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A model synthesis of the bicyclic core structure of the furanoheliangolide sesquiterpenes

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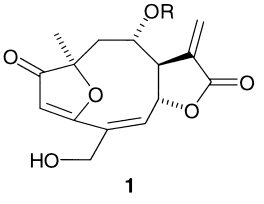
Abstract

A bicyclo[6.2.1]undecane structure, a model for the core structure of several biologically active furanoheliangolide sesquiterpenes, was synthesized through a retro–aldol reaction from a tricyclo-[6.2.1.$0^{2,7}$]undecane. The required tricyclic compound was prepared by a Diels–Alder reaction followed by minor transformations.

In the last few years we have been interested in developing methods for the synthesis of certain Brazilian biologically active natural products belonging to the class of furanoheliangolides. They are sesquiterpenoids containing a peculiar macrocyclic structure, a bicyclo[6.2.1]undecane; goyazensolide (**1**), which has cytotoxic and schistosomicidal properties,[1] is a typical example. Our recent success in preparing compound **2**, which contains most of the structural features of the bicyclic core found in these sesquiterpenes, prompted us to disclose our preliminary results.



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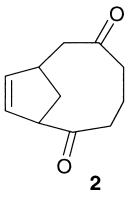

2

Our synthetic strategy consisted of preparing a tricyclo[6.2.1.$0^{2,7}$]undecane structure (**5**) through a simple Diels–Alder reaction, and breaking the bond C_2–C_7 to obtain the desired bicyclo-[6.2.1]undecane structure. Starting with cyclopentadiene and benzoquinone, adduct **5** was prepared in 90% yield (Scheme 1).[2]

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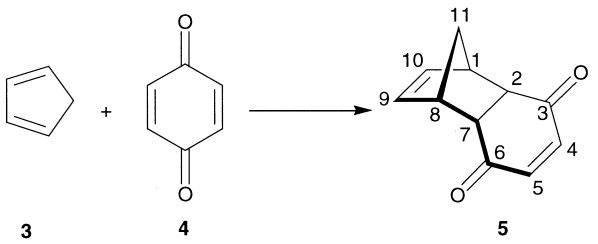
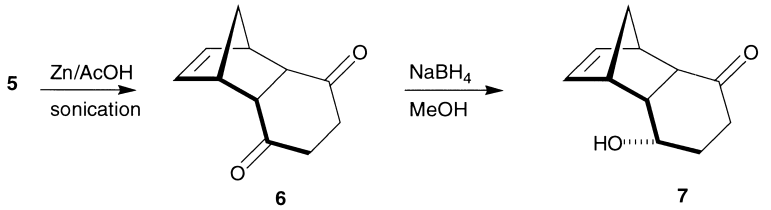


Scheme 1.

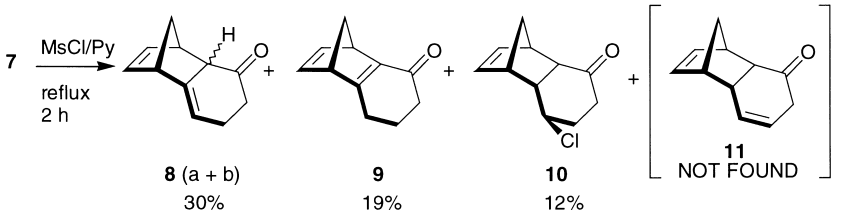
The conjugated double bond of **5** was selectively reduced with Zn/AcOH (97%),[3] and one of the carbonyls of product **6** was reduced to furnish keto-alcohol **7** in 92% yield (Scheme 2).[4] The high stereoselectivity observed in this last reduction is clearly due to the cage-like structure of **6**.



Scheme 2.

At this point we intended to move the –OH group of compound **7** to carbon 7 of the tricyclic ring system; the product thus obtained (compound **12**) (see Scheme 4) would be suitable for a retro-aldol reaction that would effect the desired C_2–C_7 bond breaking. To accomplish this 'OH shift' we decided to try the water elimination–water addition sequence, as there is some evidence that, in this kind of structure, compounds with a double bond *exo* to the bicyclic structure (as **8**) form more easily than their isomers (like **11**).[5]

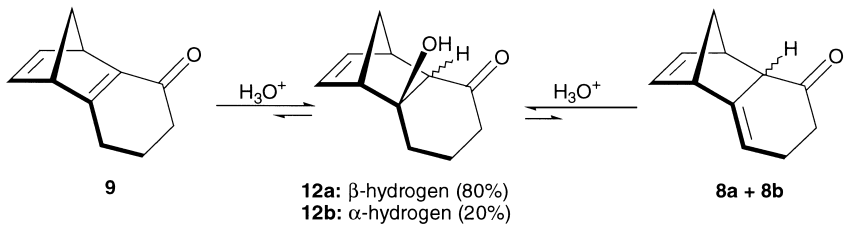
As anticipated, treatment of **7** with MsCl in pyridine under reflux produced mainly olefins **8**, as a 1:1 mixture of stereoisomers (**8a+8b**), and compound **11** was not found among the reaction products (Scheme 3).[6] The crude mixture was obtained in 94% yield (calculated as for compound **8** or **9**), and the yields in the scheme correspond to products purified by column chromatography.



Scheme 3.

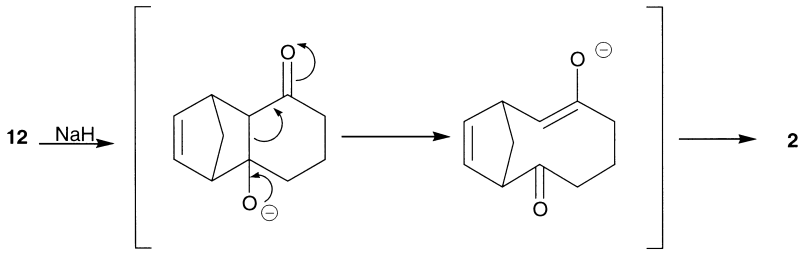
The intended further transformation of **8** into **9**, which we expected to be more stable due to conjugation, proved to be unnecessary. In fact, a considerable amount of **9** was formed in the elimination reaction, and this allowed us to isolate compounds **8** (as a mixture of isomers **8a+8b**)

and **9** and show that both can be transformed into the desired hydration product **12**, by a simple treatment with acetone/water/*p*-toluenesulfonic acid (Scheme 4). Under these conditions, either **8** or **9** is transformed in the same equilibrium mixture from which compounds **12** (as a 80:20 mixture of stereoisomers **12a** and **12b**) could be isolated in 55–60% yield, and compounds **9** (7%) and **8** (10%) could be recovered by column chromatography. Isomers **12a** and **12b** were also separated from each other (in a further column chromatography) and properly characterized, including a relative stereochemistry determination by NOE experiments.[7]



Scheme 4.

Finally, treatment of each isomer of compound **12** with NaH in toluene under reflux gave rise to a retro–aldol reaction and furnished the desired bicyclic product **2**[8] in 75% yield after column chromatography (Scheme 5).



Scheme 5.

We have also experimented on the treatment of **9** with a solution of NaOH in methanol/water, which could give a nucleophilic addition of OH^- followed by a retro–aldol reaction in the same pot; this treatment, however, furnished only methoxylated products.

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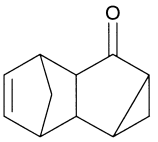
6. Treatment of the mesylate of **7** (obtained in quantitative yield from **7** with MsCl in triethylamine) with KOBu^t produced only compound **13** in good yield (69%).



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7. Compound **12a**: rel-(1*S*,7*S*,2*R*,8*R*)-7-Hydroxytricyclo[6.2.1.0^{2,7}]undec-9-en-3-one: ^{1}H NMR (300 MHz, $CDCl_3$): 1.21 (td, 1H, $J_1 = J_2 = 14$ Hz, $J_3 = 3$ Hz), 1.51 (dt, 1H, $J_1 = 9$ Hz, $J_2 = J_3 = 2$ Hz), 1.66 (m, 1H), 1.81–2.00 (m, 3H), 2.15 (m, 1H), 2.34 (ddt, 1H, $J_1 = 18$ Hz, $J_2 = 6$ Hz, $J_3 = J_4 = 2$ Hz), 2.50 (d, 1H, $J = 4$ Hz), 2.68 (m, 1H), 2.85 (br s, 1H), 3.35 (br s, 1H), 5.96 (dd, 1H, $J_1 = 6$ Hz, $J_2 = 3$ Hz), 6.12 (dd, 1H, $J_1 = 6$ Hz, $J_2 = 3$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): 18.19 (CH_2), 35.75 (CH_2), 38.89 (CH_2), 43.82 (CH), 45.78 (CH_2), 54.12 (CH), 61.57 (CH), 81.63 (C), 134.91 (CH), 138.27 (CH), 214.57 (C=O); IR (film) ν_{max}: 3441, 2692, 2887, 965, 733 cm^{-1}; MS *m*/*z* (rel. intensity): 160 [M$^+$–H_2O] (11), 132 (6), 113 (100), 66 (59), 55 (7), 39 (10). Compound **12b**: rel-(1*S*,2*S*,7*S*,8*R*)-7-Hydroxytricyclo[6.2.0^{2,7}]undec-9-en-3-one: mp 77–80°C; ^{1}H NMR (300 MHz, $CDCl_3$): 1.32 (d, 1H, $J = 10$ Hz), 1.48 (td, 1H, $J_1 = J_2 = 14$ Hz, $J_3 = 3$ Hz), 1.56 (ddt, 1H, $J_1 = 10$ Hz, $J_2 = 4$ Hz, $J_3 \cong J_4 \cong 2$ Hz), 1.81 (d, 1H, $J = 3$ Hz), 1.89 (m, 1H), 2.12 (m, 1H), 2.19–2.37 (m, 2H), 2.54 (m, 1H), 2.76 (tt, 1H, $J_1 = J_2 = 3$ Hz, $J_3 = J_4 = 2$ Hz), 6.28 (dd, 1H, $J_1 = 6$ Hz, $J_2 = 3$ Hz), 6.49 (d, 1H, $J_1 = 6$ Hz, $J_2 = 3$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): 18.38 (CH_2), 35.79 (CH_2), 38.69 (CH_2), 45.20 (CH), 48.33 (CH_2), 53.04 (CH), 61.69 (CH), 82.00 (C), 134.18 (CH), 139.27 (CH), 213.54 (C=O); IR (KBr) ν_{max}: 3441, 2962, 2887, 1692, 1455, 733 cm^{-1}; MS *m*/*z* (rel. intensity): 160 [M$^+$–H_2O] (12), 132 (6), 113 (100), 66 (59), 55 (7), 39 (10).
8. Compound **2**: rel-(1*S*,8*R*)-Bicyclo[6.2.1]undec-9-ene-2,6-dione (**4**): ^{1}H NMR (300 MHz, $CDCl_3$): 1.91 (dd, 1H, $J_1 = 14$ Hz, $J_2 = 12$ Hz), 1.92 (m, 1H), 2.13 (ddd, 1H, $J_1 = 13$ Hz, $J_2 \cong J_3 \cong 5$ Hz, $J_4 = 2$ Hz), 2.17 (d, 1H, $J = 14$ Hz), 2.43–2.53 (m, 3H), 2.55–2.75 (m, 3H), 3.16 (m, 1H), 3.39 (ddd, 1H, $J_1 = 12$ Hz, $J_2 \cong J_3 \cong 3$ Hz, $J_4 = 2$ Hz), 5.90 (dt, 1H, $J_1 = 5$ Hz, $J_2 = J_3 = 2$ Hz), 6.06 (dt, 1H, $J_1 = 5$ Hz, $J_2 = J_3 = 2$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$): 21.20 (CH_2), 33.15 (CH_2), 36.91 (CH_2), 40.73 (CH_2), 42.27 (CH), 48.36 (CH_2), 58.33 (CH), 130.86 (CH), 137.54 (CH), 211.86 (C=O), 218.35 (C=O); MS *m*/*z* (rel. intensity): 149 [M$^+$–HCO](57), 123 (9), 113 (9), 66 (100), 55 (56), 43 (56), 29 (13).