Natural Product Synthesis

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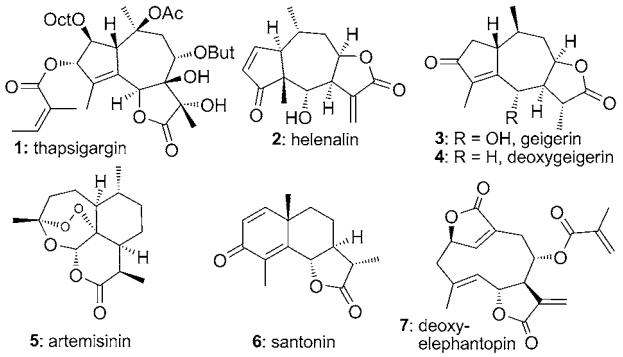
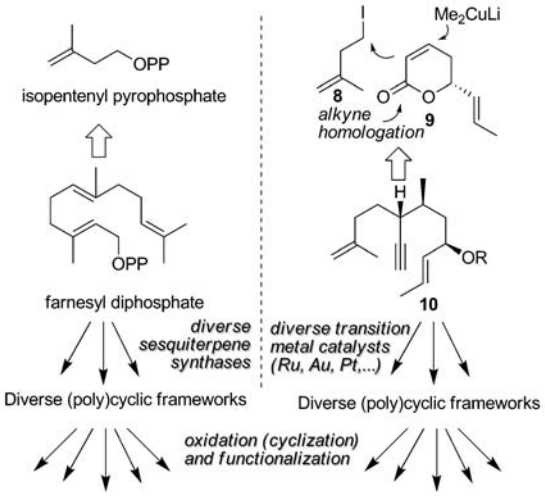
Diversity-Oriented Synthesis of Diverse Polycyclic Scaffolds Inspired by the Logic of Sesquiterpene Lactones Biosynthesis**

*Gaëlle Valot, José Garcia, Vincent Duplan, Christelle Serba, Sofia Barluenga, and Nicolas Winssinger**

Sesquiterpene lactones (SLs) are a large group of secondary plant metabolites of which more than 5000 structures are known,[1] and have historically been an important source of therapeutics.[1,2] Prominent examples of guaianolides and pseudoguaianolides are thapsigargin (**1**) and helenalin (**2**), respectively (Scheme 1). Thapsigargin inhibits the sarcoplasmic or endoplasmic reticulum Ca-ATPase pumps[3] (collectively known as SERCA) and is broadly used in cellular biology. It has been used in traditional medicine for over 6000 years and continues to attract interest from the synthetic and medicinal community.[4] Helenalin inhibits the NF-κB pathway by inhibiting p65-DNA binding[5] and is also widely used in cellular biology. It is currently used as a topical anti-inflammatory treatment and continues to attract attention from the medicinal chemistry community in light of the implication of NF-κB in human cancer.[6] Artemisinin (**5**) is currently used for the treatment of malaria,[7] while santonin (**6**) has long been used in humans to expel parasitic worms.[8] More recently, deoxyelephantopin (**7**) was shown to inhibit primary tumor growth and metastasis in mice.[9] These secondary metabolites are all produced from farnesyl diphosphate in several phases, each offering diverging reaction pathways, and thus yielding a broad array of polycyclic products with various degrees of oxygenation and unsaturation (Scheme 2).[10]



Scheme 1. Selected sesquiterpene lactones. But: butanoyl, Oct: octanoyl.



Scheme 2. Biosynthetic (left) and divergent chemical synthesis (right) of sesquiterpenes. OPP = pyrophosphate.

After the synthesis of farnesyl diphosphate, the first phase of the guaianolide biosynthesis is a cyclization catalyzed by a sesquiterpene synthase to yield germacrene A, a ten-membered hydrocarbon macrocycle. Various allylic C–H oxidations introduce the lactone and set the stage for cationic cyclizations that lead to the guaianolide or eudesmanolide frameworks. In a third phase, these products are further oxidized and functionalized. Different sesquiterpenes (such as artemisinin (**5**), santonin (**6**), and deoxyelephantopin (**7**)) originate from the same farnesyl diphosphate intermediate as the guaianolides, but are formed by different sesquiterpene synthases. This powerful diversity-oriented biosynthetic machinery is well suited to produce variations so as to optimize the function of these secondary metabolites. The terpene synthases catalyze complex reactions involving an intricate series of carbocation intermediates[11] which have historically been difficult to control in synthetic chemistry.[12] However, the same logic of multiple cyclization pathways[13] could be achieved with greater precision through the controlled reactivity of alkynes and alkenes with transition-metal catalysts.[14] Specifically, we reasoned that an acyclic chain

[*] Dr. G. Valot, Dr. J. Garcia, V. Duplan, C. Serba, Dr. S. Barluenga, Prof. Dr. N. Winssinger
Université Louis Pasteur, Strasbourg (France)
E-mail: winssinger@unistra.fr
Homepage: http://www-isis.u-strasbg.fr/winssinger/

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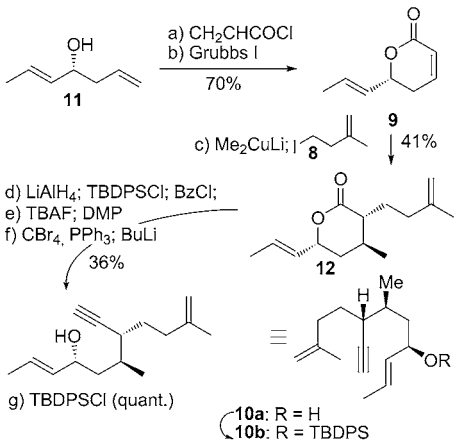
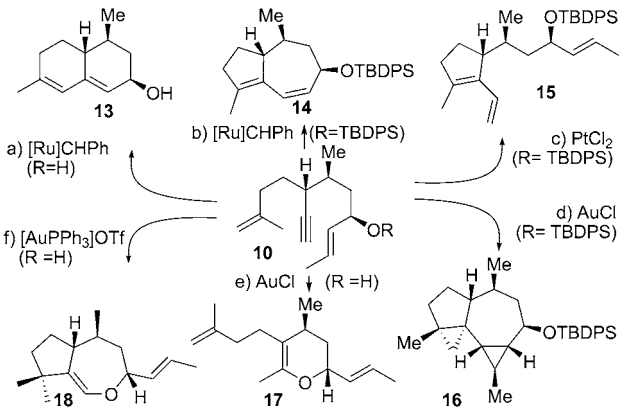
containing an ene-yne-ene motif could, in analogy to farnesyl diphosphate, be cyclized through a manifold of pathways. Notably, the guaianolide framework should be accessed from an acyclic intermediate **10** by enynene metathesis.[15] This acyclic intermediate should in turn be readily accessible from lactone **9**. As shown in Scheme 3, commercially available



Scheme 3. a) $CH_2CHCOCl$, Et_3N, Et_2O, 23 °C, 12 h, quant.; b) Grubbs I cat., CH_2Cl_2, 40 °C, 10 h, 70%; c) CuI, MeLi, Et_2O, 0 °C, 1 h; **8**, THF/HMPA, 23 °C, 2.5 h, 41%; d) $LiAlH_4$, Et_2O, 0 °C, 1 h; TBDPSCl, imidazole, CH_2Cl_2, 23 °C, 12 h; BzCl, pyridine, CH_2Cl_2, 23 °C, 3 h, 97% (three steps); e) TBAF, THF, 23 °C, 14 h; DMP, CH_2Cl_2, 23 °C, 5 h, 75% (two steps); f) CBr_4, PPh_3, CH_2Cl_2, 0 °C, 10 min; *n*BuLi, THF, 10 min, −78 °C to 23 °C, 30 min, 50% (two steps); g) TBDPSCl, imidazole, CH_2Cl_2, 23 °C, 12 h, quant. Bz = Benzoyl, DMP = Dess–Martin periodinane, HMPA = hexamethyl-phosphoramide, TBAF = tetrabutylammonium fluoride, TBDPS = *tert*-butyldiphenylsilyl, THF = tetrahydrofuran.

hepta-1,5-dien-4-ol (**11**, racemic; for resolution, see Ref. [16]) was esterified with acryloyl chloride and treated with the first-generation Grubbs catalyst[17] to obtain lactone **9** in 70% overall yield as the only isomer. The use of the second-generation Grubbs' catalyst[18] under a variety of conditions afforded mixtures of five- and six-membered-ring metathesis products. The conjugated lactone **9** was then used in a methyl cuprate conjugate addition, and the resulting enolate was treated with 4-iodoisopentene[19] (**8**) to afford **12** as a single diastereoisomer. Despite being the only product observable in the crude NMR spectrum of the reaction, it was obtained in only moderate yield (41%). While there are some precedents for the direct homologation of the lactone's carbonyl group to an alkyne,[20] the best overall yield was obtained by complete reduction of the ester ($LiAlH_4$), benzoate protection of the secondary alcohol (by temporary silylation of the primary hydroxy group), Dess–Martin oxidation, and Corey–Fuchs reaction (CBr_4, PPh_3; *n*BuLi) with concomitant cleavage of the benzoate protecting group. This sequence afforded the desired cyclization precursor **10a** in 36% yield. Attempts to convert the ester into the alkyne via the hemiacetal (obtained by reduction of ester **12** with Dibal-H) were unfruitful. Since the free hydroxy group of **10a** could act as a nucleophile or directing group in different cyclizations, it was silylated (**10b**) to provide an alternative cyclization substrate.

We then turned our attention to different transition-metal-mediated cyclizations. Treatment of acyclic enynene **10a** with the second-generation Grubbs catalyst afforded the decalin product **13** exclusively (Scheme 4) in good yield; this

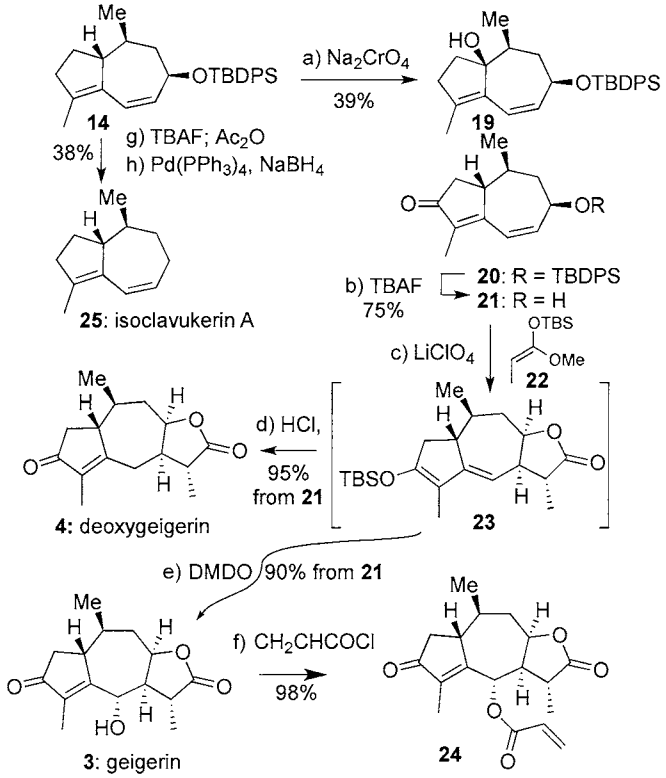


Scheme 4. a) Grubbs II cat., toluene, 100 °C, 12 h, 81%; b) same as for (a), quant.; c) $PtCl_2$, toluene, 50 °C, 2 h, quant.; d) AuCl, CH_2Cl_2, 23 °C, 20 min, 50%; e) same as for (d), quant.; f) $[AuPPh_3]OTf$, CH_2Cl_2, 23 °C, 20 min, 87%. OTf = triflate

is the basic framework of cadinenes[21] found in essential oils. The selectivity of the reaction for the decalin system may be rationalized by the directing effect of the free hydroxy group initiating the metathesis cascade on the adjacent alkene. Indeed, treatment of silyl ether **10b** under the same conditions yielded the desired [5.3.0] framework **14** exclusively. Treatment of acyclic enynene **10b** with $PtCl_2$ in toluene at 50 °C afforded the intermediate cyclization product **15** in quantitative yield (platinacyclobutane formation, reductive elimination, cyclobutene opening).[22] Reaction of the protected enynene **10b** with gold(I) chloride in CH_2Cl_2 for 20 minutes at ambient temperature led to a cascade reaction that afforded the unprecedented tetracycle **16** in 50% yield. The reaction presumably proceeds through coordination of the gold to the triple bond, thereby leading to a first cyclopropanation of the triply substituted alkene (5-*exo*-dig) with formation of a gold carbene that is judiciously positioned to undergo a second cyclopropanation.[23] The use of the same conditions with the unprotected **10a** resulted in a different reaction pathway that afforded pyran **17**, a preponderant motif in natural products.[24] In this case, the gold–alkyene complex was attacked by the free hydroxy group. Protodemetalation followed by isomerization afforded the pyran. Alternatively, treatment of **10a** with a gold(I) complex afforded the [5.3.0]oxobicyclic product **18** in 87% yield (see Figure S1 in the Supporting Information for the proposed mechanism). Palladium(0) or (II) complexes failed to effect reaction while $[Rh(PPh_3)_3OTf]$ and [CpRu(cod)Cl] yielded complex mixtures. Silver(I) had a reactivity similar to gold(I), but resulted in lower yields. Thus, the acyclic compounds **10** could be cyclized to obtain six different products, two of

which are unprecedented while the remaining four are highly common structural motifs of sesquiterpene lactones.

In analogy to the biosynthetic pathways, each of these scaffolds could be further elaborated through alkene oxidation or C–H oxidation.[25] To illustrate this potential for further functionalization to generate valuable natural product motifs we investigated the oxidation of the [5.3.0] cyclization product **14** as an entry into guaianolide analogues (Scheme 5). Different conditions were evaluated to selectively oxidize an



Scheme 5. a) Na_2CrO_4, AcOH, Ac_2O, NaOAc, benzene, 70 °C, 12 h, 39% (**19**/**20** 1:1); b) TBAF, THF, 23 °C, 12 h, 75%; c) $LiClO_4$, **22**, CH_2Cl_2, 40 °C, 5 h; d) 1 M HCl, EtOAc, 23 °C, 2 h, 95% (two steps); e) DMDO, acetone, −90 °C, 10 min, 90% (two steps); f) $CH_2CHCOCl$, Et_3N, Et_2O, 23 °C, 12 h, 98% ; g) TBAF, THF, 23 °C, 12 h; Ac_2O, pyridine, 23 °C, 12 h, 75% (two steps); h) $[Pd(PPh_3)_4]$, THF, 23 °C, 30 min; then $NaBH_4$, 2 h, 50%. DMDO = dimethyldioxirane, TBAF = tetrabutylammonium fluoride, TBS = *tert*-butyldimethylsilyl.

allylic C–H bond (Table 1). Compound **19** could be obtained in a good yield as a single isomer by using PDC. Modification of the conditions (using Na_2CrO_4)[26] resulted in a change in the regioselectivity, thereby affording **20** in addition to **19** as a separable mixture (ca. 1:1). Other sources of chromium afforded complex reaction mixtures (pyridinium chlorochromate (PCC), NaOAc)[27] or no reaction (CrO_3).[28] Classical SeO_2-based methods were disappointingly ineffective,[29] while treatment with IBX[30] led to complex mixtures. The use of a palladium-based method also proved unfruitful with this system.[31] Despite its successful use in related cases, the *N*-bromosuccinimide (NBS) based method[32] only resulted in electrophilic substitution of the alkene. The use of *t*BuOOH

Table 1: Allylic C–H oxidation of **14**.

Conditions[a]	Product	Yield [%]
PDC, $CHCl_3$, 70 °C	**19**	70
Na_2CrO_4, AcOH, Ac_2O, NaOAc, benzene, 70 °C	**19** + **20** (1:1)	39
CrO_3, assorted conditions	no reaction	–
SeO_2, dioxane, 100 °C or SeO_2, *t*BuOOH, HMPA/THF, 80 °C	no reaction	–
IBX, DMSO, 90 °C	complex mixture	–
$Pd(OAc)_2$, $(PhSOCH_2)_2$, benzoquinone, dioxane, 43 °C	complex mixture	–
Pd/C, *t*BuOOH, CH_2Cl_2, 23 °C	complex mixture	–

[a] PDC = pyridinium dichromate, IBX = 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide.

in the presence of copper catalysts[33] yielded an unidentifiable product. From intermediate **20**, access to geigerin (**3**) and deoxygeigerin (**4**) could be envisioned following the same approach used by Carret and Deprés,[34] namely a lithium perchlorate catalyzed 1,6-conjugate addition of a silyl enol ether. It was found important to deprotect the allylic alcohol **20** for the conjugate addition to proceed. Thus, treatment of **21** with silyl enol ether **22** afforded intermediate **23** in quantitative yield as a single diastereoisomer. This intermediate could be further processed with DMDO or hydrochloric acid to obtain geigerin (**3**)[35] and deoxygeigerin (**4**), respectively, in excellent yields.

Many sesquiterpene lactones exert their biological activity through the irreversible inactivation of their target by virtue of the presence of one or multiple Michael acceptors. To exemplify further functionalizations to generate preponderant structural motifs present in sesquiterpene lactones, geigerin (**3**) was derivatized with acryloyl chloride to provide an α,β-conjugated ester **24**. The key intermediate **14** to geigerin (**3**) could also be converted into isoclavukerin A[36] (**25**) by exchange of the silyl group for an acetate and a palladium-catalyzed allylic reduction ($[Pd(PPh_3)_4]$, $NaBH_4$).

To summarize, there is a high demand for efficient reaction sequences that lead to diverse and biologically relevant molecular space.[37] This study illustrates an emerging approach to broaden the diversity of known bioactive natural products through a versatile synthetic intermediate by the use of different reaction cascades in analogy to the natural biosynthetic pathway of sesquiterpene lactones. The divergent pathways emerge from distinct cyclization modes arising by the use of various transition-metal catalysts. The reaction sequence developed is suitable to access guaianolides as well as novel polycyclic frameworks, and thus provides opportunities to optimize biological and physicochemical properties beyond the biosynthetically accessible products. This general strategy should be applicable to other acyclic ene-yne-enes.

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