Reduction and Preparation of a Phthalimide Derivative from a Furo-heliangolide

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Abstract: Goyazensolide, a biologically active natural product classified as a furo-heliangolide, was transformed in a phthalimide derivative that showed an enhanced biological activity against *Tripanosoma cruzi*. The complex natural product was also reduced with high stereoselectivity by hydrogen/Wilkinson's catalyst; an epimer of this product was obtained in the reduction with hydrogen/Pd-C.

Keywords: Furo-heliangolides, Goyazensolide, Reduction, Phthalimide derivative, Wilkinson's catalyst.

Introduction

Goyazensolide is a natural product isolated from a Brazilian plant, *Eremanthus goyazensis* (Compositae, tribe Vernoniae), collected in Minas Gerais State [1,2]. It is a furo-heliangolide possessing schistosomicidal and cytotoxic properties and can usually be isolated in larger amounts than many other biologically active products of similar structure found on the same plant or in other plants of the same species. Seeking methods for the preparation of the more scarce natural products or biologically active derivatives from the relatively abundant goyazensolide, we have recently carried out some chemical transformations of this product. To this extent we have succeeded in preparing a phthalimide derivative **2** with enhanced biological activity against *Tripanosoma cruzi* and in reducing **1** with high stereoselectivity by H_2/Wilkinson's catalyst, thus obtaining compound **3**. Reduction of **1** with H_2/Pd/C produced a complex mixture from which **4**, an epimer of **3**, could be isolated.
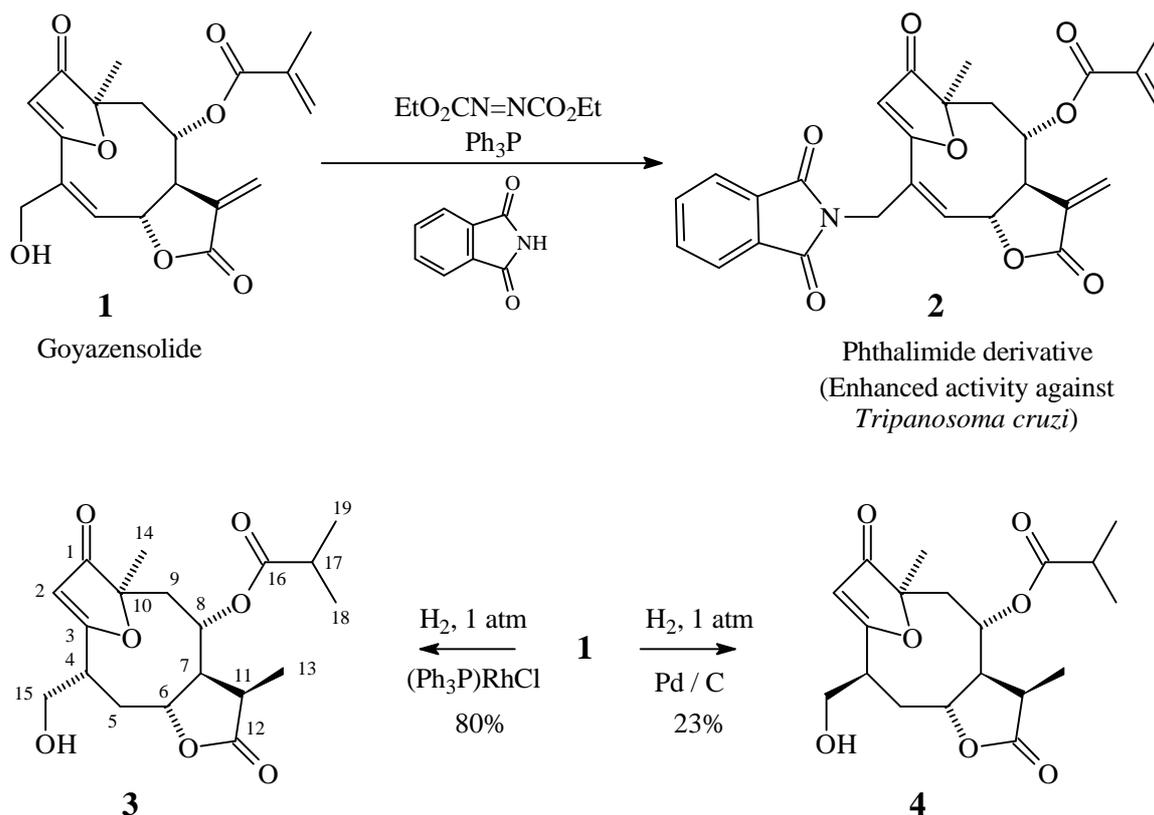
Scheme 1.

Results and Discussion

Hydrogenation of goyazensolide (**1**) (20.0 mg) at room temperature for 2 h, with Pd / C as catalyst, produced a complex mixture that was separated by column chromatography into three fractions: F1 (10.8 mg), F2 (2.8 mg) and F3 (4.7 mg). Only the third fraction, F3, was formed by a pure product (**4**, thus obtained in 23% yield); the other two fractions were still mixtures of at least 4 compounds each, which led us to the decision that it would be worthless to attempt the isolation of other pure products, as they would be obtained in too low yield. Nevertheless, ^{1}H NMR analysis of these fractions gave us some interesting information: 1) The less polar fraction F1 (obtained in higher yield) didn't show, in its ^{1}H NMR spectrum, the signals corresponding to the –CH$_2$OH group, strongly suggesting that it consisted mainly of hydrogenolysis products; 2) Most (virtually all) of the components of all fractions showed the signal corresponding to the vinylic hydrogen of the furanone ring, leading to the conclusion that the double bond in the furanone ring is the most resistant (to this hydrogenation process) of all double bonds in the molecule of goyazensolide.

In sharp contrast, when goyazensolide was hydrogenated with Wilkinson's catalyst, only one product was obtained in high yield. After the first column chromatography, to remove most of the impurities formed from the catalyst, a quantitative yield of a crude product containing essentially only **3** and some aromatic impurities was obtained. On further purification it gave 80% of pure **3**.

Compounds **3** and **4** were submitted to a careful analysis mainly by ^{1}H and ^{13}C NMR spectra. Through the further use of techniques such as COSY, J$_{res}$, double irradiation, etc., we were able to assign all chemical shifts and to measure all H / H coupling constants. The results, comparing compounds **3** and **4**, are shown in Tables 1-3.

Table 1. ^{1}H NMR chemical shifts (ppm) of isomers **3** and **4**.

H	3	4	δ(**4**) - δ(**3**)
5α	2.14	2.44	0.30
4	3.33	3.10	-0.23
5β	2.35	2.14	-0.21
7	3.06	3.26	0.20
2	5.70	5.89	0.19
15a	3.85	3.99	0.14
15b	3.80	3.93	0.13
8	4.93	5.01	0.08
9β	2.07	2.10	0.03
6	4.23	4.26	0.03
9α	2.20	2.18	-0.02
17	2.53	2.55	0.02
18	1.18	1.20	0.02
19	1.17	1.19	0.02
11	2.88	2.89	0.01
13	1.11	1.12	0.01
14	1.48	1.49	0.01

Table 2. ^{1}H NMR coupling constants (Hz) of isomers **3** and **4**.

J	3	4	J(**4**) – J(**3**)
4,5β	7.0	3.4	-3.6
8,9α	6.8	5.3	-1.5
6,7	5.5	4.1	-1.4
4,5α	10.0	8.7	-1.3
4,15a	7.9	6.7	-1.2
2,4	0.0	1.1	1.1
5α,6	8.6	9.7	1.1
7,11	8.3	9.3	1.0
5β,6	0.8	1.4	0.6
9α,9β	15.0	15.5	0.5
8,9β	2.5	3.0	0.5
7,8	9.3	9.8	0.5
17,18	7.2	6.8	-0.4
5α,5β	14.0	14.3	0.3
15a,15b	10.7	10.5	-0.2
4,15b	5.9	5.8	-0.1
11,13	7.4	7.5	0.1

Table 3. ^{13}C NMR chemical shifts (ppm) of isomers **3** and **4**.

	3	**4**
C-1	205.5	205.9
C-2	105.9	102.8
C-3	189.0	189.0
C-4	42.5	39.6
C-5	35.2	34.5
C-6	79.5	78.1
C-7	51.9	49.8
C-8	70.4	71.1
C-9	40.4	37.4
C-10	89.3	88.2
C-11	38.4	37.3
C-12	177.7	177.8
C-13	10.8	10.3
C-14	19.9	19.9
C-15	63.4	62.0
C-16	175.3	175.4
C-17	34.2	34.2
C-18	18.6	18.7
C-19	18.8	18.7

The data on Tables **1** and **2** are sorted according to decreasing absolute values of the difference between data for compound **4** and for compound **3** (last column). In this way it is easy to verify that, with a few exceptions, most of the larger differences (the values on the upper part of the tables) occur with hydrogens near to the chiral center C-4, the relative stereochemistry of which is the difference between isomers **3** and **4**. These data are reasonably consistent with literature data [3] for natural products with structures similar to **3** and **4**.

Although the general structure features of compounds **3** and **4** can be reasonably established by these data, the same can not be said about their relative stereochemistry. A few indications like the value of coupling constants $J_{2,4}$ (the larger value for isomer **4** is in agreement with the expected values when considering the involved angles [4], according to Drieding molecular models), $J_{4,5}$ and $J_{7,11}$ were considered insufficient, and we have then performed some measures of the Nuclear Overhauser Effect (NOE) for both isomers. The results, summarized in Table **4**, clearly and unambiguously establish the relative stereochemistry of compounds **3** and **4** as assigned in this paper.

Table 4. Nuclear overhauser effect on isomers **3** and **4**.

Irradiated Hydrogen	Enhanced Signals	
	Compound **3**	Compound **4**
5α (+9α+9β in **3**)	5β, 7, 15, 6 (8, through 9α and 9β)	5β, 4, 7, 6 (small)
5β (+9α+9β in **4**)	5α, 4, 15, 6	5α, 6, 15 (small) (8, through 9α and 9β)
6	5α, 5β, 13, 7	5β, 13 (small)
7	11, 5α [8, 6 small]	11, 5α
13 (+18+19)	11, 8, 6 (17, through 18 and 19)	8, 11, 6 (small) (17, through 18 and 19)
11	7, 13	7, 13
4	Not effected	15, 5α

The stereochemical outcome of these hydrogenation reactions is not surprising, particularly in the case of the chiral center C-11. Examining a 3-D model (or a stereoscopic projection such as the one found in reference 2) of goyazensolide we can see that, contrary to the first impression given by the planar representation, the methacrylate ester group is above the methylene of the lactone ring, blocking up the β-face of the double bond, thus forcing the approach of the catalysts (and the hydrogen) from the α-face. Around the center C-4 there is not a so strong sterical hindrance; the goyazensolide molecule, however, is rather bent downward and favors the approach of a bulk reagent such as the Wilkinson's catalyst from the β-face. We cannot draw many conclusions about the Pd / C catalyst because a number of unidentified products were formed in this reduction. However, the absence of **3** among the products suggests that, when Pd / C approaches goyazensolide from the β-face, hydrogenolysis products are rather formed; also, as this catalyst is not as much sensitive to sterical hindrance, a possible complexation with the oxygen of the furanone ring could account for the formation of a representative amount of isomer **4**.

Several phthalimide derivatives are known to be active against *Tripanosoma cruzi* [5]; as Mitsunobu [6,7] has described a general method for transforming alcohols into phthalimide derivatives under reasonably mild conditions, we decided to apply this method to goyazensolide. The reaction is very simple, consisting only in mixing the reagents in THF and stirring at room temperature for several hours; separation and purification of the product was not as easy because some excess reagents and by-products have R_f values similar to the R_f of the product, rendering the purification a rather laborious process.

The biological activity of derivative **2** against *Tripanosoma cruzi* (Y strain) was evaluated and compared to the activity of goyazensolide by Professor Sérgio de Albuquerque. The results [8] show that the derivative is considerably more active than goyazensolide.

Experimental

General

NMR spectra were measured using a Bruker DPX-300 (300 MHz ^{1}H NMR and 75 MHz ^{13}C NMR) instrument; deuterochloroform was used as solvent and tetramethylsilane as the internal standard. IR spectra were measured with a Perkin-Elmer 1600-FT or Nicolet 5ZDX spectrometers. TLC was performed on precoated silica gel 60 F_{254} plates (0.25 mm thick, Merck), and 70-230 mesh silica gel 60 (Merck) was used for column chromatography.

Preparation of Compound **2**

Ethyl azodicarboxylate [9,10] (15 mg, 0.088 mmol), phthalimide (13 mg, 0.091 mmol), triphenyl-phosphine (23 mg, 0.089 mmol), goyazensolide (**1**) (32 mg, 0.088 mmol) and dry THF (3 mL) were mixed and stirred at room temperature, checking the progress of the reaction by TLC. After 23 h, as no further consumption of **1** seemed to be taking place, new portions of reagents and solvent were added (same amounts as above, except that no goyazensolide (**1**) was added). Stirring was continued for an additonal 18 h period at room temperature. Column chromatography of the crude reaction product using 9:1 ethyl acetate / hexane as eluent produced 67 mg of material containing the desired product. This was again chromatographed with a different eluent (1:1 ethyl acetate / hexane) thus yielding pure **2** (26 mg, 60%).

^{1}H NMR (300 MHz, CDCl$_3$) δ 7.90 and 7.78 (AA'BB' system) (J_1 5.4 Hz, J_2 3.0 Hz), 6.22 (m, 1 H, ΣJ = 5 Hz), 6.20 (d, 1H, J 3.0 Hz), 5.99 (m, 1H, ΣJ = 6 Hz), 5.80 (s, 1H), 5.53 (m, 1H, ΣJ = 6 Hz), 5.43 (d, 1H, J 3.0 Hz), 5.29 (m, 1H, ΣJ = 12 Hz), 4.60 (dt, 1H, J_1 15.8 Hz, J_2 2.0 Hz, J_3 2.0 Hz), 4.54 (dt, 1H, J_1 15.8 Hz, J_2 2.0 Hz, J_3 2.0 Hz), 4.49 (dt, 1H, J_1 11.7 Hz, J_2 2.5 Hz, J_3 2.0 Hz), 3.72 (m, 1H, ΣJ = 14 Hz), 2.44 (dd, 1H, J_1 14.0 Hz, J_2 11.7 Hz), 2.27 (dd, 1H, J_1 14.0 Hz, J_2 2.0 Hz), 1.81 (br. s, 3H), 1.43 (s, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 204.6 (C=O); 183.4 (C), 168.6 (C=O), 167.4 (C=O), 166.8 (C=O), 137.6 (CH), 135.4 (C), 134.5 (CH), 133.0 (C), 131.7 (C), 129.3 (C), 126.6 (CH$_2$), 124.7 (CH$_2$), 123.7 (CH), 106.6 (CH), 89.9 (C), 81.4 (CH), 73.3 (CH), 50.9 (CH), 43.9 (CH), 39.6 (CH$_2$), 20.4 (CH$_3$), 18.0 (CH$_3$); IR (liquid film) ν$_{max}$ 1772, 1714, 1588, 1424, 1393, 1289, 1138, 916, 756, 722 cm^{-1}.

Preparation of Compound **3**

A solution of goyazensolide (**1**) (164 mg, 0.46 m mol) and Wilkinson's catalyst [(Ph$_3$P)$_3$RhCl] [11-13] in dry toluene (24 mL) was bubbled with nitrogen for 15 minutes to remove dissolved oxygen. Then the nitrogen atmosphere inside the system was changed to a hydrogen atmosphere (1 atm) and the reaction mixture was stirred at room temperature under hydrogen for 7.5 h. After filtration through silica gel, the solvent was removed under vacuum. The residue was chromatographed in a column of silica gel using 8:2 ethyl acetate / hexane as eluent, yielding 180 mg of a crude product containing considerable amount of aromatic impurities, but no starting material. This product was again chromatographed with the same eluent, but with higher proportion of silica gel (60 g silica gel for 1 g of crude product), sepa-

rating the pure fractions and submitting the other fractions to a new chromatography. Yield of pure **3** 134 mg (80%).

^{1}H NMR (300 MHz, CDCl$_3$) δ 5.70 (s, 1H), 4.93 (ddd, 1H, J$_1$ 9.3 Hz, J$_2$ 6.8 Hz, J$_3$ 2.5 Hz), 4.23 (ddd, 1H, J$_1$ 8.6 Hz, J$_2$ 5.5 Hz, J$_3$ 0.8 Hz), 3.85 (dd, 1H, J$_1$ 10.7 Hz, J$_2$ 7.9 Hz), 3.80 (dd, 1H, J$_1$ 10.7 Hz, J$_2$ 5.9 Hz), 3.33 (m, 1H, ΣJ = 30.5 Hz), 3.06 (dt, 1H, J$_1$ 9.3 Hz, J$_2$ 8.3 Hz, J$_3$ 5.5 Hz), 2.88 (dq, 1H, J$_1$ 8.3 Hz, J$_2$ 7.4 Hz), 2.53 (hep, 1H, J 7.2 Hz), 2.35 (ddd, 1H, J$_1$ 14.0 Hz, J$_2$ 7.0 Hz, J$_3$ 0.8 Hz), 2.20 (dd, 1H, J$_1$ 15.0 Hz, J$_2$ 6.8 Hz), 2.14 (ddd, 1H, J$_1$ 14.0 Hz, J$_2$ 10.0 Hz, J$_3$ 8.6 Hz), 2.07 (dd, 1H, J$_1$ 15.0 Hz, J$_2$ 2.5 Hz), 1.48 (s, 3H), 1.18 (d, 3H, J 7.2 Hz), 1.17 (d, 3H, J 7.2 Hz), 1.11 (d, 3H, J 7.4 Hz); ^{13}C NMR (75 MHz, CDCl$_3$) δ 205.5 (C=O), 189.0 (C), 177.7 (C=O), 175.3 (C=O), 105.9 (CH), 89.3 (C), 79.5 (CH), 70.4 (CH), 63.4 (CH$_2$), 51.9 (CH), 42.5 (CH), 40.4 (CH$_2$), 38.4 (CH), 35.2 (CH$_2$), 34.2 (CH), 19.9 (CH$_3$), 18.8 (CH$_3$), 18.6 (CH$_3$), 10.8 (CH$_3$); IR (liquid film) ν$_{max}$ 3437, 1773, 1732, 1697, 1603, 1463, 1385, 1355, 1194, 1133, 1061, 756 cm^{-1}.

Preparation of Compound **4**

A mixture of 95% ethanol (2 mL) and 5% Pd / C (1 mg) was stirred under hydrogen atmosphere (1 atm) for 2 h. A solution of goyazensolide (**1**) (20 mg, 0.056 m mol) in ethanol (1.5 mL) was then added, and stirring under hydrogen atmosphere was continued until no further comsumption of hydrogen could be detected (2 h). The reaction mixture was filtered through Celite® and the solvent was removed under vacuum. The crude product was chromatographed in a silica gel column using 8:2 ethyl acetate / hexane as eluent. Three fractions were separated: F1 (10.8 mg), F2 (2.8 mg) and F3 (4.7 mg); the first two fractions were mixtures of at least 4 products each (by ^{1}H NMR), but fraction F3 was pure compound **4**, yield 4.7 mg (23%).

^{1}H NMR (300 MHz, CDCl$_3$) δ 5.89 (d, 1H, J 0.6 Hz); 5.01 (ddd, 1H, J$_1$ 9.8 Hz, J$_2$ 5.3 Hz, J$_3$ 3.0 Hz), 4.26 (ddd, 1H, J$_1$ 9.7 Hz, J$_2$ 4.1 Hz, J$_3$ 1.4 Hz), 3.99 (dd, 1H, J$_1$ 10.5 Hz, J$_2$ 6.7 Hz), 3.93 (dd, 1H, J$_1$ 10.5 Hz, J$_2$ 5.8 Hz), 3.26 (dt, 1H, J$_1$ 9.8 Hz, J$_2$ 9.3 Hz, J$_3$ 4.1 Hz), 3.10 (m, 1H, ΣJ = 23.4 Hz), 2.89 (dq, 1H, J$_1$ 9.3 Hz, J$_2$ 7.5 Hz), 2.55 (hep, 1H, J 6.8 Hz), 2.44 (ddd, 1H, J$_1$ 14.3 Hz, J$_2$ 9.8 Hz, J$_3$ 8.4 Hz), 2.18 (dd, 1H, J$_1$ 15.5 Hz, J$_2$ 5.3 Hz), 2.14 (ddd, 1H, J$_1$ 14.3 Hz, J$_2$ 3.6 Hz, J$_3$ 2.0 Hz), 2.10 (dd, 1H, J$_1$ 15.5 Hz, J$_2$ 3.0 Hz), 1.49 (s, 3H), 1.20 (d, 3H, J 6.8 Hz), 1.19 (d, 3H, J 6.8 Hz), 1.12 (d, 3H, J 7.5 Hz); ^{13}C NMR (75 MHz, CDCl$_3$) δ 205.9, (C=O), 189.0 (C), 175.4 (C=O), 157.8 (C=O), 102.8 (CH), 88.2 (C), 78.1 (CH), 71.1 (CH), 62.0 (CH$_2$), 49.8 (CH), 39.6 (CH), 37.4 (CH$_2$), 37.3 (CH), 34.5 (CH$_2$), 34.2 (CH), 19.9 (CH$_3$), 18.7 (CH$_3$), 10.3 (CH$_3$); IR (liquid film) ν$_{max}$ 3462, 1770, 1732, 1706, 1592, 1460, 1384, 1360, 1193, 1134, 1065, 810, 733 cm^{-1}.

References and Notes

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8. The results of biological activity measurements are summarized in the table below:

Compound	% lysis		
	100	250	500 μg / mL
Negative control	0.0	0.0	0.0
Goyazensolide (**1**)	9.9	12.9	22.4
Phthalimide derivative (**2**)	50.0	52.9	61.5

*positive control gentian violet 250 μg / mL

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Sample Availability: Not available.