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Synthetic Studies Directed Towards Various Homologues of Natural Sesquiterpene-Coumarin Ethers: The Domino Approach

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A domino-based strategy was used to construct analogues containing the basic skeleton of the monocyclic sesquiterpene-coumarin ethers galbanic acid (**1**) and secodrial (**3**), through conversion of the domino adduct **19** into **10** and **11**, chosen as representative targets. ^{1}H NMR patterns, corroborated by X-ray crystallographic analysis for two of the four possible diastereomeric arrangements of the six-membered B-ring common to various A-*seco* terpenes, have been determined. The observed trends help in the design of substituent combinations that provide a tool for diastereomeric recognition, depending on the *cis*/*trans* arrangement of the adjacent methyl groups and the adopted conformations.

Introduction

In the context of our ongoing interest in the synthesis and biological evaluation of various A-*seco* terpenes, we have recently reported a diverging chiral-pool-based approach to the preparation of the sesquiterpene-coumarin ether *ent*-galbanic acid [(+)-**1**][1] and the monocyclic triterpene marneral [(+)-**4**],[2] starting from (*R*)-(+)-pulegone.[3] The structural similarity of galbanic acid and marneral points to a possible biosynthetic connection through a series of cyclizations, 1,2-hydride shifts, and methyl migrations. In view of their co-occurrence, Marner proposed marneral as a biosynthetic precursor of the iridal family.[2b] A different biogenetic origin was proposed by Appendino et al.[4] in a revision of the structure of asacoumarin B to galbanic acid, suggesting mogoltadone[5] as the biogenetic precursor of galbanic acid.

At the outset of this project, no published syntheses for any of the A-*seco* terpene targets existed. Using a chiral pool approach, we completed the synthesis of (+)-**1** by applying the protocol of Reymond et al.,[6] a modified Williamson etherification in the presence of 18-crown-6 under microwave irradiation conditions, with commercially available umbelliferone and the required B-ring C11-tosylate. Despite inefficient segment coupling, the synthesis of the antipodal galbanic acid in that previous work secured the absolute stereochemistry of the natural galbanic acid while ending the controversy around its relative stereochemistry.[7] Of the four plausible pairs of antipodes, the absolute stereostructure of natural galbanic acid was confirmed as (8*S*,9*S*,10*S*) through its first asymmetric synthesis in a convergent synthetic pathway. Since then an improved version of our chiral-pool-based entry into the naturally occurring sesquitriterpenoid area has been achieved, allowing the first synthesis of natural galbanic acid [(–)-**1**], in which Mitsunobu etherification under microwave irradiation conditions provided a considerable increase in yield while reducing the route by one step (out of ten linear steps) before coupling. The synthesis of marneral [(+)-**4**] was also significantly shortened in this same work.[8] This and the previous work from our laboratory were, to the best of our knowledge, the first published contributions in which the optically pure (or even racemic) products **1** and **4**, as well as analogues of **3** (secodrial) and **6** (secochiliotrin),[9] could be produced.[10]

Initially, the purpose of the research described below was to synthesize conveniently functionalized six-membered rings of types **1**, **2** (the revised, but erroneous, structure proposed for galbanic acid), **5**,[11] **6**(**8**), and **7**, possessing all combinations of the *R* and *S* configurations at C-8, C-9, and C-10, to resolve the still persisting structural doubt and to provide a prognostic tool for recognizing the substitution pattern simply from NMR spectroscopic data. Two of the four possible diastereomers, featuring the *trans*-methyl (**1**, **4**, **5**) and *cis*-methyl (**6**) arrangements, occur in natural products (Figure 1).

For a convenient route to the six-membered B-ring moiety we envisaged use of the lead-tetraacetate-mediated oxidative cleavage of readily available bicyclic unsaturated diols in the Hajos–Parrish series, providing direct access to stereodefined cyclohexane frameworks.[12] In this context we had previously described the development of a domino reaction[13] and its application to the synthesis of bioactive natural products.[14] Two out of four possible structures

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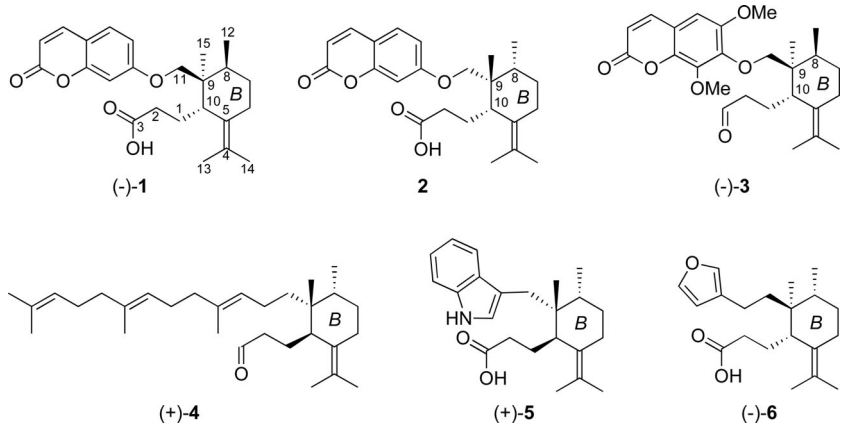


Figure 1. Structures of representative A-*seco* terpenes bearing structurally similar B-ring moieties.

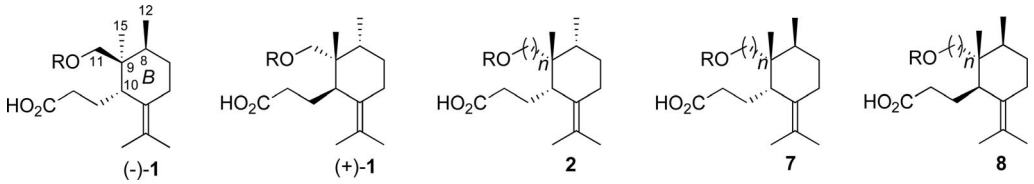
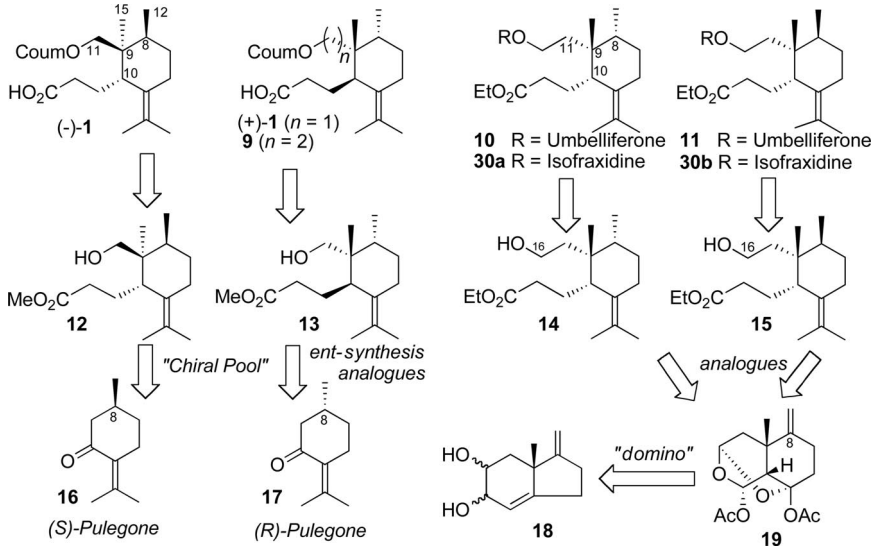


Figure 2. Originally proposed stereochemical assignment of galbanic acid **1** (both antipodes), its previously revised (albeit erroneous) proposed structure **2**, and the remaining two of the four pairs of antipodes, **7** and **8** (only one antipode is represented for **2**, **7**, and **8**).

(type **2** and type **7**, Figure 2) could be approached by use of our domino methodology as a key reaction step, setting the configurations at C-9 and C-10, while allowing for the post-domino construction of the C-8 center both in its *R* and in its *S* configuration.

In the light of our previous results relating to the synthesis of galbanic acid [(–)-**1**] and its enantiomer,[3,8] the anticipated difficulty in carrying out the coupling of the coumarin part to the crowded neopentylic center C-11 prompted us to investigate a more reactive sesquiterpene partner. We hence chose to target structures **10** and **11**, higher homologues at C-11 and epimeric to each other at C-8, synthesized by the sequence outlined in Scheme 1. The cyclohexane derivatives **14** and **15**, containing the appropriate C-8, C-9, and C-10 stereogenic centers, were to be accessed from the known domino product **19**, and this in turn was to be elaborated from the versatile building block **18**.[15] Linking to the coumarin could subsequently be performed at C-16 either directly by a Mitsunobu etherification or by conversion of the free hydroxy functionality into a tosylate leaving group followed by a Williamson etherification. With the ready accessibility of Hajos–Parrish ketone and pulegone



Scheme 1. Domino and chiral pool approaches for unequivocal structure assignments.

(both antipodes), we established access to six out of eight possible stereoisomers, although the last enantiomeric pair of type **6(8)**, characteristic of the secochiliotrin framework, still remains inaccessible.

Here we report the domino-based approach involving the stereocontrolled formation of natural product analogues. Two of them are umbelliferone-derived ethers (**10**, **11**) and the other two are isofraxidine-derived ethers (**30a**, **30b**) with the same sesquiterpenoid unit. The goal was to enable a combination of the two routes, the former chiral pool approach and the current domino approach, to provide both a means to access three out of the four possible cyclohexane core structures **1**, **2**, **7**, and **8** (Figure 2) and a reliable diagnostic model for structure assignment by NMR techniques.

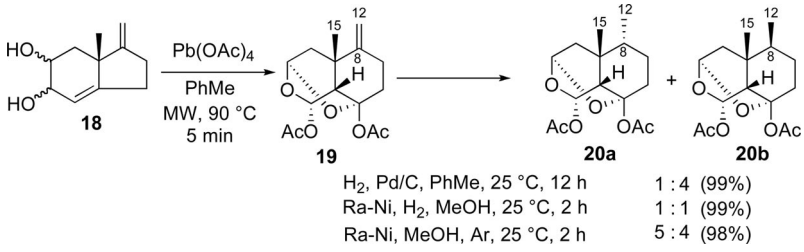
Results and Discussion

The required unsaturated diols **18** and the domino product **19** were prepared straightforwardly, in their optically pure forms, by published procedures.[15] Reduction of the exocyclic alkene was carried out first, with the installment of the coumarin moiety being left for later stages. Thus, with the large-scale acquisition of the domino derivative **19**, the crucial issue of setting up the C-12 methyl with the appropriate stereochemistry was addressed. An initial investigation for this study, based on palladium-catalyzed hydrogenation of the double bond, revealed moderate selectivity (4:1) with the major product being the C-12b epimer **20b** (Scheme 2). We then briefly studied the factors influencing the stereochemistry of the C8–C12 olefin reduction. Catalyst support and added hydrogen was investigated, the temperature was varied between 25 °C and 60 °C, and various types of solvents were employed. Although the hydrogenation was effective in terms of yield (≥98%), the formation of the C-8 methyl group proceeded with only moderate diastereoselection. To summarize, the domino intermediate **19** exhibited modest selectivity towards hydrogenation, whereas when H_2-Pd/C was replaced by Raney-Ni a slight reversal in the stereomeric ratio occurred, with the C-12α epimer being the major product in the latter case.

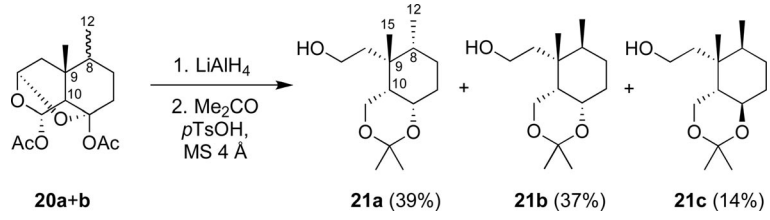
Although a method for selective production either of diastereomer **20a** or of diastereomer **20b** would ultimately be desired, a 1:1 mixture of epimers was tolerable at this point because we needed both diastereomeric types for structure elucidation.

Thus, after the preparation of **19**, in which the olefin serves as a C-12 methyl precursor, a Raney-Ni reduction afforded the C-12α- and -β-methyl groups, providing a nearly quantitative yield of **20a** and **20b** as an inseparable mixture. En route to the isopropylidene alcohols **21a**, **21b**, and **21c**, separation of the C-8 epimers was achieved through lithium aluminium hydride reduction of the thus obtained **20a** and **20b** and subsequent selective acetonide formation by standard procedures (Scheme 3). The C-8 epimeric diastereomers **21a** and **21b**/**21c** were easily separated by silica gel column chromatography and readily differentiated by ^{1}H NMR spectroscopy.

With success in the separation of C-8 epimers and large amounts available with which to press forward, the targeted B-ring building block **14**, together with its C-8 epimer **15**, was readily accessed by carrying out the sequences described in Scheme 4 and Scheme 5 in parallel. After the diastereomeric separations it becomes necessary temporarily to block the secondary hydroxy function at C-16. An ideal blocking group would be benzyl, which could be removed later by Raney nickel catalytic hydrogenolysis. Treatment of **21** with benzyl bromide in the presence of sodium hydride in dry DMF afforded the corresponding benzyl ethers, and subsequent treatment with HCl/THF (5%), selective protection of the resulting diols **22** as the corresponding *tert*-butyldimethylsilyl ethers, and Swern oxidation took the route as far as the TBS-protected aldols **23** (Scheme 4). These now require construction of the exocyclic *gem*-dimethyl olefin and further each require an additional two-carbon ho-

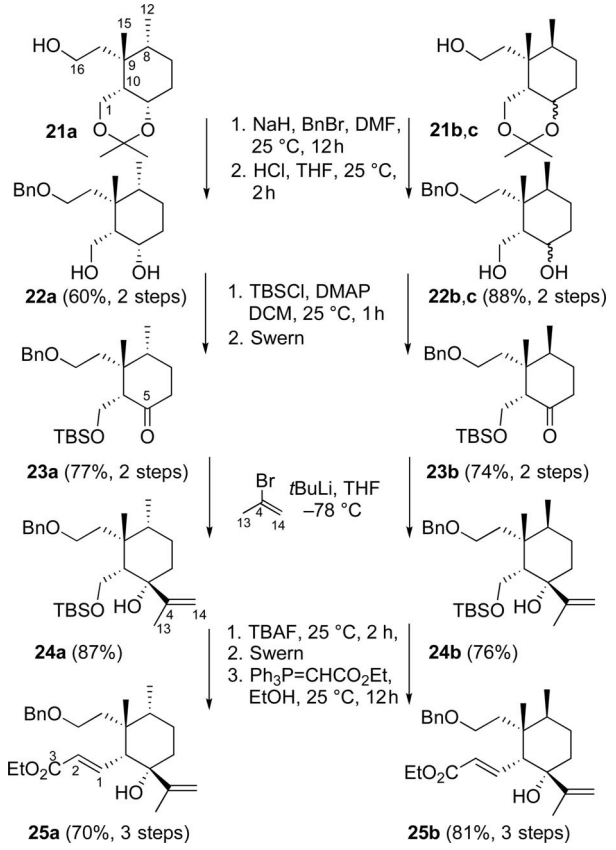


Scheme 2. Exploring the facial selectivity of the C8–C12 exocyclic olefin hydrogenation.



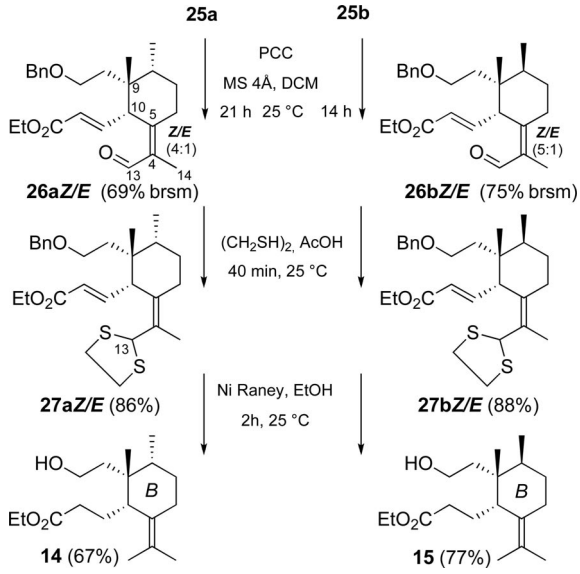
Scheme 3. Formation of the central B-ring.

mologation. Insofar as the dimethyl olefin introduction was concerned, it was initially hoped that this could be accomplished either directly through a Wittig olefination or indirectly through a Knoevenagel condensation[16] with one of the many adapted modifications for tetrasubstituted olefin formation. Attempted olefinations with **23** under a variety of conditions proved fruitless, however, and as a result an organolithium addition/oxidative rearrangement sequence, inspired by our previous iridal synthesis,[14b] was investigated. Thus, with the aim of introducing the C-4/C-13/C-14 unit, as a potential formylolefin precursor, **23** was first treated with (prop-2-enyl)magnesium bromide to afford a 54% yield of the corresponding carbinol along with unreacted starting material (23%). Alternatively, addition of isopropenyllithium (prepared in situ from 2-bromopropene and *t*BuLi in THF, –78 °C) raised the yield of the required carbinol to 87% (4% of recovered starting material). After deprotection (fluoride) and Swern oxidation, homologation of **24** was achieved by means of a Wittig-based olefination with ethyl (triphenylphosphoranylidene)-acetate, which furnished the α,β-unsaturated esters **25a** and **25b** (70% and 81% yields, respectively, over three steps, Scheme 4).



Scheme 4. Addition of the missing carbons at C-1 and C-5.

From our previous experience in the iridal synthesis, it was initially assumed that the regiochemical outcome of the Dauben–Michno rearrangement[17] would give a *Z*/*E* mixture of enals **26**. This would have no long-term significance,

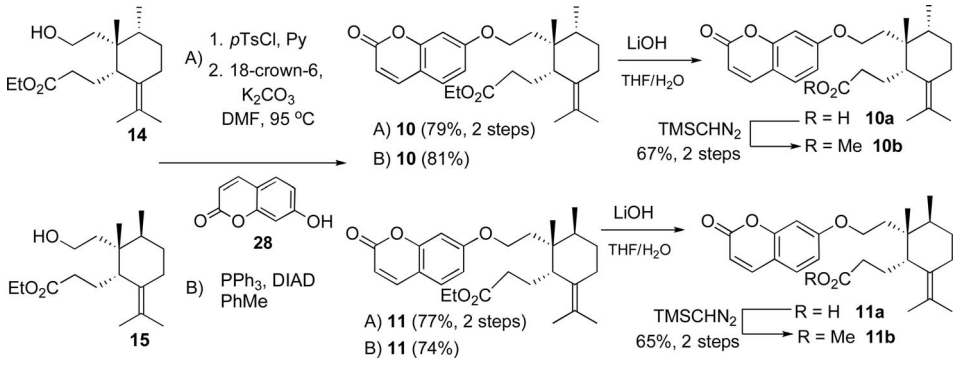


Scheme 5. Elaboration of the exocyclic dimethyl olefin and C-10 side chain (brsm = based on recovered starting material).

however, because the *Z*/*E* geometry would be destroyed in the unveiling of the *gem*-dimethyl group through removal of the dithiane at C-13 for the conversion of **27a** and **27b** into **14** and **15**. This conversion proved more beneficial than originally anticipated, because among the standard conditions surveyed, the use of Raney nickel in EtOH at 25 °C directly afforded high yields of **14** (67%) and **15** (77%). In this three-step one-pot reaction, treatment of **27a** and **27b** with Raney nickel in ethanol at ambient temperature led to debenzylation, dethioketalization, and selective reduction of the conjugated olefins (Scheme 5).

Interestingly, the Reymond protocol, which in our previous work had given low-yielding coupling with the tosylate (+)-**i** for the methylene-homologated *ent*-galbanic acid (+)-**iii**,[18] shows a configuration-controlled selectivity. Thus, once the synthesis of the B-ring moiety had been achieved, we proceeded in parallel with the two experimental coupling protocols – namely the Mitsunobu and the Williamson etherification – with the aim of investigating the reactivity patterns of various diastereomeric B-ring frameworks. Firstly, Mitsunobu couplings in which the commercially available coumarins **28** (Scheme 6) and **29** (Scheme 7) were allowed to react with the B-ring precursors **14** and **15** were tried, affording the desired coumarin ethers **10** and **11** in 81% and 74% yields, respectively.

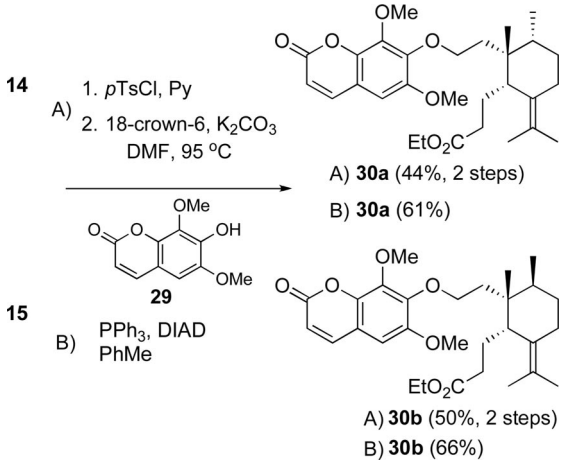
A Williamson etherification by the protocol of Reymond et al.[6] followed, with the same coumarins **28** and **29** being treated with tosylates derived from the one-carbon-homologated alcohols **14** and **15** as shown in Scheme 6 and Scheme 7. The fully elaborated skeletons of the galbanic acid analogues **10** and **11** were produced uneventfully upon attachment of umbelliferone (**28**) to **14** and **15**, respectively (Scheme 6). The ethyl homogalbanates **10** and **11** were saponified by treatment with LiOH in THF and then converted into their corresponding methyl esters **10b** and **11b**



Scheme 6. Completion of the synthesis of galbanic acid analogues.

with $TMSCHN_2$, in methanol, thus affording two more analogues, because methyl galbanate is also a natural product.[19]

In the same manner as above, isofraxidine (**29**) and the same sesquiterpenoid units **14** and **15** afforded the secodrial analogues **30a** and **30b**, respectively (Scheme 7), thus completing the synthesis of the targeted compounds.



Scheme 7. Completion of the synthesis of secodrial analogues.

As demonstrated by the above results, the segment coupling by the Raymond protocol could be accomplished cleanly and in good yields with the diastereomeric B-ring precursors **14** and **15**, as well as with several model substrates,[3] whereas with (+)-**i** as substrate it had failed,[18] which thus corroborated the influence of the configuration for a successful segment coupling pathway. Finally, although etherification with coumarins at the congested neopentylic C-11 needs further efforts, the segment coupling proceeds in good yields on moving only one carbon further away from the neopentylic center.

Stereochemical Assignments

Synthesis can bring essential insight into the stereochemical problems that may arise from the final relative configuration assignment of the target.[20] Analysis of the intermediates involved in the sequence can also clear the way for the final assignment. The task is even more arduous, however, when conformational equilibria have to be taken into account for the structural assignment, especially for small molecules that can adopt various conformations. In our case we dealt with the unknown conformation of galbanic acid, which subsequently generated confusion in its relative stereoassignment. The assignment of the vicinal stereocenters in the *trans* (**2**) and the *cis* (**7**) series as (8*R*,9*R*) and (8*S*,9*R*), respectively, had largely been based on spatial proximity effect measurements based on the 2D NOESY technique and *J*-analysis, with subsequent corroboration of two key intermediates (**22bT**, **25a**) and a target analogue (**10**) by X-ray crystallographic analysis.

The C-12/C-15 *cis*-Dimethyl Series

The triol **22bT** obtained by acetonide deprotection gave single crystals suitable for X-ray crystallographic analysis (Figure 4, below, ORTEP drawing). The depicted relative stereochemistry and preferred conformations were first deduced from the magnitudes of coupling constants and corroborated by 2D NOESY experiments (Figure 3). The ring protons have $^3J_{H,H}$ values consistent with a chair conformation, as can be seen in both Figure 3 and Figure 4.

The axially oriented Me15 group of **27b*Z*** displays correlation peaks with the protons resident on the β face of the molecule (7-H, 10-H), but also to the 13-H proton, an interaction that would not be observed if the thioketal group were in the opposite geometry. Conversely, a strong NOE was observed as a consequence of the *syn* relationship of the protons of Me14 and 6βeq-H. This assignment was also confirmed by the dipolar coupling between the olefinic proton 1-H and the axial protons 8α-H and 6α-H. Insofar as the B-ring right-half residue **15** is concerned, it can immediately be seen that the β-*cis* relationship for Me12/Me15 is in fact correct, with the six-membered ring also disposed in chair form, as in the precursor molecule **22bT**. Observation of correlation peaks between the signals for the C-13 methyl/10-H and C-14 methyl/6β-H protons (**15**) confirmed a *syn* geometry in each case. The map of diagnostic NOEs is depicted in Figure 3 for the most significant effects.

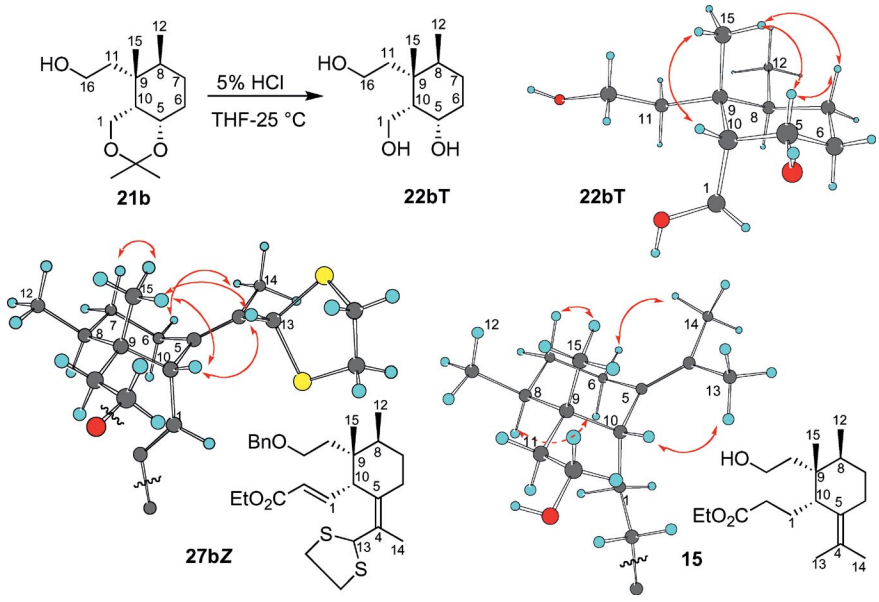


Figure 3. Key NOESY correlations used to establish the relative stereochemistries of the A-secoterpenoid B-ring residues in the Me12/Me15 *cis* series (arrows indicate diagnostic NOESY correlations for products **22bT**, **27b*Z***, and **15**). Benzyl and ethyl ester components in **15** and **27b*Z*** have been removed to permit a clearer view of the framework conformation (Chem3D output of PM3 minimized structures).

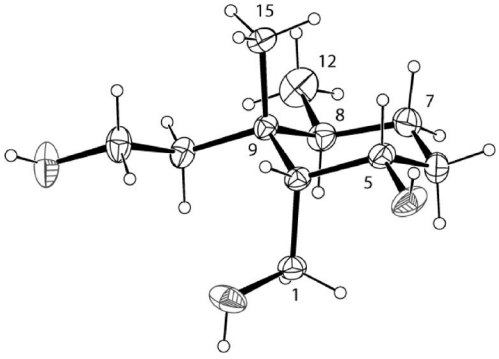


Figure 4. Ortep view of the molecular structure of triol **22bT**.

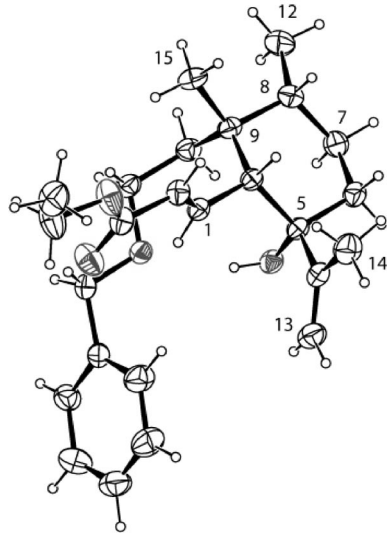


Figure 5. Ortep view of the molecular structure of conjugated ester **25a**.

The C-12/C-15 *trans*-Dimethyl Series

The missing stereochemical evidence for the target analogue **10** (Me12/Me15 *trans* relationship) was deduced after further elaboration of the "south" part, subsequent to attachment of the formyl-olefin moiety at C-5 and the homologated side chain at C-1. Upon recrystallization, the thus obtained conjugated ester **25a** afforded single crystals suitable for X-ray crystallography, which confirmed the C-8(*S*) absolute configuration for the **21a** series (Figure 5).

At this stage all three asymmetric centers of the targeted analogues **10** and **11** were established. The same chair conformation is adopted both in the solid state and in solution, as demonstrated by X-ray and *J*-analysis, as well as by facial proximity effects measured by 2D NOESY spectroscopy. The stereochemistry of the **21a** series featuring the *trans*-methyl relationship was further confirmed with two more intermediates by *J*-analysis and the observed NOEs of two later intermediates (**27a*Z*** and **14**, Figure 6).

The illustrated diagnostic NOESY interactions, together with the small vicinal coupling constants between 8β-H and 7-H (upon irradiation of the Me12 group 8β-H collapses into a triplet, J = 3.6 Hz), establish the configurations of the C-8, C-9, and C-10 stereocenters of **25a**, featuring a Me12/Me15 *trans* relationship, as (8*R*,9*R*,10*R*). Finally, additional support was also obtained from an X-ray crystallographic analysis of the target analogue **10** (Figure 7).

In summary, the assignment of the *trans* and *cis* methyl relationships in **14** and **15** was initially deduced from the NMR spectra and particularly from the *J*-analysis and the NOE data. Single-crystal X-ray diffraction analyses of the

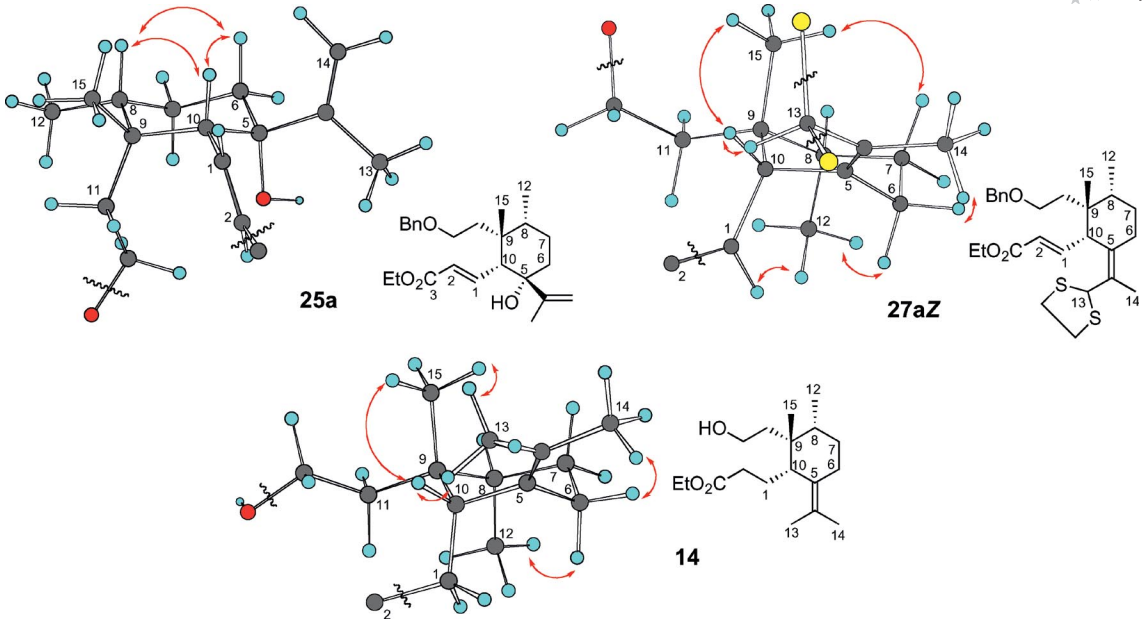


Figure 6. Key NOESY correlations used to establish the relative stereochemistries of the A-secoterpenoid B-ring residues in the Me12/Me15 *trans* series (arrows indicate diagnostic NOESY correlations for products **25a**, **27a*Z***, and **14**). Benzyl and ethyl ester parts (as well as the thioacetal moiety for **27aZ**) have been removed to permit a clearer view of the framework conformation (Chem3D output of PM3 minimized structures).

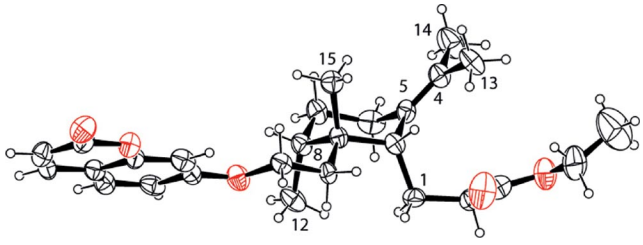


Figure 7. ORTEP drawing of the X-ray structure of **10**; the C1–C3 side chain prefers an axial orientation (allylic $A_{1,3}$ strain).

crystalline galbanate analogue **10** (Figure 7), of its precursor derivative **25a** (Figure 5), and of the triol **22bT** (Figure 4), precursor of the targeted galbanate analogue **11** with a *cis*-dimethyl relationship, enabled unequivocal stereochemical assignment and further confirmed the correctness of previous assignments by NMR techniques and molecular mechanics calculations. By comparing the ^{1}H NMR spectra of natural galbanic acid and its higher homologue with those of the analogues prepared in this work, we have been able to draw an empirical correlation between the structure of the central ring and the proton NMR spectrum. We focused our comparison on the ^{1}H NMR window that includes the chemical shifts of both Me12 and Me15, because their chemical environments vary as a function of their cyclohexane conformations. Our main objective was to be able to compare the structures of the homologated analogues **10** and **11** with that of the galbanic acid. The first validation of this analysis was provided by the resemblance of the surveyed patterns of the homogalbanic acid[8] and of natural galbanic acid. The patterns of the cyclohexane core could then be correlated with the relative configuration of Me12 and Me15 in a specific conformation (eq-eq, ax-ax, ax-eq, and eq-ax). A very important fixation point of our conformation analysis is the relative relationship between the lateral chain C1–C3 and the methyl group 13, because allylic 1,3-strain[21] pushes this lateral chain into an axial position, a fact confirmed by all our previously presented experimental data. Once the validity of this approach had been established, we were able to plan its use in structure determination in the series.

The most definitive distinguishing feature of the B-ring isomers is the ^{1}H NMR shifts for the Me12 and Me15 signals, with those of **1** appearing at δ = 0.91 ppm (Me12 doublet) and 1.15 ppm (Me15 singlet) whereas those of **10** appear at δ = 1.01 ppm (Me15 singlet) and 1.13 ppm (Me12 doublet) and those of **11** at δ = 0.79 ppm (Me12 doublet) and 0.81 ppm (Me15 singlet). It is noteworthy that compound **11**, of (8*S*,9*R*) chirality, has a more strongly upfield shift for the Me12 doublet, a trend opposite to that found in **10**, in natural secochiliotrin [**6**, at δ = 1.03 ppm (Me12 doublet), 0.97 ppm (Me15 singlet)], or in suaveolindole [**5** (see ref.[11]), at δ = 1.03 ppm (Me12 doublet), 1.01 ppm (Me15 singlet)].

As portrayed in Figure 8, this reversal of trends for the Me12/Me15 signals in A-*seco* terpenoids appears to be reliable for a fast structure assignment, including for higher homologue series, because the $\Delta\delta$ values for natural galbanic acid (**1**) and for its higher methylene homologue homogalbanic acid (δ = 0.83 ppm Me12 doublet, 1.03 ppm Me15 singlet) are only 0.08 and 0.12 ppm respectively. The striking similarities between analogue **10** and secochiliotrin

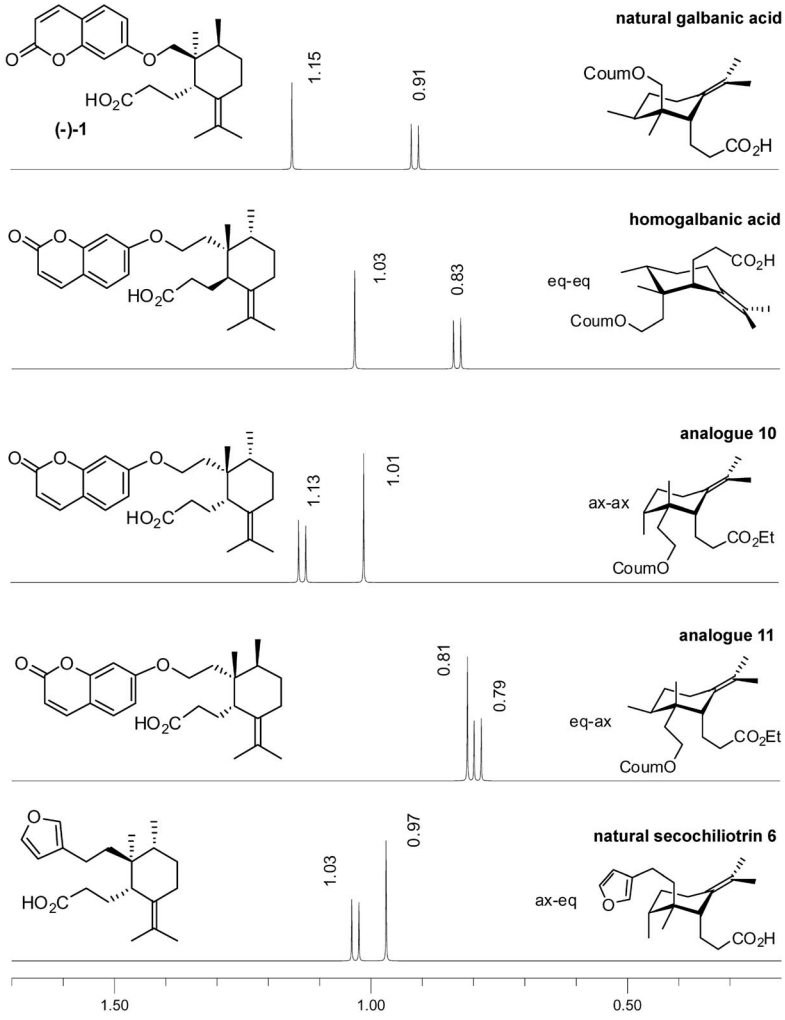


Figure 8. ^{1}H NMR spectra ($CDCl_3$, 500 MHz): Me12 (doublet) and Me15 (singlet) signals showing the upfield methyl region of natural galbanic acid (**1**) versus those of its C-11 homologue, the *trans*-dimethyl analogue **10** ("Lee-type"), the *cis*-dimethyl analogue **11**, and secochiliotrin (**6**), covering all of the four possible steroeisomeric possibilities. The conformational lock imposed by the exocyclic olefin accounts for the portrayed conformations.

(**6**), the structure of which was proposed by Bohlmann et al.,[9] call for a synthesis of the latter in order to establish its structure unequivocally.

Conclusions

The most important consequence of this work is that three out of four possible diastereomers could be produced either by the chiral pool route[8] or by the domino reaction pathway. Although the latter approach does not afford an opening to control the C-8 configuration, access to both configurational forms was gained.[22] Significant advantages are that the compounds can be obtained in high purity and that analogues can be prepared for testing, thus enabling structure/activity studies. Further, the tested synthetic routes should allow definitive verification of the proposed structures, including relative and absolute stereochemistry for the two still missing diastereomeric dispositions of the B-ring in new A-secoterpenoids awaiting isolation.

As a final note, the cell growth inhibitory activities of the synthesized analogues were evaluated against KB cells. Their insignificant levels of cytotoxicity (see the Supporting Information) make them potentially useful as biological probes.

Experimental Section

General: For general methods and standard procedures see the Supporting Information.

Raney Nickel Reduction. Completion of the Synthesis of B-Ring Precursors 14 and 15: A solution of **27a*Z*/*E*** (238 mg, 0.50 mmol, mixture of isomers) in absolute EtOH (14 mL) was added dropwise at room temperature under argon to a stirred suspension of Raney nickel (50% w/v in water, 7 mL, previously washed three times with absolute EtOH) in absolute EtOH (10 mL). The mixture was stirred for 2 h at the same temperature. The suspension was then diluted with EtOAc and filtered through a silica gel pad, with elution with further EtOAc. The solvent was evaporated under

vacuum and the residue was chromatographed on silica gel (heptane/EtOAc 3:1) to yield **14** (100 mg, 67%) as a colorless oil. $[\alpha]_D^{20}$ = –30 (*c* = 0.9, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 0.91 (s, 3 H, Me-15), 1.10 (d, *J* = 7.5 Hz, 3 H, Me-12), 1.24 (t, *J* = 7.1 Hz, 3 H, EtO), 1.35 (br. d, *J* = 13.1 Hz, 1 H, 7-H), 1.44–1.55 (m, 1 H, 8-H), 1.58 (d, *J* = 1.3 Hz, 3 H, 13-H), 1.63–1.69 (m, 1 H, 11-H), 1.70 (br. s, 3 H, Me-14), 1.73–1.87 (m, 3 H, 1-H, 2-H, 7-H), 1.92–2.09 (m, 3 H, 1-H, 2-H, 6α-H), 2.13–2.21 (m, 1 H, 2-H), 2.26–2.35 (m, 2 H, 10-H, 6β-H), 3.73 (td, *J* = 5.5, 10.1 Hz, 1 H, 16-H), 3.78 (td, *J* = 5.7, 10.1 Hz, 1 H, 16-H), 4.09 (qd, *J* = 1.6, 7.1 Hz, 2 H, EtO) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.2 (EtO), 17.1 (C-12), 20.3 (2 C, C-6, C-13), 20.5 (C-14), 24.4 (C-1), 27.0 (C-15), 30.3 (C-7), 33.2 (C-2), 36.7 (C-8), 39.6 (C-9), 41.1 (C-11), 47.0 (C-10), 59.3 (C-16), 60.2 (EtO), 124.5 (C-4), 131.3 (C-5), 174.2 (C-3) ppm. IR (film): $\tilde{\nu}$ = 3422, 1733, 1454, 1372, 1164, 1032 cm^{-1}. ESIMS (MeOH): *m*/*z* = 319.2 (100) $[M + Na]^+$. HRESIMS: calcd. for $C_{18}H_{32}O_3Na$ 319.2249; found 319.2214. Calcd. for $C_{18}H_{32}O_3$ (296.44): C 72.93, H 10.88; found C 72.89, H 10.92.

Compound 15: Raney nickel reduction of **27b** (112 mg, 0.24 mmol, mixture of *E*/*Z* isomers) as described above afforded **15** (54 mg, 77%) as a colorless oil after silica gel chromatography (heptane/EtOAc 3:1 to 2:1): $[\alpha]_D^{20}$ = –40 (*c* = 0.9, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 0.73 (s, 3 H, Me-15), 0.75 (d, *J* = 6.7 Hz, 3 H, Me-12), 1.14–1.26 (m, 1 H, 7-H), 1.24 (t, *J* = 7.1 Hz, 3 H, EtO), 1.41–1.47 (m, 1 H, 7-H), 1.57 (d, *J* = 1.9 Hz, 3 H, Me-13), 1.58–1.77 (m, 3 H, 8-H, 2×11-H), 1.66 (d, *J* = 0.9 Hz, 3 H, Me-14), 1.78–1.90 (m, 3 H, 6α-H, 2×1-H), 2.03 (dt, *J* = 8.1, 16.2 Hz, 1 H, 2-H), 2.14 (ddd, *J* = 5.8, 8.1, 16.2 Hz, 1 H, 2-H), 2.38–2.45 (m, 2 H, 6β-H, 10-H), 3.71 (td, *J* = 5.5, 10.2 Hz, 1 H, 16-H), 3.85 (td, *J* = 5.6, 10.2 Hz, 1 H, 16-H), 4.09 (q, *J* = 7.1 Hz, 2 H, EtO) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.2 (EtO), 15.7 (C-12), 17.8 (C-15), 20.2 (C-13), 20.3 (C-14), 21.7 (C-1), 24.5 (C-6), 31.6 (C-2), 31.8 (C-7), 35.0 (C-8), 39.4 (C-9), 41.0 (C-11), 44.5 (C-10), 58.8 (C-16), 60.2 (EtO), 124.6 (C-4), 130.1 (C-5), 174.3 (C-3) ppm. IR (film): $\tilde{\nu}$ = 3397, 1734, 1458, 1373, 1174, 1036 cm^{-1}. ESIMS (MeOH): *m*/*z* = 319.1 (100) $[M + Na]^+$. HRESIMS: calcd. for $C_{18}H_{32}O_3Na$ 319.2249; found 319.2236. Calcd. for $C_{18}H_{32}O_3$ (296.44): C 72.93, H 10.88; found C 72.23, H 10.97.

Preparation of Coupling Partners and Segment Coupling: Compound **14** (54 mg, 0.18 mmol) was tosylated by the general procedure to afford the crude tosylate (80 mg), which was used as such in the next reaction. The resulting tosylate (52 mg, 0.12 mmol) was coupled with **28** by the general procedure for Williamson etherification (the Reymond protocol) to afford the expected ether **10** (42 mg, 80%) after chromatography of the residue on silica gel (heptane/EtOAc 5:1 to 3:1).

Mitsunobu etherification of **14** (47 mg, 0.16 mmol) was achieved by the general procedure to give, after flash chromatography (SiO_2, heptane/EtOAc 5:1 to 3:1) the desired ether **10** (57 mg, 81%) as colorless crystals; m.p. 72.3–73.0 °C (hexane). $[\alpha]_D^{20}$ = –11 (*c* = 0.9, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 1.01 (s, 3 H, Me-15), 1.14 (d, *J* = 7.5 Hz, 3 H, Me-12), 1.24 (t, *J* = 7.1 Hz, 3 H, EtO), 1.41 (br. d, *J* = 13.0 Hz, 1 H, 7-H), 1.58–1.62 (m, 1 H, 8-H), 1.61 (br. s, 3 H, Me-13), 1.73 (br. s, 3 H, Me-14), 1.76–1.94 (m, 3 H, 1-H, 7-H, 11-H), 1.96–2.14 (m, 4 H, 1-H, 2-H, 4-H, 6α-H), 2.15–2.23 (m, 1 H, 2-H), 2.33–2.39 (m, 2 H, 6β-H, 10-H), 4.04–4.16 (m, 3 H, 16-H, EtO), 4.21 (td, *J* = 5.8, 9.3 Hz, 1 H, 16-H), 6.24 (d, *J* = 9.5 Hz, 1 H, 3′-H), 6.83–6.87 (m, 2 H, 6′-H, 8′-H), 7.36 (d, *J* = 9.1 Hz, 1 H, 5′-H), 7.63 (d, *J* = 9.5 Hz, 1 H, 4′-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.3 (EtO), 17.2 (C-12), 20.2 (C-6), 20.4 (C-13), 20.5 (C-14), 24.4 (C-1), 27.0 (C-15), 30.2 (C-7), 33.1 (C-2), 36.6 (C-8), 36.8 (C-11), 39.6 (C-9), 47.1 (C-10), 60.2 (EtO), 65.5 (C-16), 101.4 (C-8′), 112.4 (C-4a′), 112.9 (C-6′), 113.1 (C-3′), 124.9 (C-4), 128.7 (C-5′), 131.0 (C-5), 143.4 (C-4′), 156.0 (C-8a′), 161.2 (C-2′), 162.4 (C-7′), 174.0 (C-3) ppm. IR (film): $\tilde{\nu}$ = 1731, 1613, 1279, 1230, 1122, 835, 615 cm^{-1}. ESIMS (MeOH+CH_2Cl_2): *m*/*z* = 463.2 (100) $[M + Na]^+$. HRESIMS: calcd. for $C_{27}H_{36}O_5Na$ 463.2460; found 463.2461. Calcd. for $C_{27}H_{36}O_5$ (440.57): C 73.61, H 8.24; found C 73.54, H 8.36.

Formula: $C_{27}H_{36}O_5$. Unit cell parameters: *a* = 7.588(3), *b* = 6.995(3), *c* = 22.868(5), β = 95.888(5), space group *P*21.

Compound **15** (55 mg, 0.18 mmol) was tosylated by the general procedure to afford the crude tosylate (70 mg), which was used as such in the next reaction. The tosylate (70 mg, 0.15 mmol) was coupled with **28** by the general procedure for Williamson etherification (the Reymond protocol) to afford the expected ether **11** (54 mg, 77%) after chromatography of the residue on silica gel (heptane/EtOAc 5:1 to 3:1). Mitsunobu etherification of **15** (47 mg, 0.16 mmol) was achieved by the general procedure to give, after flash chromatography (SiO_2, heptane/EtOAc 5:1 to 3:1), the desired ether **11** (57 mg, 81%) as a colorless oil. $[\alpha]_D^{20}$ = –55 (*c* = 1.3, $CHCl_3$). ^1H NMR (500 MHz, $CHCl_3$): δ = 0.80 (d, *J* = 6.7 Hz, 3 H, Me-12), 0.82 (s, 3 H, Me-15), 1.24 (t, *J* = 7.1 Hz, 3 H, OEt), 1.23–1.25 (m, 1 H, 7-H), 1.46–1.51 (m, 1 H, 7-H), 1.61 (s, 3 H, Me-13), 1.69 (s, 3 H, Me-14), 1.72–1.78 (m, 1 H, 8-H), 1.82–1.90 (m, 4 H, 2×1-H, 6-H, 11-H), 1.96 (ddd, *J* = 5.2, 9.7, 14.5, Hz, 1 H, 11-H), 2.08 (td, *J* = 7.9, 16.3 Hz, 1 H, 2-H), 2.18 (ddd, *J* = 5.7, 7.6, 16.4, 7.6 Hz, 1 H, 11-H), 2.46 (dd, *J* = 3.1, 14.5 Hz, 1 H, 6-H), 2.51 (dd, *J* = 4.7, 11.0 Hz, 1 H, 10-H), 4.08–4.13 (m, 3 H, 16-H, OEt), 4.32 (dt, *J* = 6.0, 9.4 Hz, 1 H, 16-H), 6.24 (d, *J* = 9.5 Hz, 1 H, 3′-H), 6.87 (dd, *J* = 2.0, 8.6 Hz, 1 H, 6′-H), 6.89 (m, 1 H, 8′-H), 7.36 (d, *J* = 8.5 Hz, 1 H, 5′-H), 7.63 (d, *J* = 9.5 Hz, 1 H, 4′-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2 (EtO), 15.7 (C-12), 17.9 (C-15), 20.3 (C-14), 20.4 (C-13), 21.7 (C-1), 24.5 (C-6), 31.5 (C-2), 31.6 (C-7), 35.0 (C-8), 36.8 (C-11), 39.4 (C-9), 44.5 (C-10), 60.2 (OEt), 65.1 (C-16), 101.4 (C-8′), 112.4 (C-4a′), 112.9 (C-6′), 113.1 (C-3′), 125.1 (C-4), 128.7 (C-5′), 129.8 (C-5), 143.4 (C-4′), 156.0 (C-8a′), 161.3 (C-2′), 162.4 (C-7′), 174.1 (C-3) ppm. IR (film): $\tilde{\nu}$ = 1730, 1395, 1278, 1121, 1011, 834 cm^{-1}. ESIMS (MeOH+CH_2Cl_2): *m*/*z* = 463.2 (100) $[M + Na]^+$. HRESIMS: calcd. for $C_{27}H_{36}O_5Na$ 463.2460; found 463.2475.

Preparation of the Higher Homologue Acid 10a and the Corresponding Methyl Ester 10b: An aqueous solution of $LiOH·H_2O$ (21 mg in 0.5 mL) was added at 0 °C to a solution of **10** (41 mg, 0.093 mmol) in THF (2.5 mL) and the mixture was stirred overnight at 25 °C. It was then extracted with Et_2O and the organic layer was discarded. The aqueous layer was acidified to pH 1–2 and extracted with Et_2O. The combined organic layers were washed with brine and dried with $MgSO_4$ and the solvent was removed under vacuum to afford the expected acid **10a** (28 mg, 74%) as a glassy solid. $[\alpha]_D^{20}$ = –13.0 (*c* = 1.4, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 1.02 (s, 3 H, Me-15), 1.14 (d, *J* = 7.5 Hz, 3 H, Me-12), 1.23–1.29 (m, 1 H, 7-H), 1.38–1.45 (m, 1 H, 7-H), 1.56–1.63 (m, 1 H, 8-H), 1.62 (d, *J* = 1.5 Hz, 1 H, Me-13), 1.73 (br. s, 3 H, Me-14), 1.78–1.94 (m, 3 H, 1-H, 6-H, 11-H), 1.96–2.19 (m, 3 H, 1-H, 2-H, 11-H), 2.26 (ddd, *J* = 5.6, 8.5, 16.4 Hz, 1 H, 2-H), 2.34–2.41 (m, 2 H, 6-H, 10-H), 4.11 (td, *J* = 5.5, 9.3 Hz, 1 H, 16-H), 4.21 (td, *J* = 5.8, 9.3 Hz, 1 H, 16-H), 6.24 (d, *J* = 9.5 Hz, 1 H, 3′-H), 6.82–6.87 (m, 2 H, 6′-H, 8′-H), 7.36 (d, *J* = 9.2 Hz, 1 H, 5′-H), 7.63 (d, *J* = 9.5 Hz, 1 H, 4′-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.2 (C-12), 20.2 (C-6), 20.3 (C-13), 20.6 (C-14), 24.3 (C-1), 27.0 (C-15), 30.2 (C-7), 32.5 (C-2), 36.7 (C-8), 36.8 (C-4), 39.6 (C-9), 47.0 (C-10), 65.5 (C-16), 101.4 (C-8′), 112.4 (C-4a′),

112.9 (C-3′), 113.1 (C-6′), 125.2 (C-4), 128.7 (C-5′), 130.8 (C-5), 143.4 (C-4′), 156.0 (C-8a′), 161.3 (C-2′), 162.4 (C-7′), 178.5 (C-3) ppm. IR (film): $\tilde{\nu}$ = 1731, 1705, 1612, 1280, 1230, 1124, 834 cm^{-1}. ESIMS (MeOH+CH_2Cl_2): *m/z* = 435.2 (100) $[M + Na]^+$. HRESIMS: calcd. for $C_{25}H_{32}O_5Na$ 435.2147; found 435.2182.

Preparation of the Higher Homologue 10b: A solution of $TMSCHN_2$ in Et_2O (2 M, 0.22 mL, 0.44 mmol) was added at 0 °C to a solution of the carboxylic acid **10a** (28 mg, 0.068 mmol) in methanol (1 mL) and the mixture was stirred for 2 h at room temperature. The mixture was concentrated under vacuum and chromatography of the residue on silica gel (heptane/EtOAc 5:1 to 2:1) afforded the methyl ester **10b** (20 mg, 69%) as colorless crystals. M.p. 111–112 °C. $[\alpha]_D^{20}$ = –12.1 (*c* = 1.01, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 1.01 (s, 3 H, Me-15), 1.13 (d, *J* = 7.5 Hz, 3 H, Me-12), 1.40 (br. d, *J* = 14.1 Hz, 1 H, 7-H), 1.55–1.60 (m, 1 H, 8-H), 1.59 (d, *J* = 1.2 Hz, 3 H, Me-13), 1.72 (br. s, 3 H, Me-14), 1.76–1.93 (m, 3 H, 1-H, 7-H, 11-H), 1.95–2.13 (m, 4 H, 1-H, 2-H, 4-H, 6α-H), 2.17–2.25 (m, 1 H, 2-H), 2.31–2.39 (m, 2 H, 6β-H, 10-H), 3.63 (s, 3 H, OMe), 4.11 (td, *J* = 5.4, 9.4 Hz, 1 H, 16-H), 4.19 (td, *J* = 5.9, 9.4 Hz, 1 H, 16-H), 6.23 (d, *J* = 9.5 Hz, 1 H, 3′-H), 6.82–6.88 (m, 2 H, 6′-H, 8′-H), 7.36 (d, *J* = 9.3 Hz, 1 H, 5′-H), 7.63 (d, *J* = 9.5 Hz, 1 H, 4′-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 17.2 (C-12), 20.2 (C-6), 20.3 (C-13), 20.5 (C-14), 24.4 (C-1), 27.0 (C-15), 30.2 (C-7), 32.9 (C-2), 36.6 (C-8), 36.8 (C-11), 39.6 (C-9), 47.1 (C-10), 51.4 (OMe), 65.5 (C-16), 101.4 (C-8′), 112.4 (C-4a′), 112.9 (C-6′), 113.0 (C-3′), 124.9 (C-4), 128.7 (C-5′), 130.9 (C-5), 143.4 (C-4′), 155.9 (C-8a′), 161.2 (C-2′), 162.4 (C-7′), 174.4 (C-3) ppm. IR (film): $\tilde{\nu}$ = 1732, 1613, 1279, 1230, 1122, 835 cm^{-1}. ESIMS (MeOH+CH_2Cl_2): 449.2 (100) $[M + Na]^+$. HRESIMS: calcd. for $C_{26}H_{34}O_5Na$ 449.2304; found 449.2280.

Preparation of the Higher Homologue Methyl Ester 11b: Saponification/re-esterification of **11** (41 mg, 0.093 mmol) as described above afforded the methyl ester **11b** (20 mg, 69%) as colorless crystals after silica gel chromatography (heptane/EtOAc 5:1 to 2:1). $[\alpha]_D^{20}$ = –29 (*c* = 1.2, $CHCl_3$). ^1H NMR (500 MHz, $CHCl_3$): δ = 0.79 (d, *J* = 6.5 Hz, 3 H, Me-12), 0.81 (s, 3 H, Me-15), 1.22–1.28 (m, 1 H, 7-H), 1.46–1.51 (m, 1 H, 7-H), 1.59 (d, *J* = 2.0 Hz, 3 H, Me-13), 1.69 (s, 3 H, Me-14), 1.72–1.78 (m, 1 H, 8-H), 1.82–1.90 (m, 4 H, 2 × 1-H, 6-H, 11-H), 1.96 (ddd, *J* = 5.2, 10.2, 13.7, Hz, 1 H, 11-H), 2.09 (dt, *J* = 8.1, 16.5 Hz, 1 H, 2-H), 2.19 (ddd, *J* = 5.4, 7.8, 16.6 Hz, 1 H, 11-H), 2.45 (br. d, *J* = 14.3 Hz, 1 H, 6-H), 2.50 (dd, *J* = 4.2, 11.2 Hz, 1 H, 10-H), 3.64 (s, 3 H, OMe), 4.10–4.13 (td, *J* = 5.1, 9.6 Hz, 1 H, 16-H), 4.31 (td, *J* = 5.9, 9.5 Hz, 1 H, 16-H), 6.23 (d, *J* = 10.0 Hz, 1 H, 3′-H), 6.87 (dd, *J* = 2.4, 8.4 Hz, 1 H, 6′-H), 6.89 (m, 1 H, 8′-H), 7.36 (d, *J* = 8.5 Hz, 1 H, 5′-H), 7.63 (d, *J* = 9.4 Hz, 1 H, 4′-H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 15.7 (C-12), 17.8 (C-15), 20.2 (C-14), 20.4 (C-13), 21.7 (C-1), 24.4 (C-6), 31.3 (C-2), 31.6 (C-7), 35.0 (C-8), 36.7 (C-11), 39.3 (C-9), 44.5 (C-10), 51.5 (OMe), 65.1 (C-16), 101.4 (C-8′), 112.3 (C-4a′), 112.8 (C-6′), 113.0 (C-3′), 125.1 (C-4), 128.7 (C-5′), 129.7 (C-5), 143.4 (C-4′), 155.9 (C-8a′), 161.2 (C-2′), 162.4 (C-7′), 174.4 (C-3) ppm. IR (film): $\tilde{\nu}$ = 1731, 1612, 1279, 1122, 1012, 834 cm^{-1}. ESIMS (MeOH+CH_2Cl_2): *m/z* = 449.2 (100) $[M + Na]^+$. HRESIMS: calcd. for $C_{26}H_{34}O_5Na$ 449.2304; found 449.2300.

Synthesis of Secodrial Analogues

Preparation of Coupling Partners and Segment Coupling: Compound **14** (54 mg, 0.18 mmol) was tosylated by the general procedure to afford the crude tosylate (52 mg), which was used as such in the next reaction. The tosylate (14 mg, 0.031 mmol) was coupled with **29** by the general procedure for Williamson etherification (the Reymond protocol) to afford the expected ether **30a** (11 mg, 69%) after chromatography of the residue on silica gel (heptane/EtOAc 4:1 to 1:1). Mitsunobu etherification of **14** (5.0 mg, 0.017 mmol) was achieved by the general procedure to give, after flash chromatography (SiO_2, heptane/EtOAc 4:1 to 1:1) the desired ether **30a** (5.1 mg, 61%) as colorless crystals; m.p. 72.3–73.0 °C (hexane). $[\alpha]_D^{20}$ = –10 (*c* = 0.6, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 0.95 (s, 3 H, Me-15), 1.14 (d, *J* = 7.5 Hz, 3 H, Me-12), 1.24 (t, *J* = 7.2 Hz, 3 H, EtO), 1.37 (br. d, *J* = 13.3 Hz, 1 H, 7-H), 1.50–1.57 (m, 1 H, 8-H), 1.59 (br. s, 3 H, 13-H), 1.71 (br. s, 3 H, Me-14), 1.78 (tt, *J* = 4.6, 13.9 Hz, 1 H, 7-H), 1.83–1.95 (m, 2 H, 1-H, 11-H), 1.95–2.10 (m, 3 H, 1-H, 2-H, 6-H), 2.11–2.22 (m, 2 H, 2-H, 11-H), 2.28–2.37 (m, 2 H, 6-H, 10-H), 3.89 (s, 3 H, MeO), 4.04 (s, 3 H, MeO), 4.08 (q, *J* = 7.2 Hz, 2 H, EtO), 4.15–4.26 (m, 2 H, 16-H), 6.34 (d, *J* = 9.6 Hz, 1 H, 3′-H), 6.66 (s, 1 H, 5′-H), 7.61 (d, *J* = 9.6 Hz, 1 H, 4′-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.2 (EtO), 17.1 (C-12), 20.3 (2 C, C-6, C-13), 20.5 (C-14), 24.5 (C-1), 27.0 (C-15), 30.3 (C-7), 33.4 (C-2), 36.5 (C-8), 37.9 (C-4), 39.5 (C-9), 47.3 (C-10), 56.3 (MeO), 60.1 (EtO), 61.8 (MeO), 71.3 (C-16), 103.7 (C-5′), 114.4 (C-4a′), 115.2 (C-3′), 124.6 (C-4), 131.3 (C-5), 141.7 (C-8′), 143.1 (C-8a′), 143.4 (C-4′), 145.4 (C-7′), 150.6 (C-6′), 160.5 (C-2′), 174.0 (C-3) ppm. IR (film): $\tilde{\nu}$ = 1729, 1605, 1563, 1455, 1408, 1290, 1152, 1124, 1042, 983, 845 cm^{-1}. ESIMS (MeOH+CH_2Cl_2): *m/z* (%) = 523.2 (100) $[M + Na]^+$. HRESIMS: calcd. for $C_{29}H_{40}O_7Na$ 523.2672; found 523.2662.

Compound **15** (36 mg, 0.12 mmol) was tosylated by the general procedure to afford the crude tosylate (52 mg), which was used as such in the next reaction. The resulting tosylate (14 mg, 0.031 mmol) was coupled with **29** by the general procedure for Williamson etherification (the Reymond protocol) to afford the expected ether **30b** (11 mg, 69%) after chromatography of the residue on silica gel (heptane/EtOAc 4:1 to 1:1). Mitsunobu etherification of **15** (5.0 mg, 0.017 mmol) was achieved by the general procedure to give, after flash chromatography (SiO_2, heptane/EtOAc 4:1 to 1:1), the desired ether **30b** (5.2 mg, 61%) as a colorless oil. $[\alpha]_D^{20}$ = –29 (*c* = 1.0, $CHCl_3$). ^1H NMR (500 MHz, $CDCl_3$): δ = 0.79 (s, 3 H, Me-15), 0.80 (d, *J* = 7.1 Hz, 3 H, Me-12), 1.22 (t, *J* = 7.2 Hz, 3 H, OEt), 1.22–1.26 (m, 1 H, 7-H), 1.45–1.49 (m, 1 H, 7-H), 1.58 (br. s, 3 H, Me-13), 1.67 (br. s, 3 H, Me-14), 1.71–1.78 (m, 1 H, 8-H), 1.81–1.93 (m, 4 H, 2 × 1-H, 6-H, 11-H), 1.99–2.05 (m, 2 H, 2-H, 11-H), 2.13 (ddd, *J* = 5.5, 9.2, 16.2 Hz, 1 H, 2-H), 2.41–2.46 (m, 2 H, 6-H, 10-H), 3.89 (s, 3 H, OMe), 4.04 (s, 3 H, OMe), 4.07 (q, *J* = 7.1 Hz, 2 H, OEt), 4.18 (ddd, *J* = 5.2, 8.6, 10.5 Hz, 1 H, 16-H), 4.29 (ddd, *J* = 5.8, 9.0, 10.3 Hz, 1 H, 16-H), 6.34 (d, *J* = 9.5 Hz, 1 H, 3′-H), 6.66 (s, 1 H, 5′-H), 7.6 (d, *J* = 9.5 Hz, 1 H, 4′-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 14.2 (OEt), 15.7 (C-12), 17.7 (C-15), 20.2 (C-14), 20.4 (C-13), 21.9 (C-1), 24.6 (C-6), 31.6 (C-7), 32.0 (C-2), 35.1 (C-8), 37.9 (C-11), 39.4 (C-9), 44.7 (C-10), 56.3 (OMe), 60.1 (OEt), 61.8 (OMe), 71.0 (C-16), 103.6 (C-5′), 114.4 (C-4a′), 115.2 (C-3′), 124.7 (C-4), 130.1 (C-5), 141.7 (C-8′), 143.1 (C-8a′), 143.4 (C-4′), 145.4 (C-7′), 150.6 (C-6′), 160.5 (C-2′), 174.0 (C-3) ppm. IR (film): $\tilde{\nu}$ = 1732, 1559, 1457, 1409, 1289, 1150, 1124, 1042, 668 cm^{-1}. ESIMS (MeOH+CH_2Cl_2): *m/z* = 523.2 (100) $[M + Na]^+$. HRESIMS: calcd. for $C_{29}H_{40}O_7Na$ 523.2672; found 523.2670.

CCDC-746923 (for **10**), -746924 (for **22bT**), and -746925 (for **25a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see also the footnote on the first page of this article): Complete characterization data and ^1H and ^{13}C NMR spectra for all new compounds.

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

[2] Matsuda et al., see ref.[8], named this compound marneral (and its corresponding alcohol marnerol) in recognition of Marner's pioneering work on iridals. Marneral has never been isolated but was hypothesized to be the first carbocyclic precursor in the biosynthesis of iridals; a) F.-J. Marner, W. Krick, B. Gellrich, L. Jaenicke, *J. Org. Chem.* **1982**, *47*, 2531–2538; b) F.-J. Marner, *Curr. Org. Chem.* **1997**, *1*, 153–186; c) M. Lamshöft, H. Schmickler, F. J. Marner, *Eur. J. Org. Chem.* **2003**, 727–733.

[3] A. Corbu, M. Perez, M. Aquino, P. Retailleau, S. Arseniyadis, *Org. Lett.* **2008**, *10*, 2853–2856.

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

[5] T. K. Khasanov, A. I. Saidkhodzhaev, G. K. Nikonov, *Chem. Nat. Compd.* **1974**, *10*, 20–23.

[6] E. M. González-García, J. Grognux, D. Wahler, J. L. Reymond, *Helv. Chim. Acta* **2003**, *86*, 2458–2470.

[7] For the revised, though erroneous, structure of galbanic acid suggested by Lee et al., see: S. G. Lee, S. Ryu, J. W. Ahn, *Bull. Korean Chem. Soc.* **1998**, *19*, 384–386.

[8] A. Corbu, M. Aquino, M. Perez, Z. Gandara, S. Arseniyadis, *Eur. J. Org. Chem.* **2009**, 6386–6392.

[9] J. Jakupovic, S. Banerjee, F. Bohlmann, R. M. King, *Tetrahedron* **1986**, *42*, 1305–1313.

[10] With the exception of the contribution reported recently by our group there appear to have been no prior synthetic studies.

[11] a) H. D. Yoo, P. A. Cremin, L. Zeng, E. Garo, C. T. Williams, C. M. Lee, M. G. Goering, M. O'Neil-Johnson, G. R. Eldridge, J. F. Hu, *J. Nat. Prod.* **2005**, *68*, 122–124; b) E. J. Velthuisen, S. J. Danishefsky, *J. Am. Chem. Soc.* **2007**, *129*, 10640–10641.

[12] a) L. Finet, J. I. Candela Lena, T. Kaoudi, N. Birlirakis, S. Arseniyadis, *Chem. Eur. J.* **2003**, *9*, 3813–3820; b) A. Corbu, G. Gauron, J. M. Castro, M. Dakir, S. Arseniyadis, *Org. Lett.* **2007**, *9*, 4745–4748.

[13] a) L. F. Tietze, U. Beifuss, *Angew. Chem.* **1993**, *105*, 115–136; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 131–163; b) L. F. Tietze, *Chem. Rev.* **1996**, *96*, 115–136; c) L. F. Tietze, F. Haunert, in: *Stimulating Concepts in Chemistry* (Eds.: M. Shibasaki, J. F. Stoddart, F. Vögtle), Wiley-VCH, Weinheim, **2000**, pp. 39–64; d) *Domino Reactions in Organic Synthesis* (Eds.: L. F. Tietze, G. Brasche, K. M. Gericke), Wiley-VCH, **2006**; ISBN 3-527-29060-5.

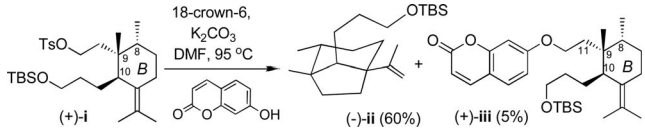
[14] a) For an application to the taxoid ABC diterpene core see: J. I. Martín Hernando, J. Quílez del Moral, M. Rico Ferreira, J. I. Candela Lena, S. Arseniyadis, *Tetrahedron: Asymmetry* **1999**, *10*, 783–797; b) For an application to the first enantioselective synthesis of iridal see: A. Corbu, M. Aquino, T. V. Pratap, P. Retailleau, S. Arseniyadis, *Org. Lett.* **2008**, *10*, 1787–1790.

[15] A. Corbu, G. Gauron, J. M. Castro, M. Dakir, S. Arseniyadis, *Tetrahedron: Asymmetry* **2008**, *19*, 1730–1743.

[16] W. Lehnert, *Tetrahedron* **1973**, *29*, 635–638. Several protocols were examined; all conditions failed in our hands.

[17] a) W. G. Dauben, D. M. Michno, *J. Org. Chem.* **1977**, *42*, 643–685; b) J. H. Babler, D. O. Olsen, W. H. Arnold, *J. Org. Chem.* **1974**, *39*, 1656–1658; c) G. Büchi, B. Egger, *J. Org. Chem.* **1971**, *36*, 2021–2023.

[18] See ref.[8]



[19] Methyl galbanate and galbanic acid were screened in an in vitro antiinfluenza A viral (H_1N_1) assay, with amantadine as a positive control. They are reported to show good potency against influenza A virus H_1N_1 (IC_{50} 0.26 and 0.45 mg mL^{-1}), with the C-3 methyl ester showing better potency than its corresponding free (galbanic) acid: C. L. Lee, L. C. Chiang, L. H. Cheng, C. C. Liaw, M. H. Abd El-Razek, F. R. Chang, Y. C. Wu, *J. Nat. Prod.* **2009**, *72*, 1568–1572.

[20] K. C. Nicolaou, S. Snyder, *Angew. Chem. Int. Ed.* **2005**, *44*, 1012.

[21] F. Johnson, *Chem. Rev.* **1968**, *68*, 375–413.

[22] The numbering throughout the text is intended to simplify discussion by maintaining a fixed designation for a particular carbon throughout a series of structures. It follows the numbering adopted by Bagirov[1] and Appendino.[4]

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