Natural Products

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# *Omnia praeclara rara*. The Quest for Ingenol Heats Up**

*Giovanni Appendino**

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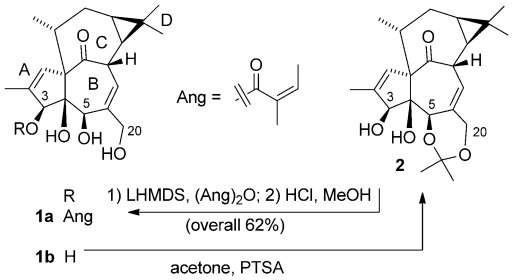
Ingenol mebutate (**1a**, ingenol 3-angelate, Picato), a plant diterpenoid used to treat solar keratosis, is an unusual drug. To start with, many ingenol esters are potent tumor promoters in rodents, and therefore are unlikely candidates for what is basically a topical form of chemoprevention.[1] Furthermore, the discovery of ingenol mebutate was the result of a reverse pharmacology logic which sounds iconoclastic in the age of rational drug discovery. Rather than by the modulation of the molecular target *du jour*, interest in ingenol mebutate was spurred by the folk use of spurges to remove warts and by anecdotal reports of self-treatment of skin cancer with their sap.[2] Finally, ingenol mebutate emerged from pharmaceutical development like Athena sprung from Zeus' head: blessed by optimization from the very beginning. In short, the materialization of a high-tech result from a low-tech approach is almost provocative in the light of the sophistication of current drug discovery methods.

Ingenol mebutate is a constituent of the petty spurge (*Euphorbia peplus* L.), an annoying weed devoid of ornamental value, whose abundance can be witnessed by any garden lover. So, why is ingenol mebutate a rarity? The problem is that the isolation from its natural source is fraught with difficulties. Not only is it isolated in very low yield (ca $\delta =$ 1 ppm),[3] but the toxicity of its plant source makes high-containment mandatory, and there is an ecological threat associated with the mass cultivation of an infesting weed which can invade agricultural and noncrop sites, kill grazing livestock, and overall reduce the quality of turf.[4] A semisynthesis of **1a** was developed from its parent polyol (ingenol, **1b**),[5] available in over 100 mg kg$^{-1}$ yield from the seeds of another spurge, *E. lathyris* L.[6] This potentially industrial supercrop is mass-cultivated to produce lamp oil, and was promoted by Melvin Calvin at the time of the oil crisis in the seventies as a renewable source of fuel.[6] Ingenol has three acylable hydroxy groups, but chemoselective formation of a 5,20-acetonide makes the monoesterification of the 3-hydroxy possible (Scheme 1). The esterification of angelic acid is a long-standing synthetic problem, plagued by isomerization to its more stable *E* isomer (tiglic acid).[5] Dual activation of angelic acid as an anhydride and of ingenol acetonide as lithium alcoholate could, however, solve this issue, with the semisynthesis being eventually optimized to a gratifying greater than 60% overall yield (Scheme 1).[5]



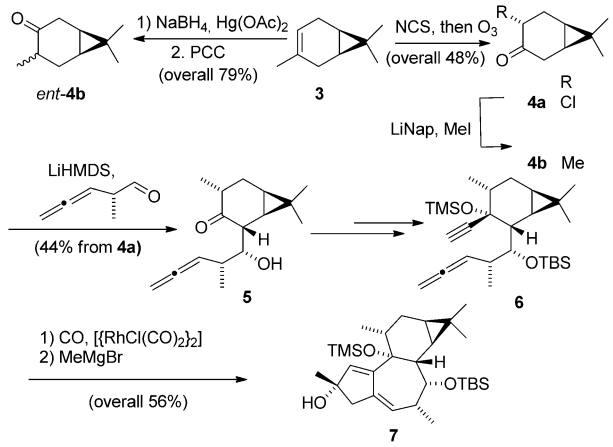

***Scheme 1.*** Semisynthesis of ingenol mebutate (**1a**) from ingenol (**1b**). LHMDS = lithium hexamethyldisilazide, PTSA = *para*-toluenesulfonic acid.

Semisynthesis has, undoubtedly, the potential to phase out the production of **1a** by isolation, but Baran and co-workers have now laid the foundation for qualifying total synthesis as an additional alternative.[7] Ingenol is an challenging synthetic target, as cogently evidenced by the synthetic steps and overall yield of the previous approaches.[8] And, with the exception of galanthamine, the total synthesis of complex natural product drugs has been industrialized essentially when no other alternative supply existed, as exemplified by the active moiety of the marine polyether halichondrin B (eribulin mesylate).[9] To go beyond the simple duplication of nature and compete with isolation and semisynthesis, an extraordinary level of efficiency had to be achieved. Baran and co-workers accepted the challenge and have developed a synthesis of ingenol, a synthesis which follows the biogenetic logic of building first a polycyclic core (cyclase stage), and then oxidatively decorating it with hydroxy groups (oxidase stage). This logic, demonstrated for taxol from the yew tree,[10] might well be of general relevance for oxygenated terpenoids because oxygen functions can interfere with cyclization reactions, thus affording oxygen bridges rather that the carbon–carbon bonds required for the formation of poycyclic scaffolds from acyclic olefin precursors.

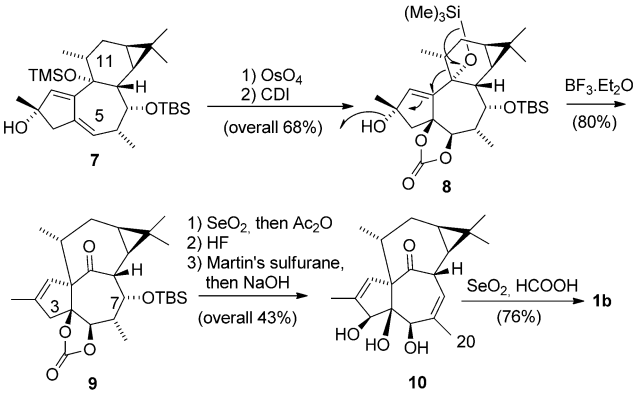
The cyclase phase uses the monoterpene (+)-3-carene (**3**) as a starting material for elaborating into a tigliane precursor

[*] Prof. G. Appendino
Dipartimento di Scienze del Farmaco
Università del Piemonte Orientale
Largo Donegani 2, 28100 Novara (Italy)
E-mail: appendino@pharm.unipmn.it

[**] All precious things are rare (Cicero, *Rhetorica. Laelius De Amicitia*, 79).




***Scheme 2.*** Cyclase phase of the synthesis. LiNap = lithium naphthalenide, NCS = *N*-chlorosuccinimide, PCC = pyridinium chlorochromate, TBS = *tert*-butyldimethylsilyl, TMS = trimethylsilyl.




***Scheme 3.*** Oxidase phase of the synthesis. CDI = carbonyldiimidazole; Martin's sulfurane = bis[α,α-bis(trifluoromethyl)benzyloxy]diphenylsulfur.

of ingenol (Scheme 2). (+)-3-Carene is available in crude form from Indian turpentine as a commodity chemical, and contains the elements of the C,D-rings of the phorboids. After expansion to a seven-membered derivative, it was used in two previous syntheses of ingenol,[8] and for the preparation of heterocyclic analogues of deoxyphorbol.[11] If the choice of the starting material seems obvious, the way it was elaborated during the cyclase phase is truly remarkable. The configuration of **3** requires a re-shuffling of the methyl substitution to comply with the chirality of ingenol, and therefore the ketone **4b**, easily available in the wrong enantiomeric form from natural (+)-3-carene (*ent*-**4b**),[11] had to be prepared in a more roundabout way by electrophilic chlorination of **3**, followed by ozonolysis and reductive alkylation. The ketone **4b** proved difficult to purify and, in the final process, it was only a transient intermediate in the one-pot telescoped process which reductively alkylated the chloroketone **4a** by methyl–chlorine exchange. Next, a regioselective intramolecular crossed aldol reaction with an allenyl aldehyde delivered **5.** After installation of the acetylenic group and protection of the hydroxy functions, the tigliane derivative **7** was eventually obtained by treatment of the allenylacetylene **6** with carbon monoxide and a $Rh^{I}$ catalyst. This allenyl Pauson–Khand carbonylation had to be carried out under high dilution (5 mM), but could, nevertheless, be scaled up to the gram level. The availability of **7** is a remarkable achievement, since it could be used to explore the many parts, which are not accessible from the pool of natural diterpenoids, of the phorboid pharmacophore.

In the oxidase phase, four hydroxy groups were inserted and the fused carbocycle system was rearranged to the bridged version of the target (Scheme 3). A tigliane-to-ingenane rearrangement is presumably involved in the biogenesis of ingenol, but this reaction had so far been observed only in the opposite direction, because ingenane derivatives rearrange to tiglianes under acidic conditions to relieve the strain associated with the in,out-bridged topology of the B,C-ring junction.[12] The way in which this reactivity was reversed is surprising in light of thermodynamic considerations of the relative stability of bridgehead and fused polycycles in general, and of the in,out and out,out configurations of the bridged junction in this particular case. Thus, the diene moiety of **7** was chemoselectively dihydroxylated at the less-hindered cycloheptene moiety, and, after protection of the glycol system as a carbonate, it was treated with $BF_3{\cdot}Et_2O$ at low temperature. A vinylogous pinacol rearrangement took place, thus delivering the ingenane derivative **8** in a rewarding 80% yield. The materialization of this apparently doubly counter-thermodynamic rearrangement is surprising, and one wonders how, in the absence of a generous sponsor like the company that developed the pharmaceutical **1a**, a proposal featuring this unpredictable reaction might have survived the conservative attitude of the grant reviewing process. Completion of the synthesis was uneventful, and involved the allylic oxidation of the methylene group at C3, dehydration of the 7-hydroxy group, and oxidation of the C20 methyl, thus concisely terminating (seven steps only) the oxidase phase of the synthesis, and relying on the cyclopropane configuration of the monoterpene **3** to establish all the remaining six stereocenters.

Can this synthesis be industrialized? While ingenious from a chemical standpoint, many cryogenic steps are technically demanding, and will probably mainly serve as a blueprint for more robust industrial modifications. Of more concern is the tag of stoichiometric metal use (also in the dihydroxylation of **7**) required in the oxidase phase. This limitation is hardly surprising, since our synthetic arsenal is more at ease at building carbon–carbon bonds than at inserting oxygen atoms into carbon–hydrogen bonds. In contrast, nature has deftly capitalized on cytochromes and iron chemistry to hydroxylate carbon atoms in a remarkably efficient and selective way, and it does not seem inconceivable that an industrial version of the synthesis, spiced up by bio-oxidation steps, could be developed. The current synthetic industrial production of the antimalarial agent artemisinin relies on a combined approach of this type, thus using biotechnology to assemble a bicyclic terpenoid skeleton, and synthesis to oxidatively degrade it.[13] Since modern science is multidisciplinary, the technological translation of its ingenuity might, undoubtedly, benefit from a similar hybrid approach.

Another issue to consider would be to simplify the access to **4b** by developing a cheap supply chain for (−)-3-carene, an abundant constituent of Scots pine (*Pinus sylvestris* L.) oil, but currently more expensive than its enantiomer from the oil of the Indian chir pine (*P. roxburghii* Sarg.).

In conclusion, the Baran synthesis of ingenol is, undoubtedly, breathtaking in terms of elegance and conciseness, and might represent a new example for the synthesis of natural products. Furthermore, the key step in which the skeleton of the target is generated is remarkable for its biogenetic implications, and its optimization might provide clues to the biogenesis of phorboids, which is currently a black box despite the outstanding biomedical relevance of this class of diterpenoids.

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