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One-step biomimetic conversion of a furanoheliangolide into an eremantholide using Stryker's reagent

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Abstract

The conversion of a furanoheliangolide structure (15-deoxygoyazensolide) into an eremantholide one (eremantholide C) was achieved by tandem hydride conjugate addition–intramolecular carbanion addition using Stryker's reagent.

Keywords: Synthesis; Natural products; Furanoheliangolides; Eremantholides; Stryker's reagent

Eremantholides are sesquiterpene lactones containing a complex polycyclic structure as shown in the example (Fig. 1). A number of these natural compounds have been found in Brazilian plants.[1–5]

The biological activity of some eremantholides, which includes trypanocidal,[6] antibacterial,[7] anti-inflammatory[8,9] and anti-tumor properties,[10] has prompted several research groups to propose syntheses, both total and partial, for these compounds.[11–18]

Nevertheless, most efforts in these synthetic works are directed toward the obtention of eremantholide A (**1**) and just a few were undertaken toward other eremantholide structures or some generic part of eremantholides structures.

Biotransformation by fungi has also been used, as described by Barrero et al.,[19] to convert lychnopholide (**6**) (a furanoheliangolide) into 16-(1-methyl-1-propenyl)eremantholide (**4**). This result supports the hypothesis that the eremantholides are biogenetically derived from furanoheliangolides. It should be noted that these authors have also tried to perform the same reaction by using

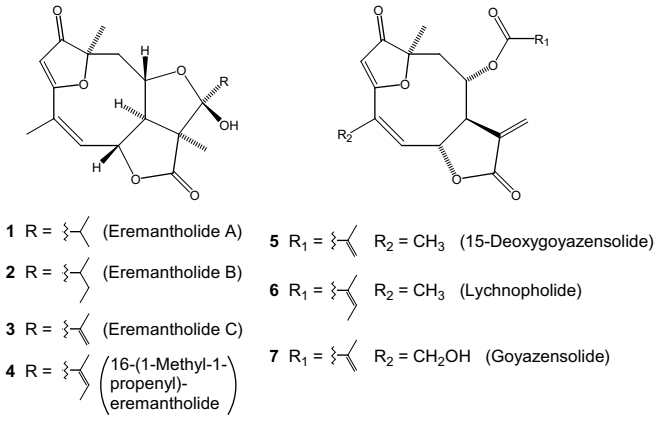

Fig. 1. Examples of eremantholides and furanoheliangolides.

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chemical reagents such as $NaBH_4$ and Bu_3SnH, but no eremantholide could be obtained in this way.

This biotransformation is formally equivalent to a hydride conjugate addition (to the lactone α-methylenic group) followed by an intramolecular addition of the intermediate carbanion to the carbonyl carbon of the nearby ester group. This is exactly the kind of transformation that can be promoted by Stryker's reagent,[20,21] as we and other research groups have recently demonstrated.[22–26]

We have thus decided to treat a sample of the natural product 15-deoxygoyazensolide[1,27–30] with the Stryker's reagent under similar conditions as used in our previous experiments. Rather surprisingly, we found that the reagent is highly selective: only the α-methylenic double bond of the lactone was affected.

Our results indicate that the conjugate addition of hydride is a faster process, producing the intermediate carbanion (**8**) in short time. Cyclization of (**8**) to form eremantholide C (**3**) is a slower process: prematurely quenching the reaction (after 5 h) produced a mixture of (**3**) and (**9**) in a ratio of 4:5.

By extending the reaction time for a further 14 h period, the ratio of **3** to **9** was raised to 64:17.[35]

The conformation of the furanoheliangolides molecules is very peculiar, as we can see with a molecular model, and is also confirmed by X-ray analysis of several natural products.[31] In Figure 2 is shown the most stable conformation for enolate **8**, as determined by molecular mechanics programs:[32] it is clear, in the picture, that the cyclization to produce eremantholide **3** is favored by the appropriate positioning of the reacting atoms (carbanion and carbonyl). Moreover, the conformation depicted in Figure 2 also shows that the stereochemistry to be expected for the cyclization product is exactly the stereochemistry of the natural eremantholide C (**3**). The cyclization product obtained in our synthesis was indeed identical to the natural product **3**.

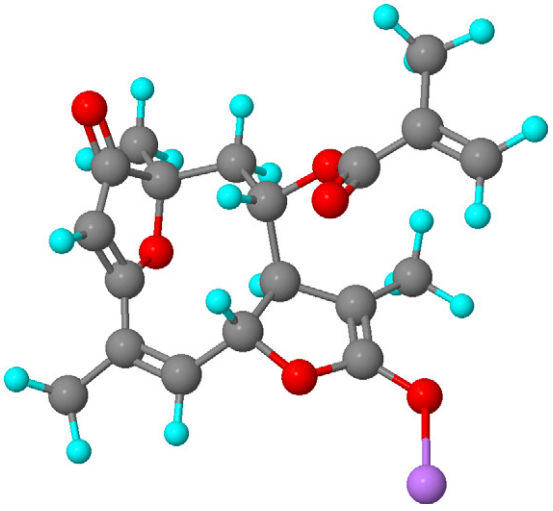


Fig. 2. Most stable conformation of enolate **8**.

The two products obtained in our reaction were separated by column chromatography and identified by NMR techniques, such as ^1H NMR, ^{13}C NMR, gCOSY, gHMQC, gHMBC, and *J-resolved*. The identity between the obtained product **3** and eremantholide C was confirmed through careful comparison of all ^1H and ^{13}C NMR data of our synthetic material with previously known and published data for the natural product,[33,34] including verification of *J* values and 2D NMR data. A perfect match was the result of this comparison.

Product **9** was initially analyzed by ^1H NMR. A remarkable similarity with the ^1H NMR spectrum of the starting material (**5**) was instantly noted. A further detailed comparison with 15-deoxygoyazensolide previously published data[30] led to the straightforward proposition of structure **9** for this product; the stereochemistry of the methyl group on position 13 was the only point that needed further clarification.

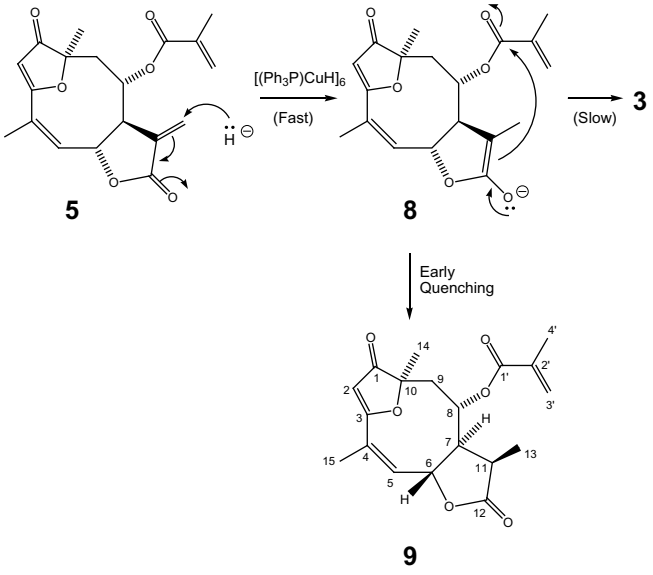
For this purpose, theoretical calculations for possible *J* values between H7 and H11 were carried out. Both possibilities were considered (H11α and H11β) and calculations were undertaken by the use of PCMODEL[32] program.

The results, shown in Table 1, leave no doubt that compound **9** has an H11 in α position, exactly as proposed in Scheme 1. By the way, this is also the stereochemistry that

Table 1
Experimental and calculated *J* values (Hz) between H7 and H11 in compound **9** and its C11 epimer

J	Calculated[a]	Experimental
J(7,11α)	8.98	—
J(7,11β)	2.06	—
J(7,11)	—	11.6

[a] PCModel.



Scheme 1. Transformation of 15-deoxygoyazensolide (**5**) into eremantholide C (**3**).

we could predict from the examination of Figure 2: the ester group is clearly blocking the upper face of the lactone ring, so we should expect the proton to be captured on the other face, thus producing **9** as shown in Scheme 1.

Compound **9** is a new product, but we should note that there are natural products with similar structure, containing the group α-methyl lactone.[5]

In conclusion, we point out that the reaction here reported, besides demonstrating a remarkable selectivity of Stryker's reagent, can be used *either* to transform furanoheliangolides into eremantholides through a biomimetic pathway *or* as a method to reduce α-methylene lactones to α-methyl lactones. We are currently investigating the application of this reaction to other natural furanoheliangolides.

Acknowledgments

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Supplementary data

The supplementary data contain ^{1}H and ^{13}C NMR spectra, including 2D spectra, and tables with summaries of NMR data. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2008.04.071.

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35. Experimental: 15-deoxygoyazensolide (**6**) (30 mg, 0.087 mmol), dry toluene (5 mL), and Stryker's reagent (90 mg, 0.044 mmol), recently prepared according to Ref. 20, were mixed and stirred at room temperature for 5 h. After this period another portion of Stryker's reagent (90 mg, 0.044 mmol) was added and the mixture was stirred for a further 14 h period, always at room temperature. The reaction was quenched with 2 mL of saturated ammonium chloride solution. The mixture was stirred for 1 h. During this period a white precipitate was formed. The reaction mixture was filtered and the residue was washed with ethyl acetate. The organic phase of the filtered mixture was separated and the aqueous phase was extracted with ethyl acetate (3×5 mL). The combined organic phases were dried with $MgSO_4$ and the solvent was removed under vacuum. The residue was purified by column chromatography on silica gel, eluting with benzene/ethyl acetate (9:1). We have thus obtained the two purified materials described below. *Eremantholide C* (**3**): 19 mg (64%) of white solid, mp 229–230 °C. ^{1}H NMR ($CDCl_3$, 500 MHz), δ (ppm): 1.19 (s, 3H); 1.49 (s, 3H); 1.90 (dd, 3H, $J_1 = 1.5$, $J_2 = 0.9$ Hz); 2.06 (dd, 1H, $J_1 = 13.6$, $J_2 = 11.9$ Hz); 2.06 (dd, 3H, $J_1 = 2.4$, $J_2 = 1.6$ Hz); 2.41 (dd, 1H, $J_1 = 13.6$, $J_2 = 2.6$ Hz); 2.85 (dd, 1H, $J_1 = 7.0$, $J_2 = 4.2$ Hz); 4.14 (dddd, 1H, $J_1 = 11.9$, $J_2 = 4.2$, $J_3 = 2.6$, $J_4 = 0.6$ Hz); 4.98 (dddq, 1H, $J_1 = 7.0$, $J_2 = 2.7$, $J_3 = 2.4$, $J_4 = 0.6$ Hz); 5.07 (dd, 1H, $J_1 = 2.0$, $J_2 = 1.5$ Hz); 5.32 (dd, 1H, $J_1 = 2.0$, $J_2 = 0.9$ Hz); 5.61 (s, 1H); 6.03 (dq, 1H, $J_1 = 2.7$, $J_2 = 1.6$ Hz). ^{13}C NMR ($CDCl_3$, 125 MHz), δ (ppm): 18.9 (CH_3); 20.3 (CH_3); 20.6 (CH_3); 21.9 (CH_3); 43.7 (CH_2);

59.8 (C); 62.5 (CH); 78.5 (CH), 81.5 (CH); 89.9 (C); 104.5 (CH); 106.2 (C); 116.1 (CH_2); 130.2 (C); 134.6 (CH); 142.0 (C); 175.4 (C=O); 186.7 (C); 205.1 (C=O). IR ν_{max} (liquid film): 3395; 2973; 2923; 1775; 1699; 1659; 1585 cm^{-1}. HRMS (ESI-TOF): calcd for $C_{19}H_{22}NaO_6^+$ (MNa+) 369.1314, found 369.1304. *11α,13-Dihydro-15-deoxygoyazensolide* (**9**): 5 mg (17%) of colorless oil. ^1H NMR ($CDCl_3$, 500 MHz), δ (ppm): 1.35 (d, 3H, $J = 6.7$ Hz); 1.50 (s, 3H); 1.91 (dd, 3H, $J_1 = 1.45$, $J_2 = 0.8$ Hz); 2,12 (dd, 3H, $J_1 = 2.4$, $J_2 = 1.7$ Hz); 2.20 (dd, 1H, $J_1 = 13.4$, $J_2 = 1.4$ Hz); 2.35 (dd, 1H, $J_1 = 13.4$, $J_2 = 11.6$ Hz); 2.40 (dq, 1H, $J_1 = 11.6$, $J_2 = 6.7$ Hz); 3.00 (ddd, 1H, $J_1 = 11.6$, $J_2 = 9.2$, $J_3 = 2.2$ Hz); 4.92 (dddd, 1H, $J_1 = 11.6$, $J_2 = 2.2$, $J_3 = 1.4$, $J_4 = 0.6$ Hz); 5.05 (dddq, 1H, $J_1 = 9.2$, $J_2 = 2.9$, $J_3 = 2.4$, $J_4 = 0.6$ Hz); 5.63 (q, 1H, $J = 1.4$ Hz); 5.78 (s, 1H); 5.99 (dq, 1H, $J_1 = 2.9$, $J_2 = 1.7$ Hz); 6.08 (dq, 1H, $J_1 = 1.4$, $J_2 = 0.8$ Hz). ^{13}C NMR ($CDCl_3$, 125 MHz), δ (ppm): 15.4 (CH_3); 18.1 (CH_3); 20.5 (CH_3); 21.6 (CH_3); 38.4 (CH); 44.8 (CH_2); 55.2 (CH); 67.9 (CH); 80.3 (CH), 88.9 (C); 105.1 (CH); 126.9 (CH_2); 128.6 (C); 133.2 (CH); 135.3 (C); 166.3 (C=O); 176.6 (C=O); 186.8 (C=O); 203.9 (C=O). IR ν_{max} (liquid film): 2979; 2941; 1779; 1716; 1665; 1576 cm^{-1}. HRMS (ESI-TOF): calcd for $C_{19}H_{23}O_6^+$ (MH+) 347.1495, found 347.1501.