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Total synthesis and anti-leishmanial activity of *R*-(−)-argentilactone

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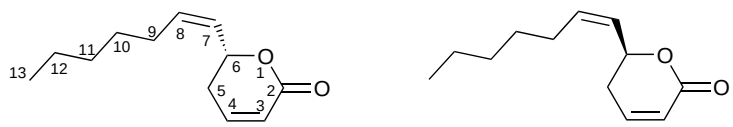
Abstract—Starting from the commercially available D-glucal (**2**), the naturally occurring α,β-unsaturated δ-lactone argentilactone (**1a**) has been synthesized. The important step is the configuration inversion at C-6 by the Mitsunobu reaction following the sugar–non-sugar–sugar strategy. The synthetic argentilactone has been tested against *Leishmania mexicana* for bioactivity.

R-(−)-Argentilactone (**1a**), an α,β-unsaturated δ-lactone, was originally isolated in 1977 from the rhizomes of *Aristolochia argentina* Gris.[1] This compound is the major constituent of the essential oil and hexane extract of *Annona haematantha*[2] and also present in the methanolic extract of the leaves of *Chorisia crispiflora*.[3] Biological studies on **1a** have revealed high anti-leishmanial[2] and cytotoxic activity against P-388 mouse leukaemia cells.[3] Moreover, it can also be used as starting material for the synthesis of interesting pheromones.[4] These features prompted some research groups to undertake the total synthesis of this compound.[5–8]

Recently, we have reported the first total synthesis of non-natural enantiomer of argentilactone (**1b**) from glucose[9] (Fig. 1). Extending our research for the synthesis of α,β-unsaturated δ-lactones based on cheap and easily available sugar templates, we describe here the total synthesis of *R*-(−)-argentilactone (**1a**). As the stereochemistry of **1a** at C-6 (pyran numbering) is *R*, a sugar from L-series is needed. This stereochemical problem was solved by converting commercially available D-glucal (**2**) into the optically active furan glycol **3a**[10] followed by inversion of configuration of the asymmetric center by the Mitsunobu reaction.[11] Although the authors used 2 equiv. of the reagent system (PPh_3, DEAD, benzoic acid) to produce the crystalline dibenzoate **4a** in 92% yield,[10] we found that the use of 1 equiv. of the reagents gave the monobenzoate **4b**[12] with the free primary hydroxyl group in more than 80% yield containing the dibenzoate **4a** in less than 5% yield. Verification that the inversion was stereospecific was obtained from the fact that the optical rotation of **3b** was identical in magnitude but opposite in sign to that of the furandiol **3a**. Compound **3b** was prepared by the hydrolysis of **4b** and **4a**.

Thus, the commercially available D-glucal (**2**) was converted into the furandiol **3a** under the conditions ($HgSO_4$, 0.002 M H_2SO_4) defined by Gonzalez and co-workers[13] in 90% yield. Inversion of the configura-



1a **1b**

Figure 1. *R*-(−)-Argentilactone (**1a**) and its non-natural enantiomer (**1b**).

Keywords: synthesis; argentilactone; Mitsunobu reaction; biological activity; *Leishmania mexicana*.

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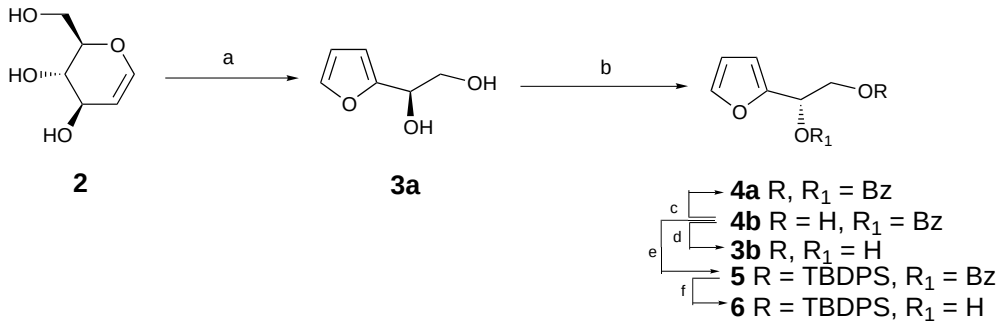
tion of the secondary alcohol in **3a** was carried out via the Mitsunobu reaction[11] by using 1.1 equiv. amounts of each, PPh_3, DEAD, and benzoic acid in dry THF. Benzoylation of the secondary hydroxyl group was indicated by the low-field absorption (δ 6.19 ppm) of H-2 in the ^1H NMR spectrum.

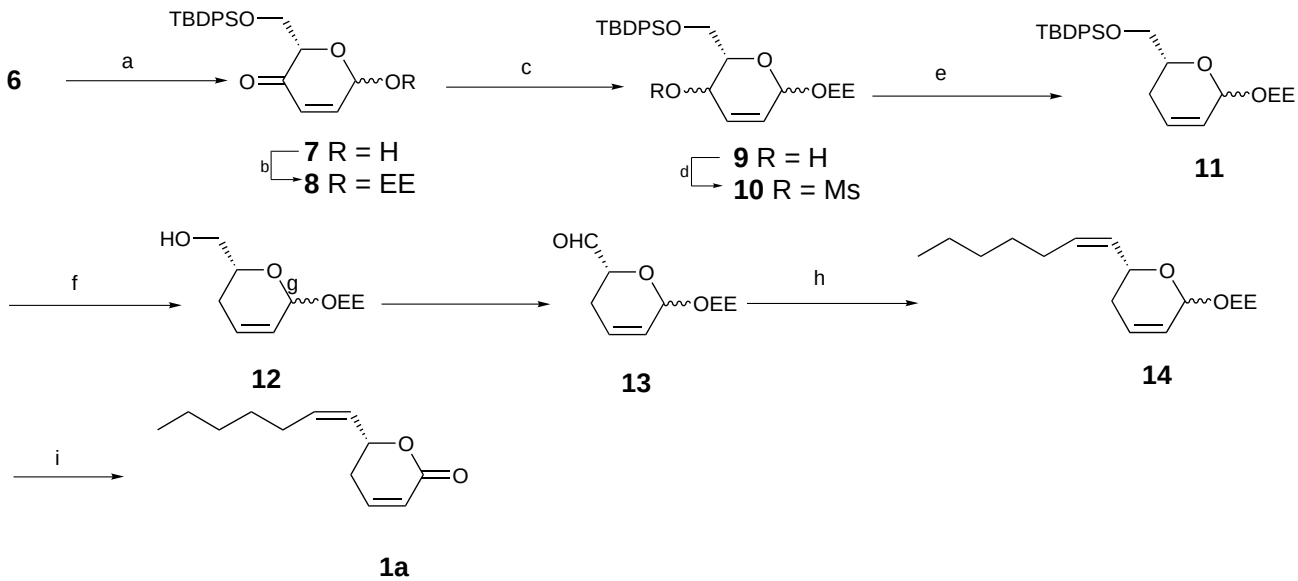
The free hydroxyl group was then protected as *tert*-butyl diphenyl silyl ether (TBDPSCl, DMF, imidazole)[14] in quantitative yield to afford **5**. Removal of the benzoyl group was tested with $MeOH/H_2O/Et_3N$, however, the yield was low and most of the starting material was recovered back even after stirring at reflux for more than 36 h. Use of lithium aluminium hydride was also not successful because it removed the TBDPS group[15] to give **3b**. Finally, catalytic amounts of sodium in methanol were used to afford the monohydroxyfuran derivative **6**, protected at the primary position with TBDPS group (Scheme 1).

Having a successful preparation of the furan alcohol **6** from D-glucal (**2**), the next step was the transformation of **6** into the L-hexenulose **7** (Scheme 2). This was accomplished smoothly by oxidation of **6** with NBS.[16] The hemiacetal **7**, having the required stereochemistry at C-6 in the target argentilactone **1a**, was obtained as a 1:1 mixture of anomers. Compound **7** was protected at the anomeric position to get the glycoside **8** as a 2:3 anomeric mixture, favouring the α-anomer as the major product.

The ketone **8** was reduced with $NaBH_4$ in methanol at −40°C in the presence of $CeCl_3 \cdot 7H_2O$ to give the allylic alcohol **9**, which was mesylated (MsCl, Py, 5°C) in excellent yield to produce **10**. The latter was treated with lithium triethylborohydride (Superhydride®) to produce the C-5-deoxygenated product **11**. The TBDPS group was removed with tetra-*n*-butylammonium fluoride in quantitative yield and the generated primary alcohol **12** was oxidized under Swern oxidation (oxalyl chloride, DMSO, Et_3N, −78°C) to produce the aldehyde **13** in 90% yield. Wittig reaction of **13** with hexyltriphenylphosphonium bromide gave the olefin **14** in the desired *cis* configuration in 78% yield as was indi-



Scheme 1. (a) H_2O/H^+, $HgSO_4$, rt, 3 h; (b) PPh_3, DEAD, benzoic acid, THF, 2 h; (c) BzCl, Py, ether; (d) $MeOH:Et_3N:H_2O$ (5:1:4), overnight at rt; (e) TBDPSCl, DMF, imidazole, 0°C to rt, 2 h; (f) NaOMe, MeOH.



Scheme 2. (a) NBS, $NaHCO_3$, $NaOAc \cdot 3H_2O$, $THF:H_2O$ (4:1), 0°C, 30 min; (b) ethyl vinyl ether, PPTS, CH_2Cl_2, rt, 2 h; (c) $CeCl_3 \cdot 7H_2O$, $NaBH_4$, MeOH, −40°C, 30 min; (d) MsCl, Py, 5°C, (e) $LiBHEt_3$, THF, 40°C, 3 h; (f) tetrabutylammonium fluoride, THF, under nitrogen, 1 h; (g) oxalyl chloride, DMSO, Et_3N, CH_2Cl_2, −78°C, 30 min; (h) hexyltriphenylphosphonium bromide, *n*-BuLi, THF, −50°C; (i) H_2O_2, MoO_3 (catalytic amounts), and then Et_3N, Ac_2O.

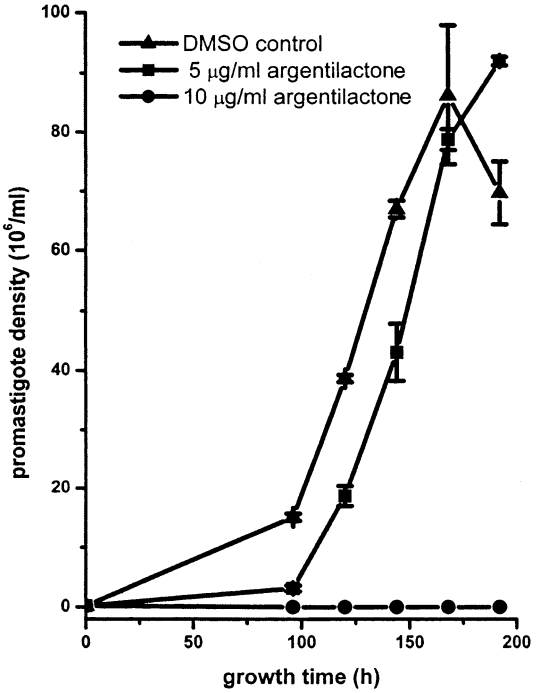


Figure 2. The effect of synthetic argentilactone on the growth of *L. mexicana*.

cated by the coupling constant $J_{7,8}=10.2$ Hz in the ^{1}H NMR spectrum of the final compound. The anomeric mixture **14** produced a very complex ^{1}H NMR spectrum and the assignments were not carried out. Finally, compound **14** was oxidized by H_2O_2 in the presence of catalytic amounts of MoO_3 to generate the target argentilactone **1a**. All physical data (MS, ^{1}H and ^{13}C NMR, optical rotation, etc.) were found identical in all respects with those reported for the natural argentilactone.[1]

Anti-leishmanial activity of 1a

In the present study, the in vitro activity of synthetic argentilactone on the growth on *L. mexicana* was also assessed[17] (Fig. 2). At 5 μg/ml, synthetic argentilactone leads to marked growth retardation in promastigote cultures, while at 10 μg/ml the parasites are unable to proliferate and die within 2–3 days, thus showing unequivocally that argentilactone is, indeed, the pharmacologically active compound of the above mentioned plant extracts. The efficiency of argentilactone against in vitro-cultured leishmania promastigotes is comparable to that of the mainly used clinical anti-leishmania drug, sodium stibogluconate.[18] This indicates that argentilactone may be used as a lead compound for the development of new anti-leishmania drug.

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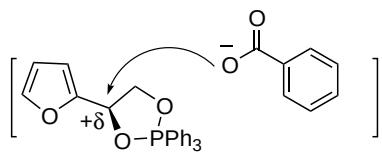
References

1. Priestap, H. A.; Bonafede, J. D.; Rúveda, E. A. *Phytochemistry* **1977**, *16*, 1579–1582.
2. Waechter, A. I.; Ferreira, M. E.; Fournet, A.; Rojas de Arias, A.; Nakayama, H.; Torres, S.; Hocquemiller, R.; Cavé, A. *Planta Med.* **1997**, *63*, 433–435.
3. Matsuda, M.; Endo, Y.; Fushiya, S.; Endo, T.; Nozoe, S. *Heterocycles* **1994**, *38*, 1229–1232.
4. Sala, L. F.; Cravero, R. M.; Signorella, S. R.; González-Sierra, M.; Rúveda, E. A. *Synth. Commun.* **1987**, *17*, 1287–1297.
5. Fehr, C.; Galindo, J.; Ohloff, G. *Helv. Chim. Acta* **1981**, *64*, 1247–1256.
6. O'Connor, B.; Just, G. *Tetrahedron Lett.* **1986**, *27*, 5201–5202.
7. Carretero, J. C.; Ghosez, L. *Tetrahedron Lett.* **1988**, *29*, 2059–2062.
8. Chidambaram, N.; Satyanarayana, K.; Chandrasekaran, S. *Tetrahedron Lett.* **1989**, *30*, 2429–2432.
9. Saeed, M.; Abbas, M.; Khan, K. M.; Voelter, W. *Z. Naturforsch.* **2000**, *56b*, 325–328.
10. Hauser, F. M.; Ellenberger, S. R.; Ellenberger, W. P. *Tetrahedron Lett.* **1988**, *29*, 4939–4942.
11. For a review on the Mitsunobu reaction, see: Mitsunobu, O. *Synthesis* **1981**, 1–28.
12. It seems that the reaction involves the intermediate **15** that undergoes an S_N2 reaction with the benzoate ion.



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13. Gonzalez, F.; Lesage, S.; Perlin, A. S. *Carbohydr. Res.* **1975**, *42*, 267–274.
14. Hanessian, S.; Lavallee, P. *Can. J. Chem.* **1975**, *53*, 2975–2977.
15. Rajashekhar, B.; Kaiser, E. T. *J. Org. Chem.* **1985**, *50*, 5480–5484.
16. Harris, J. M.; Keranen, M. D.; O'Doherty, G. A. *J. Org. Chem.* **1999**, *64*, 2982–2983.
17. *Leishmania* (L) *mexicana* LV4 (MNYC/BZ/62/M379, LEM280) promastigotes were grown in semi-defined medium 79, supplemented with 4% heat inactivated fetal calf serum at 26–27°C. To preserve their virulence, *L. mexicana* promastigotes were isolated from mouse lesion amastigotes at 8–12 week intervals. For toxicity, cultures were seeded at 10^5/ml promastigotes with the addition of either 5 or 10 μg/ml argentilactone (dissolved in 5 mg/ml in dimethylsulphoxide) or an equivalent volume of solvent. After the initial lag phase (~90 h), the promastigotes density was determined at 24 h intervals by triplicate counting of the cell numbers (for reference, see: Brun, R.; Schönenberger, M. *Acta Trop.* **1979**, *36*, 289–292.)
18. Neal, R. A. In *The Leishmaniasis in Biology and Medicine*; Peter, W.; Killick-Kendrick, R., Eds.; Academic Press: New York, 1987; Vol. 2.