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Biomimetic Total Synthesis of Gracilioethers B and C

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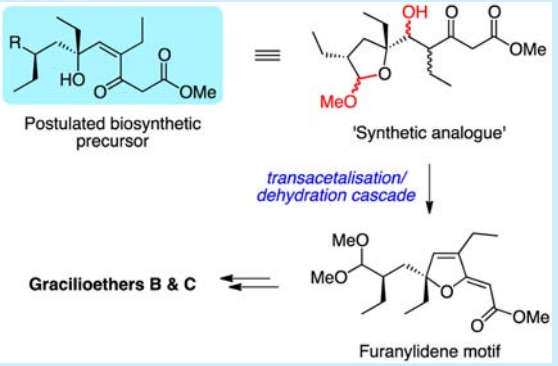
Supporting Information

ABSTRACT: Total syntheses of the marine polyketide metabolites gracilioethers B and C have been realized in 9 steps (40% overall yield) and 10 steps (34% overall yield), respectively. The [2(5*H*)-furanylidene]ethanoate (furanylidene) motif was constructed in a transacetalization/dehydration cascade of an advanced *β*-ketoester intermediate, which was designed to mimic a postulated biosynthetic precursor to the natural products. The relative and absolute configurations of gracilioethers B and C are confirmed as (6*R*,8*R*) and (6*R*,8*R*,11*S*), respectively.



The polyketide secondary metabolites gracilioethers A–K, plakilactones A–H,[1] and a number of related compounds[2] were recently isolated from marine sponges of the genera *Plakortis*, *Plakinastrella* and *Agelas*. A number of these have shown significant antimalarial activity,[1a,c] moderate inhibition of *Leishmaniasis major*,[1a,2f] pregnane-X-receptor (PXR) agonistic activity,[1d] and antifungal properties.[2g] Gracilioethers B (**1**) and C (**2**) (Figure 1) were also identified as agonists of peroxisome proliferator-activated receptor *γ* (PPAR*γ*).[1b] To date, few studies have focused on developing methods for the synthetic preparation of metabolites in this family.[3]

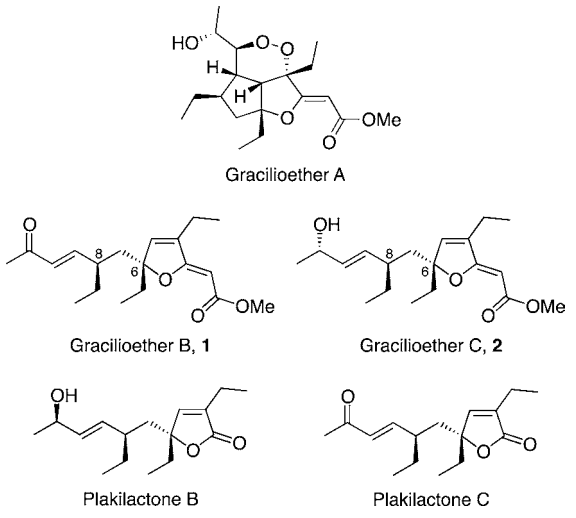
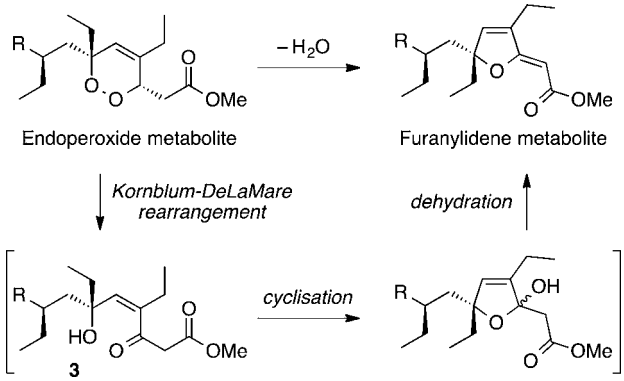


Figure 1. Reported structures of gracilioethers B and C with (*R*,*R*) configuration assumed at C6 and C8; and the oxygenated coisolates gracilioether A, plakilactone B, and plakilactone C.

We recently proposed a plausible biosynthetic origin of metabolites containing the [2(5*H*)-furanylidene]ethanoate (furanylidene) motif by Kornblum–DeLaMare rearrangement,[4] cyclization, and dehydration of related endoperoxides (Scheme 1) and demonstrated the utility of hydroxy *β*-ketoesters such as **3**

Scheme 1. Postulated Biosynthetic Origin of Furanylidene Metabolites



in the synthesis of furanylidene scaffolds.[3c] Herein we report application of this methodology to achieve total synthesis of gracilioethers B (**1**) and C (**2**).

We reasoned that the relative and absolute configurations of both gracilioethers B and C at C6 and C8 were most likely to be (*R*,*R*). Our assumption was based, first, on the total synthesis and stereochemical elucidation of a similar metabolite,[3a] '*des*-hydroxygracilioether C,' found unequivocally to have (6*R*,8*R*)

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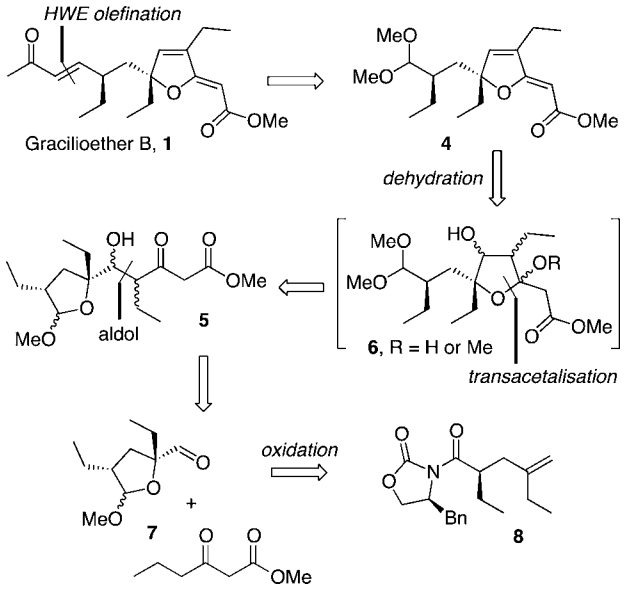
configuration and, second, the likelihood that gracilioethers B and C share a common biosynthetic origin to the endoperoxide coisolate gracilioether A, whose relative and absolute configuration was determined as (6*R*,8*R*) by chemical derivatization and NMR analysis.[1a] Compound **1** was thus identified as the structure most likely to be consistent with natural gracilioether B and became the primary target of our strategy, since selective reduction to the corresponding allyl alcohol **2** might be possible by methods of asymmetric carbonyl hydrogenation developed by Noyori.[5]

Disconnection of the unsaturated methyl ketone of **1**, which may be installed by Horner−Wadsworth−Emmons olefination, unveiled aldehyde dimethyl acetal **4** as a key late stage intermediate (Scheme 2). We envisaged that the furanylidene

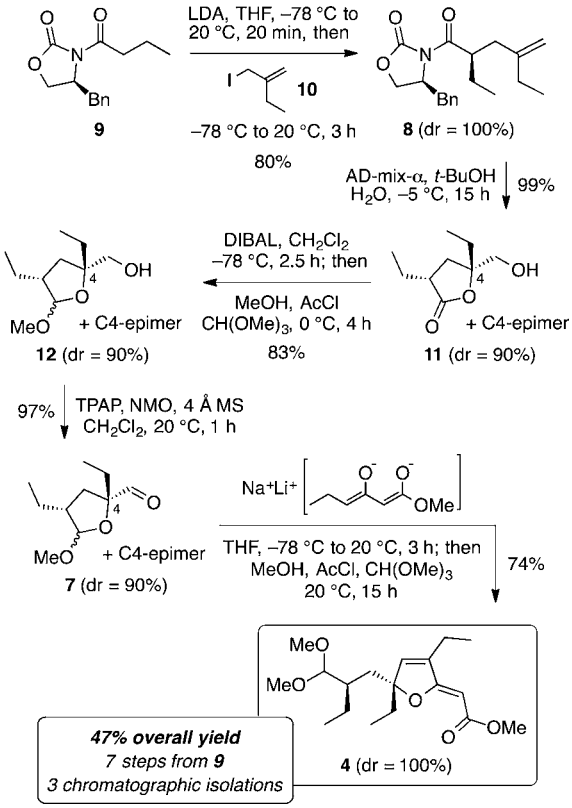
Scheme 2. Strategy for a Biomimetic Total Synthesis of Gracilioether B



ring system and correct oxidation state of **4** might be reached in a single cascade reaction of alcohol **5** (a synthetic analogue of **3**) by transacetalization to the putative intermediate **6** before dehydration. Presumably this would occur via a number of stabilized carbocation intermediates, which we have described previously.[3c] Another advantage of our design was the potential to access alcohol **5** directly from the aldol reaction of methyl 2-oxohexanoate with aldehyde **7** that could be assembled in a number of steps from olefin **8**.

To begin, **8** was prepared in good yield and as a single diastereomer by alkylation of the readily available oxazolidinone **9** with known allyl iodide **10**[6] (Scheme 3). Capitalizing on Brimble's[6] finding of reverse Sharpless-mnemonic dihydroxylation of a substrate similar to **8**, treatment with catalytic $K_2OsO_4{\cdot}2H_2O$ and $(DHQ)_2PHAL$ with K_2CO_3 and $K_3[Fe(CN)_6]$ (purchased as commercially available AD-mix-α) in a 1:1 mixture of *t*-BuOH and H_2O at −5 °C effected oxidation and concomitant lactonization with good selectivity (9:1) for the desired *syn*-lactone **11**, which was inseparable from the minor *anti*-diastereomer (with (*S*) configuration at C4).[7] Reduction with DIBAL was followed immediately by conversion of the resulting lactol isomers to the configurationally stable methyl acetal **12** (as a 3:1 mixture of acetal stereoisomers), and the corresponding C4-epimer in a combined yield of 83%. Oxidation

Scheme 3. Synthesis of Aldehyde 7, Aldol Condensation, and Transacetalization/Dehydration to Furanylidene Aldehyde Dimethyl Acetal 4



with catalytic TPAP and NMO under standard conditions developed by Ley[8] cleanly afforded aldehyde **7**, still as an inseparable mixture. Despite attempts to remove the undesired epimers produced in this sequence, separation of the C4-epimer was not possible by column chromatography.

Aldehyde **7** was then added to a solution of the sodio-lithio dianion of methyl 2-oxohexanoate, preformed by treating the parent β-ketoester with NaH followed by *n*-BuLi.[9] Gratifyingly, the anticipated aldol reaction appeared to proceed smoothly on warming from −78 °C to room temperature yielding a complex isomeric mixture of alcohol **5**. Rather than attempting to isolate intermediates, the resulting mixture was simply treated with dry HCl (generated *in situ* from acetyl chloride), MeOH, and excess $CH(OMe)_3$ at 20 °C overnight (15 h). Remarkably, NMR analysis of this final material showed that the complex series of spectral peaks observed on completion of the aldol reaction had mostly resolved to a single set, which was identified as aldehyde dimethyl acetal **4** and isolated in 74% yield as a single isomer after flash chromatography. Consistent with our previous study of furanylidene ring systems, we observed complete selectivity for *Z* geometry of the exocyclic olefin.[10]

We were also pleased to find that the aldehyde dimethyl acetal expected to arise from aldol reaction and transacetalization/dehydration of the C4-epimer of **7** was not isolated. It appears that reaction of the C4-epimeric aldehydes does not proceed readily under our reaction conditions. This has allowed us to streamline the middle section of our strategy by removing the need to attempt chromatographic isolation of **7** and **12**. Furanylidene **4**, a pivotal late stage intermediate in our strategy, was thus prepared in 47% yield over seven preparative steps from

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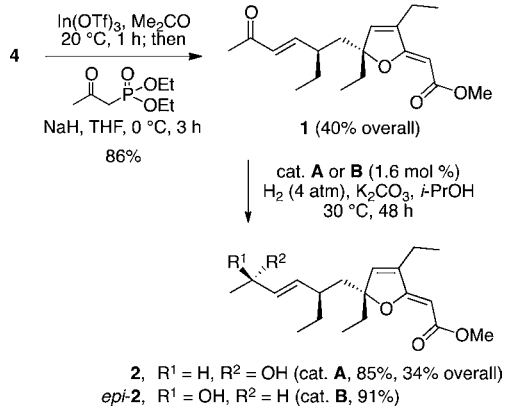
9 and requiring only three applications of chromatographic purification.

Transacetalization[11] of **4** with catalytic $In(OTf)_3$ and Me_2CO followed immediately by Horner–Wadsworth–Emmons olefination with diethyl (2-oxopropyl)phosphonate afforded **1**[12] (Scheme 4). The ^1H and ^{13}C NMR data obtained were

Scheme 4. Synthesis of 1 and 2[a]



[a]Cat. **A**: $RuCl_2$[(*R*)-Xylbinap][(*R*)-Daipen]; cat. **B**: $RuCl_2$[(*S*)-Xylbinap][(*S*)-Daipen].

consistent with that reported for natural gracilioether B,[1a,12] and optical rotation confirmed that **1** had the same absolute configuration. We were also pleased to find that reduction of the pendant methyl ketone with catalytic $RuCl_2$[(*R*)-Xylbinap][(*R*)-Daipen] under H_2 (4 atm), which has been shown to give excellent selectivity for generating the corresponding (*S*)-allyl alcohol,[5] yielded **2**[13] directly. Spectral analysis revealed overwhelming similarity with that reported for natural gracilioether C,[1a,13] and once again, optical rotation measurements confirmed the same absolute configuration. It was also possible to selectively reduce **1** with the enantiomeric catalyst $RuCl_2$[(*S*)-Xylbinap]-[(*S*)-Daipen] under H_2 (4 atm) yielding *epi*-**2**[14] and thus demonstrating that asymmetric induction is under catalyst control.[15] The ^1H and ^{13}C NMR spectra of *epi*-**2** in CD_3OD, although very similar to the spectra of **2**, were inconsistent with those of the natural material. Hence, the structures as well as relative and absolute configurations of gracilioethers B and C are confirmed as (6*R*,8*R*)-**1** and (6*R*,8*R*,11*S*)-**2**, respectively.

In summary, total syntheses of gracilioethers B and C were accomplished in 9 steps (40% overall yield) and 10 steps (34% overall yield), respectively. The [2(5*H*)-furanylidene]ethanoate (furanylidene) motif was installed in a facile biomimetic transacetalization/dehydration cascade, allowing the development of an exceptionally short and high yielding synthetic route to the natural products. The structures as well as relative and absolute configurations of gracilioethers B and C are confirmed as (6*R*,8*R*)-**1** and (6*R*,8*R*,11*S*)-**2**, respectively.

■ ASSOCIATED CONTENT

Supporting Information

Preparative procedures and copies of NMR spectral data for compounds **1**, **2**, **4**, **7**, **8**, **11**, and **12**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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(7) Relative stereochemistry established by spectral comparison to the *syn*- and *anti*-lactones reported by Brimble (see Supporting Information files for full comparison). Lactone **11** was also prepared from an olefin similar to **8** tethered with the same pseudoephedrine derived auxiliary used in Brimble's method, with similar selectivity.

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(10) Assignment of the *Z* geometry was based on ^{1}H NMR comparison of the vinyl protons with our model system previously reported (see ref 3c). The *Z* and *E* isomers are thought to equilibrate in the presence of an acid catalyst with preference for *Z* geometry (up to dr = 100%) due to steric interaction of the neighbouring vinylic ethyl group.

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(12) **1**: $[\alpha]^{20}_{D}$ −370 (*c* 0.46, MeOH); $[\theta]_{218}$ +97 640 (max), $[\theta]_{248}$ +74 530 (max), $[\theta]_{286}$ −160 420 (max); ν_{max} (thin film) 2968, 2936, 2879, 1737, 1710, 1671, 1621, 1450, 1433, 1358, 1251, 1159, 1089, 1036, 975, 870, 805, 782 cm^{-1}; δ_H (500 MHz, CD_3OD) 6.65 (1H, dd, *J* 16.0, 9.3 Hz, C*H*═CHCOCH$_3$), 6.43 (1H, s, C*H*═CCH$_2$CH$_3$), 5.85 (1H, d, *J* 16.0 Hz, C*H*COCH$_3$), 4.88 (1H, s, C*H*CO$_2$CH$_3$), 3.68 (3H, s, OC*H*$_3$), 2.26 (3H, s, COC*H*$_3$), 2.21−2.03 (4H, overlapping peaks, CH═CC*H*$_2$CH$_3$, C*H*CH$_2$CH$_3$, C*H*$_A$H$_B$CHCH$_2$CH$_3$), 2.01−1.93 (1H, m, CH$_A$*H*$_B$CHCH$_2$CH$_3$), 1.87 (1H, p, *J* 7.2 Hz, CH$_2$CC*H*$_A$H$_B$CH$_3$), 1.82 (1H, p, *J* 7.2 Hz, CH$_2$CCH$_A$*H*$_B$CH$_3$), 1.58−1.48 (1H, m, CHC*H*$_A$H$_B$CH$_3$), 1.41−1.30 (1H, m, CHCH$_A$*H*$_B$CH$_3$), 1.13 (3H, t, *J* 7.4 Hz, CH═CCH$_2$C*H*$_3$), 0.85 (3H, t, *J* 7.4 Hz, CHCH$_2$C*H*$_3$), 0.78 (3H, t, *J* 7.4 Hz, CH$_2$CCH$_2$C*H*$_3$); δ_C (125 MHz, CD_3OD) 201.3, 174.1, 169.2, 155.3, 142.1, 141.4, 131.7, 99.0, 84.3, 51.1, 43.6, 41.4, 33.0, 29.5, 26.8, 19.4, 12.0, 11.8, 8.1; HRMS (ESI): MNa$^+$, found 343.1882. $C_{19}H_{28}NaO_4^+$ requires 343.1880. See Supporting Information for detailed comparison of spectral data with those reported for gracilioether B.

(13) **2**: $[\alpha]^{20}_{D}$ −196 (*c* 0.45, MeOH); $[\theta]_{207}$ +50 390 (max), $[\theta]_{231}$ −19 420 (max), $[\theta]_{285}$ −53 660 (max); ν_{max} (thin film) 3493, 2966, 2924, 2877, 1698, 1620, 1457, 1434, 1377, 1276, 1160, 1037, 970, 861, 803 cm^{-1}; δ_H (500 MHz, CD_3OD) 6.44 (1H, s, C*H*═CCH$_2$CH$_3$), 5.29 (2H, overlapping peaks, C*H*═C*H*CHOH), 4.85 (1H, s, C*H*CO$_2$CH$_3$), 4.19−4.14 (1H, m, C*H*OH), 3.65 (3H, s, OC*H*$_3$), 2.21−2.16 (2H, m, CH═CC*H*$_2$CH$_3$), 1.95 (1H, dd, *J* 17.9, 7.1 Hz, C*H*$_A$H$_B$CHCH$_2$CH$_3$), 1.86−1.80 (1H, m, CHCC*H*$_A$H$_B$CH$_3$), 1.81−1.75 (3H, overlapping peaks, CH$_A$*H*$_B$CHCH$_2$CH$_3$, C*H*CH$_2$CH$_3$, CHCCH$_A$*H*$_B$CH$_3$), 1.42−1.37 (1H, m, CHC*H*$_A$H$_B$CH$_3$), 1.22−1.16 (7H, overlapping peaks, CH(OH)C*H*$_3$, CH═CCH$_2$C*H*$_3$, CHCH$_A$*H*$_B$CH$_3$), 0.79 (3H, t, *J* 7.6 Hz, CHCH$_2$C*H*$_3$), 0.75 (3H, t, *J* 7.2 Hz, CHCCH$_2$C*H*$_3$); δ_C (125 MHz, CD_3OD) 174.3, 169.3, 142.8, 140.7, 135.9, 135.7, 99.6, 83.8, 69.3, 51.1, 44.3, 40.7, 32.7, 30.2, 23.7, 19.5, 12.4, 11.9, 8.2; HRMS (ESI): MNa$^+$, found 345.2037. $C_{19}H_{30}NaO_4^+$ requires 345.2036. See Supporting Information for detailed comparison of spectral data with those reported for gracilioether C. The configuration of the C11 alcohol in gracilioether C was assigned in the isolation paper (ref 1a) as (11*S*) by Mosher's ester analysis, and this result is consistent with our findings.

(14) *epi*-**2**: $[\alpha]^{20}_{D}$ −271 (*c* 0.39, MeOH); $[\theta]_{209}$ +54 170 (max), $[\theta]_{231}$ −19 630 (max), $[\theta]_{285}$ −58 840 (max); ν_{max} (thin film) 3488, 2967, 2925, 2877, 1696, 1620, 1457, 1434, 1376, 1275, 1161, 1036, 971, 857, 803 cm^{-1}; δ_H (500 MHz, CD_3OD) 6.42 (1H, d, *J* 1.7 Hz, C*H*═CCH$_2$CH$_3$), 5.33 (1H, dd, *J* 15.5, 7.5 Hz, C*H*═CHCH(OH)CH$_3$), 5.27 (1H, dd, *J* 15.5, 5.4 Hz, CH═C*H*CH(OH)CH$_3$), 4.85 (1H, s, C*H*CO$_2$CH$_3$), 4.16 (1H, m, C*H*OH), 3.65 (3H, s, OC*H*$_3$), 2.18 (2H, qd, *J* 7.4, 1.7 Hz, CH═C*H*$_2$CH$_3$), 1.97−1.93 (1H, m, C*H*$_A$H$_B$CHCH$_2$CH$_3$), 1.87−1.72 (4H, overlapping peaks, CH$_A$*H*$_B$CHCH$_2$CH$_3$, C*H*CH$_2$CH$_3$, CHCC*H*$_2$CH$_3$), 1.42−1.36 (1H, m, CHC*H*$_A$H$_B$CH$_3$), 1.26−1.18 (1H, m, CHCH$_A$*H*$_B$CH$_3$), 1.19 (3H, d, *J* 6.2 Hz, CH(OH)C*H*$_3$), 1.17 (3H, t, *J* 7.4 Hz, CH═CCH$_2$C*H*$_3$), 0.80 (3H, t, *J* 7.4 Hz, CHCH$_2$C*H*$_3$), 0.75 (3H, t, *J* 7.4 Hz, CHCCH$_2$C*H*$_3$); δ_C (125 MHz, CD_3OD) 174.3, 169.3, 142.7, 140.7, 135.6 (2 peaks), 99.5, 83.8, 69.1, 51.1, 44.3, 40.6, 33.0, 30.3, 23.8, 19.5, 12.4, 11.9, 8.1; HRMS (ESI): MNa$^+$, found 345.2036. $C_{19}H_{30}NaO_4^+$ requires 345.2036.

(15) Reduction of **1** was also possible with $NaBH_4$ and $CeCl_3{\cdot}7H_2O$ in MeOH at 0 °C yielding both **2** and *epi*-**2** in approximately the ratio 1:1, further demonstrating a lack of facial bias.

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