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Total Synthesis of (–)-Mucosin and Revision of Structure

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ABSTRACT: The first total synthesis of (–)-mucosin (**6**), an unusual marine hydrindane natural product incorporating a prostaglandin-like submotif, has been achieved. As a result of the campaign, three of the four all-carbon stereocenters in the purported structure **1** have been revised. Of particular note is the excellent control over β-chirality in conjugate addition to ester (–)-**22** and the facial selectivity in the subsequent protonation of an intermediate silyl ketene acetal.

INTRODUCTION

With the current level of sophistication achieved in organic analytical techniques, it is easy to make the presumption that structural elucidation of small-molecule natural products has been made routine. Yet, alicyclic compounds adorned with multiple contiguous points of chirality can still pose a challenge when only minute amounts are available. In the absence of X-ray crystallography, the relative topology may be inferred by various NMR experiments.[1] However, the Achilles heel is the interpretation of the available data and whether or not it can provide a proper basis to unravel the architecture. Consequently, in the context of structural elucidation and total synthesis, misassignment is a looming peril and the target may prove to be an evasive entity.[2] Although, from time to time, errors are encountered,[3] the following narrative offers a particularly interesting example of how an incorrect structure and a mechanistic switch concealed within the synthetic sequence have conspired to mutually reinforce the illusion of veracity.

In 1997, following a prospection in different regions of the Mediterranean Sea, Casapullo *et al.* reported on the isolation and characterization of an unusual eicosanoid from the marine sponge *Reniera mucosa*.[4] Named pseudo-eponymously (−)-mucosin, their analysis was performed on the corresponding methyl ester. It concluded that the C_{20}-compound was structure **1**, having a *cis*-fused bicyclo[4.3.0]non-3-ene scaffold with an embedded prostaglandin-like motif (Figure 1).

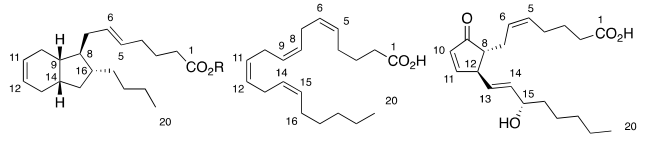


Figure 1. Proposed structure of (–)-mucosin, suggested origin and an illustrative marine prostaglandin.

Arachidonic acid (**3**) was cited as a plausible biogenetic origin. The elucidation relied primarily on 2D-NMR and the relative arrangement of the four contiguous stereogenic points was assigned on the basis of NOESY and ROESY. However, considering that the distinguishing correlations are confined to a crowded aliphatic region, the absence of any corroborative coupling patterns makes the proffered structure rest on a precarious foundation.

Given the structural attributes and the paucity of material, the isolate from *R. mucosa* merits further investigation. Ultimately, any biological evaluation hinges on the availability and identity of the analyte. For this reason, contriving a coherent synthetic strategy is essential. However, while the physiological activity spectrum of the compound is unknown, it may be noted that in the marine environment, the effect exerted by specific arachidonic acid metabolites can serve as a chemical defence. For example, the Caribbean coral *Plexaura homomalla* produces elevated levels of prostaglandin (15*S*)-PGA_2 (**4**), which acts as an emetic in predatory fish.[5]

In 2012, Whitby *et al*. communicated their total synthesis of antipodal (+)-mucosin,[6] according to the alleged configuration (*ent*-**1**).[4] The key strategic transformation depended on zirconium induced co-cyclization to install the correct topology. Thus, it was projected that the intramolecular reaction of a properly functionalized triene would furnish the complete bicyclic core, controlling the geometry at the points of substitution through formation of a zirconacycle. Bolstered by results from a model system, the reaction was then implemented in the sequence proper, encompassing 14 truncated steps to achieve the target in an overall yield of 7%. The data gathered from the prepared material was reported to align with the natural product from *R. mucosa* in all except sign of the optical rotation.[4,6,7] Paradoxically, as it became evident later on, Whitby *et al*. inadvertently came up with the correct antipode rather than achieving the total synthesis of *ent*-**1** (Figure 2).

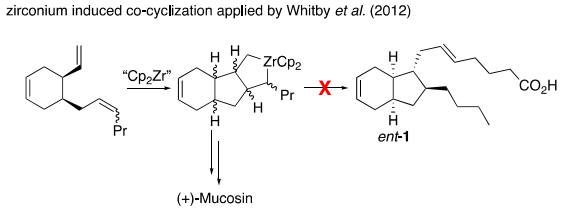


Figure 2. Preceding attempt on total synthesis of *ent*-**1**.

A few years after the apparent endorsement of the assignment published by Casapullo *et al*,[4] the authors of the present paper followed a different approach and demonstrated irrefutably that structure **1** does not represent (–)-mucosin.[8] Central to the enforced strategy was the placement of a Michael acceptor within the bicyclo[4.3.0]non-3-ene scaffold. Taking heed of the inherent conformational restrictions caused by the *cis*-fusion, it was projected that the implied conjugate addition would proceed with a bias for the targeted topology. Accordingly, the initial nucleophilic attack was anticipated to occur from the less hindered *exo* face, while protonation of the supervening enolate would be subject to kinetic *vs.* thermodynamic control. Guided by eclipsing interactions and A-values, equilibrating conditions ought to dictate *anti*-orientation on the disubstituted cyclopentane moiety. This pivotal conjecture was subsequently underpinned by a crystal structure, demonstrating how the steric effects and thermodynamic control had singled out one diastereomer. With the topology confirmed, it ultimately also contradicted the assignment of (–)-mucosin,[4] since none of the data from the final compound matched the natural product (Figure 3, eq 1).[8] Our findings even impinged the mechanistic rational provided by Whitby *et al.* for the

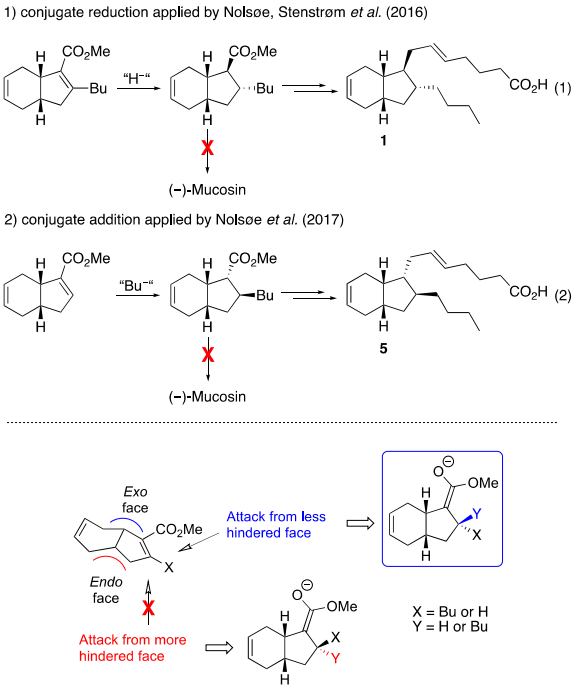


Figure 3. Total syntheses of **1** and the permutant **5**.

implementation of zirconium induced co-cyclization in the preparation of **1**.[6] Thus, assuming that the factors governing the stereochemical outcome of the featured cyclization had been misconceived, we prepared a probative structure of **1**. Applying the developed chemistry and demonstrating a stereodivergent protocol, the topology of the appended positions was examined by formation of the corresponding *anti*-permutant **5** (Figure 3, eq 2).[9] Yet, while the intended pattern was confirmed by X-ray crystallography, the probe did not match mucosin.

RESULTS AND DISCUSION

Early on in our synthetic campaign directed towards the preparation of (–)-mucosin, we voiced some concerns about the geometry at the points of fusion.[8,9] Assuming that arachidonic acid (**3**) is indeed the biogenetic progenitor, the core structure found in **1** invokes a formal disrotatory ring-closure. A survey of the known enzymes operating on this particular polyene system singled out 5-lipoxygenase (5-LOX) as a possible asymmetric promotor, catalysing stereospecific peroxidation at C5 and the concomitant formation of a 6*E*,8*Z*-diene system.[10] Taking cue from previous mechanistic discussions of 5-LOX, a tentative biosynthetic route has been contrived (Figure 4).

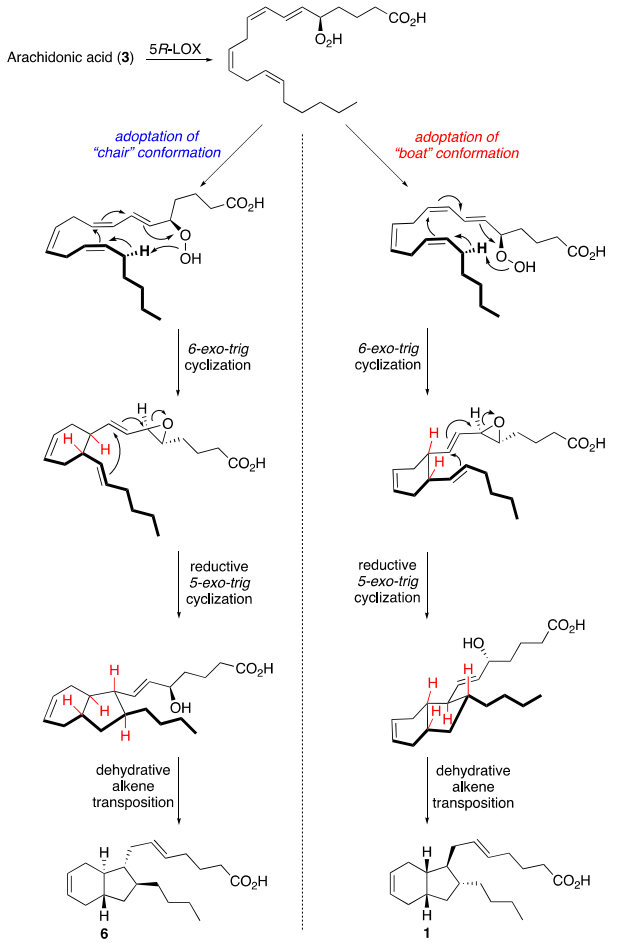


Figure 4. Hypothetical cyclization of **3** catalysed by 5*R*-LOX.

The key aspects to note are: (i) intramolecular activation of C16 by the hydroperoxide to instigate a *6-exo-trig* cyclization, leading to (ii) the stereospecific formation of a *trans*-vinyl epoxide at C8 and (iii) its subsequent reaction in a *5-exo-trig* cyclization with an *E*-alkene at C15. In detail, the activation is a suprafacial [6π+4σ] process,[11] which instigates cyclization *via* an extended π-allyl system and dictates the final geometry

at the reacting termini (C8 and C16). Governed by transannular strain in the macrocyclic transition state, the "chair" conformation is preferred over the "boat" conformation, dictating the fusion geometry in the ensuing *6-exo-trig* cyclization. At the point of initiation the *E*-alkene at C15 is a consequence of a *gauche* configuration at C16. The following *5-exo-trig* cyclization resembles a Michael addition and is under thermodynamic control. Thus, the delineated biosynthetic pathway (*vide supra*) singles out the *trans*-fused scaffold and defines an *anti*-configuration for the two substituents. Eventually, there is no ambiguity in terms of selectivity and the absence of any $A^{1,2}$ strain identifies structure **6** as the favoured diastereomer.

From a general mechanistic perspective, Gerwick has proposed epoxy allylic carbocations as conceptual intermediates in the biogenesis of marine carbocyclic oxylipins.[12] This could in principle apply to the pathway suggested by us and is easily implemented without affecting the overall stereochemical arguments. However, in its present form, it serves the intended purpose to define a plausible target in an unequivocal manner. Also, it could open up a vista onto a biomimetic approach.

To evaluate the forecast, we performed a series of DFT calculations, comparing geometry optimized structures of the *trans*-fused diastereomers **6** and **7**, as well as of the *cis*-fused diastereomers **1** and **5** (Figure 5). All the results were obtained in ORCA 4.0,[13] using the hybrid meta-functional TPSSh,[14] the def2-TZVP basis set,[15] and Grimme's D3 dispersion correction.[16] What transpired by inspecting the computations was the significance of eclipsing interactions and their impact on the relative energies: Ranked according to decreasing strain, the order was found to be structure **5**, **1**, **7** and **6**. Furthermore, observations pertaining to the synthesis executed by Whitby *et al.*, suggested that H8 and H9 are *anti*-periplanar in the natural product.[6,17] Consequently, the gathered information cemented structure **6** as the target molecule in pursuit of (–)-mucosin.

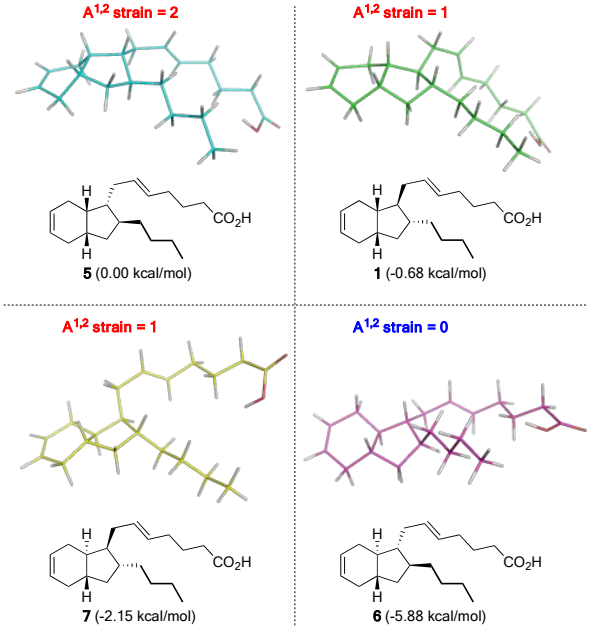
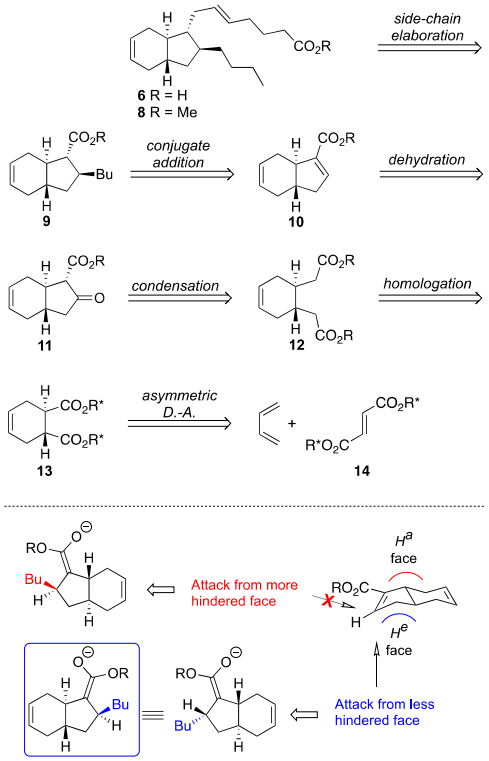


Figure 5. DFT calculations comparing geometry optimized **1** with permutants **5**, **6** and **7**.

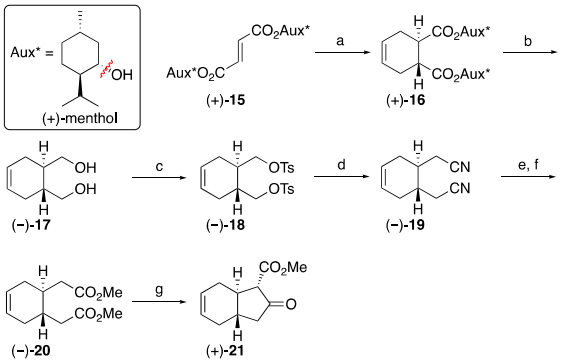
Based on our previous efforts,[8,9] we devised a flexible strategy that evolved around the application of a diastereoselective conjugate addition (Scheme 1). Relying on a known Diels- Alder protocol to furnish the asymmetric starting point,[18] the featured Michael acceptor **10** would be obtainable from the corresponding *en route* β-keto ester **11**. Compared with the *cis*-fused system, the projected conjugate addition could not call upon the same steric factors to control facial selectivity. Thus, instead of *endo*/*exo* differentiation, we invoked the presence of $A^{1,2}$ strain in the transition state to be the guiding rail.

In the execution of the outlined strategy, our total synthesis commenced with preparation of starting material (Scheme 2). Although an antipodal (–)-ethyl β-keto ester of **11** is known in the literature,[19] neither the (–)- nor the (+)-methyl β-keto ester have been described before. For the purpose of having an easily identifiable marker in ^{1}H-NMR to gauge reactions by, it was opted for methyl ester (+)-**21**. This would also allow the current findings to be assessed relative to our previous work in the campaign.[8,9] The synthetic sequence leading to methyl β-keto ester (+)-**21** was conducted in 7 steps with an overall yield of 63%. To make proper provisions for the strategy, the sequence was streamlined to supply gram quantities of starting material and to minimize chromatographic purification. Thus, subsequent to asymmetric Diels-Alder by the protocol of Furuta *et al.*,[18] and reduction of the resulting cycloadduct (+)-**16** to diol (–)-**17**, the remaining five steps leading to (+)-**21** took advantage of extractive work-up and recrystallization. Relying on the non-commercial alkene (+)-**15** to provide the featured chirality, it was easily prepared by esterification of fumaric acid with (+)-menthol. Using DIBAL-H in the reduction of cycloadduct (+)-**16** allowed recovery of the chiral auxiliary without change in optical activity.

Scheme 1. Retrosynthetic Analysis of Target Molecule 6



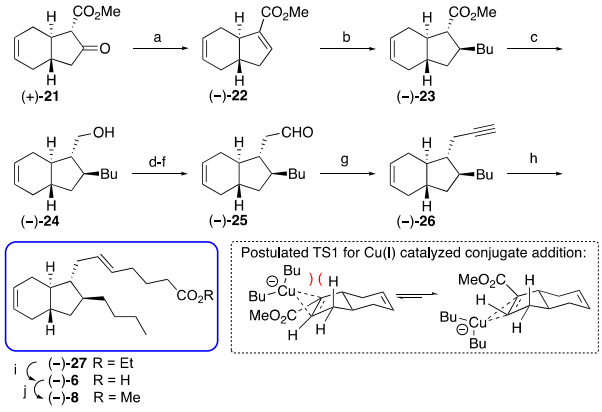
Scheme 2. Synthesis of Methyl β-Keto Ester (+)-21[a]



[a]Reagents and conditions: (a) 1,3-butadiene, DIBAL-Cl, hexane, -40 to -30 °C, 20 h, 96%; (b) DIBAL-H, hexane/CH_2Cl_2, -78 °C to rt, 16 h, 89%; (c) TsCl, pyridine, 0 °C, 12 h, 96%; (d) NaCN, EtOH, Δ, 30 h, 98%; (e) KOH, H_2O, Δ, 36 h; (f) MeOH, H_2SO_4 (cat.), 50 °C, 12 h, 86% over two steps; (g) NaH, THF, Δ,16 h, 91%.

Having previously demonstrated the ability to control topology on the *cis*-fused bicyclo[4.3.0]non-3-ene scaffold,[8,9] Cu(I) catalysed conjugate addition was cast as a fulcrum feature in the total synthesis of **6**.[20] In the preceding example, we observed a pronounced selectivity in terms of β-chirality, favouring the less hindered face. The facial selectivity may in part be accounted for by the formation of a transient and reversible metallocyclopropane undergoing oxidative addition/reductive elimination with the α,β-unsaturated system.[21] The effect is to exaggerate steric repulsion at the more congested face and is in line with the Dewar-Chatt-Duncanson model.[22] Following this reasoning, the main sequence of the total synthesis was put in train (Scheme 3). Initially, the Michael acceptor (–)-**22**

Scheme 3. Total Synthesis of (–)-Mucosin (6)[a]



[a]Reagents and conditions: (a) (i) $NaBH_4$, MeOH, 0 °C, 1 h, 95%; (ii) MsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 12 h, 96 %; (iii) DBU, toluene, r.t., 5 h, 93%; (b) BuMgCl, TMSCl, CuI (cat.), –35 °C, 2 h, then NH_4Cl (aq), –35 °C to rt, 85% with *dr* 93:7; (c) DIBAL-H, hexane, 0 °C to rt, 1 h, 88%; (d) MsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 12 h, 98 %; (e) KCN, DMSO, 70 °C, 2h, quant.; (f) DIBAL-H, hexane, –78 °C, 2 h, 91%; (g) Ohira-Bestmann reagent [dimethyl (1-diazo-2-oxopropyl)phosphonate], K_2CO_3, MeOH, 0 °C to rt, 6 h, quant.; (h) (i) Cp_2ZrCl_2, DIBAL-H, THF/hexane, 0 °C, 1 h, then (–)-**25** in THF, 0 °C to rt, 2 h; (ii) I_2 neat, rt, 1 h; (iii) 4-ethoxy-4-oxobutylzinc bromide in THF, $(Ph_3P)_4Pd$ (cat.), rt, 7 h, 64% over three steps; (i) LiOH, THF/MeOH/H_2O, rt, 12h, 96%; (j) $TMSCHN_2$, toluene/MeOH, 1h, rt, quant.

was prepared by Pd-catalysed reductive desulfonylation of the corresponding conjugate vinyl triflate.[23] However, being unable to obtain (–)-**22** in sufficient chemical purity for the critical reaction, it was opted for an efficient three-step dehydration protocol. With the unsaturated motif installed, the conjugate addition was performed using the recognised constellation of BuMgCl with TMSCl in the presence of CuI.[9] While the addition proceeded with excellent control over the β-chirality, the protonation of the intermediate silyl ketene acetal was more fickle. Thus, in the initial experiments, the adduct (–)-**23** was formed with a *dr* of 85:15. This necessitated meticulous chromatographic separation of the two α-epimers in the following step. However, minor adjustments with regard to the quenching by dropwise addition of satd. aq. NH_4Cl eventually produced (–)-**23** with a *dr* of 93:7. After reduction to carbinol (–)-**24**, the topology was subsequently confirmed by derivatization to the non-epimerizable 3,5-dinitrobenzoate (–)-**24-DNB** and performing X-ray crystallography (Figure 6). Also, before proceeding any further, the carbinol derivative (–)-**24-DNB** was subjected to HPLC analysis using a chiral column and was shown to have an *ee* in excess of 99%.

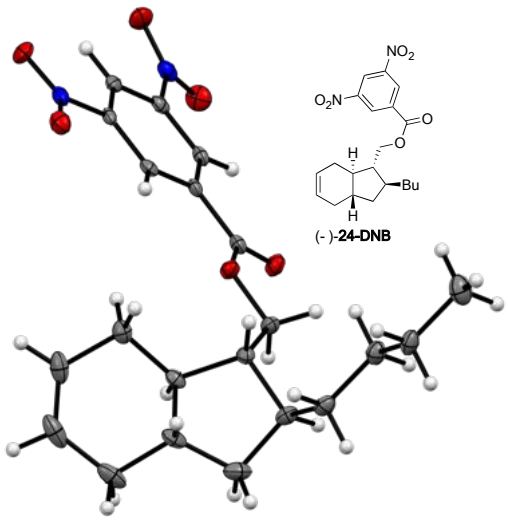


Figure 6. Single-crystal X-ray structure obtained from (–)-**24-DNB** recorded at 100K (50% probability displacement ellipsoids).

In the main synthetic route, the carbinol (–)-**24** was processed into an alkyne handle over four steps.[24] Then, capitalizing on a series of telescoped reactions developed by us,[8,9] the alkyne (–)-**26** was subjected to sequential hydrometallation, halogenation and Pd-catalysed cross-coupling to furnish the complete *E*-alkenyl sidechain present in the candidate structure. In principle, hydrolysis of ethyl ester (–)-**27** concluded the campaign by delivering (–)-**6** as the target molecule. Yet, in order to make the necessary correlation with the compound isolated by Casapullo *et al.*,[4] and the material synthesised by Whitby *et al.*,[6] the final transformation was to prepare methyl ester (–)-**8**.

Gratifyingly, when comparing all the recordings made on methyl ester (–)-**8** with the values reported in literature,[4,6,7] an excellent agreement was found. In particular, a perfect pairing

was seen when the ^{1}H- and ^{13}C-NMR spectra were overlaid with those provided by Whitby *et al.*[6,17] Furthermore, the optical rotation had both similar magnitude and sign as the methyl ester isolated from *R. mucosa*, while opposite sign of the synthetic material purporting to be the *cis*-fused *ent*-**2**. Thus, for the methyl ester (–)-**8** we registered an $[\alpha]_D^{20} = -42.9$ ($c = 0.8$, hexane), while the published values for mucosin methyl ester and the methyl ester of Whitby *et al.* had been given as $[\alpha]_D^{20} = -35.5$ and $+38.2$ ($c = 0.8$, hexane), respectively.[4,6]

The structural elucidation has revealed a subtle mechanistic switch, which has thwarted the original conception by Whitby *et al.* regarding zirconium mediated co-cyclization as a vehicle for the preparation of *cis*-fused **1**.[6], In this sense, the present work represents a manifest example of how total synthesis can serve as a mechanistic probe through side-by-side comparison of structures and outcome. As a tentative explanation for the observed disparity between the model and real system aimed at *cis*-fused **1**, we invoke the steric requirements of the allyl zirconium species (Figure 7). Thus, the difference in rate of ligation between a terminal methylene allyl (Figure 7, eq 1) and a terminal methine allyl functionality is postulated to dictate the outcome of zirconium induced co-cyclization (Figure 7, eqs 2 and 3).

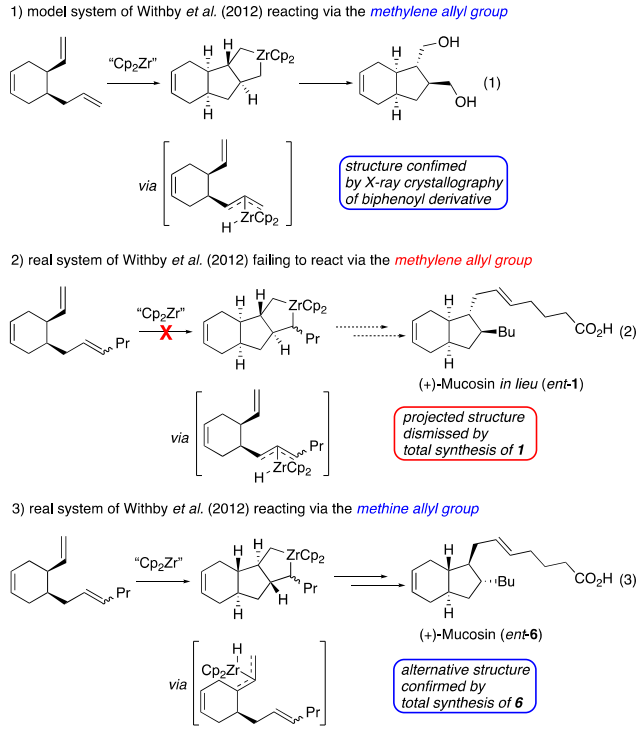


Figure 7. A mechanistic rational for the actual results obtained by Whitby *et al.* using zirconium induced co-cyclization.

CONCLUSIONS

The original assignment of (–)-mucosin as structure **1** has been soundly negated.[4] Consequently, the total synthesis that provided the topological reaffirmation relied on a flawed key transformation.[6] In the present work, the true structure of the isolated natural product from *R. mucosa* has been established as **6**. Capitalizing on a biogenetic conjecture as the key concept, which was further underpinned by comparative DFT calculations, we have executed a 14 steps linear sequence from (+)-**21** to arrive at the target structure as methyl ester (–)-**8** in an overall yield of 35% and in 10^2 mg quantities. The devised synthetic route is therefore capable of delivering sufficient material for comprehensive biological testing. Furthermore, in light of the structural assignment, some mechanistic aspects of zirconium induced co-cyclization will have to be re-evaluated. We are currently perusing this point and investigate the synthetic utility. To the mind of the authors, the unique aspects of the executed campaign show forth natural product synthesis as an enabling technology on multiple levels.

EXPERIMENTAL SECTION

General Information. All commercially available reagents and solvents were used in the form they were supplied without any further purification. (+)-Menthol (optical purity 96% *ee* by GLC) was purchased from Sigma-Aldrich. The stated yields are based on isolated material. The melting points are uncorrected. Thin layer chromatography was performed on silica gel 60 F_{254} aluminium-backed plates fabricated by Merck. Flash column chromatography was performed on silica gel 60 (40-63 µm) fabricated by Merck. NMR spectra were recorded on a Bruker Ascend™ 400 at 400 MHz for ^{1}H NMR and at 100 MHz for ^{13}C NMR. Coupling constants (*J*) are reported in hertz and chemical shifts are reported in parts per million (δ) relative to the central residual protium solvent resonance in ^{1}H-NMR ($CDCl_3$ = δ 7.27 ppm) and the central carbon solvent resonance in ^{13}C-NMR ($CDCl_3$ = δ 77.00 ppm). Mass spectra were recorded at 70 eV on Waters Prospec Q spectrometer using EI as the method of ionization. Alternatively, HRMS-ESI spectra were measured with a Bruker Apex 47e QTOF instrument. IR spectra (4000-650 cm^{-1}) were recorded on a Agilent Technologies 5500 Series FT-IR Compact spectrophotometer. UV/Vis spectra from 190-900 nm were recorded using a Biochrom Libra S32PC spectrophotometer using quartz cuvettes and the stated solvents. Optical rotations were measured using a 1 ml cell with a 1.0 dm path length on a Perkin Elmer 341 polarimeter using the stated solvents. Determination of enantiomeric excess was performed by HPLC on an Agilent Technologies 1200 Series instrument with the diode array detector set at 206 nm and equipped with a chiral stationary phase column (Chiralcel OD-H, 4.6 x 250 mm, particle size 5 µm, from Daicel Chemical Ind., Ltd) applying the conditions stated. X-ray crystallography was performed on a Bruker D8 Venture diffractometer with InCoatec ImuS Microfocus radiation source and Photon 100 CMOS detector. Data collection with Apex2,[25] data integration and cell refinement with SAINT,[25] absorption correction by SADABS,[25] structure solution with SHELXT,[26] structure refinement with SHELXL.[27] Molecular graphics from Mercury.[28] The crystal deposition identifier is CCDC 1865776. Theoretical calculations were carried out using ORCA4.[13] The detailed options in the input file were "! TPSSh RIJCOSX OPT def2-TZVP def2/J Grid6 D3BJ TightSCF". The coordinates of all final geometries are listed in the supporting information, starting at page S46. Diastereomeric ratios reported in this paper have not been validated by calibration, please consult the reference Wernerova and Hudlicky for discussions and guidelines.[29]

(*E*)-1,4-bis((1*S*,2*R*,5*S*)-2-isopropyl-5-methylcarbcyclohex-1-oxy)but-2-ene ((+)-15).[30] A mixture of fumaric acid (4.89 g, 42.2 mmol, 1.00 equiv.) and (+)-menthol (37.5 g, 240.5 mmol, 2.85 equiv.) was dissolved/suspended in benzene (50 ml). To the solution/suspension was added conc. H_2SO_4 (2.0 ml, 3.68 g, 37.5 mmol) and the resulting reaction mixture was heated to reflux. After 48h, the heating was discontinued and upon cooling the yellow mixture was washed in succession with water (2 x 50 ml), aq. saturated $NaHCO_3$ (2 x 50 ml) and brine (50 ml). The organic phase was dried over $MgSO_4$, filtered and the solvent was evaporated *in vacuo*. The residue was purified by column chromatography on silica (hexane, followed by hexane/EtOAc 90:10). This afforded the title compound as a clear, highly viscous, syrup. Yield: 15.61 g, 87%; TLC: R_f = 0.56 (Hexane/EtOAc 4:1, visualized with UV and $KMnO_4$-

dip); $[\alpha]_D^{20} = +95.2$ (c = 1.76, $CHCl_3$); IR (film): ν_{max} 2951, 2928, 2869, 1717, 1449, 1374, 1285, 1257, 1140 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 6.82 (s, 2H), 4.79 (dt, J_1 = 10.9 Hz, J_2 = 4.4 Hz, 2H), 2.00-2.05 (m, 2H), 1.82-1.93 (m, 2H), 1.66-1.74 (m, 4H), 1.40-1.58 (m, 4H), 0.98-1.13 (m, 4H), 0.88-0.94 (m, 14H), 0.76 (d, J = 6.9 Hz, 6H); ^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ 164.6, 133.8, 75.3, 47.0, 40.7, 34.1, 31.4, 26.2, 23.3, 22.0, 20.7, 16.2; HRMS (EI+): Exact mass calculated for $C_{24}H_{40}O_4$ $[M]^+$ 392.2927, found 392.2903.

(1*R*,6*R*)-Bis((1*S*,2*R*,5*S*)-2-isopropyl-5-methylcarbcyclohex-1-oxy)cyclohex-3-ene ((+)-16).[31] Diester (+)-**15** (15.61 g, 39.8 mmol, 1.00 equiv.) was first azeotroped with hexane in vacuo (2 x 100 ml) and then dissolved in dry hexane (250 ml). The solution was cooled to -40 °C and DIBAL-Cl (25% w/w in hexane, 80.0 ml, 14.4 g, 81.6 mmol, 2.05 equiv.) was added dropwise to the stirring solution, resulting in a deep orange/red complex. The generated Lewis acid-base pair was stirred at -40 °C for 0.5 h. In parallel, in a separate flask at -78 °C was added 1,3-butadiene (20 ml, 12.3 g, 0.227 mmol, 5.71 equiv.) and cooled for 0.5h. Then, the precooled diene was added dropwise to the complex of (+)-**15** via a double-tipped cannula (cooled by dry-ice wrapped in an aluminium sheet covering the exposed length of the cannula). The reaction was monitored by TLC (hexane/EtOAc 80:20, visualized by UV and $KMnO_4$-stain). According to this the starting material (R_f = 0.56, UV active) had been essentially consumed and a less lipophilic compound (R_f = 0.52, not UV active) had appeared. The temperature was then allowed to slowly equilibrate to -30 °C. As the mixture heated up, it progressively became lighter in colour. After 2 h at -30 °C, the mixture had become lemon coloured and turbid. The mixture was left at the stated temperature overnight. At this stage, TLC indicated that no starting material remained. The cooling was discontinued and the now clear yellow reaction mixture was allowed to attain ambient temperature. Using a double cannula, the reaction mixture was added dropwise into dilute aq. HCl (200 ml) with agitation. Saturated aq. Rochelle's salt (200 ml) was added and the biphasic mixture was stirred for 0.5 h. Then, the phases were separated and the aq. phase was extracted with Et_2O (4 x 50 ml). The combined organic phases were washed in succession with saturated aq. $NaHCO_3$ (200 ml) and brine (200 ml). The organic phases were dried over $MgSO_4$, filtered and the solvent was evaporated in vacuo (final bath temperature 50 °C at 3.8 mbar). This afforded the pure title compound (+)-**16** based on NMR as an opaque, highly viscous, syrup. Yield: 17.05 g, 96%; TLC (hexane/EtOAc 80:20, visualized by $KMnO_4$-stain): R_f = 0.47; $[\alpha]_D^{20} = +29.0$ (c = 2.07, $CHCl_3$); IR (film): ν_{max} 2952, 2922, 2869, 1728, 1456, 1386, 1368, 1298, 1234, 1175 cm^{-1}; 1H-NMR ($CDCl_3$, 400 MHz): δ 5.65-5.72 (m, 2H), 4.67 (dt, J_1 = 10.9 Hz, J_2 = 4.34 Hz, 2H), 2.83-2.90 (m, 2H), 2.40-2.45 (m, 2H), 2.12-2.20 (m, 2H), 1.98-2.04 (m, 2H), 1.84-1.92 (m, 2H), 1.64-1.69 (m, 4H), 1.45-1.56 (m, 2H), 1.36-1.44 (m, 2H), 0.98-1.10 (m, 4H), 0.88-0.91 (m, 14H), 0.74 (d, J = 6.92 Hz, 6H); ^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ 174.5, 125.0, 74.3, 47.0, 41.2, 40.7, 34.3, 31.4, 27.9, 25.9, 23.1, 22.0, 20.8, 15.9; HRMS (EI$^+$): Exact mass calculated for $C_{28}H_{46}O_4$ $[M]^+$ *m/z* 446.3396, found 446.3388.

(1*R*,6*R*)-Bis(hydroxymethyl)cyclohex-3-ene ((–)-17).[31] Diester (+)-**16** (17.05 g, 38.2 mmol, 2.00 equiv.) was dissolved in dry CH_2Cl_2 (100 ml) and cooled to -78 °C. DIBAL-H (1M in hexane, 195.0 ml, 195.0 mmol, 5.10 equiv.) was added via a double tipped cannula in a dropwise manner. After 2 h at the stated temperature, the reaction mixture was taken to ambient temperature and was stirred overnight. By TLC (hexane/EtOAc 80:20, visualized by $KMnO_4$-stain), the starting material (R_f = 0.47) had been consumed and two, more polar, components were visible (R_f = 0.16 and R_f = 0.00). The more lipophilic component was associated with (+)-menthol. TLC (hexane/EtOAc 50:50, visualized by $KMnO_4$-dip) revealed the relative mobility of the two components. Thus, the component associated with (+)-menthol had moved to R_f = 0.62, while the less polar component had moved to R_f = 0.09. The mixture was then cooled to 0 °C and treated with MeOH (10 ml). Then, saturated aq. Rochelle's salt (100 ml) was added, the mixture was diluted with CH_2Cl_2 (200 ml), whereupon the mixture was taken to ambient temperature and stirred for 4 h. Now, the phases were separated. Attempt to extract the aq. phase with EtOAc resulted in the formation of a gel. The gel was poured onto a sinter funnel (frit porosity P3) and repeated washing/decantation with EtOAc (in total 1.5 L) was performed. The combined organic phases were dried over $MgSO_4$, filtered and the solvent was evaporated *in vacuo*. The resulting syrupy residue was purified by column chromatography on silica (hexane, followed by hexane/EtOAc 90:10, 80:20, 50:50 and pure EtOAc). This afforded the title compound (–)-**17** as a faint off-white solid after being azeotroped with $CHCl_3$ at elevated temperature *in vacuo* (bath temperature 55 °C, 3.8 mbar). However, the solid sublimates easily under the said conditions. Yield: 4.84 g, 89%; TLC (hexane/EtOAc 50:50, visualized by $KMnO_4$-stain): R_f = 0.09; M.p.: 52-54 °C; $[\alpha]_D^{20} = -65.7$ (c = 1.48, $CHCl_3$); IR (film): ν_{max} 3329, 3026, 2891, 1438, 1068, 1023 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 5.62-5.68 (m, 2H), 3.72 (dd, J_1 = 11.1 Hz, J_2 = 3.0 Hz, 2H), 3.58 (dd, J_1 = 11.1 Hz, J_2 = 6.5 Hz, 2H), 3.30 (s, 2H), 2.00-2.07 (m, 2H), 1.81-1.89 (m, 2H), 1.64-1.73 (m, 2H); ^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ 126.0, 66.2, 39.7, 28.5; HRMS (EI$^+$): Exact mass calculated for $C_8H_{14}O_2$ $[M]^+$ *m/z* 142.0994, found 142.0992.

(1*R*,6*R*)-Bis((*p*-toluenesulfonyloxy)methyl)cyclohex-3-ene ((–)-18).[32] Diol (–)-**17** (4.50 g, 31.7 mmo, 2.00 equiv.) was dissolved in dry pyridine (25 ml) and cooled to 0 °C. *p*-Toluenesulfonyl chloride (18.1 g, 95.0 mmol) was added in portions with efficient stirring. Maintaining the cooling, the reaction mixture was stirred overnight, whereupon it was poured into dilute aq. HCl (5%, 200 ml). EtOAc (200 ml) was added to the heterogeneous mixture to dissolve precipitated material. The phases were separated and the aq. phase was extracted with EtOAc (5 x 50 ml). The combined org. extracts were dried over $MgSO_4$, filtered and the solvent was evaporated in vacuo. This afforded the title compound (–)-**18** as a white sugary solid, which was used without any further purification. Yield: 13.63 g, 96%; TLC: R_f = 0.18 (hexane/EtOAc 80:20, visualized by UV and $KMnO_4$-stain); M.p.: 107-109 °C; $[\alpha]_D^{20} = -40.0$ (c = 1.40, CHCl3); IR (film): ν_{max} 3031, 2908, 2852, 1600, 1359, 1171, 1093 cm^{-1}; 1H-NMR ($CDCl_3$, 400 MHz): δ 7.76 (d, J = 8.3 Hz, 4H), 7.36 (d, J = 8.3 Hz, 4H), 5.48-5.55 (m, 2H), 3.90-3.98 (m, 4H), 2.46 (s, 6H), 1.98-2.01 (m, 4H), 1.82-1.87 (m, 2H); ^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ 144.9; 132.7, 129.9, 127.8, 124.6, 71.2, 33.0, 25.4, 21.6; HRMS (EI$^+$): Exact mass calculated for $C_{22}H_{26}O_6S_2$ $[M]^+$ *m/z* 450.1171, found 450.1188.

(1*S*,6*S*)-Bis(cyanomethyl)cyclohex-3-ene ((–)-19).[32] Ditosylate (–)-**18** (13.6 g, 30.2 mmol, 2.00 equiv.) was dissolved in abs. EtOH (120 ml) and sodium cyanide (4.97 g, 101 mmol, 3.35 equiv.) was added. The resulting reaction mixture was heated to reflux and maintained at that temperature for 48 h. Then, the mixture was cooled to ambient temperature, decanted and the solvent was evaporated *in vacuo*. The residue was suspended/dissolved in CH_2Cl_2 (150 ml) and water (150 ml) was added. The resulting biphasic mixture was stirred for 0.5 h and then the phases were separated. The aq. phase was extracted with CH_2Cl_2 (3 x 50 ml), whereupon the combined organic phases were dried over Na_2SO_4, filtered and the solvent was removed *in vacuo*. This afforded a tanned solid, which upon analysis was shown to be the title compound (–)-**19** with some minute impurities and was subsequently used as is without further purification. Yield: 4.74 g, 98%; TLC (hexane/EtOAc 80:20, visualized by $KMnO_4$-stain): R_f = 0.09; M.p.: 86-89 °C; $[\alpha]_D^{20} = -95.6$ (c = 1.40, $CHCl_3$); IR (film): ν_{max} 3031, 2914, 2841, 2248, 1661, 1421, 1333, 1169 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 5.63-5.69 (m, 2H), 2.42-2.53 (m, 4H), 2.23-2.35 (m, 2H), 2.01-2.15 (m, 4H); ^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ 124.4, 117.6, 32.6, 28.3, 21.0; HRMS (EI$^+$): Exact mass calculated for $C_{10}H_{12}N_2$ $[M]^+$ *m/z* 160.1000 found 160.1004.

(1*S*,6*S*)-Bis((carbmethoxy)methyl)cyclohex-3-ene ((–)-20).

(i) Dicyanide (–)-**19** (4.74 g, 29.6 mmol) was dissolved in aq. KOH (33% w/v, 100 ml) and heated to reflux. Relying on olfactory, heating was terminated once the odour of ammonia was undetectable. The cooled basic solution was washed with CH_2Cl_2 (50 ml) and carefully acidified with conc. HCl to effectuate precipitation (pH = 1). To the resulting heterogeneous mixture was added EtOAc (100 ml) and the

biphasic mixture was stirred for 0.5 h. The phases were separated and the aq. phase was extracted with EtOAc (6 x 50 ml). Then, the combined organic phases were dried over Na_2SO_4, filtered and the solvent evaporated *in vacuo*. This afforded the crude diacid *pre*-**20** as a slightly off-white solid, which was used directly without any further purification. Yield: 5.36 g, 91%; TLC (EtOAc, visualized by $KMnO_4$-stain): $R_f = 0.14$.

(ii) Diacid *pre*-**20** (5.36 g, 27.0 mmol) was dissolved/suspended in MeOH (200 ml) and con. H_2SO_4 (0.5 ml) was added dropwise. The resulting reaction mixture was heated to 50 °C overnight, whereupon it was cooled to ambient temperature and aq. satd. K_2CO_3 (20 ml) was added. The solvent was concentrated *in vacuo* and the residue was treated with a mixture of aq. satd. $NaHCO_3$/water (50:50, 100 ml). The aq. phase was subsequently extracted with Et_2O (4 x 50 ml), the combined organic extracts were dried over $MgSO_4$, filtered and the solvent was evaporated *in vacuo*. This afforded a faint yellow liquid, which upon NMR analysis was shown to be the pure title compound (–)-**20**. Yield: 5.81 g, 95%; TLC (hexane/EtOAc 80:20, visualized by $KMnO_4$-stain) R_f = 0.40; $[\alpha]_D^{20} = -47.2$ (c = 1.40, $CHCl_3$); IR (film): 3028, 2978, 2908, 2846, 1729, 1436, 1269, 1159 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 5.52-5.68 (m, 2H), 3.59 (s, 6H), 2.35-2.49 (m, 2H), 2.24-2.34 (m, 2H), 2.13-2.23 (m, 2H), 1.99-2.12 (m, 2H), 1.73-1.93 (m, 2H); ^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ 173.3, 124.8, 51.5, 38.2, 33.5, 28.3; HRMS (EI$^+$): Exact mass calculated for $C_{12}H_{18}O_4$ [M]$^+$ *m/z* 226.1205 found 226.1193.

(1*R*,6*S*,9*S*)-9-Carbmethoxy-8-oxybicyclo[4.3.0]non-3-ene ((+)-21). Diester (–)-**20** (5.81 g, 25.7 mmol) was dissolved in dry THF (100 ml) and cooled to 0 °C, whereupon NaH (60% dispersion in mineral oil, 2.10 g, 51.9 mmol) was washed free of the mineral oil (hexane 3 x 25 ml) and added in portions. After the addition was complete, the reaction mixture was heated to reflux. After 16h, the heating was discontinued and aq. satd. NH_4Cl (20 ml) was added. The mixture was diluted with brine (80 ml), the phases were separated and the aq. phase was extracted with Et_2O (4 x 30 ml). The combined organic phases were dried over Na_2SO_4, filtered and the solvent was evaporated *in vacuo*. This afforded a faint yellow, viscous, liquid, which was shown to be the pure title compound (+)-**21** containing 6% of the 9-epimer by ^{1}H-NMR. Yield: 4.56 g, 91%: TLC (hexane/EtOAc 80:20, visualized by $KMnO_4$-stain): R_f = 0.32; $[\alpha]_D^{20} = +12.1$ (c = 1.40, $CHCl_3$); IR (film): ν_{max} 3021, 2951, 2904, 2834, 1755, 1724, 1436, 1321, 1269, 1234, 1125, 1047 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 5.65-5.80 (m, 2H), 3.70 (s, 3H), 2.84-2.99 (m, 1H), 2.50-2.66 (m, 1H), 2.35-2.49 (m, 2H), 2.23-2.35 (m, 1H), 1.83-2.10 (m, 4H); ^{13}C{^{1}H}-NMR ($CDCl_3$, 100 MHz): δ 209.7, 169.2, 126.5, 126.1, 61.6, 52.3, 44.8, 42.5, 36.1, 31.2, 30.3; HRMS (EI$^+$): Exact mass calculated for $C_{11}H_{14}O_3$ [M]$^+$ *m/z* 194.0943 found 194.0931.

(1*R*,6*S*)-9-Carbmethoxybicyclo[4.3.0]non-3,8-diene ((–)-22).

(i) Keto ester **9** (2.333 g, 12.0 mmol, 1.00 equiv.) was dissolved in MeOH (50 ml) and the solution was cooled to 0 °C. To the stirring mixture was added $NaBH_4$ (0.682 g, 18.0 mmol, 1.50 equiv.) in one go. The progress of the reaction was monitored by TLC (hexane/EtOAc 80:20, visualized by $KMnO_4$-stain). According to this, the starting material (R_f = 0.32) had been completely converted to a more polar compound (R_f = 0.11) after 1 h. The reaction mixture was treated dropwise with dilute aq. HCl (5 M, 25 ml) in the cold, whereupon it was concentrated *in vacuo*. The residue was diluted with brine (50 ml) and extracted with EtOAc (4 x 50 ml). The combined organic extracts were dried over Na_2SO_4, filtered and the solvent was evaporated *in vacuo*. This afforded a faint yellow oil as crude, which, according to ^{1}H-NMR ($CDCl_3$), corresponded to a diastereomeric mixture of the desired β-hydroxy ester *pre*-(–)-**22a**. Nominal yield: 2.228 g, 95%; TLC (hexane/EtOAc 80:20, visualized by $KMnO_4$-stain): 0.11.

(ii) β-Hydroxy ester *pre*-(–)-**22a** (2.228 g, 11.4 mmol, 1.00 equiv.) was dissolved in dry CH_2Cl_2 (50 ml). Then, Et_3N (3.461 g, 4.8 ml, 34.2 mmol, 3.00 equiv.) was added dropwise at ambient temperature. After 5 min, the slightly tanned mixture was cooled to 0 °C and MsCl (2.612 g, 1.76 ml, 22.8 mmol, 2.00 equiv.) was added in a dropwise manner. The reaction mixture was stirred for 10 min at the stated temperature, whereupon the cooling was discontinued. At this point a white precipitate had formed. The mixture was stirred at ambient temperature overnight, which resulted in a turbid yellow mixture. According to TLC (hexane/EtOAc 80:20, visualized by $KMnO_4$-stain), the starting material (R_f = 0.11) and the desired mesylate are indistinguishable from each other. The mixture was treated with brine (50 ml) and the volatiles were removed *in vacuo*. The aq. residue was extracted with EtOAc (4 x 40 ml) and the combined organic extracts were dried over Na_2SO_4, filtered and the solvent was evaporated *in vacuo*. This afforded a syrupy orange/red crude, which, according to ^{1}H-NMR ($CDCl_3$), corresponded to a diastereomeric mixture of the desired mesylate *pre*-(–)-**22b**. Nominal yield: 2.996 g, 96%; TLC (hexane/EtOAc 80:20, visualized by $KMnO_4$-stain): 0.11.

(iii) Mesylate *pre*-(–)-**22b** (2.996 g, 10.9 mmol, 1.00 equiv.) was dissolved in dry toluene (50 ml) and DBU (4.99 g, 4.9 ml, 32.7 mmol, 3.00 equiv.) was added in a dropwise manner at ambient temperature. The reaction mixture was stirred at the stated temperature and followed on TLC (hexane/EtOAc 80:20, visualized by UV and $KMnO_4$-stain). According to this, the starting material (R_f = 0.11) had been all but completely consumed after 1h and a more lipophilic spot (R_f = 0.54) was observed. At this stage, the mixture had taken on a biphasic character noticeable by a small amount of orange/brown oil settling at the bottom of the flask. The mixture was allowed to stir 4h at the stated temperature. Then, mixture was treated with dilute aq. HCl (2M, 25 ml) and Et_2O (25 ml), The phases were separated and the aq. phase was extracted with Et_2O (3 x 20 ml). The combined organic phases were dried over $MgSO_4$, filtered and the solvent was evaporated *in vacuo*. The residue was purified by column chromatography on silica (hexane, followed by hexane/Et_2O 75:25). This afforded the pure title (–)-**22** compound as a clear liquid (*NB! It was noted that, the liquid has a high vapour pressure and is prone to co-evaporate at 10-20 mbar*). Yield: 1.797 g, 84% over 3 steps; TLC (hexane/EtOAc 80:20, visualized by UV and $KMnO_4$-stain): R_f = 0.56; $[\alpha]_D^{20}$ = -248.8 (c = 0.8, $CHCl_3$); UV (44.9 mM in $CHCl_3$): IR (film): ν_{max} 3021, 2939, 2892, 2834, 1718, 1432, 1234, 1117, 1105 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 6.85-6.87 (m, 1H), 5.69-5.76 (m, 2H), 3.72 (s, 3H), 2.70-2.77 (m, 1H), 2.48-2.55 (m, 1H), 2.36-2.45 (m, 1H), 2.20-2.27 (m, 1H), 1.89-2.10 (m, 3H), 1.76-1.88 (m, 1H); ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ 165.7, 144.8, 139.2, 127.4, 127.3, 51.1, 45.7, 44.3, 37.0, 30.7, 30.4; HRMS (EI$^+$): Exact mass calculated for $C_{11}H_{14}O_2$ [M]$^+$ *m/z* 178.0994, found 178.0998.

(1*R*,6*S*,8*S*,9*R*)-8-Butyl-9-carbmethoxybicyclo[4.3.0]non-3-ene ((–)-23). Michael acceptor (–)-**22** (0.774 g, 4.34 mmol, 1.00 equiv.) was dissolved in dry THF (40 ml), degassed thrice and cooled to -35 °C. To the solution was added in succession CuI (0.082 g, 0.43 mmol, 0.10 equiv.) and TMSCl (1.181 g, 1.38 ml, 10.1 mmol, 2.50 equiv). The resulting heterogeneous mixture was powerfully stirred for 5 min, whereupon BuMgCl (2.0 M in THF, 6.53 ml, 13.0 mmol, 3.00 equiv.) was added in a manual dropwise manner during 1.5h. After the first few drops, the reaction mixture became homogeneous and the colour cycled between clear and yellow for each successive addition. As the reaction progressed, the yellow colour became more persistent, taking a full minute or more to revert to a turbid grey. After the addition was complete, TLC (hexane/EtOAc 80:20, visualized by UV and $KMnO_4$-stain) revealed that the starting material (R_f = 0.58) had been consumed (*NB! Prior to elution, the TLC plate was briefly fanned with a heat gun to decompose the presumed transient silyl ketene acetal formed during the reaction*). While still in the cold, the reaction mixture was treated with saturated aq. NH_4Cl (10 ml) and taken to ambient temperature. Then water (40 ml) was added, the phases were separated and the aqueous phase was extracted with EtOAc (4 x 25 ml). The combined organic phases were dried over $MgSO_4$, filtered and the solvent was evaporated *in vacuo*. The residue was purified by column chromatography on silica (hexane, followed by hexane/EtOAc 95:5) to afford the title compound (–)-**23** as clear liquid. By ^{1}H-NMR ($CDCl_3$), the isolated material contained approx. 5% of the α-epimere. Yield: 0.785 g, 85%; R_f = 0.64 (hexane/EtOAc 80:20, visualized by UV and $KMnO_4$-stain); $[\alpha]_D^{20}$ = –55.5 (c = 0.8,

$CHCl_3$); IR (film): ν_{max} 3027, 2933, 2863, 1730, 1438, 1234, 1158 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.62-5.69 (m, 2H), 3.69 (s, 3H), 2.19-2.30 (m, 3H), 2.01-2.06 (m, 1H), 1.77-1.89 (m, 2H), 1.68-1.76 (m, 1H), 1.52-1.67 (m, 3H), 1.41-1.50 (m, 1H), 1.21-1.37 (m, 5H), 0.88 (t, J = 6.92 Hz, 3H); ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ 176.5, 127.0, 126.0, 57.2, 51.5, 46.3, 41.5, 40.3, 37.1, 36.7, 32.1, 30.9, 30.2, 22.7, 14.0; HRMS (EI$^+$): Exact mass calculated for $C_{15}H_{24}O_2$ [M]$^+$ m/z 236.1776, found 236.1770.

(1*R*,6*S*,8*S*,9*R*)-8-Butyl-9-(hydroxymethyl)bicyclo[4.3.0]non-3-ene ((–)-24). Ester (–)-**23** (0.587 g, 2.48 mmol, 1.00 equiv.) was dissolved in dry CH_2Cl_2 (40 ml) and the solution was cooled to -78 °C. After 10 min, DIBAL-H (1 M in hexane, 9.93 ml, 9.93 mmol, 4.00 equiv.) was added in a dropwise manner. When the addition was complete, the reaction mixture was stirred at the stated temperature and the progression was monitored by TLC (hexane/EtOAc 80:20, visualized by $KMnO_4$-stain). According to this, the starting material (R_f = 0.68) had been consumed after 3h and a new, less lipophilic compound (R_f = 0.34) had been formed. While still in the cold, the mixture was treated with a saturated aq. solution of Rochelle's salt (50 ml) and allowed to attain ambient temperature. The mixture was diluted with CH_2Cl_2 (80 ml) and stirred overnight. The phases were separated, the aq. phase was extracted with CH_2Cl_2 (2 x 40 ml) and the combined organic phases were washed with brine (40 ml). The combined organic phases were dried over $MgSO_4$, filtered and the solvent was evaporated *in vacuo*. The residue was purified by column chromatography on silica (hexane, followed by hexane/EtOAc 90:10 and 80:20). This afforded the title compound (–)-**24** as a viscous colourless liquid/syrup. Yield: 0.457 g, 88%; TLC (hexane/EtOAc 90:10, visualized by $KMnO_4$-stain): R_f = 0.18; $[\alpha]_D^{20}$ = –65.3 (c = 0.8, $CHCl_3$); IR (film): ν_{max} 3336, 3017, 2958, 2916, 2877, 1456, 1428, 1047 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.64-5.71 (m, 2H), 3.65-3.73 (m, 2H), 2.30-2.36 (m, 1H), 2.16-2.28 (m, 1H), 1.69-1.90 (m, 3H), 1.53-1.65 (m, 2H), 1.18-1.51 (m, 10H), 0.89 (t, J = 6.76 Hz, 3H); ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ 127.2, 126.9, 65.8, 54.7, 45.0, 40.1, 39.8, 37.2, 37.1, 32.1, 31.8, 30.6, 22.9, 14.1; HRMS (EI$^+$): Exact mass calculated for $C_{14}H_{24}O$ [M]$^+$ m/z 208.1827, found 208.1822.

(1R,6S,8S,9S)-8-Butyl-9-(hydroxymethyl)bicyclo[4.3.0]non-3-ene (*epi*-(–)-**24**). Viscous colourless liquid/syrup. R_f = 0.19; $[\alpha]_D^{20}$ = –51.8 (c = 0.9, $CHCl_3$); IR (film): ν_{max} 3383, 3021, 2962, 2928, 2869, 1467, 1436, 1023 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.51-5.83 (m, 2H), 3.56-3.79 (m, 2H), 2.22-2.38 (m, 1H), 2.14-2.22 (m, 2H), 2.01-2.13 (m, 2H), 1.57-1.88 (m, 3H), 1.42-1.56 (m, 3H), 1.17-1.39 (m, 7H), 0.90 (t, J = 6.82 Hz, 3H); ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ 127.9, 127.4, 60.4, 46.9, 45.6, 41.3, 37.9, 36.1, 34.0, 31.8, 31.3, 28.6, 22.9, 14.1; HRMS (EI$^+$): Exact mass calculated for $C_{14}H_{24}O$ [M]$^+$ m/z 208.1827, found 208.1845.

(1*R*,6*S*,8*S*,9*R*)-8-Butyl-9-((methylsulfonyloxy)methyl)bicyclo[4.3.0]non-3-ene (*pre*-(–)-25a). Carbinol (–)-**24** (0.365 g, 1.75 mmol, 1.00 equiv.) was dissolved in dry CH_2Cl_2 (15 ml) and Et_3N (0.355 g, 0.49 mL, 3.50 mmol, 2.00 equiv.) was added to the solution at ambient temperature. After 10 min, the mixture was cooled to 0 °C and MsCl (0.602 g, 0.41 ml, 5.26 mmol, 3.00 mmol) was added dropwise. After an additional 10 min, the reaction mixture was brought to ambient temperature and the progress was monitored by TLC (hexane/EtOAc 80:20, visualized by UV and $KMnO_4$-stain). According to this, traces of starting material (R_f = 0.29) were left after 8h and a new, more lipophilic, compound (R_f = 0.34) had been formed. The reaction was left overnight and was then deemed complete. Brine (20 ml) was added in a dropwise manner, followed by a mixture of brine and EtOAc (50:50, 80 ml). The phases were separated and the aq. phase was extracted with EtOAc (4 x 30 ml). The combined organic phases were dried over $MgSO_4$, filtered and the solvent was evaporated *in vacuo*. The residue was purified by column chromatography on silica (hexane, followed by hexane/EtOAc 80:20). This afforded the title compound *pre*-(–)-**25a** as a clear, syrupy, liquid. Yield: 0.493 g, 98%; TLC (hexane/EtOAc 80:20, visualized by UV and $KMnO_4$-stain): R_f = 0.34; $[\alpha]_D^{20} = -46.5$ (c = 0.8, $CHCl_3$); IR (film): ν_{max} 3025, 2963, 2924, 2869, 1467, 1444, 1350, 1175 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.53-5.82 (m, 2H), 4.25-4.33 (m, 1H), 4.18-4.24 (m, 1H), 3.01 (s, 3H), 2.29-2.41 (m, 1H), 2.18-2.29 (m, 1H), 1.71-1.92 (m, 3H), 1.49-1.70 (m, 3H), 1.38-1.49 (m, 2H), -1.19-1.38 (m, 6H), 0.90 (t, J = 6.82 Hz, 3H); ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ 127.1, 126.5, 72.3, 51.3, 45.3; 40.0, 39.8, 37.2, 36.9, 36.6, 32.0, 31.3, 30.4, 22.8, 14.1; HRMS (ESI$^+$): Exact mass calculated for $C_{15}H_{26}O_3SNa$ [M + Na]$^+$ m/z 309.1495, found 309.1495.

(1*R*,6*S*,8*S*,9*R*)-8-Butyl-9-(cyanomethyl)bicyclo[4.3.0]non-3-ene (*pre*-(–)-25b). Mesylate *pre*-(–)-**25a** (0.490 g, 1.71 mmol, 1.00 equiv.) was dissolved in dry DMSO (30 ml), solid KCN (0.659 g, 10.3 mmol, 6.00 equiv.) was added in one go and the resulting faint yellow, homogenous, mixture was heated to 70 °C. After stirring overnight, a yellow homogeneous mixture had been obtained and the heating was discontinued. Upon equilibration to ambient temperature, water (5 ml) was added in a dropwise manner, resulting in a decolourization, and the mixture was poured into water/EtOAc (50:50, 50 ml). The phases were separated and the aq. phase was extracted with EtOAc (4 x 25 ml). The combined organic phases were washed with brine, dried over $MgSO_4$, filtered and the solvent was evaporated *in vacuo*. The residue was purified by column chromatography on silica (hexane, followed by hexane/Et_2O 75:25). This afforded the title compound *pre*-(–)-**25b** as a clear liquid. Yield: 0.370 g, quant.; TLC (hexane/EtOAc 80:20, visualized by $KMnO_4$-stain): R_f = 0.58; $[\alpha]_D^{20} = -52.9$ (c = 0.80, $CHCl_3$); IR (film): ν_{max} 3017, 2955, 2924, 2830, 2238, 1636, 1456, 1428 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.59-5.78 (m, 2H), 2.40-2.53 (m, 2H), 2.30-2.40 (m, 1H), 2.19-2.30 (m, 1H), 1.70-1.87 (m, 3H), 1.54-1.69 (m, 2H), 1.43-1.54 (m, 2H), 1.19-1.42 (m, 7H); 0.91 (t, , J = 6.94 Hz, 3H); ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ 127.3, 126.1, 119.0, 48.0, 46.9, 42.8, 39.8, 36.6, 36.0, 32.2, 30.5, 30.4, 22.9, 20.3, 14.1; HRMS (EI$^+$): Exact mass calculated for $C_{15}H_{23}N$ [M]$^+$ m/z 217.1830, found 217.1834.

(1*R*,6*S*,8*S*,9*R*)-8-Butyl-9-(formylmethyl)bicyclo[4.3.0]non-3-ene ((–)-25). Nitrile *pre*-(–)-**25b** (0.370 g, 1.71 mmol, 1.00 equiv.) was dissolved in dry hexane (25 ml) and cooled to -78 °C. After 10 min, the resulting solution was treated with DIBAL-H (1.0 M in hexane, 2.57 ml, 2.57 mmol, 1.50 equiv.) in a dropwise manner. The reaction was monitored by TLC (hexane/EtOAc 80:20, visualized by $KMnO_4$-stain). As only one spot was discernible (R_f = 0.57), which could not be unequivocally ascribed to starting material or product, more DIBAL-H (1.0 M in hexane, 2.57 ml, 2.57 mmol, 1.50 equiv.) was added after 1 h. Finally, more DIBAL-H (1.0 M in hexane, 2.57 ml, 2.57 mmol, 1.50 equiv.) was added after a further 0.5 h. Then, after a total of 2 h, the reaction mixture was treated with a saturated aq. solution of Rochelle's salt (40 ml) and taken to ambient temperature. The mixture was diluted with hexane (40 ml) and stirred for 1 h. Then the phases were separated and the aq. phase was extracted with hexane (2 x 40 ml). The combined organic phases were washed with brine (20 ml), dried over Na_2SO_4, filtered and the solvent was evaporated *in vacuo*. The residue was purified by column chromatography on silica (hexane, followed by hexane/Et_2O 75:25). This afforded the title compound (–)-**25** as a slightly opaque oil. Yield: 0.340 g, 91%; TLC (hexane/EtOAc 4:1, visualized by $KMnO_4$-stain): R_f = 0.57; $[\alpha]_D^{20} = -57.6$ (c = 0.8, $CHCl_3$); IR (film): ν_{max} 3017, 2963, 2922, 2834, 2717, 1724, 1460, 1438 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.81 (t, J = 2.66 Hz, 1H), 5.53-5.80 (m, 2H), 2.40-2.57 (m, 2H), 2.10-2.31 (m, 2H), 1.71-1.88 (m, 2H), 1.52-1.71 (m, 4H), 1.38-152 (m, 2H), 1.12-1.38 (m, 6H), 0.89 (t, J = 6.94 Hz, 3H); ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ 203.1, 127.3, 126.5, 48.5, 48.0, 46.8, 43.5, 39.9, 36.6, 36.0, 32.4, 31.0, 30.6, 22.8, 14.1; HRMS (EI$^+$): Exact mass calculated for $C_{15}H_{24}O$ [M]$^+$ m/z 220.1827, found 220.1829.

(1*R*,6*S*,8*S*,9*R*)-8-Butyl-9-(prop-2-yn-1-yl)bicyclo[4.3.0]non-3-ene ((–)-26). Aldehyde (–)-**25** (0.340 g, 1.54 mmol, 1.00 equiv.) was dissolved in MeOH (15 ml) and cooled to 0 °C. Ohira-Bestmann reagent (0.593 g, 3.09 mmol, 2.00 equiv.) in MeOH (5 ml) was added in one go to afford a colourless homogeneous mixture. Then, K_2CO_3 (0.533 g, 3.86 mmol, 2.50 equiv.) was added in one go, which resulted in a phosphorescent yellow, heterogeneous, mixture. The cooling was discontinued and the reaction mixture was stirred at

ambient temperature. According to TLC (hexane/EtOAc 80:20, visualized with $KMnO_4$-stain), the starting material (R_f = 0.57) had been consumed after 6 h and a new more lipophilic compound (R_f = 0.71) had been formed. To decompose the excess of Ohira-Bestmann reagent, acetone (10 ml) was added, followed by aq. saturated $NaHCO_3$ (40 ml). The mixture was partitioned with pentane (30 ml) and the aq. phase was extracted with pentane (3 x 30 ml). The combined organic phases were dried over Na_2SO_4, filtered and the solvent was evaporated *in vacuo* (reduced pressure at 150 mbar, bath temperature at 0 °C). The residue was purified by column chromatography on silica (pentane, followed by pentane/Et_2O 90:10). This afforded the title compound (–)-**26** as a colourless oil. Yield: 0.430 g, quant.; TLC (hexane/EtOAc 80:20, visualized by $KMnO_4$-stain): R_f = 0.71; $[\alpha]_D^{20} = -51.5$ (c = 0.8, hexane); IR (film): ν_{max} 3308, 3021, 2951, 2916, 2828, 1456, 1428 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.57-5.84 (m, 2H), 2.29-2.45 (m, 3H), 2.18-2.27 (m, 1H), 1.91 (t, J = 2.68 Hz, 1H), 1.70-1.88 (m, 3H), 1.39-1.65 (m, 4H), 1.16-1.39 (m, 7H), 0.90 (t, J = 6.99 Hz, 3H); ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ 127.2, 126.9, 83.4, 68.8, 50.3, 46.5, 42.2, 39.9, 36.9, 36.4, 32.4, 31.0, 30.6, 22.9, 21.4, 14.1; HRMS (EI$^+$): Exact mass calculated for $C_{16}H_{24}$ [M]$^+$ m/z 216.1878, found 216.1874.

(1*R*,6*S*,8*S*,9*R*)-8-Butyl-9-((*E*)-6-(carbethoxy)hex-2-en-1-yl)bicyclo[4.3.0]non-3-ene ((–)-27).

(i) Cp_2ZrCl_2 (0.892 g, 3.05 mmol, 2.00 equiv.) was dissolved in dry THF (15 ml) and the resulting homogeneous solution was cooled to 0 °C and protected from light. DIBAL-H (3.05 ml, 3.05 mmol, 2.00 equiv.) was added in a dropwise manner to obtain a heterogeneous mixture with a slightly yellow hue. After 1 h at 0 °C, the mixture had taken on an eggshell colour. Then, alkyne (–)-**26** (0. 330 g, 1.53 mmol, 1.00 equiv.) was dissolved in dry THF (10 ml) and added in a dropwise manner to the preformed reagent. Upon heating to ambient temperature, the reaction mixture became homogeneous within 10 min to yield a translucent watered-down orange appearance. The resulting mixture was stirred for 2 h.

(ii) The above mixture was cooled to 0 °C and iodine (0.581 g, 2.29 mmol, 1.50 equiv.) was added in one go to afford a deep purple medium. The reaction mixture was then allowed to attain ambient temperature and was stirred for 1 h, while maintaining protection from light. At the end, the colour had turned a light reddish purple.

(iii) To above mixture at ambient temperature was added 4-ethoxy-4-oxobutylzinc bromide (0.5 M in THF, 6.1 ml, 3.05 mmol, 2.00 equiv.) in a dropwise manner. When approx. 1/6 of the volume had been added, the mixture had attained a faint yellow colour, which persisted during the rest of the addition. Then, $Pd(PPh_3)_4$ (0.088 g, 0.075 mmol, 0.05 equiv.) was added, which after a few min resulted in a reddish orange mixture. The reaction was monitored by TLC (hexane/EtOAc 80:20, visualized by $KMnO_4$-stain). According to this, the starting alkyne (R_f = 0.77) had been consumed within 1 h and a slightly more polar compound had appeared (R_f = 0.67). The reaction was left for 6 h at the stated conditions to ensure completion. The reaction mixture was then treated with dilute aq. HCl (1 M, 40 ml). The phases were separated and the aq. phase was extracted with Et_2O (4 x 40 ml). The combined organic phases were dried over $MgSO_4$, filtered and the solvent was evaporated *in vacuo*. The residue was purified by column chromatography on silica (hexane, followed by hexane/EtOAc 95:5) to afford the title compound (–)-**27** as a clear oil (*NB! Traces of co-eluting ethyl butanoate, originating from the zinc reagent, was removed by prolonged heating at 55 °C and reduced pressure set at 10 mbar. However, loss of some product was encountered due to high vapour pressure*). Yield: 0.327 g, 64%; TLC (hexane/EtOAc 80:20, visualized by $KMnO_4$-stain): R_f = 0.61; $[\alpha]_D^{20} = -43.3$ (c = 0.8, $CHCl_3$); UV (24.1 mM, $CHCl_3$); λ_{max} 252 nm (1.349 AU); IR (film): ν_{max} 3021, 2963, 2921, 2864, 1736, 1439, 1374, 1292, 1175 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.60-5.73 (m, 2H), 5.32-5.52 (m, 2H), 4.13 (q, J = 7.15 Hz, 2H), 2.15-2.33 (m, 4H), 2.07-2.15 (m, 2H), 1.99-2.07 (m, 2H), 1.64-1.80 (m, 4H), 1.46-1.64 (m, 3H), 1.30-1.46 (m, 3H), 1.07-1.30 (m, 9H), 0.89 (t, J = 6.88 Hz, 3H); ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ 173.7, 130.2, 129.9, 127.2, 127.1, 60.1, 52.2, 47.2, 42.3, 40.1, 36.9, 36.71, 36.65, 33.7, 32.4, 31.9, 31.6, 30.7, 24.8, 22.9, 14.2, 14.1; HRMS (ESI$^+$): Exact mass calculated for $C_{22}H_{36}O_2Na$ [M + Na]$^+$ m/z 355.2607, found 355.2608.

(–)-Mucosin ((–)-6). Ethyl ester (–)-**27** (0.160 g, 0.48 mmol, 1.00 equiv.) was dissolved in THF (4.0 ml), whereupon MeOH (4.0 ml) and water (2.0 ml) was added. To the stirring solution at ambient temperature was added LiOH · H_2O (0.707 g, 16.8 mmol, 35.0 equiv.) and the resulting reaction mixture was stirred overnight. At this point, analysis by TLC (hexane/EtOAc 80:20, visualized by $KMnO_4$-stain) indicated that the starting material (R_f = 0.61) had been consumed and that a new polar component had been formed (R_f = 0.14). The mixture was diluted with Et_2O (25 ml) and the pH was adjusted to approx. 2 with dilute aq. HCl. The phases were separated and the aq. phase was extracted with EtOAc (4 x 20 ml), whereupon the combined organic phases were dried over $MgSO_4$, filtered and the solvent was evaporated *in vacuo*. The residue was purified by column chromatography on silica (hexane, followed by hexane/EtOAc 60:40). This afforded the title compound **6** as a clear oil. Yield: 0.140 g, 96%; TLC (hexane/EtOAc 80:20, visualized by $KMnO_4$-stain): R_f = 0.14; $[\alpha]_D^{20} = -46.3$ (c = 0.8, $CHCl_3$); $[\alpha]_D^{20} = -45.2$ (c = 1.0, hexane); UV (26.3 mM, $CHCl_3$): λ_{max} 245 nm (1.220 AU), 275 nm (0.970 AU); IR (film): ν_{max} 3027, 2963, 2924, 2869, 1713, 1444, 1296, 1245 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 11.45 (brs, 1H), 5.60-5.73 (m, 2H), 5.43-5.54 (m, 1H), 5.33-5.43 (m, 1H), 2.32-2.41 (m, 2H), 2.09-2.32 (m, 4H) 2.02-2.09 (m, 2H), 1.66-1.81 (m, 4H), 1.47-1.66 (m, 3H), 1.05-47 (m, 9H), 0.89 (t, J = 6.88 Hz, 3H); ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ 180.0, 130.5, 129.6, 127.3, 127.1, 52.2, 47.2, 42.3, 40.1, 37.0, 36.74, 36.67, 33.3, 32.4, 31.8, 31.6, 30.7, 24.4, 22.9, 14.1; HRMS (ESI$^+$): Exact mass calculated for $C_{20}H_{32}O_2Na$ [M + Na]$^+$ m/z 327.2295, found 327.2294.

(1*R*,6*S*,8*S*,9*R*)-8-Butyl-9-((*E*)-6-(carbmethoxy)hex-2-en-1-yl)-bicyclo[4.3.0]non-3-ene ((–)-8). Acid (–)-**8** (0.130 g, 0.43 mmol, 1.00 equiv.) was dissolved in MeOH (8.0 ml), whereupon toluene (12.0 ml) was added. To the stirring solution at ambient temperature was added trimethylsilyldiazomethane (2.0 M in hexane, 0.43 ml, 0.85 mmol, 2.00 equiv.) in a dropwise manner. During the addition, instantaneous decolourization of the added reagent was noticed, accompanied by evolution of gas. At the end, a faint yellow colour persisted. The resulting reaction mixture was stirred at the stated temperature and the progress was monitored by TLC (hexane/EtOAc 80:20, visualized by $KMnO_4$-stain). According to this, the starting material (R_f = 0.14) had been completely consumed after 0.5 h and a more lipophilic material (R_f = 0.60) had appeared. The reaction mixture was treated with dilute aq. HCl (1.0 M, 20 ml), followed by addition of brine (20 ml) and pentane (20 ml). The mixture was stirred for 0.25 h, whereupon the phases were separated and the aq. phase was extracted with pentane (3 x 25 ml). The combined organic phases were dried over $MgSO_4$, filtered and the solvent was evaporated *in vacuo*. The residue was purified by column chromatography on silica (hexane, followed by hexane/EtOAc 95:5) to afforded the pure title compound as a faintly yellow oil. Yield: 0.135 g, quant.; TLC (hexane/EtOAc 80:20, visualized by $KMnO_4$-stain): R_f = 0.60; $[\alpha]_D^{20} = -42.9$ (c = 0.8, hexane); UV (25.1 mM, hexane): λ_{max} 219 nm (3.504 AU), 272 nm (1.070); IR (film): ν_{max} 3021, 2958, 2921, 2864, 1743, 1436, 1366, 1249, 1210, 1171 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 5.60-5.74 (m, 2H), 5.31-5.53 (m, 2H), 3.67 (s, 3H), 2.29-2.34 (m, 2H), 2.14-2.29 (m, 2H), 2.08-2.14 (m, 2H), 2.00-2.07 (m, 2H), 1.65-1.80 (m, 4H), 1.46-1.65 (m, 3H), 1.24-1.46 (m, 5H), 1.07-1.24 (m, 4H), 0.89 (t J = 6.92 Hz, 3H); ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ 174.1, 130.3, 129.8, 127.2, 127.1, 52.2, 51.4, 47.2, 42.3, 40.1, 36.9, 36.72, 36.65, 33.4, 32.4, 31.9, 31.6, 30.7, 24.7, 22.9, 14.1; Exact mass calculated for $C_{21}H_{34}O_2Na$ [M + Na]$^+$ m/z 341.2451, found 341.2451.

(1*R*,6*S*,8*S*,9*R*)-8-Butyl-9-((3,5-dinitrobenzoyl)oxymethyl)bicyclo[4.3.0]non-3-ene ((–)-24-DNB). Carbinol (–)-**24** (0.036 g, 0.17 mmol) in dry CH_2Cl_2 (10 ml) and Et_3N (0.070 g, 0.096 ml, 0.69 mmol, 4.00 equiv.) was added to the solution at ambient temperature. After 10 min, the mixture was cooled to 0 °C and 3,5-dinitrobenzoyl chloride l (0.080 g, 0.35 mmol, 2.00 equiv.) was added in one portion. The reaction mixture was allowed to reach

ambient temperature overnight. Water (20 ml) was added to the reaction mixture and diluted with CH_2Cl_2 (20 ml). The phases were separated and the aq. phase was extracted with CH_2Cl_2 (3 x 20 ml). The combined organic phases were washed with brine (30 ml), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by column chromatography on silica (hexane/EtOAc, 95:5) to afford the title compound (–)-**24-DNB** as white, tiny, fern-like needles. Yield: 0.061 g, 88%; M.p.: 64-65 °C; TLC (hexane/EtOAc 80:20, visualized by $KMnO_4$-stain): R_f = 0.52; $[\alpha]_D^{20} = -28.1$ (*c* = 1.0, $CHCl_3$); UV (26.8 mM, $CHCl_3$): λ_{max} 260 nm (1.984 AU), 295 nm (1.968 AU), 381 nm (1,252); IR (film): ν_{max} 3104, 3020, 2956, 2925, 2858, 1734, 1633, 1544, 1465, 1342, 1275, 1169, 1074 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$): δ 9.24 (t, *J* = 2.12 Hz, 1H), 9.16 (d, *J* = 2.12 Hz, 2H), 5.62-5.75 (m, 2H), 4.49-4.57 (m, 1H), 4.42-4.49 (m, 1H), 2.31-2.42 (m, 1H), 2.22-2.31 (m, 1H), 1.89-2.01 (m, 1H), 1.75-1.89 (m, 2H), 1.61-1.89 (m, 3H), 1.42-1.55 (m, 2H), 1.24-1.42 (m, 6H), 0.84-0.94 (m, 3H); ^{13}C{^{1}H}-NMR (100 MHz, $CDCl_3$): δ 162.6, 148.7, 134.1, 129.3, 127.3, 126.4, 122.3, 70.2, 51.1, 45.9, 40.6, 40.1, 37.2, 37.0, 32.0, 31.6, 30.6, 22.9, 14.1; HRMS (ESI$^+$): Exact mass calculated for $C_{21}H_{26}N_2O_6Na$ [*M* + Na]$^+$ *m/z* 425.1683, found 425.1684. The enantiomeric excess was determined by chiral-phase HPLC analysis (Chiralcel OD-H, hexanes/iPrOH, 95:5, 1 mL/min, 206 nm): t_R(major) = 17.42 min and t_R(minor) = 19.20, *ee*: > 99%.

Supporting Information

^{1}H- and ^{13}C-NMR spectra of all compounds listed in the experimental section ((–)-**6** to (–)-**27**). HRMS (ESI+), IR and UV/vis spectra of (–)-**6**, (–)-**8**, (–)-**24-DNB** and (–)-**27**. Chromatograms from HPLC analysis to determine enantiomeric excess and X-ray crystallographic data recorded for single-crystal of (–)-**24-DNB**.

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J.M.J.N. is the main contributor of this work.

Notes

The authors declare no competing financial interest.

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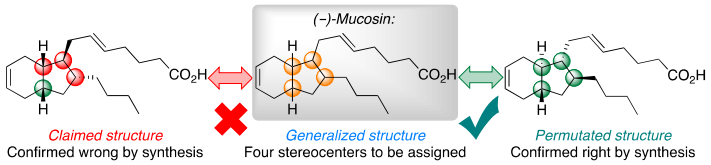
(–)-Mucosin:
CO2H
CO2H
CO2H
Claimed structure
Confirmed wrong by synthesis
Generalized structure
Four stereocenters to be assigned
Permutated structure
Confirmed right by synthesis