleophilic substitution, annulations with epoxides or alkene-mediated cyclizations [2].

However, despite its simplicity and atom economy efficiency, very few reported methods are based on the intramolecular cyclization of an alkenol in the presence of Brønsted [3] or Lewis [4] acids. In order to overcome the lack of generality (and frequent side reactions that result in low yields) of this type of cyclizations [5], we herein propose the use of organosilanes to reduce the undesirable reactions of this process [6]. In this paper, we present a regio- and stereoselective methodology for the synthesis of tetrahydropyrans based on an intramolecular acid catalysed cyclization of alkenyl alcohols which bear a silyl group [7].

2. Methods

2.1. General Procedure of Silylcupration of Alkynes and Reaction with *A,B*-Unsaturated Ketone

To a suspension of CuCN (12 mmol) in dry THF (8 mL), 12 mmol of phenyldimethylsilyllithium were added and the mixture stirred at 0 °C for 30 min. The solution was then cooled to -40 °C and 12 mmol of the alkyne were added. After 1 h at this temperature, BF₃·Et₂O was added and the solution stirred for 10 min. The ketone (8.4 mmol) was then dropped in and the mixture stirred at -40 °C for 1 h. After warming to 0 °C, the mixture was quenched with a saturated solution of NH₄Cl/NH₃. The aqueous layer is extracted three times with Et₂O. Organic layers, together, are washed with saturated solution of NH₄Cl/NH₃; dried over MgSO₄, filtered and evaporated in vacuo. Products are purified by flash chromatography (hexane/EtOAc 20:1) to give:

2.1.1. (E)-6-Dimethylphenylsilyl-4-phenyl-5-trimethylsilylhex-5-en-2-one 1

¹H RMN (400 MHz, CDCl₃) δ 7.63–7.52 (m, 2H, Ph), 7.37–7.29 (m, 3H, Ph), 7.21–7.08 (m, 3H, PhMe₂Si), 6.99–6.87 (m, 2H, PhMe₂Si), 6.29 (s, 1H, CH=C), 4.44 (dd, *J* = 11.2, 3.6 Hz, 1H, CH-Ph), 3.13 (dd, *J* = 17.3, 11.2 Hz, 1H, CH₂), 2.33 (dd, *J* = 17.3, 3.6 Hz, 1H, CH₂), 1.90 (s, 3H, CH₃), 0.52 (s, 3H, PhMe₂Si), 0.46 (s, 3H, PhMe₂Si), -0.21 (s, 9H, SiMe₃); ¹³C RMN (101 MHz, CDCl₃) δ 206.5 (C=O), 169.0 (C=), 141.0 (CH=), 139.5 (C, Ph), 133.9 (CH, Ph), 133.8 (C, Ph), 128.9 (CH, Ph), 128.1 (CH, Ph), 127.9 (CH, Ph), 127.6 (CH, Ph), 126.2 (CH, Ph), 47.6 (CH-Ph), 46.6 (CH₂), 29.6 (CH₃), 0.6 (3xCH₃, Me₃Si), -0.6 (CH₃, PhMe₂Si), -1.1 (CH₃, PhMe₂Si).

2.1.2. (Z)-5-Butyl-6-dimethylphenylsilyl-4-phenyl-hex-5-en-2-one 2

¹H RMN (500 MHz, CDCl₃) δ 7.61 (m, 2H, Ph), 7.36 (m, 3H, Ph), 7.22–7.10 (m, 3H, PhMe₂Si), 6.95 (m, 2H, PhMe₂Si), 5.48 (s, 1H, CH=C), 4.30 (dd, *J* = 10.9, 4.2 Hz, 1H, CH-Ph), 3.09 (dd, *J* = 16.8, 10.9 Hz, 1H, CH₂), 2.39 (dd, *J* = 16.8, 4.2 Hz, 1H, CH₂), 1.87 (s, 3H, CH₃), 1.32–1.25 (m, 2H, CH₂, Bu), 1.18–1.13 (m, 2H, CH₂, Bu), 0.87–0.85 (m, 2H, CH₂, Bu), 0.78 (t, *J* = 7.1 Hz, 3H, CH₃, Bu), 0.52 (s, 3H, PhMe₂Si), 0.46 (s, 3H, PhMe₂Si); ¹³C RMN (126 MHz, CDCl₃) δ 206.6 (C=O), 162.0 (C=), 140.8 (C, Ph), 139.9 (C, Ph),

134.0 (CH, Ph), 128.9 (CH, Ph), 128.2 (CH, Ph), 127.9 (CH, Ph), 127.5 (CH, Ph), 126.2 (CH, Ph), 121.8 (CH=), 46.9 (CH-Ph), 46.1 (CH₂), 33.2 (CH₂, Bu), 30.8 (CH₂, Bu), 29.6 (CH₃), 22.5 (CH₂, Bu), 13.95 (CH₃, Bu), -0.63 (CH₃, PhMe₂Si), -1.0 (CH₃, PhMe₂Si).

2.1.3. (Z)-4-Isopropyl-6-phenyldimethylsilyl-5-hexen-2-one 3

¹H NMR (CDCl₃, 300 MHz) δ = 7.60–7.57 (m, 2 H), 7.37–7.35 (m, 3 H), 6.24 (dd, *J* = 14.0, 10.5 Hz, 1 H), 5.71 (d, *J* = 14.0 Hz, 1 H), 2.60–2.52 (m, 1 H), 2.42 (dd, *J* = 15.2, 5.9 Hz, 1 H), 2.25 (dd, *J* = 15.2, 7.5 Hz, 1 H), 1.99 (s, 3 H), 1.58 (sept., *J* = 6.3 Hz, 1 H), 0.82 (d, *J* = 6.3 Hz, 3 H), 0.80 (d, *J* = 6.3 Hz, 3 H), 0.45 (s, 6 H); ¹³C NMR (CDCl₃, 150 MHz) δ = 208.3 (C), 151.1 (CH), 139.8 (C), 134.0 (CH), 129.0 (CH), 128.7 (CH), 127.9 (CH), 46.5 (CH₂), 44.6 (CH), 31.8 (CH), 30.7 (CH₃), 20.0 (CH₃), 19.2 (CH₃), -0.6 (CH₃), -0.8 (CH₃).

2.2. Synthesis of Alkenyl Ketones

Vinylmagnesiumbromide (9 mmol) is added during 10 min to a solution of CuI (3 mmol) in dry THF (40 mL) and the mixture stirred under N₂ at -5 °C for 15 min. Then, the reaction mixture is cooled to -30 °C and a solution of the ketone (3 mmol) in dry THF (10 mL) is slowly added for 1 h. 30 min after the addition is completed the reaction is quenched with 20 mL of a saturated solution of NH₄Cl. The aqueous layer is extracted three times with Et₂O. Organic layers, together, are washed with saturated solution of NH₄Cl, first, and NaCl, second; dried over MgSO₄, filtered and evaporated in vacuo. Products are purified by flash chromatography (hexane/EtOAc 10:1) to give:

4.- Phenylhex-5-en-2-one 4

¹H RMN (400 MHz, CDCl₃) δ 7.32–7.26 (m, 2H, Ph), 7.22–7.16 (m, 3H, Ph), 5.95 (ddd, *J* = 17.1, 10.3, 6.8 Hz, 1H, CH=), 5.05 (dd, *J* = 10.3, 1.3 Hz, 1H, CHH=), 5.00 (dd, *J* = 17.1, 1.3 Hz, 1H, CHH=), 3.92–3.89 (m, CH-Ph), 2.85 (dd, *J* = 16.3, 8.0 Hz, 1H, CHH), 2.80 (dd, *J* = 16.3, 6.9 Hz, 1H, CHH), 2.07 (s, 3H, CH₃); ¹³C RMN (101 MHz, CDCl₃) δ 207.0 (C=O), 142.8 (C, Ph), 140.5 (CH=), 128.6 (CH, Ph), 127.6 (CH, Ph), 126.6 (CH, Ph), 114.6 (CH₂=), 49.0 (CH₂), 44.5 (CH-Ph), 30.6 (CH₃).

2.3. General Procedure for the Synthesis of Alkenyl Epoxides

To a solution of trimethylsulfonium iodide (2 mmol) in dry THF (15 mL), n-BuLi (2 mmol) was added dropwise and the mixture was stirred under N₂ at 0 °C for 1 h. Then, a solution of the ketone (1.35 mmol) in dry THF (10 mL) was added. The reaction is quenched with saturated solution of NaCl (15 mL). The aqueous layer is extracted three times with Et₂O. Organic layers are washed with saturated solution of NaCl; dried over MgSO₄, filtered and evaporated in vacuo. Products are purified by flash chromatography (hexane/EtOAc 20:1) to give:

2.3.1. (E)-2-Methyl-6-dimethylphenylsilyl-4-phenyl-5-trimethylsilylhex-5-ene 5

¹H RMN (500 MHz, CDCl₃) δ 7.65–7.60 (m, 2H, Ph), 7.39–7.33 (m, 3H, Ph), 7.20–7.16 (m, 2H, PhMe₂Si), 7.14–7.10 (m, 1H, PhMe₂Si), 7.05–7.00 (m, 2H, PhMe₂Si), 6.23 (s, 1H, CH=C), 3.90 (dd, *J* = 10.6, 3.8 Hz, 1H, CH-Ph), 2.43 (dd, *J* = 15.2, 10.6 Hz, 1H, CHH), 2.38 (d, *J* = 4.6 Hz, 1H, CHH-O), 2.38 (d, *J* = 4.6 Hz, 1H, CHH-O), 1.94 (dd, *J* = 15.2, 3.8 Hz, 1H, CHH), 1.21 (s, 3H, CH₃), 0.54 (s, 3H, PhMe₂Si), 0.51 (s, 3H, PhMe₂Si), -0.21 (s, 9H, SiMe₃); ¹³C RMN (126 MHz, CDCl₃) δ 170.0 (C=), 141.8 (C, Ph), 140.0 (CH=), 139.8 (C, Ph), 133.9 (CH, Ph), 128.9 (CH, Ph), 128.3 (CH, Ph), 127.9 (CH, Ph), 127.8 (CH, Ph), 126.0 (CH, Ph), 55.8 (C-O), 53.5 (CH₂-O), 47.8 (CH-Ph), 37.9 (CH₂), 22.5 (CH₃), 0.7 (3xCH₃, Me₃Si), -0.7 (CH₃, PhMe₂Si), -0.7 (CH₃, PhMe₂Si).

2.3.2. (Z)-5-Butyl-2-methyl-6-dimethylphenylsilyl-4-phenyl-1,2-epoxy-hex-5-ene 6

¹H RMN (500 MHz, CDCl₃) δ 7.65–7.60 (m, 2H, Ph), 7.40–7.35 (m, 3H, Ph), 7.20–7.10 (m, 3H, PhMe₂Si), 7.00–6.96 (m, 2H, PhMe₂Si), 5.40 (s, 1H, CH=C), 3.83 (dd, *J* = 10.1, 4.7 Hz, 1H, CH-Ph), 2.36–2.31 (m, 3H), 1.92 (dd, *J* = 14.9, 4.7 Hz, 1H, CHH), 1.91–1.87 (m, 1H), 1.75–1.69 (m, 1H), 1.29–1.24 (m, 1H, CH₂, Bu), 1.18–1.09 (m, 3H, CH₂, Bu), 1.13 (s, 3H, CH₃), 0.77 (t, *J* = 7.2 Hz, 3H, CH₃, Bu), 0.52 (s, 3H, PhMe₂Si),

0.49 (s, 3H, PhMe₂Si); ¹³C RMN (126 MHz, CDCl₃) δ 163.0 (C=), 141.7 (C, Ph), 140.2 (C, Ph), 134.0 (CH, Ph), 128.9 (CH, Ph), 128.0 (CH, Ph), 128.0 (CH, Ph), 127.9 (CH, Ph), 126.1 (CH, Ph), 120.9 (CH=), 55.9 (C-O), 53.4 (CH₂-O), 47.4 (CH-Ph), 37.8 (CH₂), 32.9 (CH₂), 30.9 (CH₂), 22.6 (CH₂), 22.2 (CH₃), 14.0 (CH₃, Bu), -0.5 (CH₃, PhMe₂Si), -0.6 (CH₃, PhMe₂Si).

2.3.3. (Z)- 4-Isopropyl-6-phenyldimethylsilyl-2-methy-1,2-epoxy-5-hexene 7

¹H RMN (300 MHz, CDCl₃) δ 7.59–7.56 (m, 2H), 7.38–7.37 (m, 3H), 6.24 (dd, *J* = 14.0 y 10.5 Hz, 1H), 5.70 (d, *J* = 14.0 Hz, 1H), 2.55 (d, *J* = 4.8 Hz, 1H), 2.51–2.42 (m, 1H), 2.28–2.08 (m, 1H), 1.78 (dd, *J* = 13.6 y 3.9 Hz, 1H), 1.72–1.61 (m, 1H), 1.27–1.19 (m, 1H), 1.12 (s, 3H), 0.85–0.79 (m, 6H), 0.43 (s, 6H); ¹³C-RMN (CDCl₃, 150 MHz) δ 153.9 (CH), 139.7 (C), 134.0 (CH), 129.1 (CH), 128.0 (CH), 127.8 (CH), 56.4 (C), 54.7 (CH₂), 45.3 (CH), 39.3 (CH₂), 32.6 (CH), 21.0 (CH₃), 19.4 (CH₃), 19.3 (CH₃), -0.27 (CH₃), -0.51 (CH₃).

2.3.4. 2-. methyl-2-(2-phenylbut-3-en-1-yl)oxirane 8

¹H RMN (400 MHz, CDCl₃) δ 7.32–7.28 (m, 2H, Ph), 7.20 (m, 3H, Ph), 6.06–5.97 (m, 1H, CH=), 5.08–4.99 (m, 2H, CH₂=), 3.49–3.42 (m, 1H, CH-Ph), 2.62 (d, *J* = 4.7 Hz, 1H, CH₂-O), 2.54 (d, *J* = 4.7 Hz, 1H, CH₂-O), 2.18–2.15 (m, 1H, CHH), 1.83–1.76 (m, 1H, CHH), 1.30 (s, 3H, CH₃); ¹³C RMN (101 MHz, CDCl₃) δ 143.5 (C, Ph), 141.8 (CH=), 128.5 (CH, Ph), 127.6 (CH, Ph), 126.5 (CH, Ph), 114.1 (CH₂=), 55.8 (C-O), 54.2 (CH₂-O), 46.4 (CH-Ph), 42.8 (CH₂), 21.1 (CH₃).

2.4. Procedure of Synthesis of Primary Alcohols

To a solution of triphenylphosphine (0.078 mmol) in dry hexane (10 mL), was added a solution of the epoxide (0.65 mmol) in dry hexane (1 mL). Then, trimethylaluminium (1.95 mmol) is added dropwise and the reaction stirred for 1 h. The reaction is then quenched with saturated solution of NaCl (10 mL). The aqueous layer is extracted three times with Et₂O. Organic layers are washed with saturated solution of NaCl; dried over MgSO₄, filtered and evaporated in vacuo. Stable products are purified by flash chromatography (hexane/EtOAc 10:1) and characterised by spectroscopy techniques to give:

2.,2-. dimethyl-4-phenylhex-5-en-1-ol 12

¹H RMN (400 MHz, CDCl₃) δ 7.28 (m, 2H, Ph), 7.22–7.14 (m, 3H, Ph), 5.98 (ddd, *J* = 17.7, 10.2, 7.9 Hz, 1H, CH=), 5.01–4.89 (m, 2H, CH₂=), 3.44–3.39 (m, 1H, CH-Ph), 3.24 (d, *J* = 11.1 Hz, 1H, CHH-OH), 3.18 (d, *J* = 11.1 Hz, 1H, CHH-OH), 1.79 (dd, *J* = 14.3, 6.7 Hz, 1H, CHH), 1.74 (dd, *J* = 14.3, 6.5 Hz, 1H, CHH), 0.88 (s, 3H, CH₃), 0.83 (s, 3H, CH₃); ¹³C RMN (101 MHz, CDCl₃) δ 145.8 (C, Ph), 144.2 (CH=), 128.6 (CH, Ph), 127.5 (CH, Ph), 126.2 (CH, Ph), 113.3 (CH₂=), 71.4 (CH₂-OH), 46.3 (CH-Ph), 44.0 (CH₂), 36.1 (C), 24.6 (CH₃), 14.5 (CH₃).

2.5. Synthesis of Tetrahydropyrans

To a stirred solution of one of the previous synthesised alcohols (0.3 mmol) in dry DCM (5 mL) was added the acid. The reaction progress is followed by TLC. When the reaction is over, it was quenched with saturated solution of NaCl (5mL). The aqueous layer is extracted three times with Et₂O. Organic layers are washed with saturated solution of NaCl; dried over MgSO₄, filtered and evaporated in vacuo. Products are purified by flash chromatography (hexane/EtOAc 20:1) and characterised by spectroscopy techniques to give:

2.5.1. 3-. Isopropyl-5,5-dimethyl-2-dimethylphenylsilylmethyltetrahydropyran 13

¹H NMR (300 MHz, CDCl₃) δ 7.55–7.52 (m, 2H), 7.34–7.32 (m, 3H), 3.35 (dd, *J* = 11.0, 2.7 Hz, 1H), 3.06 (td, *J* = 10.3, 3.1 Hz, 1H), 2.92 (d, *J* = 11.0, 1H), 1.89–1.82 (m, 1H), 1.38–1.32 (m, 1H), 1.30–1.25 (m, 1H), 1.17 (dd, *J* = 14.8, 3.1 Hz, 1H), 0.98 (s, 3H, CH₃), 1.00–0.97 (m, 1H), 0.90 (dd, *J* = 14.8, 10.3 Hz, 1H), 0.81 (d, *J* = 7.0 Hz, 3H, CH₃), 0.78 (s, 3H, CH₃), 0.63 (d, *J* = 6.9 Hz, 3H, CH₃), 0.31 (s, 3H, CH₃-Si), 0.30 (s, 3H, CH₃-Si); ¹³C NMR (75 MHz, CDCl₃) δ 140.5 (C), 133.6 (CH), 128.5 (CH), 127.6 (CH), 79.1 (CH), 77.9

(CH₂), 44.1 (CH), 35.7 (CH₂), 30.7 (C), 27.6 (CH), 26.9 (CH₃), 24.4 (CH₃), 21.0 (CH₃), 20.3 (CH₂-Si), 15.3 (CH₃), -1.4 (CH₃), -2.5 (CH₃).

2.5.2. 2-. Butyl-2,5,5-trimethyl-3-phenyltetrahydropyran 14

¹H RMN (500 MHz, CDCl₃) δ 7.28–7.24 (m, 2H, Ph), 7.22–7.17 (m, 3H, Ph), 3.48 (dd, *J* = 11.5, 0.9 Hz, 1H, CH₂-O), 3.25 (dd, *J* = 11.5, 2.6 Hz, 1H, CH₂-O), 3.05 (dd, *J* = 13.5, 3.8 Hz, 1H, CH-Ph), 1.99 (t, *J* = 13.5 Hz, 1H, CHH), 1.55–1.49 (m, 1H, CHH), 1.44–1.33 (m, 4H, CH₂), 1.26–1.22 (m, 2H, CH₂), 1.12 (s, 3H, CH₃), 1.07 (s, 3H, CH₃), 0.89 (s, 3H, CH₃), 0.88 (t, *J* = 7.0 Hz, 3H, CH₃); ¹³C RMN (126 MHz, CDCl₃) δ 142.8 (C, Ph), 129.1 (CH, Ph), 127.8 (CH, Ph), 126.4 (CH, Ph), 76.31 (C-O), 71.3 (CH₂-O), 45.8 (CH-Ph), 41.3 (CH₂), 39.6 (CH₂), 27.5 (CH₃), 24.9 (CH₂), 24.1 (CH₃), 23.3 (CH₂), 22.6 (C), 16.4 (CH₃), 14.2 (CH₃, Bu).

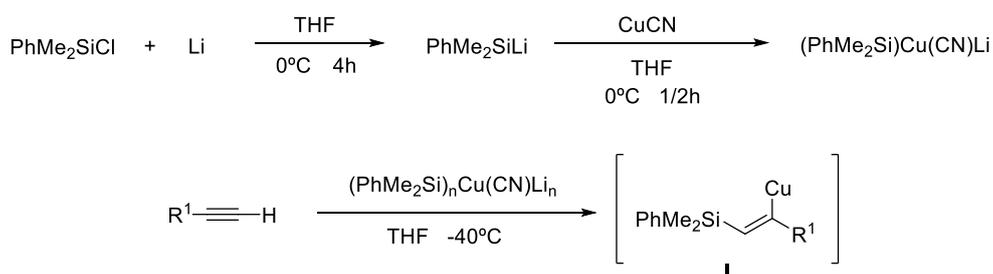
3. Results and Discussion

The vinylsilyl alcohols needed for the synthesis of tetrahydropyrans were prepared in three steps with an initial silylcupration of alkynes followed by reaction with α,β -unsaturated ketones. The subsequent preparation of the epoxide derivative was then followed by the opening of the epoxide to obtain the primary alcohol.

3.1. Silylcupration of Alkynes and Reaction with α,β -Unsaturated Ketone

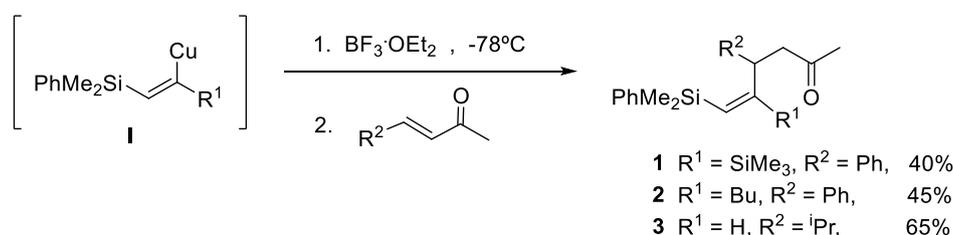
The silylcuprate needed for the silylcupration of alkynes was prepared in two steps. Thus, phenyldimethylsilylchloride reacts with an excess of metallic lithium producing quantitative phenyldimethylsilyllithium, which reacts with cyanide copper (I) to give the desired silylcuprate.

This reagent reacts with substituted acetylenes, by *syn*-addition, affording intermediate I.



Scheme 1. Silylcupration of alkynes.

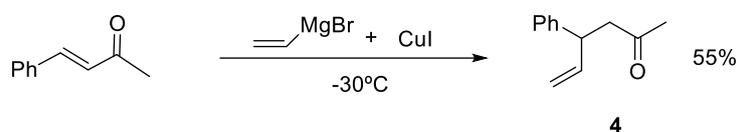
Later, the intermediate I (activated by BF₃·OEt₂) reacts with the corresponding α,β -unsaturated ketone. The activation produces a yield increment due to the formation of a new intermediate (RCu·BF₃), described by Yamamoto [8] and Lipshutz [9], whose selectivity and reactivity are higher than the initial silylcuprate. Even though the composition and structure of this intermediate is not well established, it has an important role in conjugate additions.



Scheme 2. Preparation of vinylsilyl ketones.

3.2. Synthesis of Alkenyl Ketones

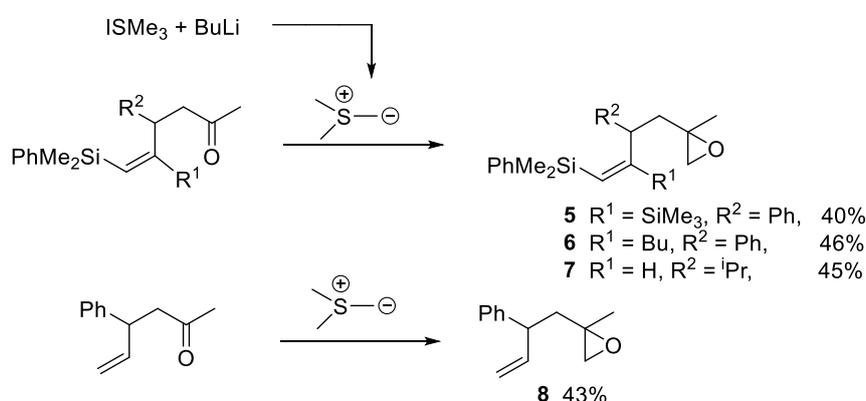
To synthesise ketone **4**, a Michael addition is used. The reaction gives the desired ketone in good yield [10].



Scheme 3. Formation of alkenyl ketone **4**.

3.3. Synthesis of Alkenyl Epoxides

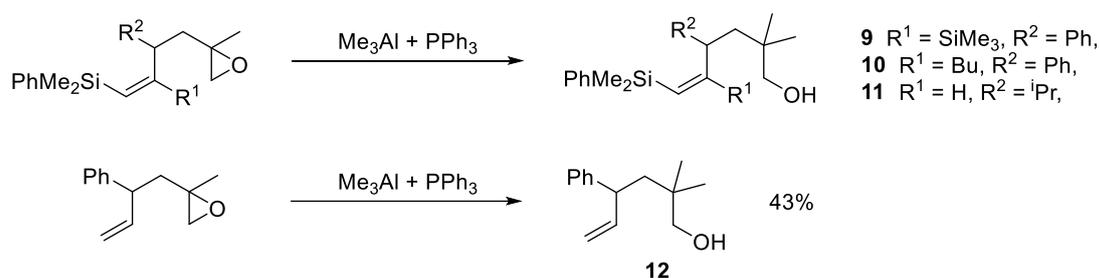
The ketones previously prepared were treated with trimethylsulphonium ylide (prepared in situ from trimethylsulfonium iodide and butyllithium) to yield the desired epoxides.



Scheme 4. Synthesis of alkenyl epoxides.

3.4. Formation of Primary Alkenyl Alcohols

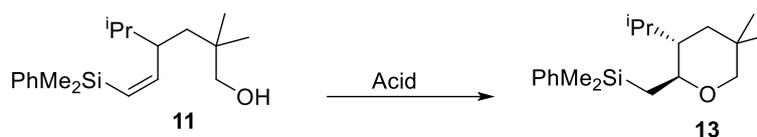
To obtain primary alcohols, a nucleophile has to attack the more substituted position of the epoxide. For this purpose, we have used trialkylaluminium coordinated to a Lewis base (PPh_3) [11,12], following Schneider's studies [13], which produced satisfactory results.



Scheme 5. Opening of epoxides. Alcohol **12** is stable under chromatography conditions and can be purified, however alcohols **9–11** are unstable and they are used in next step without further purification.

3.5. Intramolecular Cyclization of Vinylalcohols

We then studied the scope of the acid-catalyzed cyclization of these vinylsilyl alcohols, evaluating the influence of the acid (either protonic or Lewis acid) in the process. For this process we used vinylsilyl alcohol **11**. Results are shown in Table 1.

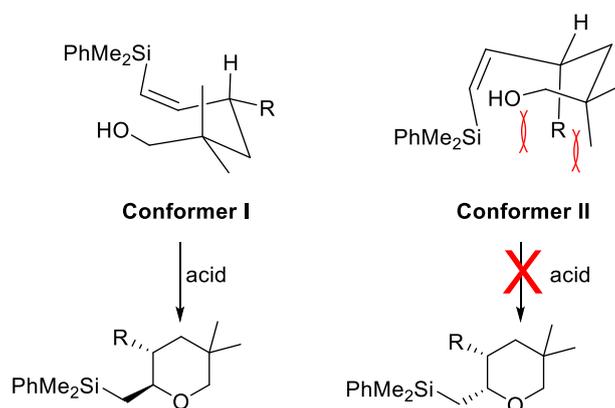
Table 1. Optimization of the cyclization of vinyl alcohol **11**.

| Acid | Temperature/°C | Solvent | Yield/% |
|-----------------------------------|----------------|---------------------------------|-----------------|
| TMS-OTf | -78 | CH ₂ Cl ₂ | Complex mixture |
| TMS-OTf | -78 | Et ₂ O | Complex mixture |
| p-TsOH | 40 | CH ₂ Cl ₂ | 64 |
| BF ₃ ·OEt ₂ | -78 | CH ₂ Cl ₂ | n.r. |

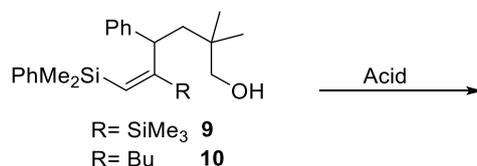
n.r.: no reaction.

Reactions with TMSOTf gaved a complex mixture in which no cyclization products could be identified. When the acid was changed to BF₃·OEt₂, the starting alcohol was obtained untransformed. The best results were obtained when p-TsOH in dichloromethane was employed. Under these conditions the desired tetrahydropyran **13** was obtained in good yield and with very high stereocontrol (a single diastereoisomer with a 2,3-*trans* relative stereochemistry could be detected).

To explain the high stereoselectivity associated to this process we proposed a chair-like reactive conformation in which destabilizing 1,3-diaxial interactions are avoided.

**Scheme 6.** Stereoselectivity of the cyclization.

Once the optimal conditions for the cyclization were determined, we proceed to study the influence of the vinyl alcohol substituents in the cyclization. For this purpose, two alcohols with an additional substituent in the double bond were selected. Table 2 shows the results.

Table 2. Cyclization of substituted vinylalcohols.

| R | Acid | Quantity/Eq | Temperature/°C | Product (Yield) |
|--------------------|--------|-------------|----------------|--------------------|
| Bu | p-TsOH | 1 | r.t. | 14 (51) |
| Me ₃ Si | p-TsOH | 1 | r.t. | n.r. |
| Me ₃ Si | p-TsOH | 1 | 40 | n.r. |

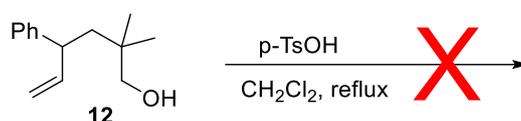
| | | | | |
|--------------------|-----------------------------------|------|----|-----------------|
| Me ₃ Si | BF ₃ ·OEt ₂ | 1 | 0 | n.r. |
| Me ₃ Si | TfOH | 0.05 | 40 | Complex mixture |

n.r.: no reaction.

The cyclization of a trisubstituted alkenyl alcohol in which an alkyl group (R = Bu) is the additional substituent (**9**), took place in a short time producing a unique polisubstituted tetrahydropyran **14** where the phenyldimethylsilyl group is lost. As this reaction is fast at room temperature, it confirms that the presence of an alkyl substituent in the double bond increases its reactivity.

However, when a bulky trimethylsilyl group is bonded to the alkene (**10**), the reaction with p-TsOH or BF₃·OEt₂ gave unreacted starting alcohol either at room temperature or at reflux, while in the presence of a stronger acid, such as TfOH, a complex mixture was obtained in which no known compound could be identified. This fact seems to indicate the great influence of steric factors in this cyclization.

Finally, in order to study the role of the silyl group in this cyclization, we have tried the cyclization of an analogue alcohol which lacks the silyl group substituent (**12**). Under the standard conditions, cyclization didn't take place, which seems to confirm that an electron-rich alkene moiety is needed for the acid catalysed hydroalkoxylation to occur.



Scheme 7. Influence of the silyl group in the cyclization.

4. Conclusions

In conclusion, a new efficient method for the synthesis of polisubstituted tetrahydropyrans by acid-catalysed cyclization of vinylsilyl alcohols has been developed. Moreover, it has been shown that the presence of a silyl substituent in the double bond is required for the reaction to proceed. In addition, the high stereoselectivity of this cyclizations can be explained by steric factors. Further transformation of the tetrahydropyrans can develop in new interesting synthetic routes.

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