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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 developing 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: Heterocycles; cyclizations; organosilanes; tetrahydropyrans

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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 (Figure 1), 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 heterocycle. In addition, synthesizing 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.

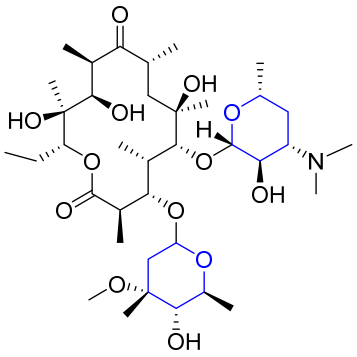


Figure 1. Erythromycin.

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 cyclization [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 catalyzed 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 tetrahydrofuran (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, $BF_3.Et_2O$ 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 NH_4Cl/NH_3. The aqueous layer was extracted three times with Et_2O. Organic layers, together, were washed with saturated solution of NH_4Cl/NH_3; dried over $MgSO_4$, filtered, and evaporated in vacuo. Products were 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**)

^{1}H RMN (400 MHz, $CDCl_3$) δ 7.63–7.52 (m, 2H, Ph), 7.37–7.29 (m, 3H, Ph), 7.21–7.08 (m, 3H, $PhMe_2Si$), 6.99–6.87 (m, 2H, $PhMe_2Si$), 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, CH_2), 2.33 (dd, *J* = 17.3, 3.6 Hz, 1H, CH_2), 1.90 (s, 3H, CH_3), 0.52 (s, 3H, $PhMe_2Si$), 0.46 (s, 3H, $PhMe_2Si$), −0.21 (s, 9H, $SiMe_3$); ^{13}C RMN (101 MHz, $CDCl_3$) 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 (CH_2), 29.6 (CH_3), 0.6 (3xCH_3, Me_3Si), −0.6 (CH_3, $PhMe_2Si$), −1.1 (CH_3, $PhMe_2Si$).

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

^{1}H RMN (500 MHz, $CDCl_3$) δ 7.61 (m, 2H, Ph), 7.36 (m, 3H, Ph), 7.22–7.10 (m, 3H, $PhMe_2Si$), 6.95 (m, 2H, $PhMe_2Si$), 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, CH_2), 2.39 (dd, *J* = 16.8, 4.2 Hz, 1H, CH_2), 1.87 (s, 3H, CH_3), 1.32–1.25 (m, 2H, CH_2, Bu), 1.18–1.13 (m, 2H, CH_2, Bu), 0.87–0.85 (m, 2H, CH_2, Bu), 0.78 (t, *J* = 7.1 Hz, 3H, CH_3, Bu), 0.52 (s, 3H, $PhMe_2Si$), 0.46 (s, 3H, $PhMe_2Si$); ^{13}C RMN (126 MHz, $CDCl_3$) 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 (CH_2), 33.2 (CH_2, Bu), 30.8 (CH_2, Bu), 29.6 (CH_3), 22.5 (CH_2, Bu), 13.95 (CH_3, Bu), −0.63 (CH_3, $PhMe_2Si$), −1.0 (CH_3, $PhMe_2Si$).

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

^{1}H NMR ($CDCl_3$, 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); ^{13}C NMR ($CDCl_3$, 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 (CH_2), 44.6 (CH), 31.8 (CH), 30.7 (CH_3), 20.0 (CH_3), 19.2 (CH_3), −0.6 (CH_3), −0.8 (CH_3).

2.2. Synthesis of Alkenyl Ketones

Vinylmagnesiumbromide (9 mmol) was added for 10 min to a solution of CuI (3 mmol) in dry THF (40 mL) and the mixture stirred under N_2 at −5 °C for 15 min. Then, the reaction mixture was cooled to −30 °C and a solution of the ketone (3 mmol) in dry THF (10 mL) was slowly added for 1 h. Thirty minutes after the addition is completed the reaction was quenched with 20 mL of a saturated solution of NH_4Cl. The aqueous layer was extracted three times with Et_2O. Organic layers, together, were washed with saturated solution of NH_4Cl, first, and NaCl, second; dried over $MgSO_4$, filtered, and evaporated in vacuo. Products were purified by flash chromatography (hexane/EtOAc 10:1) to give:

2.2.1. 4-Phenylhex-5-en-2-one (**4**)

^{1}H RMN (400 MHz, $CDCl_3$) 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, C*H*H=), 5.00 (dd, *J* = 17.1, 1.3 Hz, 1H, CH*H*=), 3.92–3.89 (m, C*H*-Ph), 2.85 (dd, *J* = 16.3, 8.0 Hz, 1H, C*H*H), 2.80 (dd, *J* = 16.3, 6.9 Hz, 1H, CH*H*), 2.07 (s, 3H, CH_3); ^{13}C RMN (101 MHz, $CDCl_3$) 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 (CH_2=), 49.0 (CH_2), 44.5 (CH-Ph), 30.6 (CH_3).

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 N_2 at 0 °C for 1 h. Then, a solution of the ketone (1.35 mmol) in dry THF (10 mL) was added. The reaction was quenched with saturated solution of NaCl (15 mL). The aqueous layer was extracted three times with Et_2O. Organic layers were washed with a saturated solution of NaCl; dried over $MgSO_4$, filtered, and evaporated in vacuo. Products were 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**)

^{1}H RMN (500 MHz, $CDCl_3$) δ 7.65–7.60 (m, 2H, Ph), 7.39–7.33 (m, 3H, Ph), 7.20–7.16 (m, 2H, $PhMe_2Si$), 7.14–7.10 (m, 1H, $PhMe_2Si$), 7.05–7.00 (m, 2H, $PhMe_2Si$), 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, CH_3), 0.54 (s, 3H, $PhMe_2Si$), 0.51 (s, 3H, $PhMe_2Si$), −0.21 (s, 9H, $SiMe_3$); ^{13}C RMN (126 MHz, $CDCl_3$) 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 (CH_2-O), 47.8 (CH-Ph), 37.9 (CH_2), 22.5 (CH_3), 0.7 (3xCH_3, Me_3Si), −0.7 (CH_3, $PhMe_2Si$), −0.7 (CH_3, $PhMe_2Si$).

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

^{1}H RMN (500 MHz, $CDCl_3$) δ 7.65–7.60 (m, 2H, Ph), 7.40–7.35 (m, 3H, Ph), 7.20–7.10 (m, 3H, $PhMe_2Si$), 7.00–6.96 (m, 2H, $PhMe_2Si$), 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, CH_2, Bu), 1.18–1.09 (m, 3H, CH_2, Bu), 1.13 (s, 3H, CH_3), 0.77 (t, *J* = 7.2 Hz, 3H, CH_3, Bu), 0.52 (s, 3H, $PhMe_2Si$), 0.49 (s, 3H, $PhMe_2Si$); ^{13}C RMN (126 MHz, $CDCl_3$) 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 (CH_2-O), 47.4 (CH-Ph), 37.8 (CH_2), 32.9 (CH_2), 30.9 (CH_2), 22.6 (CH_2), 22.2 (CH_3), 14.0 (CH_3, Bu), −0.5 (CH_3, $PhMe_2Si$), −0.6 (CH_3, $PhMe_2Si$).

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

^{1}H RMN (300 MHz, $CDCl_3$) 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); ^{13}C-RMN ($CDCl_3$, 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 (CH_2), 45.3 (CH), 39.3 (CH_2), 32.6 (CH), 21.0 (CH_3), 19.4 (CH_3), 19.3 (CH_3), −0.27 (CH_3), −0.51 (CH_3).

2.3.4. 1,2-epoxy-2-methyl-4-phenylhex-5-ene (**8**)

^{1}H RMN (400 MHz, $CDCl_3$) 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, CH_2=), 3.49–3.42 (m, 1H, C**H**-Ph), 2.62 (d, *J* = 4.7 Hz, 1H, CH_2-O), 2.54 (d, *J* = 4.7 Hz, 1H, CH_2-O), 2.18–2.15 (m, 1H, C**H**H), 1.83–1.76 (m, 1H, CH**H**), 1.30 (s, 3H, CH_3);^{13}C RMN (101 MHz, $CDCl_3$) δ 143.5 (C, Ph), 141.8 (CH=), 128.5 (CH, Ph), 127.6 (CH, Ph), 126.5 (CH, Ph), 114.1 (CH_2=), 55.8 (C-O), 54.2 (CH_2-O), 46.4 (CH-Ph), 42.8 (CH_2), 21.1 (CH_3).

2.4. Procedure of Synthesis of Primary Alcohols

A solution of the epoxide (0.65 mmol) in dry hexane (1 mL) was added to a solution of triphenylphosphine (0.078 mmol) in dry hexane (10 mL). Then, trimethylaluminium (1.95 mmol) was added dropwise and the reaction stirred for 1 h. The reaction was then quenched with a saturated solution of NaCl (10 mL). The aqueous layer was extracted three times with Et_2O. Organic layers were washed with saturated solution of NaCl; dried over $MgSO_4$, filtered, and evaporated in vacuo. Stable products were purified by flash chromatography (hexane/EtOAc 10:1) and characterized by spectroscopy techniques to give.

2.4.1. 2,2-dimethyl-4-phenylhex-5-en-1-ol (**12**)

^{1}H RMN (400 MHz, $CDCl_3$) 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, CH_2=), 3.44–3.39 (m, 1H, C**H**-Ph), 3.24 (d, *J* = 11.1 Hz, 1H, C**H**H-OH), 3.18 (d, *J* = 11.1 Hz, 1H, CH**H**-OH), 1.79 (dd, *J* = 14.3, 6.7 Hz, 1H, C**H**H), 1.74 (dd, *J* = 14.3, 6.5 Hz, 1H, CH**H**), 0.88 (s, 3H, CH_3), 0.83 (s, 3H, CH_3); ^{13}C RMN (101 MHz, $CDCl_3$) δ 145.8 (C, Ph), 144.2 (CH=), 128.6 (CH, Ph), 127.5 (CH, Ph), 126.2 (CH, Ph), 113.3 (CH_2=), 71.4 (CH_2-OH), 46.3 (CH-Ph), 44.0 (CH_2), 36.1 (C), 24.6 (CH_3), 14,5 (CH_3).

2.5. Synthesis of Tetrahydropyrans

The acid was added to a stirred solution of one of the previous synthesized alcohols (0.3 mmol) in dry dichloromethane (5 mL). The reaction progress was followed by TLC (thin layer chromatography) When the reaction was over, it was quenched with a saturated solution of NaCl (5mL). The aqueous layer was extracted three times with Et_2O. Organic layers were washed with saturated solution of NaCl; dried over $MgSO_4$, filtered,

and evaporated in vacuo. Products were purified by flash chromatography (hexane/EtOAc 20:1) and characterized by spectroscopy techniques to give:

2.5.1. 3-Isopropy-5,5-dimethyl-2-dimethylphenylsilylmethyltetrahydropyran (**13**)

^{1}H NMR (300 MHz, $CDCl_3$) 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, CH_3), 1.00–0.97 (m, 1H), 0.90 (dd, *J* = 14.8, 10.3 Hz, 1H), 0.81 (d, *J* = 7.0 Hz, 3H, CH_3), 0.78 (s, 3H, CH_3), 0.63 (d, *J* = 6.9 Hz, 3H, CH_3), 0.31 (s, 3H, CH_3-Si), 0.30 (s, 3H, CH_3-Si); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.5 (C), 133.6 (CH), 128.5 (CH), 127.6 (CH), 79.1 (CH), 77.9 (CH_2), 44.1 (CH), 35.7 (CH_2), 30.7 (C), 27.6 (CH), 26.9 (CH_3), 24.4 (CH_3), 21.0 (CH_3), 20.3 (CH_2-Si), 15.3 (CH_3), −1.4 (CH_3), −2.5 (CH_3).

2.5.2. 2-Butyl-2,5,5-trimethyl-3-phenyltetrahydropyran (**14**)

^{1}H RMN (500 MHz, $CDCl_3$) 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, CH_2-O), 3.25 (dd, *J* = 11.5, 2.6 Hz, 1H, CH_2-O), 3.05 (dd, J = 13.5, 3.8 Hz, 1H, CH-Ph), 1.99 (t, J = 13.5 Hz, 1H, C*H*H), 1.55–1.49 (m, 1H, CH*H*), 1.44–1.33 (m, 4H, CH_2), 1.26–1.22 (m, 2H, CH_2), 1.12 (s, 3H, CH_3), 1.07 (s, 3H, CH_3), 0.89 (s, 3H, CH_3), 0.88 (t, *J* = 7.0 Hz, 3H, CH_3); ^{13}C RMN (126 MHz, $CDCl_3$) δ 142.8 (C, Ph), 129.1 (CH, Ph), 127.8 (CH, Ph), 126.4 (CH, Ph), 76.31 (C-O), 71.3 (CH_2-O), 45.8 (CH-Ph), 41.3 (CH_2), 39.6 (CH_2), 27.5 (CH_3), 24.9 (CH_2), 24.1 (CH_3), 23.3 (CH_2), 22.6 (C), 16.4 (CH_3), 14.2 (CH_3, Bu).

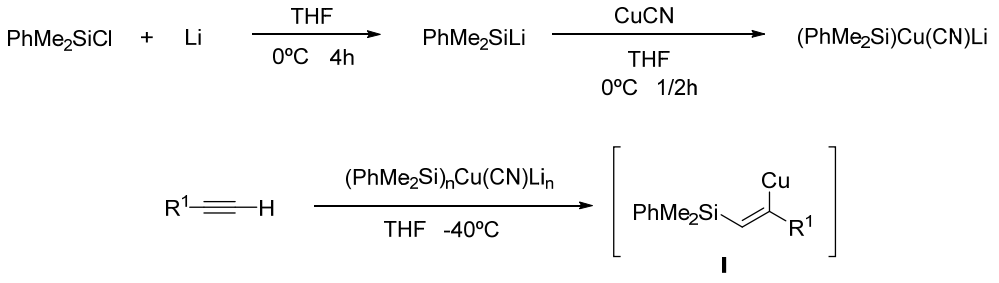
3. Results and Discussion

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

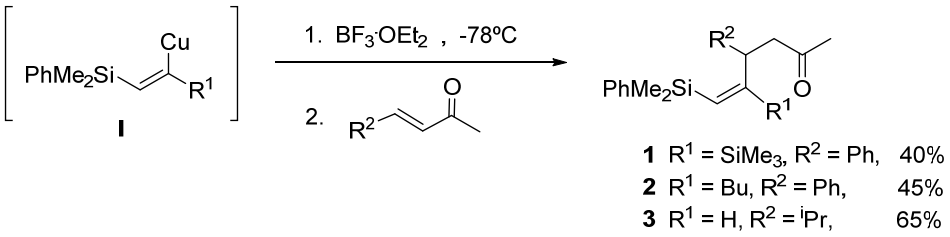
The silylcuprate needed for the silylcupration of alkynes was prepared in two steps. Thus, phenyldimethylsilylchloride reacted with an excess of metallic lithium producing quantitative phenyldimethylsilyllithium, which reacted with cyanide copper (I) to give the desired silylcuprate.

This reagent reacted with substituted acetylenes, by *syn*-addition, affording intermediate **I** (Scheme 1).



Scheme 1. Silylcupration of alkynes.

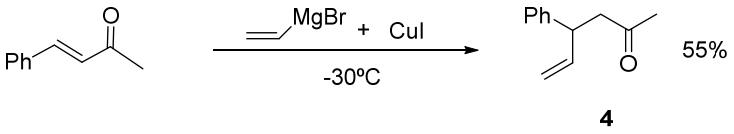
Later, the intermediate **I** (activated by BF_3.OEt_2) reacted with the corresponding α,β-unsaturated ketone (Scheme 2). The activation produces a yield increment due to the formation of a new intermediate (RCu·BF_3), described by Yamamoto [8,9] and Lipshutz [10], whose selectivity and reactivity are higher than the initial silylcuprate. Even though the composition and structure of this intermediate was not well established, it had an important role in conjugate additions.



Scheme 2. Preparation of vinylsilyl ketones.

3.2. Synthesis of Alkenyl Ketones

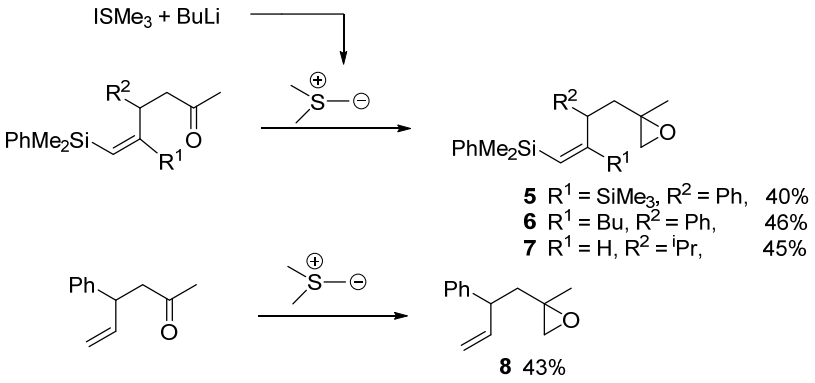
To synthesize ketone **4**, a Michael addition was used. The reaction gave the desired ketone in good yield [11] (Scheme 3).



Scheme 3. Formation of alkenyl ketone 4.

3.3. Synthesis of Alkenyl Epoxides

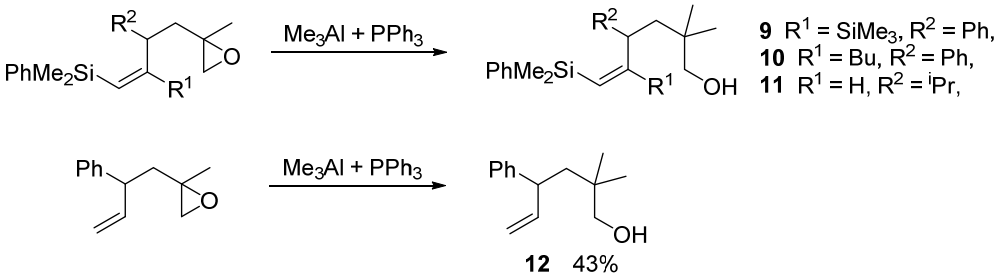
The ketones previously prepared were treated with trimethylsulphonium ylide (prepared in situ from trimethylsulfonium iodide and butyllithium) to yield the desired epoxides (Scheme 4).



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 used trialkylaluminium coordinated to a Lewis base (PPh_3) [12–17], following Schneider's studies [18], which produced satisfactory results (Scheme 5).



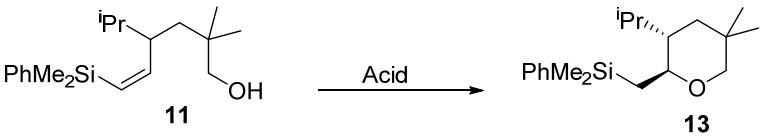
Scheme 5. Opening of epoxides.

Alcohol **12** was stable under chromatography conditions and could be purified, however, alcohols **9–11** were unstable and they were used in the 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 [19], 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.**

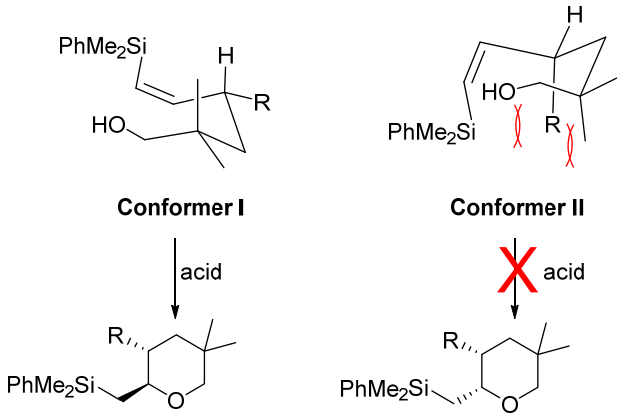


Acid	Temperature/°C	Solvent	Yield/%
TMS·OTf	−78	CH_2Cl_2	Complex mixture
TMS·OTf	−78	Et_2O	Complex mixture
p-TsOH	40	CH_2Cl_2	64
$BF_3{\cdot}OEt_2$	−78	CH_2Cl_2	n.r.

n.r.: no reaction.

Reactions with TMSOTf (trimethylsilyl trifluoromethanesulfonate) gave a complex mixture in which no cyclization products could be identified. When the acid was changed to $BF_3{\cdot}OEt_2$, 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).

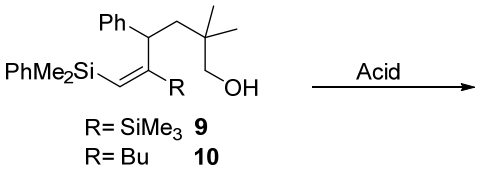
To explain the high stereoselectivity associated to this process, we proposed a chair-like reactive conformation in which destabilizing 1,3-diaxial interactions were avoided (Scheme 6).

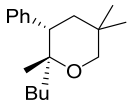


Scheme 6. Stereoselectivity of the cyclization.

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

Table 2. Cyclization of substituted vinylalcohols.



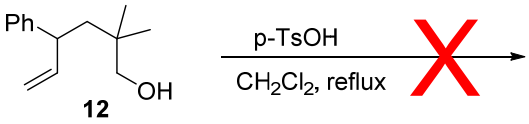
R	Acid	Quantity/Eq	Temperature/°C	Product (Yield)
Bu	p-TsOH	1	r.t.	 **14** (51)
Me_3Si	p-TsOH	1	r.t.	n.r.
Me_3Si	p-TsOH	1	40	n.r.
Me_3Si	$BF_3{\cdot}OEt_2$	1	0	n.r.
Me_3Si	TfOH	0.05	40	Complex mixture

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 was lost. As this reaction was fast at room temperature, it confirmed that the presence of an alkyl substituent in the double bound increases its reactivity.

However, when a bulky trimethylsilyl group was bonded to the alkene (**10**), the reaction with p-TsOH or $BF_3{\cdot}OEt_2$ 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 tried the cyclization of an analogue alcohol which lacks the silyl group substituent (**12**). Under the standard conditions, cyclization did not take place, which seems to confirm that an electron-rich alkene moiety is needed for the acid catalyzed hydroalkoxylation to occur (Scheme 7).



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

Institutional Review Board Statement: Not applicable.

References

1. Lohsen, S.; Stephens, D.S. *Antibiotic Drug Resistance*; John Wiley & Sons: Hoboken, NJ, USA, 2020; pp. 97–117, ISBN 978-1-119-28254-9.
2. Larrosa, I.; Romea, P.; Urpi, F. Synthesis of six-membered oxygenated heterocycles through carbon–oxygen bond-forming reactions. *Tetrahedron* **2008**, *64*, 2683–2723.
3. Coulombel, L.; Duñach, E. Triflic acid-catalysed cyclisation of unsaturated alcohols. *Green Chem*. **2004**, *6*, 499–501.
4. Coulombel, L.; Favier, I.; Duñach, E. Catalytic formation of C–O bonds by alkene activation: Lewis acid-cycloisomerisation of olefinic alcohols. *Chem. Commun.* **2005**, 2286–2288.
5. Rosenfeld, D.C.; Shekharm, S.; Takemiya, A.; Utsunomiya, M.; Hartwig, J.F. Hydroamination and Hydroalkoxylation Catalyzed by Triflic Acid. Parallels to Reactions Initiated with Metal Triflates. *Org. Lett.* **2006**, *8*, 4179–4182.
6. Diez-Varga, A.; Barbero, H.; Pulido, F.J.; González-Ortega, A.; Barbero, A. Competitive Silyl–Prins Cyclization versus Tandem Sakurai–Prins Cyclization: An Interesting Substitution Effect. *Chem. Eur. J.* **2014**, *20*, 14112–14119.
7. Díez-Poza, C.; Barbero, A.; Diez-Varga, A. The Silyl-Prins Reaction as an Emerging Method for the Synthesis of Heterocycles. In *Progress in Heterocyclic Chemistry*; Elsevier: Oxford, UK, 2018; Volume 30, pp. 13–41.
8. Yamamoto, Y. Selective Synthesis by Use of Lewis Acids in the Presence of Organocopper and Related Reagents. New Synthetic Methods. *Angew. Chem. Int. Ed. Engl*. **1986**, *25*, 947–959.
9. Ibuka, T.; Yamamoto, Y. *Organocopper Reagents. A Practical Approach*; Taylor, R.J.K., Ed.; Oxford University Press: Oxford, UK, 1994; Chapter 7.
10. Lipshutz, B.H.; Ellsworth, E.L.; Siahaan, T.J. The role of boron trifluoride etherate in reactions of lower order (Gilman) organocuprates. *J. Am. Chem. Soc*. **1989**, *111*, 1351–1358.
11. Rüedi, G.; Hansen H.-J. Diradical-Promoted Two-Carbon Ring-Expansion Reactions by Thermal Isomerization: Synthesis of Functionalized Macrocyclic Ketones. *Helv. Chim. Acta* **2004**, *87*, 1628–1665.
12. Suzuki, T.; Saimoto, H.; Tomioka, H.; Oshima, K.; Nozaki, H. Regio- and stereoselective ring opening of epoxy alcohols with organoaluminium compounds leading to 1,2-diols. *Tetrahedron Lett.* **1982**, *23*, 3597–3600.
13. Roush, W.R.; Adam, M.A.; Peseckis, S.M. Regioselectivity of the reactions of trialkylaluminum reagents with 2,3-epoxyalcohols: application to the synthesis of α-chiral aldehydes. *Tetrahedron Lett.* **1983**, *24*, 1377–1380.
14. Pfaltz, A.; Mattenberger, A. Regioselective Opening of α- and β-Alkoxyepoxides with Trimethylaluminum. *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 71–72.
15. Miyashita, M.; Hoshino, M.; Yoshikoshi, A. Stereospecific methylation of γ,δ-epoxy acrylates by trimethylaluminum: a method for the iterative construction of polypropionate chains. *J. Org. Chem.* **1991**, *56*, 6483–6485.
16. Miyazawa, M.; Ishibashi, N.; Ohnuma, S.; Miyashita, M. Stereospecific internal alkylation of terminal γ,δ-epoxy acrylates. *Tetrahedron Lett.* **1997**, *38*, 3419–3422.
17. Abe, N.; Hanawa, H.; Maruoka, K.; Sasaki, M.; Miyashita, M. Highly efficient alkylation of epoxides with R_3Al/H_2O systems based on the double activation of epoxy oxygens. *Tetrahedron Lett.* **1999**, *40*, 5369–5372.
18. Schneider, C.; Brauner, J. Lewis Base-Catalyzed Addition of Trialkylaluminum Compounds to Epoxides. *Eur. J. Org. Chem*. **2001**, 4445–4450.
19. Díez-Poza, C.; Val, P.; Pulido, F.J.; Barbero, A. Synthesis of Polysubstituted Tetrahydropyrans by Stereoselective Hydroalkoxylation of Silyl Alkenols. En Route to Tetrahydropyranyl Marine Analogues. *Mar. Drugs* **2018**, *16*, 421.