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Total Synthesis of the Cytotoxic 1,10-*seco*-Eudesmanolides Britannilactone and 1,6-*O*,*O*-Diacetylbritannilactone

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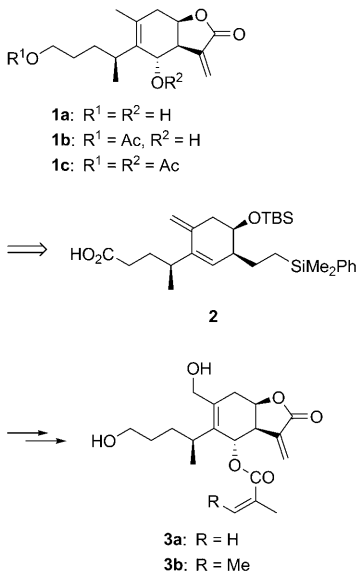
Dedicated to Professor Alberto Brandi on the occasion of his 60th birthday

Britannilactone (**1a**), 1-*O*-acetylbritannilactone (**1b**), and 1,6-*O*,*O*-diacetylbritannilactone (**1c**) are members of the 1,10-*seco*-eudesmanolide family of sesquiterpene lactones, which have been isolated from the plant *Inula britannica* syn. *Inula japonica*; a traditional Chinese medicinal herb (xuan fu hua) used for the treatment of bronchitis and inflammation (Scheme 1).[1,2] Compounds **1a**–**1c** display interesting bioactivities such as cytotoxicity in cancer cells.[3,4] Moreover, compound **1b** and particularly **1c** are anti-inflammatory agents;[5] compound **1c** effects cell-cycle arrest at the G_2+M phase and also affects the polymerization of microtubules.[3b] Herein, we report the first total synthesis of **1a** and **1c** by using the readily available carboxylic acid **2**, which has already served as an important intermediate in the synthesis of the more highly oxygenated 1,10-*seco*-eudesmanolides (−)-eriolanin (**3a**) and (−)-eriolangin (**3b**).[6] Since the absolute configuration of **2** was unambiguously established, our synthetic access to **1a** and **1c** has also proved the absolute configuration of these natural products.



Scheme 1. Structures and retrosynthesis of the cytotoxic 1,10-*seco*-eudesmanolides **1a**, **1b**, and **1c**. TBS = *tert*-butyldimethylsilyl.

Carboxylic acid **2** was treated with bis(*sym*-collidine)iodine(I) hexafluorophosphate[7] in toluene followed by reduction[8,9] of the intermediate allyl iodides in a one-pot procedure to give a 4.8:1 mixture of ε-lactones **4** and **5** (Scheme 2). Since separation was not accomplished at this stage, the mixture was reduced with lithium borohydride to give triol **6**, which was easily isolated as the major product. Chemoselective tritylation of the primary alcohol and subsequent Dess–Martin oxidation[10] of the resultant tritylether **7** afforded ketone **8**. X-ray diffraction analysis of **8** (using anomalous scattering) provided further independent proof of its absolute configuration.[11] Mild desilylation[12] of **8** led to the β-hydroxy ketone **9**, which was subjected to a hydroxyl-directed[13] reduction with sodium bis(2-methoxyethoxy)-aluminum hydride (Red-Al) to give the desired 6α (eudesmane numbering) allyl alcohol **10**. Next, the modified Tamao–Fleming oxidation[6,14] of **10** was used to give triol **11** (Scheme 2). This sequence enables the formation of the completely oxygenated skeleton of the target molecules with the correct configuration at all stereogenic centers, as confirmed by X-ray diffraction analysis.[11]

N-chlorosuccinimide (NCS)[15] proved to be a better cooxidant than bisacetoxyiodobenzene[6,16] for the TEMPO-mediated chemoselective oxidation of triol **11** to give the hydroxy γ-lactone **12** (Scheme 3). After protection of the secondary alcohol, a one-step α-methylenation of lactone **13** succeeded with sodium hydride and paraformaldehyde. Although the original methodology[17] for attachment of the requisite α-methylene unit did not work well for **13**, changing the solvent from THF to DMF allowed a fast methylenation at room temperature, and following desilylation, lactone **14** was isolated. Detritylation to give **1a** proceeded uneventfully to give (+)-britannilactone, which proved to be identical to the natural product by comparison of the spectral and op-

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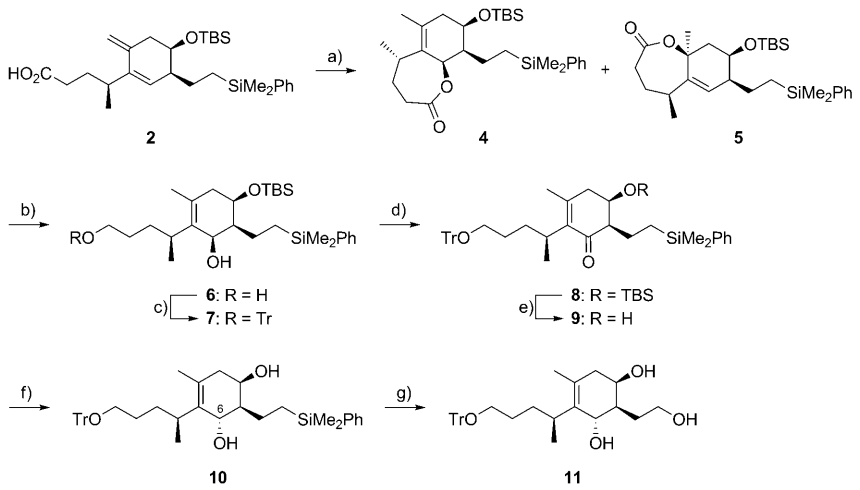
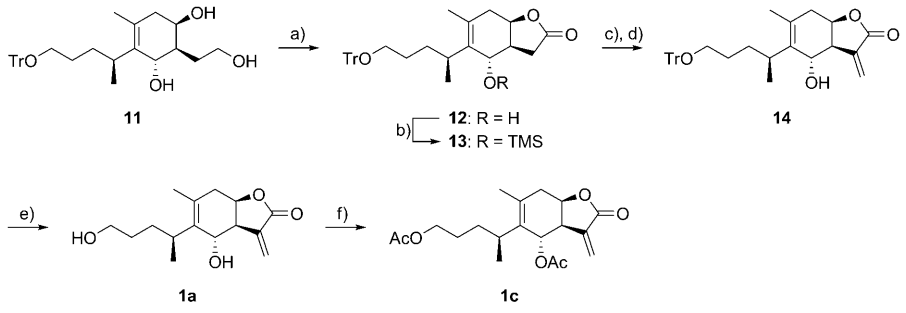
[+] X-ray diffraction analysis

Supporting information for this article (including full experimental details and compound characterization) is available on the WWW under http://dx.doi.org/10.1002/chem.201002927.



Scheme 2. Synthesis of triol **11** from carboxylic acid **2**. a) i) $I(col)_2PF_6$, toluene, 0 °C, ii) Bu_3SnH, AIBN, toluene, 75 °C, 73 % **4**/**5** (4.8:1); b) $LiBH_4$, THF, 0 °C→RT, 82 % (2 steps); c) TrCl, DMAP, pyridine, CH_2Cl_2, RT, 100 %; d) Dess–Martin periodinane, pyridine, CH_2Cl_2, RT, 98 %; e) Bu_4NF, AcOH, THF, RT, 100 %; f) Red-Al, CH_2Cl_2, toluene, −20 °C→RT, 83 %; g) i) Bu_4NF, MS (4 Å), THF, 85 °C (sealed tube) ii) KF, H_2O_2, $NaHCO_3$, THF, MeOH, 85 °C (sealed tube), 91 %. Tr = triphenylmethyl, col = *sym*-collidine, AIBN = azobisisobutyronitrile, DMAP = 4-(*N*,*N*-dimethylamino)pyridine, Red-Al = sodium bis(2-methoxyethoxy)aluminum hydride, MS = molecular sieves.



Scheme 3. Completion of the synthesis of **1a** and **1c**. a) TEMPO (50 mol %), NCS, Bu_4NCl (10 mol %), CH_2Cl_2, H_2O, pH 8.6, RT, 77 %; b) TMSCl, imidazole, CH_2Cl_2, 0 °C, 100 %; c) NaH, paraformaldehyde, DMF, RT; d) Bu_4NF, THF, 0 °C, 35 % (2 steps); e) TsOH, MeOH, RT, 100 %; f) Ac_2O, pyridine, RT, 67 %. TEMPO = 2,2,6,6-tetramethylpiperidine-1-oxyl (free radical), NCS = *N*-chlorosuccinimide, TMSCl = Trimethylsilyl chloride , TsOH = toluenesulfonic acid.

tical rotation data.[18] To determine without any doubt if the relative configuration of (+)-britannilactone depicted in the literature[1a] should be revised to that of **1a**, we repeated the published procedure for isolation[1a] of this sesquiterpene lactone from *Inula britannica* flowers.[19] As anticipated, the X-ray diffraction analysis of natural **1a** obtained in this way unambiguously verified the 6α orientation of the secondary hydroxyl group.[11] Finally, conversion of synthetic **1a** to the diacetate also gave (−)-**1c**, which, by comparison of the spectral and optical rotation data, was also found to be identical to the natural product.[20]

In conclusion, a short enantioselective route to britannilactone (**1a**) and 1,6-*O*,*O*-diacetylbritannilactone (**1c**) has been developed that also confirmed the relative and absolute configuration of these bioactive natural products.

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Keywords: antitumor agents · natural products · structure elucidation · terpenoids · total synthesis

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[11] CCDC-794897 (**8**), 794895 (**11**), and 794896 (natural **1a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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[18] Synthetic **1a**: $[\alpha]_D^{25} = +86.0$ ($c = 0.57$ in $CHCl_3$); natural **1a** (see Ref. [1a]): $[\alpha]_D^{25} = +91.3$ ($c = 0.092$ in $CHCl_3$).
[19] *Inula britannica* flowers were purchased from Ancient Way Acupuncture & Herbs, Inc., 219 Pine St, Klamath Falls, Oregon 97601, USA. Britannilactone (**1a**) was isolated from these flowers as described in Ref. [1a].
[20] Synthetic **1c**: $[\alpha]_D^{25} = -38.4$ ($c = 0.50$ in $CHCl_3$); natural **1c** (see Ref. [21]): $[\alpha]_D^{25} = -36.9$ ($c = 0.64$ in $CHCl_3$).
[21] Measured with an authentic sample of natural **1c** kindly provided by Prof. Dr. M. M. Rafi, Rutgers University, New Brunswick, USA. The positive specific optical rotation reported in Ref. [1a] is evidently due to a typing error.

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