Sesquiterpene Lactones

Enantioselective Total Synthesis of the Highly Oxygenated 1,10-*seco*-Eudesmanolides Eriolanin and Eriolangin**

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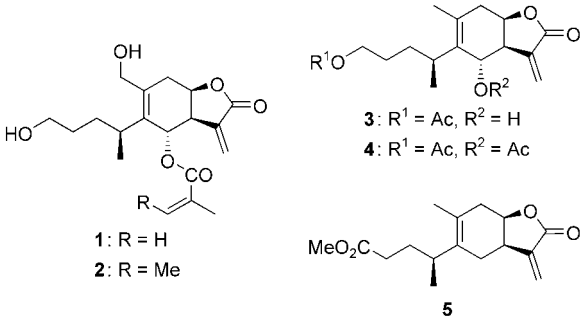
Dedicated to Professor Johann Mulzer on the occasion of his 60th birthday

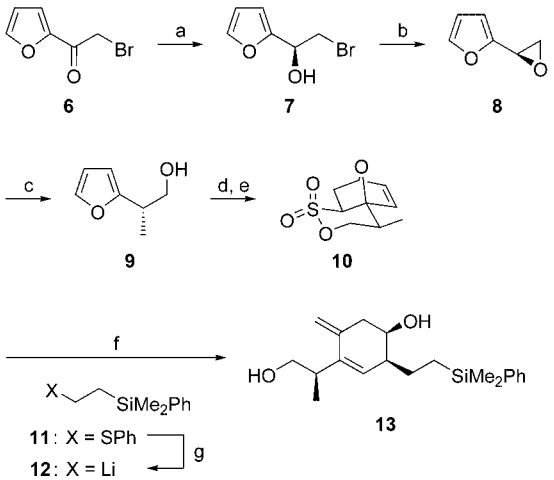
The highly oxygenated 1,10-*seco*-eudesmanolides eriolanin (**1**) and eriolangin (**2**, Scheme 1) isolated from the plant



Scheme 1. Representatives of the 1,10-*seco*-eudesmanolides.

Eriophyllum lanatum inhibit the growth of the human KB tumor cell line in vitro and additionally display a significant antileukemic activity in vivo in mice.[1] While several syntheses for racemic **1**[2,3] and one for racemic **2** have been published,[2] the absolute configuration of these sesquiterpene lactones was unknown prior to our work. Here we report an efficient enantioselective sultone route[4] to **1** and **2** that also opens a synthetic access toward the less highly oxygenated, cytotoxic britannilactone derivatives **3** and **4**.[5–7] As the central intermediate, δ-sultone **10** (Scheme 2) was employed, the racemic mixture of which already enabled a short and highly diastereoselective synthesis of the 1,10-*seco*-eudesmanolide ivangulin (**5**).[8]

Alcohol **9**,[9] required as the starting material for the enantiomerically pure sultone **10**, was available on a multigram scale by catalytic enantioselective transfer hydrogenation[10] of 2-bromo-1-(2-furyl)ethanone (**6**)[11] to **7** (> 98.5% *ee* according to capillary GC), mild basic treatment to give epoxide **8**, and subsequent ring opening with full regioselectivity and complete inversion of configuration[12] (Scheme 2). By treatment of **9** with β-chloroethanesulfonic acid chloride[13] and triethylamine, a mixture of **10** and a further *exo* sultone isomer was formed in a domino process consisting of elimination, esterification, and intramolecular Diels–Alder reaction, from which pure **10** could be isolated in excellent yield after thermal equilibration.[8] Conversion of **10** to methylenecyclohexene **13** succeeded by a sequential transformation consisting of elimination, alkoxide-directed 1,6-addition of lithiosilane **12**,[14,15] and desulfurization with simultaneous methylenation in a one-pot procedure.[16] In a single synthetic operation, the prefunctions for a γ-lactone were unfolded, activation for 1,4-dioxygenation was created by virtue of the 1,3-diene, and the primary hydroxy group was liberated for side-chain elongation.



Scheme 2. Sultone route to 1,3-diene **13**. a) 0.2 mol% [Cp*RhCl((*R*,*R*)-tsdpen)], HCO_2H, Et_3N, 0°C; b) K_2CO_3, MeCN, RT; c) MeCu(CN)Li, Et_2O, −78°C→RT, 50% over three steps; d) β-chloroethanesulfonic acid chloride, Et_3N, CH_2Cl_2, RT; e) cat. BHT, EtOAc, 120°C, microwaves, 81% over two steps; f) 1. MeLi, THF, −78°C, 2. **12**, −78°C→−20°C, 3. ICH_2MgCl, THF, −78°C→RT, 61%; g) LiDBB, THF, −78°C. BHT = 2,6-di-*tert*-butyl-4-methylphenol, Cp* = pentamethylcyclopentadienyl, LiDBB = lithium 4,4′-di-*tert*-butylbiphenylide, tsdpen = *N*-(4-toluenesulfonyl)-1,2-diphenylethylenediamine.

For side-chain elongation, diol **13** was first bissilylated, and then the primary hydroxy group was selectively deprotected (Scheme 3). After conversion[17] of the resulting alcohol **15** to iodide **16**, the required C_2 unit was attached by alkylation with dimethyl malonate in the presence of proazaphosphatrane **17**[18,19] and demethoxycarbonylation[8,20] of **18**. An intramolecular protocol was eventually decisive for the efficient generation of the enediol fragment of the target molecules. Carboxylic acid **20**, obtained after saponification of **19**, was treated successively with bis(*sym*-collidine)iodine(I) hexafluorophosphate[21] followed by silver acetate in dimethylformamide[22] in a one-pot procedure, whereupon the formyloxy ε-lactone **21**[23] was isolated as the major product. Substitution of the formylation by a reduction[24,25] of the intermediate allyl iodide should allow concise access to

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[+] X-ray diffraction analysis

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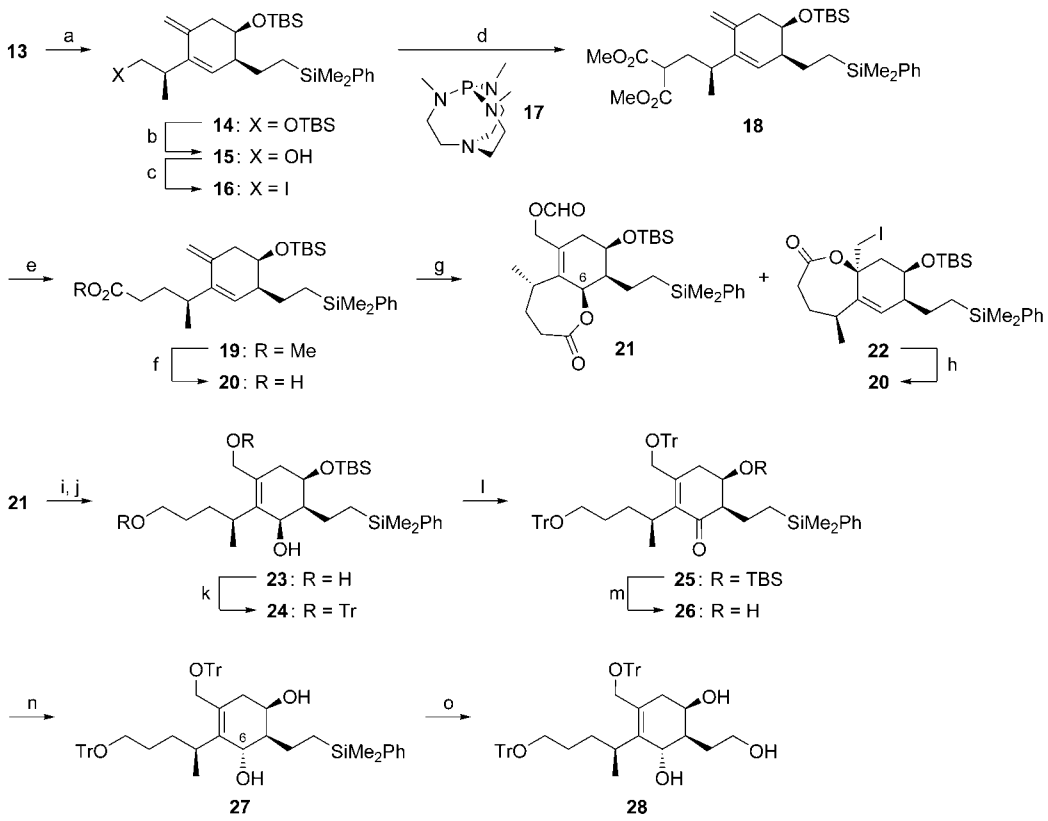
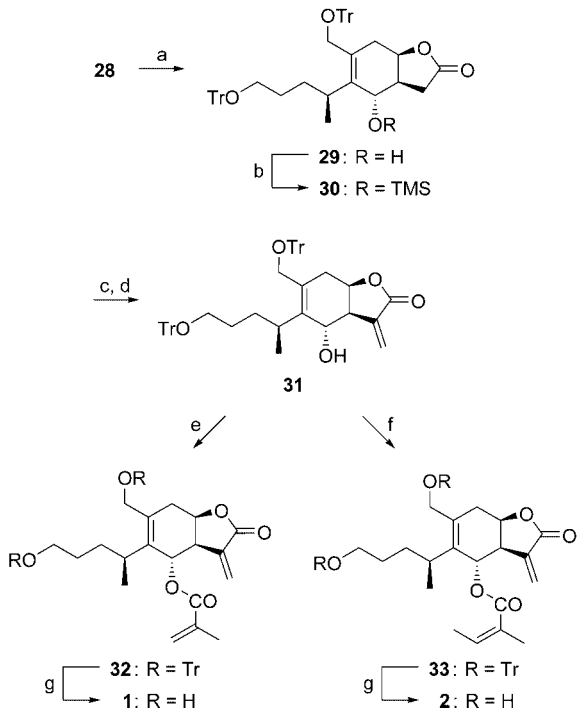


Scheme 3. Synthesis of the completely oxygenated basic skeleton **28**. a) TBSCl, imidazole, DMAP, DMF, RT, 99%; b) TBAF, THF, 0°C, 81% **15** + 17% **13**; c) I_2, Ph_3P, imidazole, THF, MeCN, −20°C→RT, 84%; d) **17**, dimethyl malonate, MeCN, RT, 91%; e) PhSH, K_2CO_3, DMF, 90°C, 89%; f) KOH, MeOH, H_2O, reflux, 100%; g) 1. $I(col)_2PF_6$, PhMe, 0°C, 2. AgOAc, DMF, PhMe, RT, 67% **21** + 15% **22**; h) zinc dust, HOAc, H_2O, THF, 0°C→RT, 86%; i) $LiAlH_4$, Et_2O, 0°C; j) $LiBH_4$, Et_2O, −10°C, 91% over two steps; k) TrCl, DMAP, pyridine, CH_2Cl_2, RT, 91%; l) Dess–Martin periodinane, pyridine, CH_2Cl_2, RT, 99%; m) TBAF, HOAc, THF, RT, 96%; n) Red-Al, CH_2Cl_2, PhMe, −20°C→RT, 90%; o) 1. TBAF, MS 4 Å, THF, reflux, 2. KF, H_2O_2, $NaHCO_3$, THF, MeOH, reflux, 99%. col = *sym*-collidine, DMAP = 4-(*N*,*N*-dimethylamino)pyridine, MS = molecular sieves, Red-Al = sodium bis(2-methoxyethoxy)aluminum hydride, TBAF = tetrabutylammonium fluoride, TBS = *tert*-butyldimethylsilyl, Tr = triphenylmethyl.

britannilactones **3** and **4**. Iodolactone **22**, which was formed in small amounts next to **21**, can be reductively eliminated[26] to return **20**. The undesired configuration at C6 (eudesmane numbering) in **21** set up in a completely stereoselective fashion during the sequential iodolactonization/allyl formiate generation from **20** was subsequently corrected by an oxidation/reduction strategy.[27] Reduction of diester **21** with lithium aluminum hydride to give a hydroxy lactol[28] and further reduction with lithium borohydride afforded triol **23**. Chemoselective tritylation of the two primary hydroxy groups (→**24**), Dess–Martin oxidation[29] (→**25**), and mild desilylation[30] led to β-hydroxy ketone **26**. Hydroxy-directed[31] reduction of the latter with the sodium aluminum dihydride Red-Al furnished the desired 6α allyl alcohol **27** with excellent diastereoselectivity.[32] After Tamao–Fleming oxidation,[33,34] the completely oxygenated skeleton of the target molecules with correct configuration at all stereogenic centers was finally available in the form of triol **28**.

The final stage of the synthesis was initiated with a chemoselective oxidation[35] of triol **28** to give hydroxy γ-lactone **29** (Scheme 4). After protection of the secondary hydroxy group, a one-step α-methylenation of lactone **30** succeeded with sodium hydride and paraformaldehyde,[36] and following desilylation, lactone **31** was isolated in good overall yield. Preparation[2] of methacrylate **32** as well as detritylation to give **1** proceeded uneventfully and delivered (−)-eriolanin, which proved to be identical to the natural product by comparison of optical rotation data.[37] Thus, our synthesis of **1** also clarifies the previously unknown absolute configuration of this sesquiterpene lactone, since the absolute configuration of **9** was unambiguously established.[9] In addition, an X-ray diffraction analysis of our synthetic product **1** provided a further independent proof of the absolute configuration by anomalous X-ray scattering.[38] Using a modified Yamaguchi esterification,[39] **31** could also be transformed smoothly to angelate **33** without *Z*/*E* isomerization. Deblocking to give **2** delivered (−)-eriolangin, which also turned out to be identical to the natural product by comparison of optical rotation data.[40]

Due to the sultone strategy applied, our enantioselective route to the 1,10-*seco*-eudesmanolides **1** and **2** requires only 26 steps from 2-bromo-1-(2-furyl)ethanone (**6**). Average yields of 87% for **1** and 86% for **2** highlight the efficacy of the route reported. Moreover, the selective manipulation of the diverse hydroxy groups on the 1,10-*seco*-eudesmanolide framework possible here offers great flexibility with respect



Scheme 4. Final steps of the synthesis of (−)-eriolanin (**1**) and (−)-eriolangin (**2**). a) BAIB, cat. TEMPO, CH_2Cl_2, RT, 75%; b) TMSCl, imidazole, CH_2Cl_2, RT, 96%; c) NaH, paraformaldehyde, THF, 100°C (sealed tube); d) TBAF, THF, 0°C, 61% over two steps; e) methacrylic acid anhydride, Et_3N, DMAP, THF, 0°C→RT, 85%; f) 1. angelic acid, 2,4,6-trichlorobenzoyl chloride, Et_3N, PhMe, RT, 2. **31**, 100°C, 60%; g) cat. *p*-TsOH, MeOH, RT, 97% **1** from **32**, 85% **2** from **33**. BAIB = bisacetoxyiodobenzene, TEMPO = 2,2,6,6-tetramethylpiperidin-1-oxyl (free radical), TMS = trimethylsilyl, *p*-TsOH = *p*-toluenesulfonic acid.

to the assembly of synthetic analogues. A synthesis of the britannilactone derivatives **3** and **4** is in preparation.

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[38] Crystal dimensions $0.25 \times 0.20 \times 0.20\ mm^3$, orthorhombic, space group $P2_12_12_1$ (No. 19), $a = 8.251(1)$, $b = 10.895(1)$, $c = 20.845(2)$ Å, $V = 1873.9(3)$ Å^3, $\rho_{calcd} = 1.242\ g\,cm^{-3}$, $Cu_{K\alpha}$ radiation, $\lambda = 1.54178$ Å, $\omega/2\theta$ scans, $T = 233$ K, 4186 reflections measured, 3823 independent ($R_{int} = 0.031$), of which 3369 were observed [$I \geq 2\sigma(I)$], $\mu = 7.58\ cm^{-1}$, empirical absorption correction ($0.833 \leq T \leq 0.863$), $Z = 4$, 230 refined parameters, hydrogen atoms calculated and refined as riding atoms, $R = 0.041$, $wR^2 = 0.106$, largest difference peak and hole $0.15/-0.20\ e\,Å^{-3}$, Flack parameter 0.04(19). Programs used: EXPRESS, MolEN, SHELXS-97, SHELXL-97, SCHAKAL. CCDC-239240 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

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