Natural Products

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Access to Guaianolides: Highly Efficient Stereocontrolled Total Synthesis of (±)-Geigerin**

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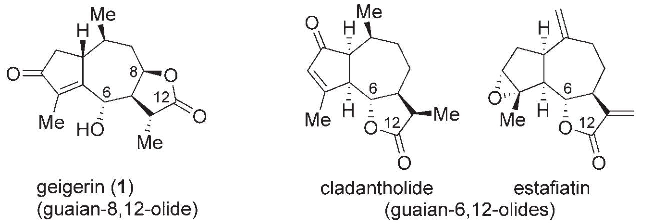
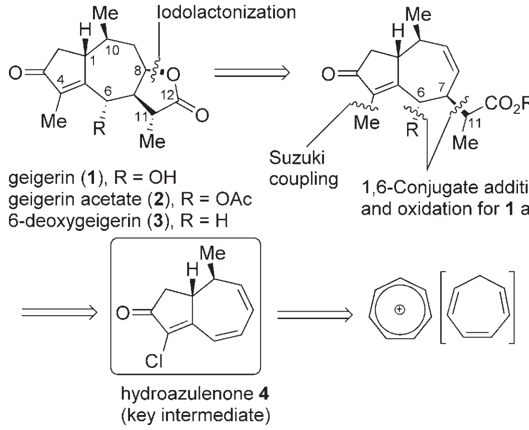
In memory of André Rassat

Guaianolides, which possess a bicyclo[5.3.0]decane skeleton, represent one of the largest groups of naturally occurring sesquiterpene lactones.[1a] They exist in two forms, guaian-6,12-olides and guaian-8,12-olides (Scheme 1), and show important, diverse biological activities.[1b,c] Geigerin (**1**, Scheme 1), a member of the guaian-8,12-olide class, was initially isolated in 1936 from *G. aspera Harv.*, a South African species of *Geigeria*, known colloquially as the vermeerbos ("vomiting bush").[2] The structure of **1**, which exhibits six stereogenic centers, was first proposed in 1958 on the basis of an elegant series of degradation studies by Barton and Levisalles[3a] and confirmed in 1960 by X-ray analysis of the 1-bromo derivative of geigerin acetate (**2**, Scheme 2).[3b] In 1964, a partial synthesis of **2** from artemisin, through oxidation of deoxygeigerin (**3**) (0.1–0.3% yield), was reported by Barton et al.,[3c] and this constitutes the only successful preparation of this compound to date. In 1992, Jacobi et al.[4] presented a new synthetic approach to geigerin (**1**) through a Diels—Alder/retro-Diels–Alder transformation of an acetylenic oxazole, but they were unable to complete the synthesis.



Scheme 1. Guaian-8,12- and -6,12-olide families.

One of the challenges in modern organic chemistry, from both academic and industrial points of view,[5] is the rapid elaboration of molecular complexity and diversity from simple substrates,[6] owing to economic[7,8] as well as environmental[9] considerations. Over the past several decades, many strategies have been proposed to access guaian-6,12- and -8,12-olides, but they have involved numerous steps and lacked sufficient flexibility to reach both families. For example, Lee et al.[10] reported in 1997 the total synthesis of (+)-cladantholide and (−)-estafiatin from (−)-carvone in 16 and 12 steps, respectively, which represented the shortest construction of naturally occurring guaianolides (Scheme 1). Our objective has been to develop a versatile, regio- and stereoselective synthetic approach to both guaianolide classes from inexpensive starting materials in fewer than 10 steps and without protecting-group chemistry. Through a second-generation synthesis of (±)-6-deoxygeigerin (**3**) and the first total synthesis of (±)-geigerin (**1**) and (±)-geigerin acetate (**2**), we now demonstrate such an approach (Scheme 2).



Scheme 2. Retrosynthetic analysis.

As shown retrosynthetically in Scheme 2, the approach is based on hydroazulenone **4**, a versatile intermediate[11,12] that is easily obtained in three steps (43% overall yield) from commercially available tropylium cation[13] through a highly regio- and stereocontrolled [2+2] cycloaddition[14]/ring-expansion/elimination sequence[15] (Scheme 3).

It was initially decided to attempt a key 1,6-conjugate addition with a ketene acetal to introduce the lactone in a single step and a Suzuki cross-coupling for the introduction of the C4 methyl group. This would substantially improve our previous total synthesis of (±)-6-deoxygeigerin (**3**)[11a] (Scheme 3). Conjugate addition of the (*E*)-*tert*-butyldimethylsilyl ketene acetal[16,17] derived from *tert*-butyl propionate to α-chloro trienone **4** in the presence of a catalytic amount of

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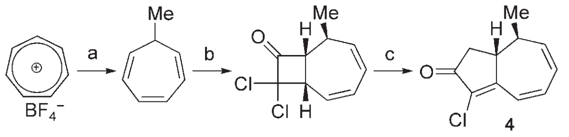
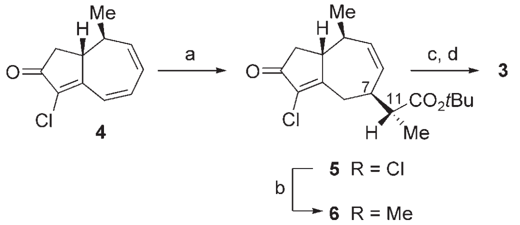


Scheme 3. Synthesis of hydroazulenone **4**. Reagents and conditions: a) MeLi, Et_2O, 0→20°C, 83% (after distillation); b) Cl_3CCOCl, Et_2O, 25–28°C, ultrasound, 1–2 h; c) CH_2N_2, Et_2O/MeOH; DMSO, RT, 16–18 h, 52% overall from 7-methylcycloheptatriene. DMSO = dimethyl sulfoxide.

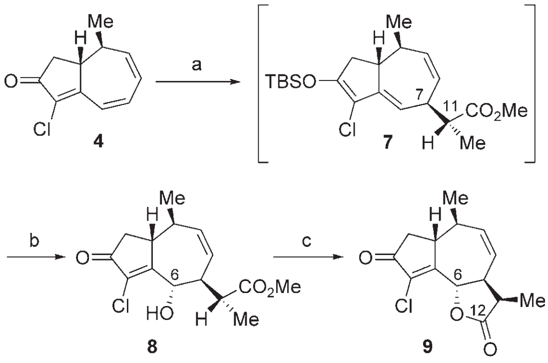
$TiCl_4$ at −78°C afforded the β 1,6-adduct **5** in 74% yield with a high regio- and stereoselectivity (d.r. at C7: >98:2, d.r. at C11: 5:1). The methylation at the C4 position to give **6** was achieved in 70% yield by using methylboronic acid and the Suzuki coupling catalyst system developed by Buchwald et al.[18] Finally, iodolactonization under mild, neutral conditions,[19] followed by immediate reduction with nBu$_3$SnH installed the final stereocenter and afforded in 88% yield 6-deoxygeigerin (**3**) as a 5:1 mixture of epimers at the C11 position (Scheme 4). The minor,[20] undesired isomer was easily removed by flash chromatography to give pure 6-deoxygeigerin[21,11a] (**3**) in only seven steps and with 13.6% overall yield from the tropylium cation. This new synthetic route to **3** represents a major improvement in guaianolide total synthesis as the number of steps of the previous shortest route to a naturally occurring guaianolide has been almost halved and the yield more than doubled.



Scheme 4. Synthesis of (±)-6-deoxygeigerin (**3**). Reagents and conditions: a) (E)-MeCH=C(OTBS)(OtBu), $TiCl_4$, CH_2Cl_2, −78°C (d.r. at C7: >98:2) 74%; b) $MeB(OH)_2$, $Pd(OAc)_2$, dpdb, K_3PO_4, toluene, 60°C, 70%; c) I_2, MeCN, RT, 14 h. d) nBu$_3$SnH, Et_3B, O_2, 0°C, toluene/THF, 88% overall (two steps). TBS = *tert*-butyldimethysilyl, dpdb = dicyclohexylphosphano-2′,6′-dimethoxybiphenyl.

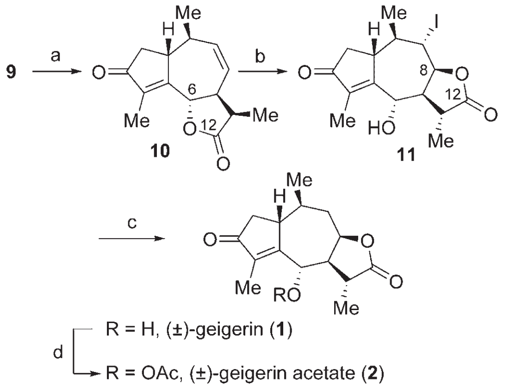
Having achieved this efficient, second-generation total synthesis of (±)-6-deoxygeigerin (**3**), we focused our efforts on the first total synthesis of (±)-geigerin (**1**). As shown in the retrosynthetic analysis (Scheme 2), the approach to geigerin (and guaian-6,12-olides) is based on two highly selective transformations: a regio- and stereocontrolled 1,6-conjugate addition like that described above and a regio- and stereoselective oxidation at the C6 position.

First, conjugate addition of the (E)-*tert*-butyldimethylsilyl ketene acetal derived from methyl propionate[16] to the α-chloro trienone **4** in the presence of a catalytic amount of $LiClO_4$[22] at room temperature afforded the β 1,6-adduct **7** with high regio- and stereoselectivity (d.r. at C7: 85:15) (Scheme 5). From a 98:2 E/Z mixture of silyl ketene acetals, the diastereoselectivity at the C11 position is 4:1, while from a 85:15 E/Z mixture, the diasteroselectivity is lower (d.r. at C11:[23] 2:1). Next, oxidation of the intermediate **7** proceeded with remarkable selectivity with dimethyldioxirane (DMDO)[24a–c] to furnish only the expected C6 α-hydroxylated product **8**.[25] Of the several different oxidizing agent screened (mCPBA, Davis oxaziridine,[24d] chromyl chloride,[24e] osmium tetroxide,[24f] methyltrifluoromethyldioxirane,[24g] and DMDO), DMDO was the most efficacious. The hydroxylated product **8** underwent lactonization on silica gel purification or acid treatment to provide **11** in 49% overall yield.[26] Not only does this highly selective conjugate-addition/oxidation/lactonization sequence constitute a key part of the synthesis of geigerin, but it also affords an exceptionally direct access to the tricyclic guaian-6,12-olide framework **9**.



Scheme 5. Synthesis of the tricyclic guaian-6,12-olide framework **9**. Reagents and conditions: a) (E)-MeCH=C(OTBS)(OMe), $LiClO_4$ (cat.), CH_2Cl_2, RT, (d.r. at C7: 85:15); b) DMDO, acetone, −90°C; c) TSA (cat.), THF, 49% overall. DMDO = 2,2-dimethyldioxirane, TSA = *para*-toluenesulfonic acid.

The next important transformation in the synthesis, methylation at C4 of the lactone intermediate **9**, could be accomplished by using Suzuki cross-coupling[18] to afford the desired compound **10** in 58% yield (Scheme 6). The same



Scheme 6. Synthesis of (±)-geigerin (**1**) and (±)-geigerin acetate (**2**). Reagents and conditions : a) $MeB(OH)_2$, $Pd(OAc)_2$, dpdb, K_3PO_4, toluene, 60°C, 58%; b) $LiOH{\cdot}H_2O$, CO_2, THF; I_2, KI, $NaHCO_3$, MeCN; c) nBu$_3$SnH, Et_3B, O_2, 0°C, toluene/THF, 53% overall (two steps); d) Ac_2O, py, DMAP, THF, 5 h, 95%. py = pyridine, DMAP = 4-dimethylaminopyridine.

coupling conditions applied to the either allylic alcohol **8** or the corresponding acetate derivative led to coupling followed by elimination to give the α-methyltrienone.

As before, the remaining stereocenter was installed by a stereoselective *trans*-iodolactonization[27] under mild, basic conditions (LiOH, H_2O/THF, CO_2) (Scheme 6). The crude iodo lactone **11** was immediately reduced with tributyltin hydride to afford (±)-geigerin (**1**) as the major component of 4:1 mixture of the C11 diastereomers. The natural product[3c] (m.p. 167 °C) was easily separated from this mixture by flash chromatography and isolated in 42 % overall yield from **10** (the C11 epimer of **1** was also isolated in 11 % yield). Acetylation of **1** gave the naturally occurring geigerin acetate (**2**)[3c,28] in racemic form in 95 % yield. The ^{1}H NMR spectrum of (±)-geigerin acetate (**2**) was identical to that reported in the literature for the natural product;[28] additionally, the X-ray crystal analysis[25] of geigerin confirmed the relative stereochemistry in both synthetically derived products.

In conclusion, we have successfully developed a highly efficient second-generation total synthesis of (±)-6-deoxygeigerin (**3**) in seven steps (13.6 % overall yield) and the first total synthesis of (±)-geigerin (**1**) (easily converted to (±)-geigerin acetate (**2**)) in only eight steps (4.9 % overall yield) from the tropylium cation without the need of protecting groups. Both approaches were achieved with high regio- and stereoselectivity owing to very effective 1,6-conjugate additions of ketene acetals and an oxidation, which generated the desired lactone with the correct configurations at C7, C11, and C6. This versatile methodology, which provides access to both guaian-6,12- and -8,12-olides classes, could also provide a reasonably short route to pseudoguaianolides through stereoselective 1,4-conjugate addition[29] to **11** or one of its derivatives.

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ent reflections, 2940 reflections used with $I > 2.0\sigma$, diffractometer: CAD4-Enraf-Nonius. CCDC-636014 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre (www.ccdc.cam.ac.uk/data_request/cif).

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