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Abstract: We report on the regio- and stereoselective synthesis of tetrahydrofurans by reaction between epoxides and alkenes in the presence of a Lewis acid. This is an unprecedented formal [3+2] cycloaddition reaction between an epoxide and an alkene. The chemical reaction represents a very concise synthesis of tetrahydrofurans from accessible starting compounds.

Keywords: lignans; epoxides; cycloaddition

1. Introduction

Diaryl dimethyltetrahydrofurans lignans (Figure 1) are an important group of natural products displaying anti-apoptotic, anticancer, and anti-inflammatory properties [1–3] and interesting new examples have been found during the last few years [4]. Reported synthetic approaches to these compounds are usually step intensive, including functional group manipulations [5,6].

Formal [3+2] cycloadditions represent an interesting synthetic approach for the preparation of tetrahydrofurans. Some interesting examples have been recently reported, for example, the combination of allylic silanes and aldehydes in the presence of a Lewis acid [7], the reaction between ketenes and vinyl cyclopropanes under palladium catalysis [8] or the cycloaddition between a palladium-oxyallyl complex and a diene [9]. On the other hand, epoxides are versatile intermediates in organic synthesis. Ring opening of epoxides by the use of an acid catalyst are attractive reactions which require effective ways to control the regioselectivity [10]. Disubstituted tetrahydrofurans have been prepared by reaction between epoxides and alkenes [11]. Cascade cyclizations of polyepoxides stand as one of the most beautiful and efficient reactions in organic synthesis [12]. In some of these intramolecular reactions, an alkene is the initiating nucleophile that attacks the first epoxide which will trigger the process.

Inspired by these transformations, we envisioned the combination of an epoxide and an alkene under acidic conditions as a straightforward synthetic approach to tetrasubstituted tetrahydrofurans (Figure 1). The concept of this reaction revolves around the idea of the epoxide as an oxygenated cationic synthon and the alkene as a 1,2-dipole to afford a tetrasubstituted tetrahydrofuran (Figure 1).
2. Results

We report herein the preparation of tetrahydropyrans by combination of an epoxide and an alkene in the presence of a Lewis acid.

Scheme 1. Reaction between methyl isoeugenol and its epoxide.

We began our study by combining one equivalent of methyl isoeugenol and one equivalent of its corresponding epoxide with boron trifluoride (30 mol %) in dichloromethane. These conditions were chosen based on previous results reported by us [10]. We were pleased to see that the reaction afforded the desired compound as a 7:3 mixture of stereoisomers 1a and 2a (Scheme 1), although the chemical yield was not satisfactory. Under these conditions, undesired byproducts were also formed, including cyclobutane resulting from self-condensation of the alkene. In order to increase the yield, the reaction was performed using 2 equivalents of the alkene and 1 equivalent of the epoxide but this resulted in a lower yield. Furthermore, if more equivalents of the epoxide than the alkene were added, the chemical yield did not improve. Higher chemical yield and similar stereoselection were obtained by using aluminum chloride as a Lewis acid instead of boron trifluoride (Scheme 1). Aluminum chloride is a cheap Lewis acid and it was therefore advantageous that it worked well in this purpose.

Figure 1. (A) Retrosynthesis of tetrahydropyrans. (B) Examples of neolignans.
To study the scope of the reaction, various β-methyl styrenes and epoxides were subjected to the optimized reaction conditions (Scheme 2). We started by combining methyl isoeugenol oxide with less electron-rich alkenes. Methyl isoeugenol oxide was reacted with β-methyl styrene affording compound 1b in similar chemical yield and stereo-selectivity as 1a (Scheme 2). However, the reaction with styrene afforded an equimolecular mixture of three isomeric compounds 1d (Scheme 2). Comparison of the selectivity of 1b and 1d denotes that the substituent at the beta position of the alkene is important for stereocorelution. We then assayed the reaction with epoxides derived from less electron-rich alkenes. When stilbene oxide was combined with methyl isoeugenol, tetrahydrofuran 1c was obtained at very low yield (Scheme 2), affording instead 2,2-diphenylacetaldehyde as a main product. This compound results from Meinwald rearrangement of starting stilbene oxide under acid catalysis. The reaction between styrene oxide and methyl isoeugenol oxide gave a complex mixture of compounds, but no tetrahydrofuran could be isolated. When other electron-rich alkenes different from methyl isoeugenol are used, the cycloaddition process then takes place. Tetrahydrofurans 1e and 1f derived from the combination of methyl isoeugenol oxide with α-asarone or isoeugenol were prepared. The antiantisyn isomer was the major one in both cases. In addition, compound 1g containing a carboxylic ester was obtained by reaction between methyl 3-arylglycidate and methyl isoeugenol. The selectivity of this reaction is similar to the one obtained when using methyl isoeugenol oxide (Scheme 2).

For all cases except for compound 1d, the main stereoisomer could be isolated by chromatography. Further investigation of the reaction with other substitution patterns is currently underway.

3. Discussion

Unambiguously established 2,3-anti, 3,4-anti, 4,5-syn configuration of the natural product magnosalicin [13] enabled us to use its NMR data as our standard for tentative stereochemical assignment. Chemical shifts and coupling constants of 1a, 1b, 1e, 1f and 1g were very similar to magnosalicin (Figure 2). In addition, the NOE data (see Supplementary Materials) denote the stereochemistry to be antiantisyn (Figure 2). The structure of the minor isomers is antianti as assigned by comparison of 1H NMR spectrum with already reported epi-magnosalicin: as compared to 2a, a downfield shift of the C-2 CH₃ signal, and an upfield shift of the H-3 signal are observed.
Interestingly, relative 2,4-\textit{syn} configuration has also been reported for the preparation of disubstituted tetrahydrofurans under similar conditions \cite{11}.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Figure2}
\caption{Coupling constants and NOE effects measured in 1a and 1e as compared to magnosalicin.}
\end{figure}

Chemical correlation of compound 1g with 1a was done through a three-step sequence. The first step is the reduction of the ester group, then activation of the resulting alcohol as a $p$-toluenesulfonate ester and, finally, conversion to methyl (Scheme 3).

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{Scheme3}
\caption{Synthesis of compound 1a from 1g.}
\end{figure}

In order to explain the reaction between an alkene and an epoxide a two-step mechanism is proposed. Initial attack of $\beta$-carbon of alkene to $\alpha$-carbon of activated epoxide would afford a benzylic carbocation, stabilized by para-quinone methide structures, which upon ring closure would give the tetrahydrofuran (Scheme 4). Stereocontrol would result from the first step through a less strained transition state resulting from the combination of both planar reactants and subsequent cyclization through attack of the oxygen atom on the less hindered face of the carbocation (Scheme 4).
4. Materials and Methods

4.1. General Information

Unless otherwise specified, all reactions were carried out under nitrogen atmosphere with magnetic stirring. All solvents and reagents were obtained from commercial sources and were purified according to standard procedures before use. $^1$H and $^{13}$C NMR spectra were measured in CDCl$_3$ ($^1$H, 7.24 ppm; $^{13}$C 77.0 ppm) solution at 30 °C on a 300 or 400 MHz NMR spectrometer (Bruker, Rheinstetten, Germany). Mass spectra (Waters, Milford, MA, USA) were measured in a QTOF I (quadrupole–hexapole–TOF) mass spectrometer with an orthogonal Z-spray–electrospray interface. EM Science Silica Gel 60 was used for column chromatography while Thin Layer Chromatography (TLC) (Merck, Darmstadt, Germany) was performed with precoated plates (Kieselgel 60, F$_{254}$, 0.25 mm).

4.2. Preparation of Epoxides 2-(3,4-dimethoxyphenyl)-3-methyloxirane and 2,3-diphenyloxirane

A stirred solution of the alkene (5.61 mmol) in dichloromethane (20 mL) at 0–5 °C (ice-bath) was treated with sodium carbonate (10% aqueous solution) (40 mL). Then, a solution of $m$-chloroperbenzoic acid (12.4 mmol) in dichloromethane (20 mL) was added dropwise to the previous mixture. The resulting mixture was stirred for 20 min, then was poured into a separatory funnel. The organic layer was separated and washed sequentially with sodium carbonate (10% aqueous solution) (5 × 25 mL) and dried over Na$_2$SO$_4$. Finally, the solvent was evaporated and the residue was purified by column chromatography (silicagel, n-hexane/ethyl acetate; 9:1).

4.3. Preparation of Methyl 3-(3,4-dimethoxyphenyl)oxirane-2-carboxylate

Sodium (62 g) was added to dry methanol (900 mL) and the resulting solution was cold to –10 °C. Then, a solution of veratraldehyde (1.8 mol) and methyl chloroacetate (293 g) in methanol (mL) was added dropwise over a period of 3 h with vigorous stirring. The resulting mixture was stirred for 2 h at –5 °C and then for 3 h at room temperature. The mixture was poured into a flask containing a mixture of water, ice and acetic acid (20 mL) (total volume of the mixture was 3.5 L). The desired compound precipitated as a white powder, and was filtered, washed with cold water and dried. The solid was recrystallized from methanol to afford a white solid (65–66 °C).

4.4. General Experimental Procedure for the Preparation of Tetrahydrofurans

To an ice-bath cold solution of alkene (0.56 mmol) in dichloromethane (1 mL) the corresponding epoxide was added (0.56 mmol, 1 equiv), then aluminum chloride (0.168 mmol, 0.3 equiv) was added.
The resulting mixture was stirred cold with an ice-bath for 30 min. An indicative color change was observed after this time. Water (10 mL) was then added followed by extraction with dichloromethane (3 × 20 mL). Combined organic layers were dried (Na₂SO₄), filtered and concentrated to afford an oil which was purified through silica gel column.

**(2R,3R,4S,5R)-2,4-bis(3,4-dimethoxyphenyl)-3,5-dimethyltetrahydrofuran 1a** and **(2R,3R,4S,5S)-2,4-bis(3,4-dimethoxyphenyl)-3,5-dimethyltetrahydrofuran 2a.** (156 mg, 75%) (hexane/ethyl acetate, 75/25 and 60/40). 1a: ¹H NMR (300 MHz, CDCl₃) δ 7.00 (m, 2H), 6.86 (m, 2H), 6.72 (m, 2H), 4.46 (m, 1H), 3.92 (s, 3H), 3.87 (s, 3H), 3.18 (dd, J = 9.6, 8.5 Hz, 1H), 2.32 (m, 1H), 1.05 (d, J = 6.5 Hz, 3H), 0.97 (d, J = 6.5 Hz, 3H) ppm; ¹³C NMR (75 MHz, CDCl₃) d 149.2, 149.0, 148.8, 148.0, 134.3, 132.2, 120.8, 118.7, 112.4, 111.3, 111.2, 109.8, 87.7, 77.6, 77.4, 56.8, 56.2, 56.1, 56.0, 46.8, 19.1, 15.3 ppm. HRMS (ESI) calcd for C₂₂H₂₂O₂Na (M + Na⁺) 395.1834, found 395.1831.

**(2R,3S,4R,5R)-2,4-bis(3,4-dimethoxyphenyl)-2,4-dimethyl-5-phenyltetrahydrofuran 1b** and **(2R,3S,4R,5S)-2,4-bis(3,4-dimethoxyphenyl)-2,4-dimethyl-5-phenyltetrahydrofuran 2b.** (108 mg, 62%) (hexanes/ethyl acetate, 75/25 and 60/40). 1b: ¹H NMR (300 MHz, CDCl₃) d 7.29–7.45 (m, 5H), 6.68–6.82 (m, 3H), 4.46 (m, 1H), 4.49 (d, J = 9.1 Hz, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.18 (dd, J = 9.6, 8.2 Hz, 1H), 2.31 (m, 1H), 1.05 (d, J = 6.5 Hz, 3H), 0.97 (d, J = 6.5 Hz, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) d 148.8, 147.5, 141.5, 131.9, 128.2, 127.6, 126.0, 120.6, 111.9, 111.0, 87.5, 56.6, 55.7, 47.0, 18.8, 15.0 ppm. HRMS (ESI) calcd for C₂₀H₂₀O₂Na (M + Na⁺) 335.1623, found 335.1625.

**(2S,3R,4S,5R)-2-(3,4-dimethoxyphenyl)-3-methyl-4,5-diphenyltetrahydrofuran 1c.** (31 mg, 15%) (hexanes/ethyl acetate, 75/25 and 60/40). ¹H NMR (500 MHz, CDCl₃) d 6.56–6.79 (m, 6H), 6.90–6.93 (m, 2H), 7.19–7.33 (m, 5H), 4.04 (d, J = 9.6 Hz, 1H), 3.88 (d, J = 9.2 Hz, 1H), 3.82 (s, 3H), 3.70–3.79 (m, 1H), 3.75 (s, 3H), 2.13 (m, 1H), 0.96 (d, J = 6.4 Hz, 3H) ppm; ¹³C NMR (100 MHz, CDCl₃) d 149.1, 147.7, 143.2, 139.9, 138.5, 137.5, 129.9, 129.3, 128.9, 127.2, 126.2, 126.1, 122.1, 112.2, 111.0, 78.0, 77.2, 56.0, 55.9, 53.7, 43.3, 16.0 ppm. HRMS (ESI) calcd for C₂₀H₂₀O₂Na (M + Na⁺) 397.1780, found 397.1779.

**(2R,3S,4R,5R)-2-(3,4-dimethoxyphenyl)-2-methyl-5-phenyltetrahydrofuran 1d.** (95 mg, 57%) (hexanes/ethyl acetate, 75/25 and 70/30). ¹H NMR (300 MHz, CDCl₃) δ 7.63–7.17 (m, 8H), 6.96–6.62 (m, 5H), 5.23 (dd, J = 12.0, 5.6 Hz, 1H), 5.07 (dd, J = 9.5, 6.7 Hz, 1H), 4.52–4.39 (m, 1H), 4.24 (dq, J = 9.1, 6.0 Hz, 1H), 4.12 (dq, J = 8.8, 6.0 Hz, 1H), 3.62 (dd, J = 15.8, 7.8 Hz, 1H), 3.06 (dd, J = 11.6, 9.2, 6.8 Hz, 1H), 2.94 (q, J = 8.9 Hz, 1H), 2.78 (dd, J = 12.5, 6.5 Hz, 1H), 2.74 (dd, J = 12.6, 2.2 Hz, 1H), 2.60 (t, J = 8.7 Hz, 1H), 2.56 (t, J = 8.7 Hz, 1H), 2.40 (dd, J = 8.8, 5.5 Hz, 1H), 2.35 (dd, J = 8.8, 5.4 Hz, 1H), 2.18 (dt, J = 22.1, 11.1 Hz, 1H), 2.25 (m, 1H), 1.40 (d, J = 6.0 Hz, 2H), 1.36 (d, J = 6.0 Hz, 1H), 1.00 (d, J = 6.4 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) d 149.1, 149.1, 148.7, 148.0, 147.9, 147.6, 143.8, 143.6, 142.7, 128.5, 128.4, 128.4, 125.8, 125.7, 125.6, 119.6, 119.5, 111.7, 111.4, 111.0, 110.9, 110.7, 82.8, 82.3, 80.1, 79.9, 79.8, 78.5, 55.9, 55.9, 55.8, 54.1, 51.8, 48.6, 44.7, 43.8, 41.1, 19.6, 19.1, 18.0 ppm. HRMS (ESI) calcd for C₂₀H₂₀O₂Na (M + Na⁺) 321.1468, found 321.1468.

**(2R,3S,4R,5R)-3-(3,4-dimethoxyphenyl)-2,4-dimethyl-5-(2,4,5 trimethoxyphenyl)tetrahydrofuran 1e.** (92 mg, 41%) (hexanes/ethyl acetate, 75/25 and 60/40). ¹H NMR (300 MHz, CDCl₃) δ 7.07 (s, 1H), 6.73 (s, 1H), 6.62–6.67 (m, 2H), 6.46 (s, 1H), 4.86 (d, J = 9.0 Hz,1H), 4.36 (dq, J = 8.2, 6.5 Hz, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.79 (s, 3H), 3.78 (s, 3H), 3.73 (s, 3H), 3.09 (dd, J = 9.1, 8.4 Hz, 1H), 2.31 (m, 1H), 0.98 (d, J = 6.6 Hz, 3H), 0.89 (d, J = 6.5 Hz, 3H) ppm; ¹³C NMR (75.5 MHz, CDCl₃) d 151.8, 149.0, 148.8, 147.7, 143.4, 132.4, 97.7, 81.0, 77.2, 56.9, 56.7, 56.5, 56.2, 55.9, 55.9, 46.5, 18.8, 15.4 ppm. HRMS (ESI) calcd for C₂₃H₃₀O₆Na (M + Na⁺) 425.1940, found 425.1939.
4-((2R,3R,5R)-4-(3,4-dimethoxyphenyl)-3,5-dimethyltetrahydrofuran-2-yl)-2-methoxyphenol 1f and 4-((2R,3R,5S)-4-(3,4-dimethoxyphenyl)-3,5-dimethyltetrahydrofuran-2-yl)-2-methoxyphenol 2f. (70 mg, 35%) (hexanes/ethyl acetate, 75/25 and 60/40). 1f: 1H NMR (300 MHz, CDCl$_3$) $\delta$ 6.91 (s, 1H), 6.85 (s, 1H), 6.62–6.78 (m, 3H), 5.57 (br s, 1H), 4.36 (dd, $J$ = 8.1, 6.5 Hz, 1H), 4.35 (d, $J$ = 9.2 Hz, 1H), 3.84 (s, 3H), 3.80 (s, 3H), 3.79 (s, 3H), 3.10 (dd, $J$ = 9.9, 8.2 Hz, 1H), 2.22 (m, 1H), 0.96 (d, $J$ = 6.5 Hz, 3H), 0.89 (d, $J$ = 6.5 Hz, 3H) ppm; 13C NMR (75.5 MHz, CDCl$_3$) d 148.8, 147.8, 146.6, 146.3, 133.4, 132.0, 120.6, 119.3, 114.2, 112.1, 111.8, 87.7, 56.5, 55.9, 55.9, 46.6, 18.9, 15.1 ppm. HRMS (ESI) calcd for C$_{21}$H$_{23}$O$_3$Na (M + Na$^+$) 381.1678, found 381.1679. 2f: 1H NMR (300 MHz, CDCl$_3$) $\delta$ 6.89 (s, 1H), 6.84 (s, 1H), 6.62–6.78 (m, 3H), 5.57 (br s, 1H), 4.47 (d, $J$ = 9.4 Hz, 1H), 4.2 (dq, $J$ = 9.4, 6.0 Hz, 1H), 3.86 (s, 3H), 3.82 (s, 3H), 3.80 (s, 3H), 2.46 (dd, $J$ = 11.1, 9.4 Hz, 1H), 2.22 (m, 1H), 1.22 (d, $J$ = 6.0 Hz, 3H), 0.85 (d, $J$ = 6.5 Hz, 3H) ppm.

Methyl (2S,3S,4R,5R)-3,5-bis(3,4-dimethoxyphenyl)-4-methyltetrahydrofuran-2-carboxylate 1g and methyl (2R,3S,4R,5S)-3,5-bis(3,4-dimethoxyphenyl)-4-methyltetrahydrofuran-2-carboxylate 2g. (105 mg, 45%) (hexanes/ethyl acetate, 75/25 and 60/40). 1g: 1H NMR (300 MHz, CDCl$_3$) $\delta$ 7.55 (d, $J$ = 1.9 Hz, 1H), 7.10 (m, 1H), 6.88–6.71 (m, 4H), 4.81 (d, $J$ = 9.4 Hz, 1H), 4.55 (d, $J$ = 9.7 Hz, 1H), 3.97 (s, 3H), 3.90 (s, 3H), 3.87 (s, 3H), 3.86 (s, 3H), 3.84 (s, 3H), 3.43 (dd, $J$ = 11.9, 9.4 Hz, 1H), 2.67–2.50 (m, 1H), 0.92 (d, $J$ = 6.5 Hz, 3H) ppm; 13C NMR (75 MHz, CDCl$_3$) d 172.6, 149.4, 149.0, 148.5, 133.1, 128.3, 120.4, 119.5, 111.5, 111.2, 110.7, 110.3, 89.2, 80.9, 56.5, 55.8, 51.4, 45.3, 13.0 ppm. HRMS (ESI) calcd for C$_{31}$H$_{35}$O$_4$Na (M + Na$^+$) 449.1732, found 449.1702. 2g: 1H NMR (300 MHz, CDCl$_3$) $\delta$ 7.55 (d, $J$ = 1.9 Hz, 1H), 6.92 (m 5H), 4.71 (d, $J$ = 9.1 Hz, 1H), 4.68 (d, $J$ = 8.2 Hz, 1H), 3.97 (s, 3H), 3.92 (s, 3H), 3.89 (s, 3H), 3.87 (s, 3H), 3.86 (s, 3H), 3.16 (dd, $J$ = 10.8, 8.6 Hz, 2H), 2.19 (m, 1H), 0.95 (d, $J$ = 6.5 Hz, 3H) ppm.

5. Conclusions

In summary, tetrasubstituted tetrahydrofurans can be prepared in a highly regio- and diastereoselective fashion when equimolecular amounts of styrenes and styrene oxides are treated with a Lewis acid catalyst, which represents a convenient method of preparing tetrahydrofurans from accessible starting compounds. The reaction opens new possibilities for the preparation of biomedically interesting tetrahydrofurans.

Supplementary Materials: Graphical NMR spectra of all compounds. This material is available online.

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References


**Sample Availability:** Samples of the compounds 1a–1g are available from the authors.

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