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Enantioselective Total Synthesis of Macfarlandin C, a Spongian Diterpenoid Harboring a Concave-Substituted cis-Dioxabicyclo[3.3.0]octanone Fragment

Tyler K. Allred, André P. Dieskau, Peng Zhao, Gregory L. Lackner, and Larry E. Overman*

In memory of Ronald C. D. Breslow

Abstract: The enantioselective total synthesis of the rearranged spongian diterpenoid (–)-macfarlandin C is reported. This is the first synthesis of a rearranged spongian diterpenoid in which the bulky hydrocarbon fragment is joined via a quaternary carbon to the highly hindered concave face of the cis-2,8-dioxabicyclo[3.3.0]octan-3-one moiety. This mode of conjugation is suggested to be important for the Golgi phenotype of these natural products.

A diverse group of marine diterpenoids are believed to arise by fragmentation and rearrangement of the steroid-like spongian skeleton. A distinctive set of these rearranged spongian diterpenoids harbor a cis-2,8-dioxabicyclo[3.3.0]octan-3-one fragment (1) attached at C-6 to a quaternary carbon of a hydrophobic fragment (Figure 1). These diterpenoids can be further subdivided into two families that differ by the orientation of the hydrocarbon fragment. In the largest collection, the hydrocarbon moiety resides on the more sterically hindered concave face of the cis-dioxabicyclo[3.3.0]octan-3-one fragment, exemplified by macfarlandin C (2), whereas cheloviolène A (3) is representative of members in which the hydrocarbon unit resides on the convex face.

Our interest in these structures was initially piqued by Sütterlin’s observations of the unique Golgi-altering activity of macfarlandin E, a structurally related diterpenoid in which the cis-dioxabicyclooctanone fragment is replaced by a 2,7-dioxabicyclo[3.2.1]octan-3-one subunit. Macfarlandin E, and some simplified congeners having either a cis-2,8-dioxabicyclo[3.3.0]octan-3-one or a 2,7-dioxabicyclo[3.2.1]octan-3-one subunit, uniquely induce irreversible fragmentation of the Golgi apparatus with retention of fragments in the pericentriolar region of the cell. The fused and bridged dioxabicyclooctanone moieties degrade in the presence of primary amine functionalities to form pyrrole products via putative 1,4-dialdehyde intermediates.

The central challenge in the synthesis of the marine diterpenoids exemplified in Figure 1 is fashioning the α-bond that links the two chiral fragments in a stereocorected fashion. This challenge is heightened significantly in members such as macfarlandin C (2) wherein the bulky hydrocarbon unit resides on the sterically demanding concave face of cis-2,8-dioxabicyclooctanone fragment. This steric congestion is apparent in the X-ray model of macfarlandin C (Figure 1), and strikingly illustrated in the unusually long length (1.577 Å) of the C-8/C-14 α-bond that joins the two fragments. In contrast, this bond in cheloviolène A (3) is quite standard (1.546 Å). In addition, this steric congestion results in significant distortion of the cis-2,8-dioxabicyclooctanone fragment of macfarlandin C (2) as compared to that of cheloviolène A (3).

When we initiated studies to develop a chemical synthesis of macfarlandin C (2), only the related structural archetypes cheloviolène A (3) and cheloviolène B having the hydrocarbon fragment positioned on the convex face of the cis-2,8-dioxabicyclo[3.3.0]octan-3-one unit had been synthesized. The
approach employed in these syntheses to access the 6-
substituted cis-2,8-dioxabicyclo[3.3.0]octan-3-one moiety relied
on the coupling of a tertiary radical with a 5-alkoxy butenolide.[9]
Although this approach allowed for facile access to diterpenoids
bearing the C-6 hydrophobic fragment on the convex face of the
cis-2,8-dioxabicyclo[3.3.0]octan-3-one unit, we were unable to
tune this coupling to access the alternate stereoisomer.[8b] We
report herein the development of a synthetic approach to cis-2,8-
dioxabicyclo[3.3.0]octan-3-ones attached at C-6 to a quaternary
carbon of a bulky hydrophobic fragment that allows for the
divergent synthesis of either C-6 substituted stereoisomeric from
the product of fragment coupling (Scheme 1). The utility of this
strategy is exemplified by the enantioselective total synthesis of
(--)-macfarlandin C (2).

We initiated exploratory model studies with lactone 11,
which is readily available from the coupling of cesium oxalate 9
and 5-methoxybutenolide (10).[8b] Our original aim was to explore
the feasibility of directly installing a carboxymethyl substituent cis
to the bulky 1-methylcyclohexyl substituent of 11. This goal has
proven to be exceptionally challenging and has not yet been
realized. One approach we examined was to introduce the side
chain as an alkylidene fragment, with the hope that the double
bond could be reduced selectively from the face anti to the
adjacent hydrocarbon side chain. Aldol reaction of lactone 11 with
ethyl glyoxylate yielded a mixture of aldol adducts, which was
dehydrated to provide in high overall yield alkylidene product 12
as a mixture of E and Z stereoisomers. Unfortunately, under no
conditions that we examined was the stereoisomeric
hydrogenation product having the 1-methylcyclohexyl and
carboxymethyl substituents cis formed selectively. Among
the conditions examined were heterogeneous catalytic hydrogenation
using Pd, Pt and Rh catalysts, homogeneous hydrogenation
using Rh or Ir catalysts, Cu and Ni-promoted hydride reduction.[10]
and several recent and older hydrogenation methods that likely
proceed by initial hydrogen atom transfer.[11,12]

We turned to a strategy in which the ester side chain would be
"locked" into a cis relationship with the bulky hydrophobic
substituent by incorporation of a hydroxyl group at the α-position
of a butyrolactone intermediate.[13] Mukaiyama hydration of
alkylidene lactone 12 took place with complete regioselectivity
from the lactone face opposite the 1-methylcyclohexyl substituent
to give alcohol intermediate 13.[14] The transformation of alcohol
13 to concave-functionalized cis-2,8-dioxabicyclo[3.3.0]octan-3-
one 17 was initially accomplished by way of three isolated
intermediates. After initial silyl protection of the hydroxyl
substituent, reaction with excess (iBu)2AlH provided a mixture of
lactol epimers, which were then allowed to react with excess acetic
anhydride at room temperature. The intermediate diacetate, which could be
observed in the crude product by NMR analysis, converted
completely to elimination product 16 by simple treatment with
silica gel. Conjugate-silane reduction of this unsaturated lactone
by the method of Buchwald then provided cis-2,8-
dioxabicyclo[3.3.0]octan-3-one 17 in good yield.

Our application of this strategy to construct (--)-macfarlandin
C (2) is summarized in Schemes 3 and 4. The route commences
with the enantioselective synthesis of octahydronaphthalene
tertiary alcohol 28 in nine steps from 4,4-dimethylcyclohexen-1-
one (18), iodination of 18, followed by catalytic enantioselective
reduction of α-iodocyclohexenone 19 by a variant of the Corey-
Bakshi–Shibata reduction afforded (S)-cyclohexenol 20 in high
yield and 98% ee.[18,19] After conversion to allylic phosphate 21,
anti-Saxx2 allylic displacement by reaction with an excess of the
organocupper intermediate generated in situ from CuCN and
Grignard reagent 22 gave vinyl iodide 23 in high yield.[19] Enantioselective HPLC analysis showed that the displacement
took place with complete transfer of chirality.

As a prelude to forming the (E)-ethylidene side chain that is
required for the pivotal intramolecular cyclization to fashion the
cyclohexaphenanthrene fragment,[20] iodide 23 was advanced by
Negishi vinylation to diene 24.[21] Exposure of 24 to 75 atm of
hydrogen in the presence of catalytic (η5-naphthalene)chromium
tricarbonyl occasioned selective delivery of hydrogen to the
termini of the diene to give exclusively the (E)-ethylidene product
25 in 95% yield from vinylicde 23.[22] Treatment of this
unsaturated acetal with catalytic PPTS in aqueous acetone at

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**Scheme 1:** General and divergent approach to 6-substituted cis-2,8-dioxabicyclo[3.3.0]octan-3-ones.

**Scheme 2:** Model studies toward accessing concave 6-substituted cis-2,8-dioxabicyclo[3.3.0]octan-3-one 17. (d)(+CF3)2py = 2-(2,4-difluorophenyl)-5-
trifluoromethylpyridine, dbbpy = 4,4′-diphenyl-2,2′-bipyridine, DME = dimethoxyethane, THF = tetrahydrofuran, LHMDS = lithium hexamethyldisilazide, TF AA = trifluoroacetic anhydride, DBU = 1,8-
dioxabicyclo[5.4.0]undec-7-ene acac = acetylacetonate, TMSCl = chlorotrimethylsilane, PCC = pyridinium chlorochromate, Ipr = 1,3-bis(2,6-
diisopropylphenyl)-1,3-dihydropyridin-2-ylidene, PMHS = poly(methylhydroxiloxane).

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70 °C promoted stereoselective intramolecular carbonyl-ene cyclization of the corresponding aldehyde to give alcohol 26 harboring the octahydronaphthalene core of macfarlandin C in 69% yield. The secondary alcohol of 26 was then oxidized using Dess-Martin periodinane to ketone 27, which was transformed with high selectivity to equatorial tertiary alcohol 28 upon sequential treatment with an excess of Yamamoto’s MAD reagent (methylaluminum bis(2,6-di-tert-butyl-4-methylphenoxide) and methylimagnesium bromide.

The pivotal fragment coupling step and advancement of the coupled product in eight steps to (–)-macfarlandin C are summarized in Scheme 4. Alcohol 28 was converted first to the oxalate radical precursor 29 by sequential reaction at room temperature with methyl chlorooxalate and cesium hydroxide. Irradiation of a solution of oxalate salt 29, O-menthol-derived chlorobutenolide 30 and 2 mol% of the iridium photocatalyst with high-intensity blue LEDs for 20 h at 60 °C, followed by addition of excess tri-n-butylamine and irradiation for an additional 6 h gave coupled product 31 in 74% overall yield from alcohol 28. This product was then advanced in high yield to vinylogous β-alkoxyacyl ester 33 by the aldol-dehydration sequence developed in our earlier model studies (Scheme 2). Mukaiyama hydration of 33 proceeded with high regio- and stereoselectivity to deliver alcohol intermediate 34, leaving the electron-rich trisubstituted double bond untouched. The highest yields in this conversion were realized using the more active catalytic system reported by Shenvi.

To our surprise, α-hydroxy lactone 34, and alcohol-protected variants thereof, proved remarkably resilient to reduction by a variety of hydride reagents. Fortunately, reaction with a large excess of lithium aluminum hydride at 0 °C gave rise to a mixture bicyclic lactols, which upon direct oxidation with excess PCC provided dioxabicyclooctanone 35 in 72% yield. Without purification of intermediates, the menthoxy group was removed under acidic conditions, the resulting diol product was peracetylated and then exposed to DMAP to provide butenolide intermediate 36. Silane reduction promoted by a N-heterocyclic-carbene copper complex then delivered (–)-macfarlandin C (2) in 38% yield over three steps. Spectroscopic properties and optical rotation of synthetic (–)-macfarlandin C (2) are indistinguishable from those reported for the dorid nudibranch isolate.
In summary, the first total synthesis of rearranged spongian diterpenoids having a bulky hydrocarbon positioned on the highly congested concave face of the cis-2,8-dioxabicyclo[3.3.0]octan-3-one fragment is reported. This sequence was exemplified in the first total synthesis of the structurally elaborate diterpenoid (macfarlandin C (2)), an enantioselective synthesis that rigorously establishes the absolute configuration of the natural product, which previously had been proposed only on the basis of biosynthetic conjecture. Three transformations are critical to the successful synthesis of 2: a) stereoselective carbonyl-ene cyclization to fashion the octahydronaphthalene fragment, b) high-yielding fragment coupling between a tertiary alcohol-derived tertiary radical and an electron-deficient alkene resulting in the formation of a new quaternary and tertiary stereocenters, and c) a stereo-and diastereoselective Mukaiyama hydration that allows the concave-substituted cis-2,8-dioxabicyclo[3.3.0]octan-3-one unit to be elaborated from the product of fragment coupling.

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Keywords: C–C coupling • natural product synthesis • photoredox chemistry • terpene synthesis • radical chemistry

Scheme 4: Photoredox-mediated fragment coupling for the generation of lactones 31 and elaboration to macfarlandin C (1). \( \text{(DMAP = N,N-dimethyl-4-aminopyridine, dF(CF}_3\text{ppy) = 2-(2,4-difluorophenyl)-5-trifluoromethylpyridine, dbu = 4,4,4-di-tert Bu-2,2-bipyridine, LiHMDS = lithium hexamethyldisilazide, TFAA = trifluoroacetic anhydride, DBU = 1,8-diazabicyclo[5.4.0]jundec-7-ene, dpn = dipivaloylmethane, PCC = pyridinium chlorochromate, PMHS = polymethylhydrosiloxane).} \)


c) Cheloviene A CDDC ref. codes SIZIKZ and SIZIKZ1. b) The other diterpenoid in the convex-linked series whose structure has been determined by single-crystal X-ray analysis, cheloviene B, also shows a typical value of 1.545 Å for the length of the linking bond (CDDC ref. code HEFVIA).}


Many of these attempts are summarized in: a) the Supporting Information of reference 8b, and b) G. L. Lackner, PhD thesis, University of California, Irvine (USA), 2016.

See the supporting information for details.


The partial isomerization of the desired (less stable) hydrogenation product formed from 12 under some of the reduction conditions we had examined, in part, led us to this approach.[8b,11]


[16] a) Regio- and stereoselectivity was quite high, as no additional alcohol products were detected during chromatographic purification of 13. b) Single-crystal X-ray analysis confirmed the relative configuration of 13 (CCDC ID 1972398).


[26] As we have observed earlier in related reactions,[21] the yield of the coupling reaction is enhanced when the butenolide contains an α-chloro substituent. Stereoselection in the fragment coupling was extremely high, as no stereoisomers were detected upon chromatographic purification of 31.

[27] When the oxalate derived from the corresponding axial tertiary alcohol is subjected to the fragment coupling conditions, the major product arises from cyclization of the alkoxycarbonyl radical intermediate onto the pendent trisubstituted double bond to form a γ-butyrolactone.[21b]

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