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Total Synthesis and Structural Confirmation of *ent*-Galbanic Acid and Marneral

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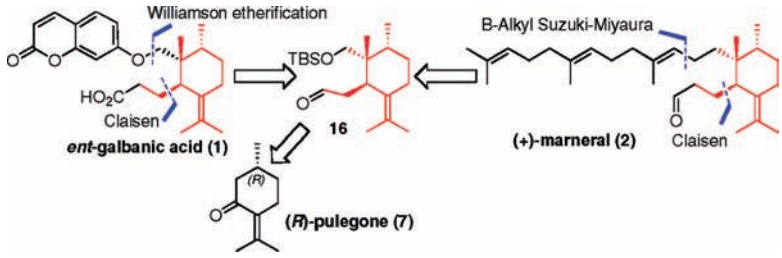
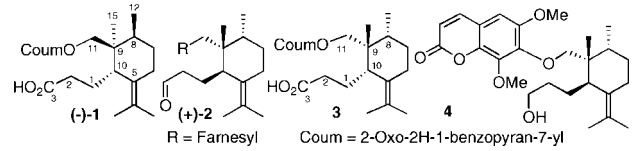
ABSTRACT



By capitalizing on a highly selective Claisen rearrangement, *ent*-galbanic acid 1 and (+)-marneral 2 have been synthesized. The relative configurations of (+)-1 and (+)-2 were unambiguously established by X-ray crystallographic analysis of the precursors 11a and 20, with the absolute configuration ensuing from their derivation from *R*-pulegone. In this way, the controversial issue of the configuration of galbanic acid was unequivocally settled.

Galbanic acid, a known constituent of the gum-resins galbanum[1] and asafetida,[2] is a sesquiterpene coumarin ether, showing antibiotic[3] and hepatoprotective properties.[4] It occurs in plants from the genus *Ferula*, accompanied by coumarins with acyclic as well as monocyclic sesquiterpene skeleta, and was assigned structure (−)-**1** (Scheme 1). Although originally described as an antibiotic principle, galbanic acid was recently demonstrated to synergize the activity of antibiotics rather than simply mimick their antibacterial activity[5] opening up interesting applications for the treatment of MRSA (methicillin-resistant *Staphylococcus aureus*) infections, a scourge currently accounting for more deaths each year than AIDS in the U.S.[6] Surprisingly, the structure of galbanic acid is still debated. The original assignment made by Bagirov et al. was later revised by Lee et al.[7] who proposed structure **3**, reverting the relative configurations at C8 and C9, after extensive NMR investigations.

Scheme 1



This structure revision has been mentioned in several articles, but to the best of our knowledge, neither a total

(1) Structure and stereochemistry of galbanic acid from *galbanum*: Bagirov, V. Y.; Scheichenko, V. I.; Veselovskaya, N. V.; Sklyar, Y. E.; Savina, A. A.; Kir'yanova, I. A. *Khim. Prir. Soedin.* **1980**, *16*, 620–623.

(2) (a) Isolation from *asafetida*: Appendino, G.; Tagliapetra, S.; Nano, G. M.; Jakupovic, J. *Phytochemistry* **1994**, *35*, 183–186. (b) Appendino, G.; Maxia, L.; Bascope, M.; Houghton, P. J.; Sanchez-Duffhues, G.; Muñoz, E.; Sterner, O. *J. Nat. Prod.* **2006**, *69*, 1101–1104.

(3) (a) Racnicer, S. K.; Veeravally, J. *Chem. Ind. (London)*; 1975; *Vol. 431, No 12*. (b) Artamonov, A. F.; Nusipbekova, K. A.; Nigmatullina, F. S.; Dzhienbaev, B. Zh. *Chemistry of Natural Compounds*; 1997; *Vol. 33, No 2*, pp 162−164.

(4) Syrov, V. N.; Khushbactova, Z. A.; Nabiev, A. N. *Farmakol. Toksikol.* **1990**, *53*, 41.

(5) Shahverdi, A. R.; Fakhimi, A.; Zarrini, G.; Dehghan, G.; Iranshahi, M. *Biol. Pharm. Bull.* **2007**, *30*, 1805–1807.

(6) Bancroft, E. A. *J. Am. Med. Assoc.* **2007**, *298*, 1803–1804.

(7) Lee, S.-G.; Ryu, S. Y.; Ahn, J. W. *Bull. Korean Chem. Soc.* **1998**, *19*, 384–386.

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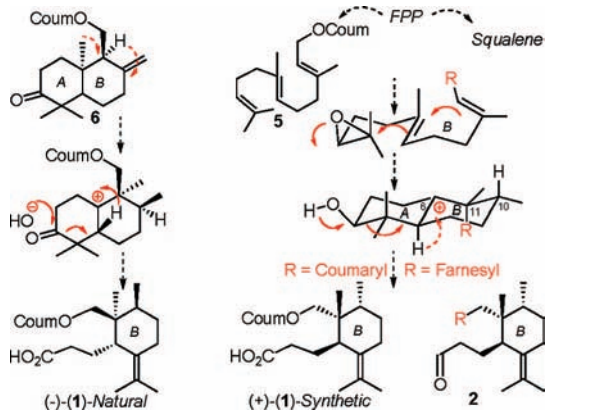


Figure 1. Simplified schematic representation of Appendino's and Marner's biogenetic proposals.

synthesis nor the ambiguity inherent in the structural revision[8] has yet been addressed. Galbanic acid **1** bears structural similarities with marneral **2**,[9] an alleged precursor of triterpenoid iridals, themselves precursors of irones, which suggests a common biogenetic origin. Marneral has been suggested to derive from an acyclic precursor through a series of cyclizations, 1,2-hydride, shifts and methyl migrations (Figure 1),[10] and one could assume a similar biosynthetic sequence for the derivation of galbanic acid from umbelliprenin (**5**). The squalene to C10-*epi* marnerol sequence has been successfully reproduced in a laboratory setting by Marner and co-workers by using van Tamelen's biomimetic cyclization of 2,3-epoxysqualene,[11] while Matsuda et al.[12] have validated the Marner proposal that oxidosqualene cyclizes en route to iridals via a B-ring boat intermediate to marneral **2**, providing the first experimental proof of a Grob fragmentation in triterpene synthesis. On the other hand, Appendino et al., while revising the structure of asacoumarin B to galbanic acid, proposed a different biogenetic origin for this compound,[2a] via a fragmentative, rather than a cyclizative route, suggesting mogoltadone **6** as the biogenetic precursor of galbanic acid (Figure 1).

In this communication, we have developed a divergent strategy to both galbanic acid and marneral, based on the coupling of commercially available (*R*)-pulegone-derived right halves **19** and **31** with umbelliferone **8** (Scheme 2) and

(8) The three stereogenic centres of galbanic acid are contiguous, with the central one being tetrasubstituted. Within this structural context, it is difficult to translate dipolar interactions into a configurational assignment.

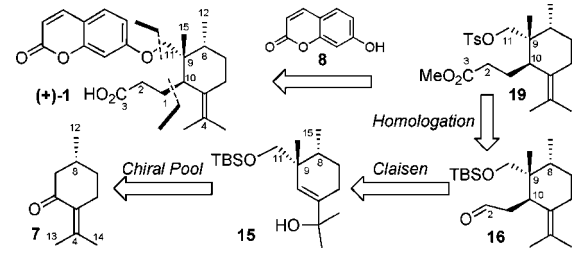
(9) Matsuda et al. (see ref 11) named this compound Marneral (and its corresponding alcohol **33** Marnerol) in recognition of the pioneering work of Marner on iridals. **2** has never been isolated but was hypothesized to be the first carbocyclic precursor in the biosynthesis of iridals. (a) Marner, F.-J.; Krick, W.; Gellrich, B.; Jaenicke, L.; Winter, W. *J. Org. Chem.* **1982**, *47*, 2531–2538. (b) Marner, F.-J. *Curr. Org. Chem.* **1997**, *1*, 153–186. (c) Lamshoft, M.; Schmickler, H.; Marner, F.-J. *Eur. J. Org. Chem.* **2003**, 727–733.

(10) Marner, F.-J.; Longerich, I. *Liebigs Ann. Chem.* **1992**, 269–272.

(11) (a) Marner, F.-J.; Kasel, T. *J. Nat. Prod.* **1995**, *58*, 319–323. (b) Sharpless, K. B.; van Tamelen, E. E. *J. Am. Chem. Soc.* **1969**, *91*, 1848–1849.

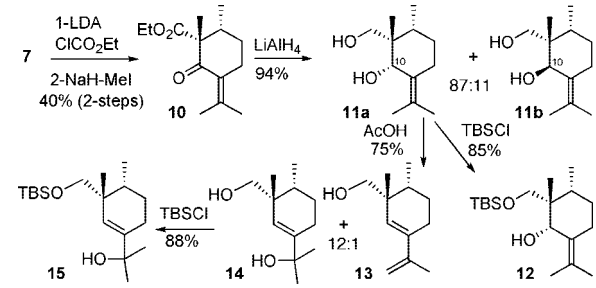
(12) Xiong, Q.; Wilson, W. K.; Matsuda, S. P. T. *Angew. Chem., Int. Ed.* **2006**, *45*, 1285–1288.

Scheme 2



(*E*)-vinyl iodide **9** (Scheme 8), respectively. The key step in our route involved the mercury-catalyzed Claisen rearrangement of allyl-alcohol **15**, itself accessible in five straightforward steps from **7**. This should allow the stereoselective introduction of the side chain at C10, which would be ultimately one-carbon homologated to **19**. Linking to the coumarin could be subsequently performed at C11 by converting the free hydroxyl functionality into a tosylate leaving group followed by an ether formation.

Scheme 3



Elaboration of **7** began with the installation of the methyl and ester groups at C9 using standard literature conditions to afford **10** and its C-/O-biscarboxymethylated counterpart, which was recycled by basic treatment (see Supporting Information). After chromatographic separation, standard reduction with $LiAlH_4$ produced the primary−secondary diol intermediates **11a** and **11b** in quantitative yield and 87:11 ratio, respectively. The major diol (**11a**) was protected as its *tert*-butyldimethylsilyl ether **12** to be used in the allyl-Claisen reaction (Scheme 3).

The stereochemistry of **11a** was unequivocally established by an X-ray crystallographic analysis (Figure 2). The one-pot allyl-Claisen rearrangement conditions, reported by Dams et al.[13] on *cis*-pulegol derivatives, did not work with **12**. Instead, the stereoselective introduction of the side chain at C10 has been cleanly achieved by first inducing the rearrangement of **11a** in AcOH[14] leading to **14** along with diene **13** (75% yield, 12:1 ratio, Scheme 3).

(13) $CH_3C(OEt)_3$, $C_2H_5CO_2H$, H_2O, 3 h at 138 °C: Dams, I.; Bialonska, A.; Ciunik, Z.; Wawrzenczyk, C. *Tetrahedron: Asymmetry* **2005**, *16*, 2087–2097.

(14) Eschinasi, E. H. *J. Org. Chem.* **1970**, *35*, 2010–2012.

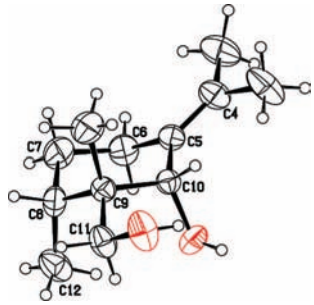
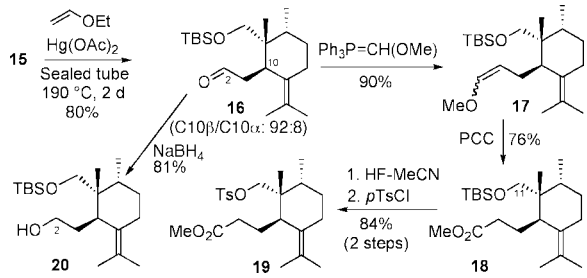


Figure 2. ORTEP view of the molecular structure of **11a**.

The rearranged diol **14**, subsequent to a TBS-protection at C11, underwent the desired Claisen rearrangement upon heating at 190 °C in the presence of vinyl ether and mercuric acetate as a catalyst,[15] affording **16** in 80% yield along with its C10-α epimer (92:8 ratio, Scheme 4).[16]

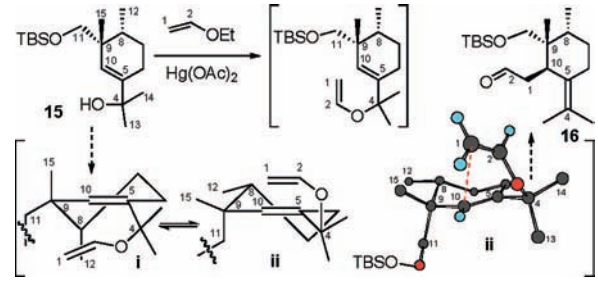
Scheme 4



Having secured the requisite C8, C9, C10 pattern for the core cyclohexane subunit **16**, a common intermediate for galbanic acid **1** and marneral **2**, the stage was set for chain elongation prior to etherification for the former and double chain elongation prior to coupling for the latter. Thus, alkoxymethylenation of **16** afforded the corresponding enol ether **17** as a mixture of *E*/*Z* isomers, which was subsequently converted to the required ester **18**.[17] The latter was desilylated to its corresponding C11 alcohol, which was taken to the required tosylate **19** (Scheme 4).

To account for the stereochemical outcome of the Claisen rearrangement, we could consider that the reaction proceeds through one of the two half-chair conformers **i** and **ii**, with the latter reacting faster, as it contains a pseudoequatorial methyl at C9 and an equatorial methyl at C8, compared to the energetically unfavorable conformer **i**. It is therefore proposed that C10−C1 bonding occurs through the more accessible *β*-face of conformer **ii** (PM3 minimized most reactive transition structure involved in this process) leading preferentially to **16** (Scheme 5).

Scheme 5



The stereochemistry of **16** was established by an X-ray crystallographic analysis on **20**, obtained by reduction of the aldehyde at C2 (Figure 3).

Initial efforts to couple **19** with **8** under conventional heating for the etherification met with total failure. Degradation of starting material was detected, and no reasonably clean product could be isolated from the reaction mixture. Coupling of the precursor alcohol with umbelliferone under Mitsunobu conditions (DIAD, PPh_3, ROH)[18] did not proceed either, yielding only starting materials. On the basis of these negative outcomes, we turned our attention to a microwave-assisted coupling. Hence, applying Williamson etherification conditions in the presence of 18-Crown-6[19] produced a clean transformation affording the desired coupling of **8** and **19**, though in very low yield (6%, along with 70% of recovered starting material).

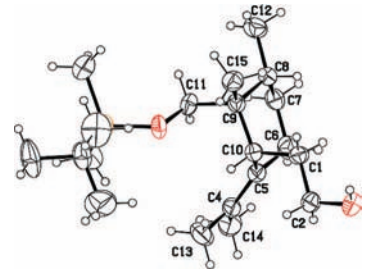


Figure 3. ORTEP view of the molecular structure of **20**.

The methyl galbanate **21** thus obtained (Scheme 6), which is also a natural product and which showed identical spectral data with the one we prepared starting from natural galbanic acid ($[\alpha]_D$ +24 (*c* 1.00, $CHCl_3$), lit.:[20] $[\alpha]_D$ −25.8 (*c* 1.16, $CHCl_3$)), was then saponified to the target **1**. A comparison of the physical properties of the natural and synthetic galbanic acid finally assessed its relative configuration,

(15) Burgstahler, A. W.; Nordin, I. C. *J. Am. Chem. Soc.* **1961**, *83*, 198–206.

(16) For closely related Claisen rearrangements, see: Ireland, R. E.; Varney, M. D. *J. Org. Chem.* **1983**, *48*, 1829–1833.

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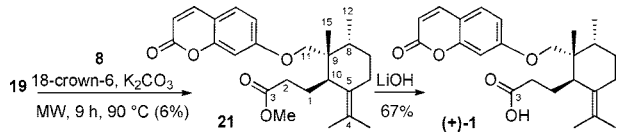
(19) Gonzales-Garcia, E. M.; Grognux, J.; Wahler, D.; Reymond, J.-L. *Helv. Chim. Acta* **2003**, *86*, 2458–2470.

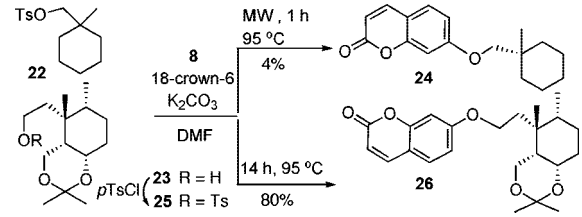
(20) The observed specific rotation of synthetic galbanic acid **1** ($[a]_D$ +26 (*c* 1.00, $CHCl_3$)) was found to be opposite in sign with that of the natural product ($[a]_D$ −23 (*c* 1.00, $CHCl_3$)), thus establishing the absolute configuration of galbanic acid as (8*S*), (9*S*), (10*S*).

Scheme 6



confirming the original one proposed by Bagirov.[21] In further trials to establish the viability of coumarine-ether formation on a model available to us from our previous studies, we have again encountered a high level of difficulty implementing the segment coupling (Scheme 7). In particular C−O bond formation at the sterically congested center has been

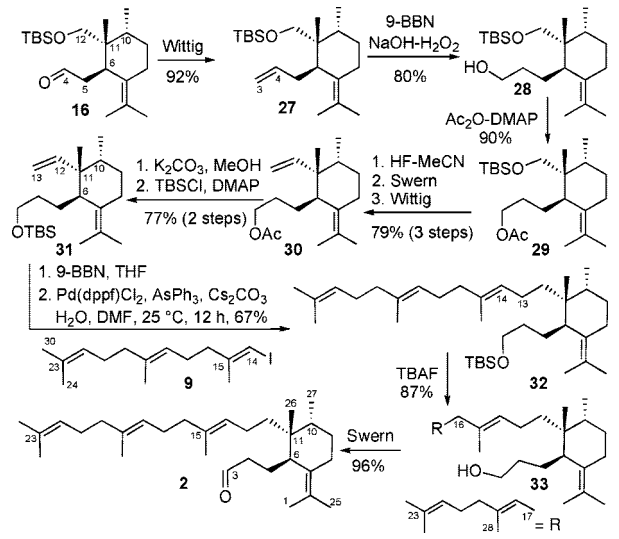
Scheme 7



difficult on **22**[22] containing a similar α-neopentylic substitution pattern. Coumarin-ether **24** was obtained in still lower yield (4%). Further model studies employed cyclohexyl tosylate **25**. Moving only one carbon farther from the neopentylic center, segment coupling proceeded smoothly under conventional heating to give the galbanic acid analogue (**26**) in high yield (80%).

With a route to common intermediate **16** established, we turned to the one-carbon homologation at C12 (from this point on, squalene numbering proposed by Marner et al. is used) prior to the key B-alkyl Suzuki coupling[23] en route for marnerol **33** and marneral **2**. The alkyl-borane precursor **31** was prepared by the efficient eight-step sequence, as depicted in Scheme 8. Wittig methylenation of **16** into C3−C4 olefin **27** and subsequent hydroboration−oxidation furnished the requisite alcohol **28**, which was acetyl-protected at C3 to afford **29** in 67% yield over three steps. The presence of orthogonal protecting groups on the side chains at C3 and C12 positions provides the opportunity to extend the chain at C12 via a selective TBS-deprotection of the latter. Swern oxidation and finally a second Wittig olefination afforded **30**, which was taken to the required boronate precursor for the B-alkyl Suzuki−Miyaura coupling, providing **31** after

Scheme 8



protecting group interchange at C3. Treatment of the latter with 9-BBN in THF, followed by addition of $PdCl_2$(dppf) and the geometrically pure vinyl iodide **9**,[24] afforded the desired coupling product **32** in 67% isolated yield. TBS deprotection of the latter afforded marnerol **33**, which was converted by a Swern oxidation to marneral **2**, both spectroscopically indistinguishable from the oxidosqualene cyclase generated biosynthetic substances.[12]

The work described in this paper has secured both the relative and the absolute configuration of galbanic acid (**1**) and marneral (**2**). Starting from an (*R*)-pulegone-derived cyclohexane core, subunit coupling for *ent*-galbanic acid (+)-**1** was accomplished in very low yield by using microwave-assisted etherification, while the B-alkyl Suzuki−Miyaura coupling afforded marneral **2** in good yield. Though no optimization was done, the route followed is operationally simple and validated the structure of both targets. The confirmation of the original stereostructure of galbanic acid warns against over-relying on NMR data even in apparently simple molecular contexts.[25]

Acknowledgment. We thank Professor Giovanni Appendino Universita del Piemonte Orientale, Novara, for supplying natural galbanic acid and helpful discussions and Dr J. Arteaga, Universidad de Huelva (Spain), for helping in preliminary experiments to prepare starting materials **10**−**12**.

Supporting Information Available: Experimental details and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(25) Six-membered rings can adopt various conformations, while a shortage of functional groups causes extensive signal overlapping.