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PAPER

Selectivity in reduction of natural furanoheliangolides with Stryker's reagent†

Daiane C. Sass,[a] Vladimir C. G. Heleno,[b] Gustavo O. Morais,*[b] João L. C. Lopes,[c] Norberto P. Lopes*[c] and Mauricio G. Constantino*[a]

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Reduction of the natural sesquiterpene lactones furanoheliangolides with Stryker's reagent is an effective process for producing eremantholides through a biomimetic pathway. Other reduction products are also formed. Oxygenated functions at C-15 of the furanoheliangolide produce an increase in the velocities of the reactions and reduce the chemoselectivity of the reagent.

Furanoheliangolides and eremantholides (Fig. 1) are natural sesquiterpene lactones[1] that show a number of interesting biological activities, *e.g.* trypanocidal, antibacterial, antiinflammatory, antitumor, *etc*.[2] Several compounds of this class have been isolated from Brazilian plants.[3]

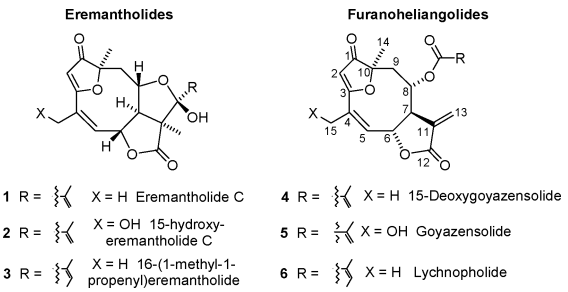


Fig. 1 Examples of eremantholides and furanoheliangolides.

It is believed that these biological activities are mediated chemically by α,β-unsaturated carbonyl structures, such as an α-methylene-γ-lactone, an α,β-unsaturated cyclopentenone or a conjugated ester.[1a,4] Kupchan has shown that for many antitumor active sesquiterpenoids having an α-methylene-γ-lactone function, activity is associated with the ability of this group to accept nucleophilic attack by sulfhydryl groups, in a Michael-type addition reaction.[5] The sesquiterpenoids presenting this α-methylene-γ-lactone function were shown to be toxic for clinical use. However, the eremantholides maintain these activities despite the absence of an α-methylene lactone, and are more selective and, thus, less toxic.[6]

Due to their importance, several research groups have proposed total syntheses or structural modifications of those substances.[7] Some papers reported chemical transformations in furanoheliangolides of type **4** with several reducing agents such as $NaBH_4$, Bu_3SnH, $H_2/Pd/C$ and H_2/Wilkinson's catalyst,[7d,7e] attempting to selectively reduce these compounds to prepare more rare natural products or derivatives with enhanced biological activity.

We have been particularly interested in biomimetically[8] transforming furanoheliangolides (found in larger amounts in plants) into eremantholides, which would require a reducing agent capable of selectively delivering a hydride to the conjugated system α-methylene-γ-lactone producing an enolate that would attack the nearby carbonyl of the ester group.

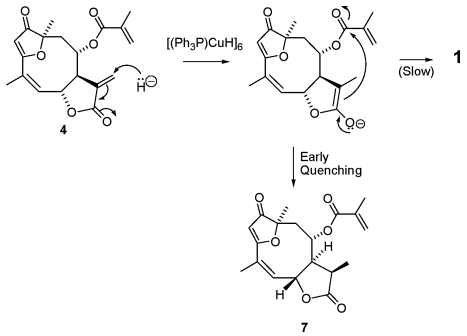
A review of the available methods of selective reduction revealed that Stryker's reagent $[Ph_3PCuH]_6$[9] is highly regioselective and chemoselective in conjugate reductions of various α,β-unsaturated carbonyl derivatives, including unsaturated ketones, esters and aldehydes. These reductions can usually be carried out under very mild reaction conditions.[10] In the presence of additional electrophilic centers, this reagent can also promote, after the 1,4-reduction, a second reaction consisting of an inter- or intramolecular addition.[11]

So we have decided to investigate the use of Stryker's reagent in reduction reactions with these sesquiterpene lactones, and verify how selective it can be in the presence of their several electrophilic centers, which include unsaturated ketones and esters.

We have recently published a preliminary study conducted with a sample of the natural product 15-deoxygoyazensolide (**4**) (Scheme 1).[12] Stryker's reagent showed very high chemoselectivity: we could find only products from the reduction of the α-methylene-lactone; the unsaturated ketone of the furanone ring, as well as the unsaturated ester, remained untouched. In this reaction we obtained eremantholide C (**1**) and the reduced product α-methyl-lactone **7**.

[a]*Departamento de Química, Faculdade de Filosofia, Ciências e Letras de Ribeirão Preto, Universidade de São Paulo, Av. Bandeirantes 3900, 14040-901, Ribeirão Preto–SP, Brazil. E-mail: mgconsta@usp.br*
[b]*Núcleo de Pesquisas em Ciências Exatas e Tecnológicas, Universidade de Franca, Avenida Dr Armando de Salles Oliveira, 201, 14404-600, Franca–SP, Brazil. E-mail: vheleno_05@yahoo.com.br*
[c]*Departamento de Física e Química, Faculdade de Ciências Farmacêuticas de Ribeirão Preto, Universidade de São Paulo, Avenida do Café s/n, 14040-903, Ribeirão Preto–SP, Brazil. E-mail: npelopes@fcfrp.usp.br*

† Electronic supplementary information (ESI) available: Copies of NMR (^1H and ^{13}C, including some gCOSY, gHMQC, gHMBC and NOESY) analyses of compounds **1**, **2**, **3**, **7**, **10**, **11**, **12**, **13**, **14**, **15** and **16**. See DOI: 10.1039/c1ob05734k



Scheme 1 Transformation of 15-deoxygoyazensolide (**4**) into eremantholide C (**1**).

Encouraged by this favorable result, we decided to extend our studies to other furanoheliangolides. We now report the results of this research.

When we treated compounds **4**, **5**, **6**, **8** and **9** (Fig. 2) with Stryker's reagent (0.5 equiv.) at two different temperatures (0 °C and 25 °C) for a period of 2 h, we found that the reducing agent was still selective, but we obtained a larger variety in the results.

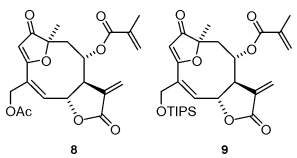


Fig. 2 Derivatives prepared from goyazensolide (**5**).

Though rather confusing at first sight, this variety can be better understood if we consider that an oxygenated function at C-15 has a strong influence on the behavior of Stryker's reagent, producing two remarkable changes: (1) the velocity of the reactions is increased; (2) the α,β,γ,δ-unsaturated system of the furanone can now be also reduced.

Two of our substrates, the natural products 15-deoxygoyazensolide (**4**) and lychnopholide (**6**), contained no oxygen at C-15 and gave similar results (Table 1). The reactions were relatively slow, as evidenced by the recovery of starting material, and the reagent attacked only the α-methylene-γ-lactone, producing the corresponding eremantholide by cyclization and the corresponding α-methyl-γ-lactone by quenching before the intermediate enolate could cyclize (Scheme 1). From the yields in Table 1, calculated based on the transformed starting material, we can easily observe that the cyclization of the enolate is considerably faster for the substrate **4** than for **6**. This is possibly due to an increased steric hindrance in **6** produced by the additional methyl group in the ester moiety.

The other substrates, **5**, **8** and **9**, contain oxygenated functions at C-15 and gave more complex results. Compound **5** is the natural sesquiterpene lactone goyazensolide, and **8** and **9** are simple derivatives, acetate and triisopropylsilyl ether, prepared from **5**.

The increase in the velocity of all reactions is evident by the high consumption of the starting materials, quantitative in all cases except one. We can also observe that the amounts of α-methyl-γ-lactones is much smaller in Table 2 than in Table 1, indicating that there was an increase also in the velocity of cyclization of the intermediate enolates.

Table 1 Reactions of C-15-non-oxygenated sesquiterpene lactones (**4** and **6**) with $[Ph_3PCuH]_6$

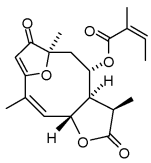
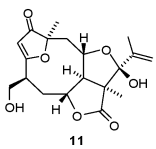
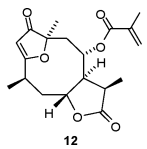
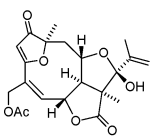
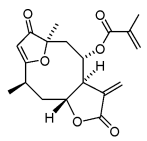
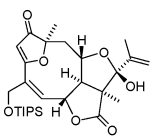
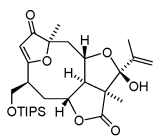
SM	*T*/°C	Consumed SM	Products and yields	
4			**1** (eremantholide)	**7** (α-methyl-lactone)
	0	72%	44%	32%
	25	87%	49%	36%
6			**3** (eremantholide)	 **10** (α-methyl-lactone)
	0	48%	—	77%
	25	75%	15%	63%

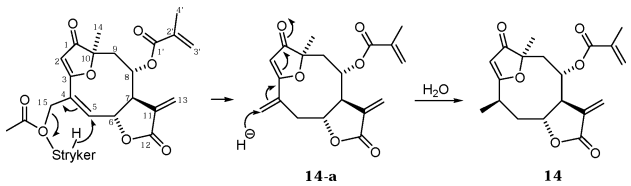
Table 2 Reactions of C-15-oxygenated sesquiterpene lactones (**5**, **8** and **9**) with $[Ph_3PCuH]_6$

SM	*T*/°C	Consumed SM	Products and yields	
5			**2**  **11**	 **12**
	0	100%	45%	41%
	25	100%	48%	37%
8			 **13**	 **14**
	0	88%	32%	48%
	25	100%	28%	62%
9			 **15**	 **16**
	0	100%	46%	39%
	25	100%	Complex mixture	

In all cases (except for substrate **9** at 25 °C, which gave a complex mixture) the expected eremantholide was formed in reasonable yield (**2** from **5**, **13** from **8**, **15** from **9**). In all cases were also obtained products of reduction of the allylic system conjugated with the furanone.

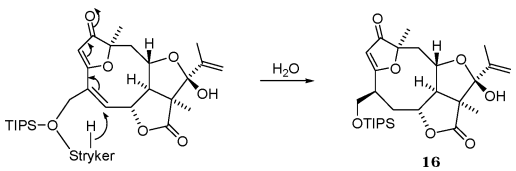
These results can be explained by assuming that a complexation of the Stryker's reagent with the allylic oxygen at C-15 would somehow enhance the reactivity of the reagent, of the substrate or both. This complexation would also force the proximity of the reactants in such a way that the reduction of the allylic system would become an important process.

Depending on the oxygenated group at C-15, this reduction can occur in one of two ways. If the oxygen group in C-15 is a part of a good leaving group (*e.g.* acetate, as in compound **8**), the oxygenated function can be reduced first, possibly through an allylic rearrangement, forming an intermediate that can accept conjugate addition of a hydride, giving a reduced product without oxygen in C-15 (product **14**), as suggested in Scheme 2. It is also possible that **14-a** is formed by 1,6-conjugate addition of hydride followed by elimination of acetate.



Scheme 2 Proposed mechanism for formation of compound **14**.

On the other hand, if the oxygen in C-15 is a part of a bad leaving group (*e.g.* triisopropylsilyl ether, as in compound **9**), the conjugate addition of hydride to the conjugated system becomes the main process, forming products still containing oxygen in C-15 (*e.g.* **16**), as suggested in Scheme 3. It is not possible to decide if this reduction took place before or after the reduction of the α-methylene-γ-lactone and cyclization to form the eremantholide moiety.



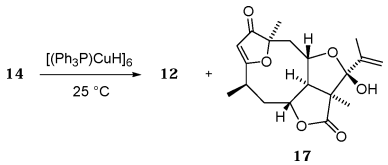
Scheme 3 Proposed mechanism for formation of compound **16**.

The OH group of goyazensolide (**5**) is, like the triisopropylsilyl ether, a bad leaving group, and the still oxygenated eremantholide **11** is the major of the two products that had the conjugated furanone system reduced. However, under the more strained conditions (25 °C), a small amount of **12** was also formed, suggesting that the complexation with Stryker's reagent could have transformed the OH into a somewhat better leaving group.

The formation of compound **14** in the reduction of **8** is rather surprising, because our experimental results indicate clearly that the α-methylene-γ-lactone is the more reactive group of these molecules. It is possible that this methylene-lactone has withstood reduction because in the reaction medium the furanone function was in its enolate form. In fact, in a control experiment we found that pure compound **14** is easily reduced to give **12** together with the corresponding eremantholide **17**[13] when treated with Stryker's reagent under the same reaction conditions used in this paper (25 °C) (Scheme 4).

Conclusions

In conclusion we can say that, considering the complexity of these substrates, the reduction of furanoheliangolides (having the appropriate relative stereochemistry at C-6, C-7, C-8) with Stryker's reagent is an efficient method for preparing eremantholides. When the substrate furanoheliangolide is oxygenated at C-15, the reactions are faster and the eremantholides are still obtained in acceptable yield, but other reduction products are also formed. This is an inconvenience from the point of view of classical synthetic methods, but can also be regarded as an advantage for applying the methodology of biological activity screening usually associated with combinatorial synthesis.



Scheme 4 Control experiment showing that **14** can be reduced.

Experimental

General methods

Reagents and starting materials were purchased from commercial sources and used as received or were synthesized when convenient. Natural products starting materials were isolated from natural sources as described in the literature. If necessary, solvents were purified following standard literature procedures. The reactions were carried out under an atmosphere of argon as specified in the experimental procedures. The NMR spectra were recorded using a Bruker DPX-500 instrument (500 MHz ^{1}H NMR and 125 MHz ^{13}C NMR); $CDCl_3$ and mixtures of $CDCl_3$ and DMSO-d_6 were used as solvent with TMS as internal standard. IR spectra were measured with a Perkin-Elmer Spectrum RX IFTIR System. High resolution mass spectra (HRMS) were obtained on an ESI-TOF Mass Spectrometer. TLC was performed on precoated silica gel 60 F254 plates (0.25 mm thick, Merck), and silica gel 60 (70–230 mesh, Merck) was used for column chromatography.

Synthesis of Stryker's reagent $[PPh_3CuH]_6$

This was performed, with some modifications, as described in the literature.[8] Copper(I) chloride (0.9930 g, 10.03 mmol), potassium *t*-butoxide (1.124 g, 10.02 mmol) and triphenylphosphine (2.623 g, 20.00 mmol) were weighed into a dry septum-capped round-bottomed flask inside a dry-box. The flask was charged with 50 mL toluene (distilled from CaH_2 and degassed for 20 min) and the contents were stirred for 40 min under argon to produce a slightly cloudy, yellow solution. 1,1,2,2-Tetramethyl-disiloxane (1.84 mL, 10.0 mmol) was then added by syringe. The colour of the reaction mixture changed from yellow to very dark red. After stirring for 2 h, the mixture was transferred to a large Schlenk filter containing 1 cm Celite *via* cannula. The red filtrate was concentrated *in vacuo* to about 15 mL. Dry degassed acetonitrile (40 mL) was slowly layered onto the top of the toluene solution *via* cannula to induce crystallization of the product. After standing overnight, the red crystals thus obtained were isolated by filtration, washed with 3 × 10 mL dry acetonitrile and dried under vacuum to give 2.1 g (64%)

of bright to dark red crystals. ^{1}H NMR (500 MHz, C_6D_6) δ (ppm): 7.65 (36H, t, J = 8.1 Hz), 6.93 (18H, t, J = 7.3 Hz), 6.72 (36H, t, J = 7.5 Hz), 3.49 (6H, br s).

General procedure for reduction of sesquiterpene lactones with Stryker's reagent

A 9.5×10^{-3} M solution of the sesquiterpene lactone (n mmol) in toluene and recently prepared Stryker's reagent (n/2 mmol), were mixed together and stirred at room temperature or 0 °C for 2 h. The reaction was quenched with 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 was separated and the aqueous phase was extracted with ethyl acetate. 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. The yields are shown in Tables 1 and 2.

(2a*S*,3*R*,4a*S*,6*R*,11a*R*,11b*R*)-3-Hydroxy-3-isopropenyl-2a,6,10-trimethyl-2a,3,5,6,11a,11b-hexahydro-2*H*-6,9-epoxy-1,4-dioxacyclodeca[*cd*]pentalene-2,7(4a*H*)-dione (eremantholide C) (1)

Obtained from reduction of **4**. Purified by column chromatography in silica gel using a 9 : 1 mixture of toluene/ethyl acetate as eluent. White solid, mp (229 °C - 230 °C). ^{1}H NMR ($CDCl_3$, 500 MHz), δ (ppm): 1.19 (3H, s); 1.49 (3H, s); 1.90 (3H, dd, J = 1.5, 0.9 Hz); 2.06 (1H, dd, J = 13.6, 11.9 Hz); 2.06 (3H, dd, J = 2.4, 1.6 Hz); 2.41 (1H, dd, J = 13.6, 2.6 Hz); 2.57 (1H, br.s); 2.85 (1H, dd, J = 7.0, 4.2 Hz); 4.14 (1H, dddd, J = 11.9, 4.2, 2.6, 0.6 Hz); 4.98 (1H, dddq, J = 7.0, 2.7, 2.4, 0.6 Hz); 5.08 (1H, dd, J = 2.0, 1.5 Hz); 5.33 (1H, dd, J = 2.0, 0.9 Hz); 5.62 (1H, s); 6.03 (1H, dq, J = 2.7, 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); 186.8 (C); 205.2 (C═O). IR ν_{max} (liquid film): 3395; 2973; 2923; 1775; 1699; 1659; 1585 cm^{-1}. HRMS (ESI-TOF): calcd for $C_{19}H_{22}O_6Na^+$ (MNa^+) 369.1308, found 369.1304.

(3*R*,3a*R*,4*S*,6*R*,11a*R*)-3,6,10-Trimethyl-2,7-dioxo-2,3,3a,4,5,6,7,11a-octahydro-6,9-epoxycyclodeca[*b*]furan-4-yl 2-methylacrylate (7)

Obtained from reduction of **4**. Purified by column chromatography in silica gel using a 9 : 1 mixture of toluene/ethyl acetate as eluent. Colourless oil. ^{1}H NMR ($CDCl_3$, 500 MHz), δ (ppm): 1.34 (3H, d, J = 6.7 Hz); 1.50 (3H, s); 1.91 (3H, dd, J = 1.45, 0.8 Hz); 2.12 (3H, dd, J = 2.4, 1.7 Hz); 2.19 (1H, dd, J = 13.4, 1.4 Hz); 2.35 (1H, dd, J = 13.4, 11.6 Hz); 2.40 (1H, dq, J = 11.6, 6.7 Hz); 3.00 (1H, ddd, J = 11.6, 9.2, 2.2 Hz); 4.92 (1H, dddd, J = 11.6, 2.2, 1.4, 0.6 Hz); 5.05 (1H, dddq, J = 9.2, 2.9, 2.4, 0.6 Hz); 5.63 (1H, q, J = 1.4 Hz); 5.78 (1H, s); 5.99 (1H, dq, J = 2.9, 1.7 Hz); 6.09 (1H, dq, J = 1.4, 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); 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.

(2a*S*,3*R*,4a*S*,6*R*,11a*R*,11b*R*)-3-Hydroxy-2a,6,10-trimethyl-3-[(1*Z*)-1-methylprop-1-en-1-yl]-2a,3,5,6,11a,11b-hexahydro-2*H*-6,9-epoxy-1,4-dioxacyclodeca[*cd*]pentalene-2,7(4a*H*)-dione (3)

Obtained from reduction of **6**. Purified by column chromatography in silica gel using a 9 : 1 mixture of toluene/ethyl acetate as eluent. Colourless oil. ^{1}H NMR ($CDCl_3$, 500 MHz), δ (ppm): 1.17 (3H, s); 1.42 (3H, s); 1.70–1.71 (3H, m); 1.76 (3H, br.s); 1.97–2.02 (4H, m); 2.39 (1H, dd, J = 13.6, 2.4 Hz); 2.75 (1H, dd, J = 7.2, 4.4 Hz); 2.88 (1H, br.s); 4.07–4.09 (1H, m); 4.90–4.91 (1H, m); 5.25–5.55 (2H, m); 5,96 (1H, br.s). ^{13}C NMR ($CDCl_3$, 125 MHz), δ (ppm): 15.3 (CH_3); 20.3 (CH_3); 20.5 (CH_3); 21.4 (CH_3); 21.9 (CH_3); 43.7 (CH_2); 61.2 (C); 62.0 (CH); 78.9 (CH), 81.4 (CH); 90.0 (C); 104.5 (CH); 127.9 (CH); 130.1 (C); 131.7 (C); 134.8 (CH); 175.6 (C═O); 187.0 (C); 205.4 (C═O). IR ν_{max} (liquid film): 3402; 2960; 2926; 2855; 1773; 1733; 1699; 1585 cm^{-1}. HRMS (ESI-TOF): calcd for $C_{20}H_{24}O_6Na^+$ (MNa^+) 383.1460, found 383.1476.

(3*R*,3a*R*,4*S*,6*R*,11a*R*)-3,6,10-Trimethyl-2,7-dioxo-2,3,3a,4,5,6,7,11a-octahydro-6,9-epoxycyclodeca[*b*]furan-4-yl (2*Z*)-2-methylbut-2-enoate (10)

Obtained from reduction of **6**. Purified by column chromatography in silica gel using a 9 : 1 mixture of toluene/ethyl acetate as eluent. Yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz), δ (ppm): 1.26 (3H, d, J = 7.0 Hz); 1.44 (3H, s); 1.78 (3H, s); 1.91 (3H, d, J = 7.0 Hz); 2.05 (3H, s); 2.10–2.13 (1H, m); 2.26–2.33 (2H, m); 2.89–2.94 (1H, m); 4.85–4.87 (1H, m); 5.02–5.04 (1H, m); 5.71 (1H, s); 5.93 (1H, br.s); 6.10–6.15 (1H, m). ^{13}C NMR ($CDCl_3$, 125 MHz), δ (ppm): 15.4 (CH_3); 15.9 (CH_3); 20.3 (CH_3); 20.5 (CH_3); 21.6 (CH_3); 38.4 (CH); 44.9 (CH_2); 55.1 (CH); 67.1 (CH); 80.4 (CH), 89.0 (C); 105.1 (CH); 133.2 (CH); 141.6 (CH); 166.6 (C═O); 176.8 (C═O); 187.0 (C); 204.2 (C═O). IR ν_{max} (liquid film): 2983; 2934; 1770; 1732; 1682; 1574 cm^{-1}. HRMS (ESI-TOF): calcd for $C_{20}H_{24}O_6Na^+$ (MNa^+) 383.1460, found 383.1469.

(2a*S*,3*R*,4a*S*,6*R*,11a*R*,11b*R*)-3-Hydroxy-10-(hydroxymethyl)-3-isopropenyl-2a,6-dimethyl-2a,3,5,6,11a,11b-hexahydro-2*H*-6,9-epoxy-1,4-dioxacyclodeca[*cd*]pentalene-2,7(4a*H*)-dione (15-hydroxy-eremantholide C) (2)

Obtained from reduction of **5**. Purified by column chromatography in silica gel using a 1 : 1 mixture of hexane/ethyl acetate as eluent. Colourless oil. ^{1}H NMR ($CDCl_3$, 500 MHz), δ (ppm): 1.20 (3H, s); 1.50 (3H, s); 1.90 (3H, br.s); 2.05–2.10 (1H, m); 2.42 (1H, dd, J = 13.7, 2.3 Hz); 2.68 (1H, br.s); 2.91 (1H, dd, J = 7.3, 4.1 Hz); 4.17–4.19 (1H, m); 4.36–4.42 (2H, m); 5.05–5.06 (1H, m); 5.08 (1H, br.s); 5.33 (1H, br.s); 5.72 (1H, s); 6.31 (1H, br.s). ^{13}C NMR* ($CDCl_3$, 125 MHz), δ (ppm): 19.1 (CH_3); 20.7 (CH_3); 21.8 (CH_3); 43.8 (CH_2); 62.1 (CH); 63.3 (CH_2); 78.3 (CH), 81.3 (CH); 90.1 (C); 106.4 (CH); 106.8 (C); 116.1 (CH); 116.2 (CH_2); 134.5 (C); 135.3 (CH); 141.7 (C); 175.3 (C═O); 184.0 (C); 205.0 (C═O). IR ν_{max} (liquid film): 3422; 2979; 2930; 1778; 1713; 1659; 1584; 1451; 1377; 918 cm^{-1}. HRMS (ESI-TOF): calcd for $C_{19}H_{22}O_7Na^+$ (MNa^+) 385.1258, found 385.1269.

(2a*S*,3*R*,4a*S*,6*R*,10*S*,11a*R*,11b*R*)-3-Hydroxy-10-(hydroxymethyl)-3-isopropenyl-2a,6-dimethyl-2a,3,5,6,10,11,11a,11b-octahydro-2*H*-6,9-epoxy-1,4-dioxacyclodeca[*cd*]pentalene-2,7(4a*H*)-dione (11)

Obtained from reduction of **5**. Purified by column chromatography in silica gel using a 1 : 1 mixture of hexane/ethyl acetate as eluent. Yellow oil. ^{1}H NMR ($CDCl_3$ + 10% DMSO-d_6, 500 MHz), δ (ppm): 1.16 (3H, s); 1.44 (3H, s); 1.87 (3H, br.s); 2.04 (1H, dd, J = 14.0, 11.7 Hz); 2.24–2.31 (1H, m); 2.35 (1H, dd, J = 14.0, 2.3 Hz); 2.41–2.44 (1H, m); 2.54 (1H, dd, J = 6.7, 4.3 Hz); 2.99–3.04 (1H, m); 3.80 (1H, dd, J = 10.5, 6.4 Hz); 3.92 (1H, dd, J = 10.5, 6.7 Hz); 3.98–4.01 (1H, m); 4.32–4.36 (1H, m); 5.01 (1H, br.s); 5.26 (1H, br.s); 5.67 (1H, br.s); 5.71 (1H, br.s). ^{13}C NMR ($CDCl_3$ + 10% DMSO-d_6, 125 MHz), δ (ppm): 18.6 (CH_3); 20.7 (CH_3); 22.0 (CH_3); 36.0 (CH_2); 38.5 (CH); 43.7 (CH_2); 59.9 (C); 60.8 (CH_2); 66.2 (CH), 75.9 (CH); 80.1 (CH); 88.5 (C); 104.1 (CH); 105.8 (C); 114.3 (CH_2); 142.2 (C); 175.9 (C═O); 190.4 (C); 205.5 (C═O). IR ν_{max} (liquid film): 3445; 1762; 1681; 1583; 1049; 1025; 997; 827; 765 cm^{-1}. HRMS (ESI-TOF): calcd for $C_{19}H_{24}O_7Na^+$ (MNa^+) 387.1414, found 387.1412.

(3*R*,3a*S*,4*S*,6*R*,10*R*,11a*R*)-3,6,10-Trimethyl-2,7-dioxo-2,3,3a,4,5,6,7,10,11,11a-decahydro-6,9-epoxycyclodeca[*b*]furan-4-yl 2-methylacrylate (12)

Obtained from reduction of **5**. Purified by column chromatography in silica gel using a 1 : 1 mixture of hexane/ethyl acetate as eluent. Colourless oil. ^{1}H NMR ($CDCl_3$, 500 MHz), δ (ppm): 1.33 (3H, d, J = 6.7 Hz); 1.42 (3H, d, J = 7.3 Hz); 1.45 (3H, s); 1.91 (3H, br.s); 2.16–2.40 (5H, m); 2.50–2.55 (1H, m); 3.06–3.08 (1H, m); 4.37–4.40 (1H, m); 4.77–4.80 (1H, m); 5.62 (1H, br.s); 5.73 (1H, br.s); 6.07 (1H, br.s). ^{13}C NMR ($CDCl_3$, 125 MHz), δ (ppm): 16.0 (CH_3); 16.1 (CH_3); 18.1 (CH_3); 20.7 (CH_3); 31.3 (CH); 38.5 (CH); 41.5 (CH_2); 46.5 (CH_2); 59.4 (CH); 68.2 (CH), 79.2 (CH); 88.4 (C); 104.8 (CH); 126.9 (CH_2); 135.4 (C); 166.3 (C═O); 177.1 (C═O); 194.1 (C); 204.9 (C═O). IR ν_{max} (liquid film): 2961; 2926; 2853; 1773; 1718; 1707; 1591; 1261; 1191; 805 cm^{-1}. HRMS (ESI-TOF): calcd for $C_{19}H_{24}O_6Na^+$ (MNa^+) 371.1465, found 371.1483.

[(2a*S*,3*R*,4a*S*,6*R*,11a*R*,11b*R*)-3-Hydroxy-3-isopropenyl-2a,6-dimethyl-2,7-dioxo-2a,3,4a,5,6,7,11a,11b-octahydro-2*H*-6,9-epoxy-1,4-dioxacyclodeca[*cd*]pentalen-10-yl]methyl acetate (13)

Obtained from reduction of **8**. Purified by column chromatography in silica gel using a 8 : 2 mixture of toluene/ethyl acetate as eluent. Yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz), δ (ppm): 1.19 (3H, s); 1.48 (3H, s); 1.88 (3H, br.s); 1.99–2.06 (1H, m); 2.10 (3H, s); 2.41 (1H, dd, J = 13.5, 2.5 Hz); 2.78 (1H, br.s); 2.89 (1H, dd, J = 7.1, 4.1 Hz); 4.10–4.17 (1H, m); 4.76 (2H, br.s); 5.02–5.07 (2H, m); 5.31 (1H, br.s); 5.70 (1H, s); 6.32–6.33 (1H, m). ^{13}C NMR ($CDCl_3$, 125 MHz), δ (ppm): 18.9 (CH_3); 20.5 (CH_3); 21.7 (CH_3); 22.7 (CH_3); 43.7 (CH_2); 59.7 (C); 62.0 (CH); 63.5 (CH_2); 78.3 (CH), 81.2 (CH); 90.2 (C); 106.2 (C); 106.5 (CH); 116.2 (CH_2); 129.6 (C); 138.0 (CH); 141.8 (C); 170.2 (C═O); 175.2 (C═O); 183.1 (C); 205.0 (C═O). IR ν_{max} (liquid film): 3412; 2961; 2925; 2855; 1767; 1746; 1712; 1589; 1449; 1373; 1259; 1097; 1046; 812 cm^{-1}. HRMS (ESI-TOF): calcd for $C_{21}H_{24}O_8Na^+$ (MNa^+) 427.1363, found 427.1368.

(3a*S*,4*S*,6*R*,10*R*,11a*R*)-6,10-Dimethyl-3-methylene-2,7-dioxo-2,3,3a,4,5,6,7,10,11,11a-decahydro-6,9-epoxycyclodeca[*b*]furan-4-yl 2-methylacrylate (14)

Obtained from reduction of **8**. Purified by column chromatography in silica gel using a 8 : 2 mixture of toluene/ethyl acetate as eluent. Yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz), δ (ppm): 1.36 (3H, d, J = 7.0 Hz); 1.42 (3H, s); 1.75 (3H, br.s); 2.05–2.07 (1H, m); 2.27–2.30 (1H, m); 2.38–2.43 (2H, m); 2.95–3.01 (1H, m); 3.28–3.30 (1H, m); 4.26–4.29 (1H, m); 4.42–4.45 (1H, m); 5.37–5.38 (1H, m); 5.46 (1H, br.s); 5.62 (1H, br.s); 5.93 (1H, br.s); 6.12 (1H, d, J = 3.1 Hz). ^{13}C NMR ($CDCl_3$, 125 MHz), δ (ppm): 16.5 (CH_3); 17.9 (CH_3); 21.2 (CH_3); 31.2 (CH); 41.4 (CH_2); 45.4 (CH_2); 54.7 (CH); 72.0 (CH), 80.2 (CH); 89.7 (C); 104.7 (CH); 124.3 (CH_2); 126.4 (CH_2); 133.9 (C); 135.6 (C); 166.8 (C═O); 168.9 (C═O); 193.8 (C); 205.1 (C═O). IR ν_{max} (liquid film): 2959; 2931; 2854; 1774; 1709; 1588; 1455; 1377; 1242; 1141; 1041; 944; 817 cm^{-1}. HRMS (ESI-TOF): calcd for $C_{19}H_{22}O_6Na^+$ (MNa^+) 369.1309, found 369.1308.

(2a*S*,3*R*,4a*S*,6*R*,11a*R*,11b*R*)-3-Hydroxy-3-isopropenyl-2a,6-dimethyl-10-{[(triisopropylsilyl)oxy]methyl}-2a,3,5,6,11a,11b-hexahydro-2*H*-6,9-epoxy-1,4-dioxacyclodeca[*cd*]pentalene-2,7(4a*H*)-dione (15)

Obtained from reduction of **9**. Purified by column chromatography in silica gel using a 5 : 1 : 4 mixture of chloroform/ethyl acetate/hexane as eluent. Colourless oil. ^{1}H NMR ($CDCl_3$, 500 MHz), δ (ppm): 1.00 (18H, d, J = 6.7 Hz); 1.04–1.09 (3H, m); 1.13 (3H, s); 1.40 (3H, s); 1.83 (3H, br.s); 1.97–2.02 (1H, m); 2.35 (1H, dd, J = 13.5, 2.3 Hz); 2.65 (1H, br.s); 2.84 (1H, dd, J = 7.3, 4.2 Hz); 4.07–4.11 (1H, m); 4.34–4.41 (2H, m); 4.98–5.01 (2H, m); 5.26 (1H, br.s); 5.61 (1H, s); 6.20 (1H, br.s). ^{13}C NMR ($CDCl_3$, 125 MHz), δ (ppm): 11.9 (CH–Si); 17.9 (CH_3); 18.9 (CH_3); 20.5 (CH_3); 21.8 (CH_3); 43.7 (CH_2); 59.8 (C); 62.3 (CH); 63.7 (CH_2); 78.4 (CH), 81.6 (CH); 90.1 (C); 106.2 (C); 106.4 (CH); 116.0 (CH_2); 133.4 (CH); 134.4 (C); 142.1 (C); 175.5 (C═O); 184.8 (C); 205.3 (C═O). IR ν_{max} (liquid film): 3376; 2960; 2926; 2866; 1779; 1699; 1576; 1457; 1378; 1260; 1099; 1024; 919; 798 cm^{-1}. HRMS (ESI-TOF): calcd for $C_{28}H_{42}O_7SiNa^+$ (MNa^+) 541.2592, found 541.2597.

(2a*S*,3*R*,4a*S*,6*R*,10*S*,11a*R*,11b*R*)-3-Hydroxy-3-isopropenyl-2a,6-dimethyl-10-{[(triisopropylsilyl)oxy]methyl}-2a,3,5,6,10,11,11a,11b-octahydro-2*H*-6,9-epoxy-1,4-dioxacyclodeca[*cd*]pentalene-2,7(4a*H*)-dione (16)

Obtained from reduction of **9**. Purified by column chromatography in silica gel using a 5 : 1 : 4 mixture of chloroform/ethyl acetate/hexane as eluent. Yellow oil. ^{1}H NMR ($CDCl_3$, 500 MHz), δ (ppm): 1.00 (18H, d, J = 6.2 Hz); 1.04–1.10 (3H, m); 1.14 (3H, s); 1.39 (3H, s); 1.82 (3H, br.s); 1.94–1.99 (1H, m); 2.21–2.27 (2H, m); 2.33–2.36 (1H, m); 2.39–2.41 (1H, m); 2.50 (1H, dd, J = 6.5, 4.7 Hz); 3.90–3.99 (3H, m); 4.33–4.37 (1H, m); 4.99 (1H, br.s); 5.25 (1H, br.s); 5.64 (1H, br.s). ^{13}C NMR ($CDCl_3$, 125 MHz), δ (ppm): 11.8 (CH–Si); 18.0 (CH_3); 18.9 (CH_3); 21.2 (CH_3); 22.6 (CH_3); 36.8 (CH_2); 39.2 (CH); 44.0 (CH_2); 60.2 (C); 63.1 (CH_2); 66.4 (CH); 77.0 (CH), 80.7 (CH); 89.1 (C); 104.8 (CH); 106.4 (C); 115.9 (CH_2); 142.2 (C); 175.8 (C═O); 190.4 (C); 205.9 (C═O). IR ν_{max} (liquid film): 3396; 2926; 2866; 1771; 1740; 1695; 1586; 1456; 1373; 1242; 1107; 917; 882; 804; 683 cm^{-1}. HRMS (ESI-TOF): calcd for $C_{28}H_{44}O_7SiNa^+$ (MNa^+) 543.2748, found 543.2748.

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