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Total Synthesis and Structure Confirmation of Elatenyne: Success of Computational Methods for NMR Prediction with Highly Flexible Diastereomers

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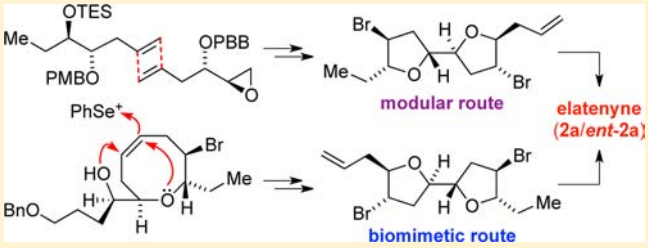
Supporting Information

ABSTRACT: Elatenyne is a small dibrominated natural product first isolated from *Laurencia elata*. The structure of elatenyne was originally assigned as a pyrano[3,2-*b*]pyran on the basis of NMR methods. Total synthesis of the originally proposed pyrano[3,2-*b*]pyran structure of elatenyne led to the gross structure of the natural product being reassigned as a 2,2′-bifuranyl. The full stereostructure of this highly flexible small molecule was subsequently predicted by Boltzmann-weighted DFT calculations of ^{13}C NMR chemical shifts for all 32 potential diastereomers, with the predicted structure being in accord with the proposed biogenesis outlined below. Herein we report two complementary total syntheses of elatenyne, which confirm the computer-predicted stereostructure. Additionally, the total syntheses of (*E*)-elatenyne and a related 2,2′-bifuranyl, laurendecumenyne B, are reported. This work has not only allowed the full structure determination of all of these natural products but also provides excellent supporting evidence for their proposed biogenesis. The total synthesis of elatenyne demonstrates that DFT calculations of ^{13}C NMR chemical shifts coupled with biosynthetic postulates, comprise a very useful method for distinguishing among large numbers of highly flexible, closely related molecules.



INTRODUCTION

The use of DFT calculations to predict the spectroscopic properties of organic molecules has emerged as a powerful additional tool for structure determination. In particular, the use of ab initio methods to calculate NMR chemical shifts has proven beneficial in both gross structural assignment as well as stereochemical assignment. The technique, which was pioneered by Bifulco[1,2] and co-workers, has played a key role in the structure assignment or reassignment of a number of natural products or natural product fragments.[3−5] Moreover, Goodman and Smith[4] have developed a statistical method, the DP4 probability, to aid structure assignment from a range of candidate structures.[5] The majority of these DFT studies for the prediction of ^{13}C NMR chemical shifts have been conducted with relatively rigid molecules, although increasingly these techniques are being successfully used with flexible molecules.[1a,2,6] Herein, we report two complementary total syntheses of the highly flexible 2,2′-bifuranyl natural product elatenyne, which demonstrate the success of DFT calculations of GIAO ^{13}C NMR chemical shifts, and biosynthetic postulates, to predict the correct stereostructure of a highly flexible natural product from a set of 32 possible diastereomers.

Elatenyne is a C_{15} dibrominated marine natural product isolated by Hall and Reiss in 1983 from *Laurencia elata* and assigned the pyrano-[3,2-*b*]-pyran structure **1** (Chart 1).[7−9] On the basis of total synthesis and a ^{13}C NMR chemical shift/structure correlation, we reassigned the gross structure of the natural product from a pyrano[3,2-*b*]-pyran to a 2,2′-bifuranyl **2**.[10,11] Elatenyne contains six stereocenters, and hence the stereostructure of the natural product is one of 32 possible diastereomers. In collaboration with Dr. Jonathan Goodman (University of Cambridge, UK) we predicted the stereostructure of elatenyne by comparison of the ^{13}C NMR chemical shifts of the natural product with the Boltzmann-weighted GIAO ^{13}C NMR chemical shifts calculated using DFT methods.[12] Several structural features made elatenyne challenging to study computationally: (i) two highly flexible THF rings, (ii) an inter-ring torsion, (iii) side-chain torsions, (iv) the presence of bromine atoms, and (v) the presence of sp-hybridized carbon atoms. Nevertheless, analysis of the computational data by comparison of the average difference in the chemical shift across a number of carbon atoms between the computed data and the natural product data (mean average error, MAE)[1,12] gave four promising candidates for the stereostructure of elatenyne (diastereomers **2a**−**d**) with structure **2a** being the most likely structure of the natural product. What was particularly encouraging about the computer

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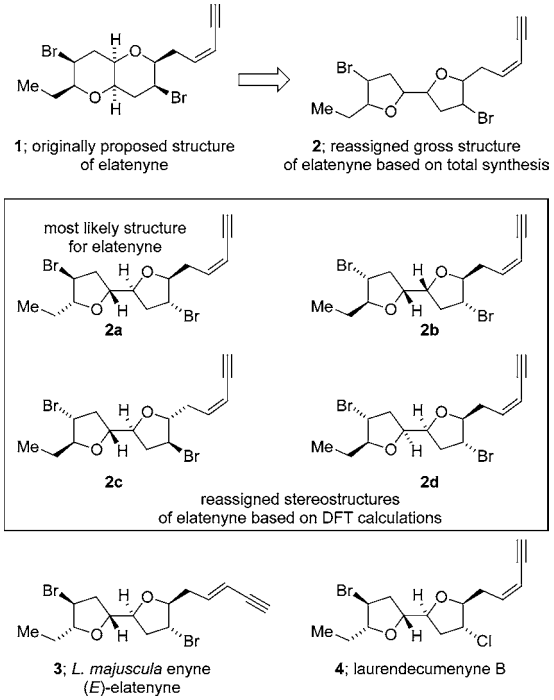
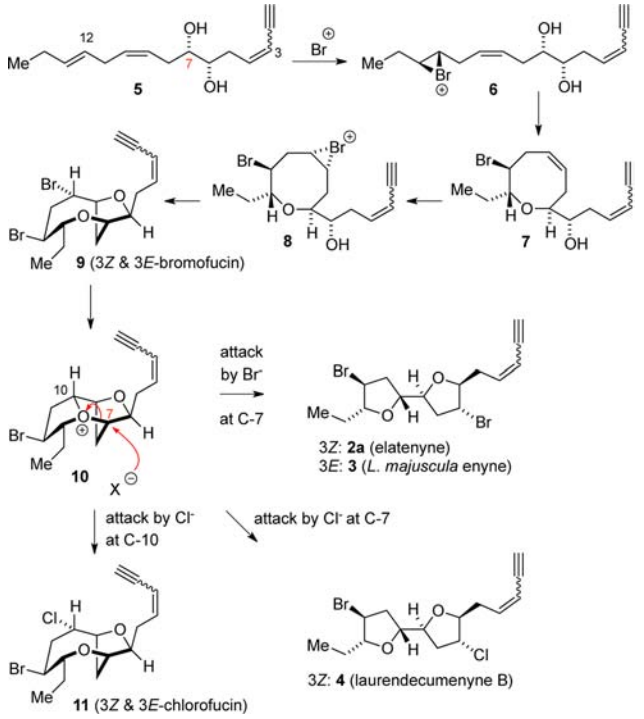
Chart 1. Proposed Structures of Elatenyne and Other Natural Products from *L.* spp. (relative configurations)



prediction was that the most likely stereostructure was in keeping with that predicted from a plausible biosynthetic pathway (vide infra). In this article, we report both a 'modular' and a 'biomimetic' total synthesis of the most likely structure of elatenyne, which confirms the relative configuration of natural elatenyne as **2a**. Most importantly however, this work demonstrates that DFT calculations of GIAO ^{13}C NMR chemical shifts coupled with biosynthetic postulates are an excellent method for distinguishing among a large number of highly flexible diastereomers. Additionally, we report the total synthesis and hence full stereostructure, of a second dibrominated enyne from *L. majuscula*,[13] which, on the basis of this work, corresponds to (*E*)-elatenyne **3**, and laurendecumenyne B **4**,[9a,b] a bromo−chloro enyne from *L. decumbens*, which is assigned the same relative configuration as that of elatenyne **2a**.

Proposed Biosynthesis and Absolute Configuration. The biosynthesis of C_{15} halogenated natural products from *L.* spp. has been widely studied.[14] Murai has demonstrated that a number of C_{15} halogenated natural products can be derived from laurediol (e.g., **5**)[15] via bromoperoxidase-mediated bromonium ion-induced cyclizations. Based on the above precedent[14] and analogous to the proposed biosynthesis of the natural product notoryne,[14b] a biosynthesis for elatenyne may be outlined as follows. (3*Z*, 12*E*)-Laurediol **5**, would be converted into the corresponding bromonium ion **6** by the action of bromide and a bromoperoxidase[16] which would undergo cyclization to give **7**, a diastereomer of deacetyl laurencin.[17] Bromoperoxidase-mediated *endo*-cyclic bromonium ion formation, giving **8**, followed by etherification would deliver the natural product (*Z*)-bromofucin (*Z*)-**9**.[18] Transannular displacement of bromide would give the tricyclic oxonium ion (*Z*)-**10** which would be opened by bromide at C-7 to give the specific elatenyne diastereomer **2a**.[19] Similarly, the tricyclic oxonium ion (*E*)-**10** derived from (*E*)-bromofucin (*E*)-**9**[20] would give (*E*)-elatenyne **3**. The above transannular biosynthetic rearrangements find precedent in the work of Suzuki,[14b] Fukuzawa,[21] and, more recently, Braddock[22] and our own work.[23,24] The natural products (3*Z*)-[25] and (3*E*)-chlorofucin **11**[26] are most likely biosynthesized by an analogous route from laurediol **5** by opening of the tricyclic oxonium ion **10** at C-10 with chloride. The absolute configuration of (3*E*)-chlorofucin (*E*)-**11** has previously been assigned by X-ray crystallography[26a] that, by analogy, would give elatenyne the absolute configuration shown in Scheme 1. However, the

Scheme 1. Proposed Biosynthesis



absolute configuration of the natural product (3*Z*)-chlorofucin (*Z*)-**11** has not been unequivocally determined, and the isolation chemists noted that there is the possibility of its being enantiomeric with (3*E*)-chlorofucin (*E*)-**11**.[25] Considering the fact that the laurediols exist naturally as unequal mixtures of (3*E*/*Z*, 12*E*/*Z*, *RR*/*SS*) stereoisomers[15] and that the absolute configuration of the bromofucins **9** and (3*Z*)-chlorofucin (*Z*)-**11** have not been unequivocally determined,[27] it was deemed prudent for the Oxford and Seoul groups to pursue the total synthesis of opposite enantiomers of elatenyne.

■ STRATEGY AND RETROSYNTHESIS

The computational analysis had predicted the most likely structure for elatenyne as **2a**[12] that also corresponded to one of the diastereomers predicted on the basis of biosynthetic arguments. We were confident, therefore, that **2a** was indeed the structure of elatenyne; however, we deemed it prudent to design a modular synthesis of elatenyne, which could, with minimum modification, allow the synthesis of *any* of the 32 diastereomers of the natural product. At the same time we pursued a biomimetic synthesis of diastereomer **2a**. Given the inherent difficultly in unambiguously assigning the relative configuration of flexible, polysubstituted 5-membered rings, we elected to introduce the stereocenters of elatenyne using stereochemically unambiguous reactions, namely the Sharpless

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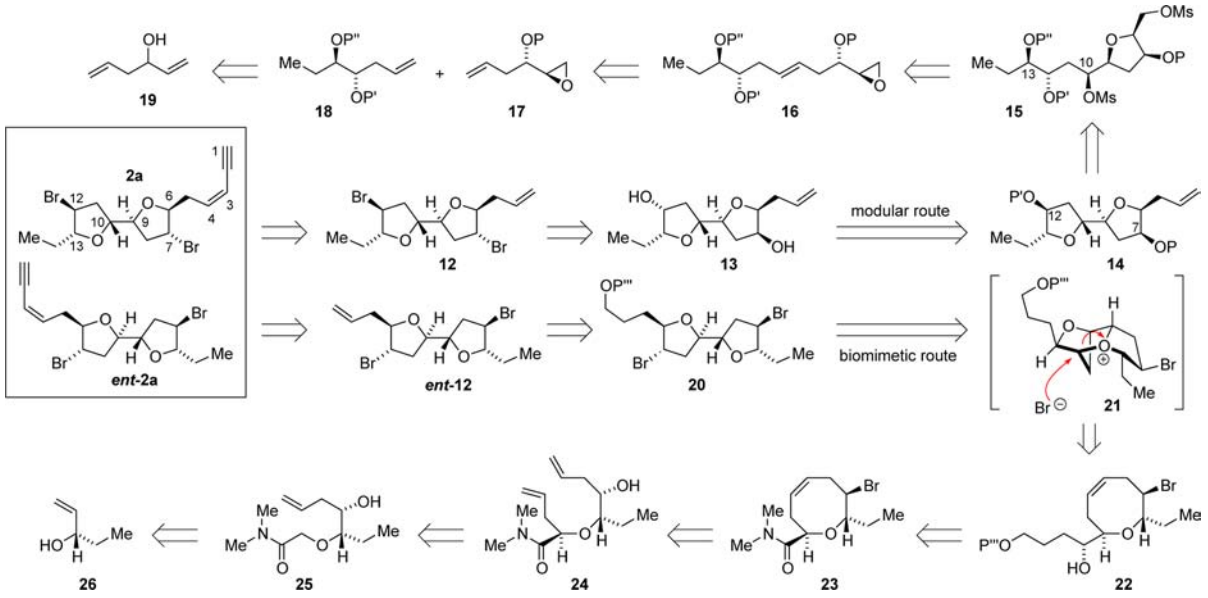

Figure 1. Retrosynthetic analysis of both enantiomers of elatenyne **2a** showing both modular and biomimetic routes.

asymmetric epoxidation (SAE)[28] and Sharpless asymmetric dihydroxylation (SAD),[29] and to manipulate the installed stereocenters using stereochemically unequivocal reactions (e.g., S_N2-reactions). Use of either enantiomer/*pseudo*-enantiomer of ligand in the SAE and SAD reactions, followed by further manipulation of stereocenters would allow us to introduce the necessary diversity into the synthesis such that we could, in principle, synthesize any of the 32 diastereomers of elatenyne.

In concert with this modular approach, we devised a route to elatenyne which would serve not only to secure the structure of the natural product but also to give additional weight to the biosynthesis of halogenated 2,2′-bifuranyls isolated from *L.* spp. Retrosynthetic analyses of both enantiomers of elatenyne **2a**/***ent*-2a** are shown in Figure 1. Thus, the enyne was to be readily installed from the terminal olefin **12**/***ent*-12** as previously demonstrated in related systems.[10,30] In the "modular" route, the dibromide **12** was to be prepared from the diol **13** by bromination with inversion of configuration, with the diol, in turn, being available from the 2,2′-bifuranyl **14** following C-12 inversion of configuration.[31] The 2,2′-bifuranyl would then be synthesized from the alkene epoxide **16** by an SAD reaction[29] with concomitant THF formation giving **15**, followed by C-13 alkoxy to C-10 cyclization. The key alkene **16** was to be prepared by cross-metathesis[32] of substrates **17** and **18** both of which would be available from 1,5-hexadien-3-ol **19** by an SAE reaction. The modularity of the route arises from the use of either enantiomer/*pseudo*-enantiomer of ligand in both the SAE and SAD reactions coupled with the formation of the 2,2′-bifuranyl and the installation of the bromine atoms with either overall inversion or retention of configuration. With the "biomimetic" route, the common intermediate dibromide ***ent*-12** was to be available from the protected alcohol **20**. The key "biomimetic" step involves formation of the tricyclic oxonium ion **21** from the bromooxocene **22** followed by regioselective opening of **21** with bromide to give the 2,2′-bifuranyl **20** with all of the stereocenters of elatenyne installed. The brominated oxocene **22** was to be prepared using methodology previously developed within the Seoul group, and utilized in the total synthesis of numerous natural products.[23,33] The bromooxocene **22** would be prepared from the amide **23** which, in turn, would be available by ring-closing-metathesis of the diene **24**.[32b,c] Diastereoselective alkylation of the amide **25**, using methodology developed by the Seoul group,[33b] would deliver the diene **24**, with the amide itself, being prepared from the known allylic alcohol **26**.[34]

Synthesis of the Dibromide 12 - Modular Route. The "modular" route to elatenyne **2a** began with the known SAE (kinetic resolution) of 1,5-hexadien-3-ol **19**[35] which we prepared in 100 g batches by Barbier coupling of allyl bromide and acrolein according to the procedure of Barfield (Scheme 2).[36] The epoxy alcohol **27** was converted into the PMB-protected epoxide,[37] and the epoxide opened at the terminal position with methylmagnesium bromide in the presence of a copper(I) catalyst[35c] to give the C-10−C-15 fragment of elatenyne **28** on protection with triethylsilyl chloride. For the second cross metathesis partner corresponding to **17**, we required a protecting group that could be removed in the presence of a terminal olefin. We elected to use the 4-bromobenzyl protecting group rather than the more usual benzyl protecting group, as it would give us added flexibility on deprotection if required.[38] Moreover, the 4-bromobenzyl group had the added advantage of giving the majority of our intermediates a clear isotope signature in the mass spectrum, thus greatly simplifying reaction analysis. Cross metathesis[32a] of **28** with **29** required careful optimization. Ultimately we found that treatment of 4 equiv of **29** and 1 equiv of **28** with the second-generation Grubbs−Hoveyda catalyst **30** (10 mol %)[39] and 1,4-benzoquinone (25 mol %)[40] in DCM at reflux gave the alkene **31** as a 3:1 mixture of geometrical isomers in 60% yield;[41] the (*E*)-isomer of **31** could be separated in pure form by chromatography on silver nitrate-impregnated silica gel (45% yield from **28**).[42] The alkene **31** underwent clean, albeit slow, SAD[28] with super AD-mix-α employed by Nicolaou and co-workers in their synthesis of zaragozic acid,[43] which gave the corresponding diols in 88% yield as a 4:1 mixture of *syn*-diastereomers; diol **32** could be isolated in pure form in 71% yield.[44] Cyclization of the C-9 hydroxy group onto the epoxide under acidic conditions required careful optimization so that loss of the C-13 silyl protecting group was minimized. In the

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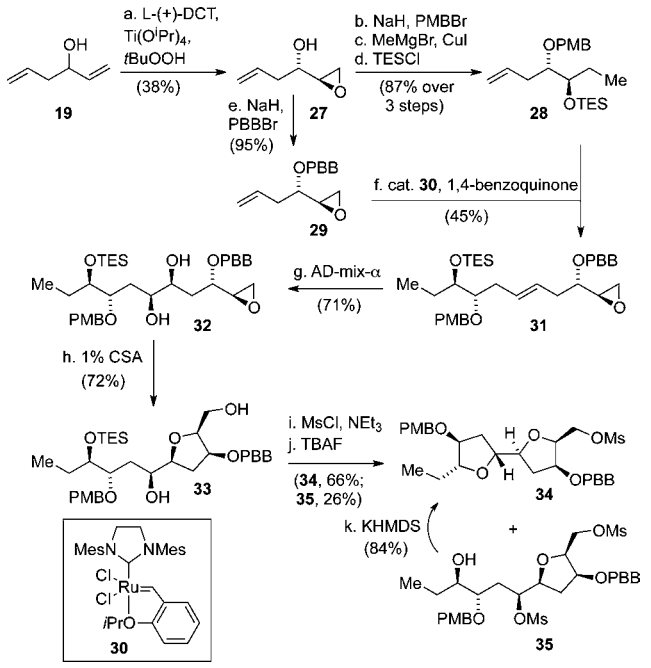
Scheme 2. Synthesis of the 2,2′-Bifuranyl 34[a]

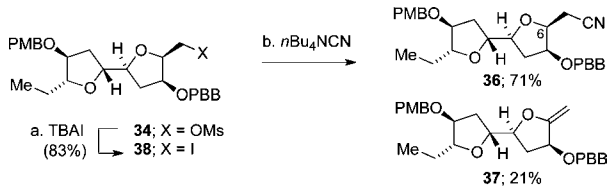


[a]Reagents and conditions: (a) L-(+)-Dicyclohexyl tartrate (DCT), $Ti(OiPr)_4$, *t*BuOOH, 4 Å molecular sieves, CH_2Cl_2, −20 °C, 42 h, 38%; (b) NaH, PMBBr, TBAI, THF, −78 °C to rt, 16 h; (c) MeMgBr, CuI, THF, −23 °C, 1 h, 90% for two steps; (d) TESCl, imidazole, DMAP, CH_2Cl_2, rt, 16 h, 97%; (e) *p*-bromobenzyl bromide (PBBBr), NaH, TBAI, THF −78 °C to rt, 17 h, 95%; (f) Grubbs−Hoveyda II **30**, 1,4-benzoquinone, CH_2Cl_2, reflux, 45%; (g) $K_2OsO_4(OH)_4$, $K_3Fe(CN)_6$, $(DHQ)_2PHAL$, K_2CO_3, $MeSO_2NH_2$, *t*BuOH, water, 0 °C, 96 h, 71%; (h) CSA, CH_2Cl_2, 0 °C, 3 h, 72% (87% brsm); (i) MsCl, Et_3N, CH_2Cl_2, 0 °C, 10 min.; (j) TBAF, THF, rt, 16 h, **34**, 66% (for two steps), and **35**, 26%; (k) KHMDS, THF, rt, 20 min, 84%.

event, exposure of the diol epoxide **32** to (±)-10-camphorsulfonic acid at 0 °C in DCM gave the THF **33** in 72% yield along with 15% recovered starting material. The diol **33** was readily converted into the corresponding bis-mesylate, which on treatment with TBAF gave a mixture of the 2,2′-bifuranyl **34** and bis-mesylate **35**; the bis-mesylate **35** could be coaxed into cyclizing to give **34** on treatment with potassium bis(trimethylsilyl)amide.

A stereocontrolled route to the 2,2′-bifuranyl **34** having been secured, all that remained was to introduce the bromine atoms and the (*Z*)-enyne. Our initial strategy for enyne introduction involved installation of a nitrile, which would serve as a surrogate aldehyde from which the enyne could be introduced by Wittig−Peterson olefination strategies.[10] Surprisingly, under a range of conditions, the mesylate **34** was unreactive toward substitution by cyanide anion. Heating the mesylate **34** with tetrabutylammonium cyanide in acetonitrile at reflux gave trace amounts of a product with molecular mass corresponding to **36** (Scheme 3); however, we were unable to obtain further supporting evidence that substitution by cyanide anion had indeed occurred. Surprised by the recalcitrant nature of the mesylate **34** toward substitution by cyanide, we investigated the substitution with the more nucleophilic iodide anion. Conventional Finkelstein reaction conditions (sodium iodide, acetone, reflux) gave the desired iodide **38** in 25% yield. Ultimately, it was found that exposure of the mesylate **34** to excess tetrabutylammonium iodide in toluene at reflux gave the

Scheme 3. Nitrile Introduction[a]

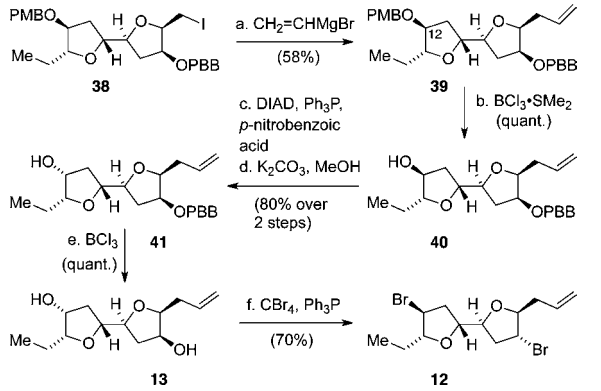


[a]Reagents and conditions: (a) TBAI, toluene, reflux, 16 h, 83%; (b) nBu_4NCN, MeCN, reflux, 4 h, **36**, 71%, **37**, 21%.

corresponding iodide **38** in 83% yield. Exposure of the iodide to tetrabutylammonium cyanide in acetonitrile at reflux gave the desired nitrile **36**[45] in 71% yield along with the enol ether **37** (21%). Although we had secured a route to the desired nitrile **36**, the enol ether **37** was also formed in significant quantities under the basic reaction conditions.[45,46] We therefore sought an alternative method of enyne introduction.

Given that the iodide **38** was more prone to nucleophilic substitution than the mesylate **34**, we attempted to displace the iodide directly with a vinyl anion from which the enyne could be installed by both Wittig−Peterson olefination reactions from the corresponding aldehyde,[10] or using metathesis based reactions directly from the alkene.[30] In the event, exposure of the iodide **38** to excess vinylmagnesium bromide in benzene/THF at 40 °C gave the terminal alkene **39** in 58% yield along with 26% recovered starting material (Scheme 4).[47] It was now

Scheme 4. Synthesis of the Dibromide 12[a]



[a]Reagents and conditions: (a) CH_2=CHMgBr, benzene, THF, 40 °C, 4 h 58% (84% brsm); (b) BCl_3·SMe_2, CH_2Cl_2, rt, 10 min, quant.; (c) DIAD, Ph_3P, *p*-nitrobenzoic acid, THF, 0 °C, 2 h, 85%; (d) K_2CO_3, MeOH, 0 °C to RT, 2 h, 94%; (e) BCl_3, CH_2Cl_2, rt, 30 min, quant.; (f) CBr_4, Ph_3P, toluene, 80 °C, 75 min, 70%.

necessary to invert the configuration at C-12, as we deemed attempted introduction of the bromide directly from the corresponding alcohol with retention of configuration was unlikely to prove successful.[48] The PMB group was readily removed in the presence of the less electron-rich PBB group on exposure of **39** to boron trichloride-dimethyl sulfide complex.[49] Mitsunobu reaction[50] followed by ester removal gave the inverted secondary alcohol **41** in 80% overall yield from the 2,2′-bifuranyl **40**. The PBB group was now removed on exposure of the alcohol to the stronger Lewis acid, boron trichloride,[51] which gave the diol **13** in quantitative yield. Exposure of the diol to standard Hooz bromination conditions (CBr_4, PPh_3) cleanly gave the desired dibromide **12** in 70% yield.[52]

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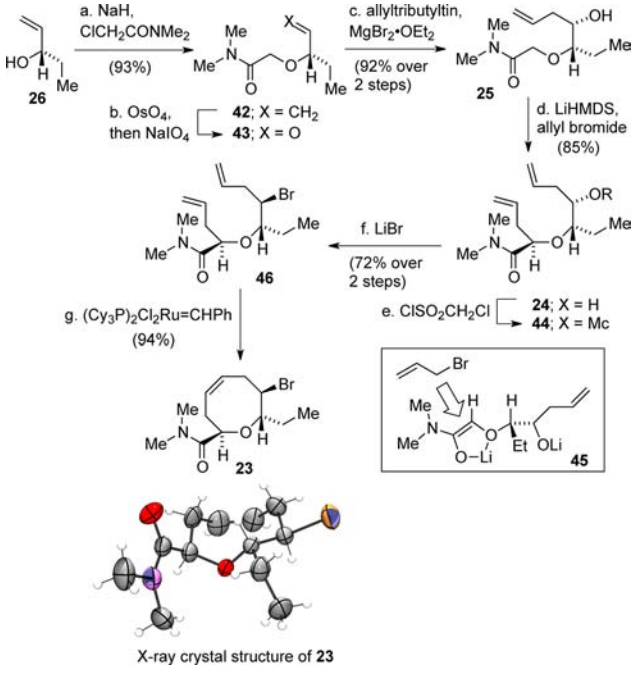
Synthesis of the Dibromide *ent*-12 - Biomimetic Route. The proposed "biomimetic" synthesis of elatenyne ***ent*-2a** required the preparation of an *α,α′-trans*-disubstituted oxocene **22** which was to undergo electrophile-mediated rearrangement to give the desired dibrominated 2,2′-bifuranyl corresponding to **20**. The oxocene **22** was to be prepared from **23**, which, in turn would be synthesized by a ring closing metathesis of the bis-terminal alkene **24** followed by bromination with inversion of configuration. The bis-terminal alkene **24** was to be prepared by an *α,α′-anti*-selective alkylation of the dianion derived from the amide **25**. Both of these steps have been developed and used by us in the synthesis of a large number of natural products, and we were confident that this robust methodology would provide an efficient route to the desired oxocene.[23,33b−d] The amide **24** was to be prepared from the known secondary allylic alcohol **26** by a diastereoselective allylation of the dianion derived from the amide **25**. Thus, known allylic alcohol **26**[34] was alkylated with 2-chloro-*N,N*-dimethylacetamide to give the amide **42** in 93% yield (Scheme 5). Cleavage of the alkene **42** by a Lemieux−Johnson oxidation

Scheme 5. Synthesis of the Bromoamide 23[a]



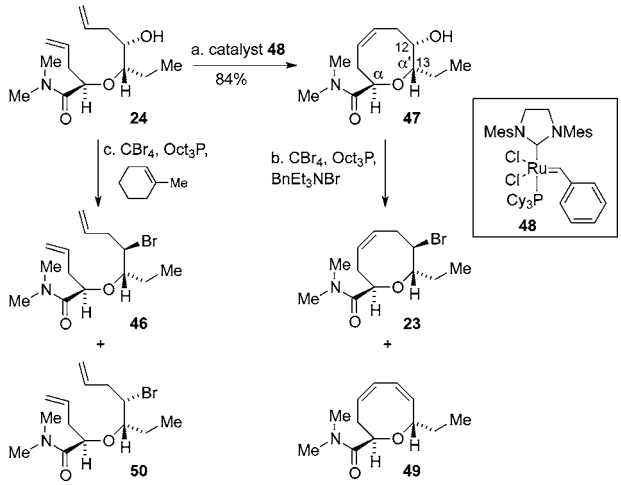
[a]Reagents and conditions: (a) $ClCH_2CONMe_2$, NaH, THF, 0 °C to rt, 3 h, 93%; (b) OsO_4, NMO, acetone, rt, 18 h, then $NaIO_4$, acetone/H_2O (3:1), rt, 3 h; (c) allyltributyltin, $MgBr_2{\cdot}Et_2O$, CH_2Cl_2, −78 °C to rt, 15 h, 92% for 2 steps, *syn*/*anti* = 18:1; (d) LiHMDS, CH_2=$CHCH_2Br$, THF, −78 °C to −40 °C, 2 h, 85%, *anti*/*syn* = 9.3:1; (e) $ClSO_2CH_2Cl$, 2,6-lutidine, CH_2Cl_2, 0 °C, 1.5 h; (f) LiBr, Et_2O/THF (10:1), rt, 6 h, 72% for 2 steps; (g) $(Cy_3P)_2Cl_2Ru$=CHPh, CH_2Cl_2, 40 °C, 2 h, then DMSO, rt, 12 h, 94%.

gave the aldehyde **43**. Chemoselective chelation controlled nucleophilic addition of allyltributylstannane to the aldehyde in the presence of the α-alkoxy amide, yielded the hydroxy amide **25** as an 18:1 mixture of diastereomers (92% from **42**) setting the stage for the pivotal dianion alkylation.

Treatment of the hydroxy amide **25** with LiHMDS followed by allyl bromide produced the desired *α,α′-anti*-isomer **24** in 85% yield with 9.3:1 *anti*/*syn* stereoselectivity, in accord with our previous work on the synthesis of (+)-microcladallene B.[33b] The stereocontrol of this selective alkylation presumably arises by alkylation of the (*Z*)-enolate via pretransition state assembly **45** with the electrophile approaching from the least hindered side in the H,H-eclipsed conformation. After extensive experimentation it was found that the desired bromide **46** could be formed by the displacement of the corresponding chloromesylate **44** by bromide (vide infra).[53] Formation of the oxocene **23** occurred efficiently on treatment of the bromide **46** with Grubbs' first-generation catalyst at ambient temperature (94%).[32b] The structure of the bromoamide **23** was confirmed by X-ray crystallographic analysis.

Our extensive experience[54−57] in the field suggested bromination of *α,α′-trans*-12,13-*syn*-oxocene alcohol **47** with inversion of configuration might be problematic. Thus, the alcohol **24** underwent efficient ring-closing-metathesis on exposure to Grubbs' second-generation catalyst **48** to give the oxocene **47** in 84% yield.[32b,c] As anticipated, attempted Hooz bromination[52] of **47** gave the desired bromide **23** along with the diene **49** as a 1:1 mixture (by 500 MHz, ^{1}H NMR) in 54% combined yield.[56] Therefore, in order to overcome the obstacle of this seemingly straightforward transformation, the synthesis of the bromide **46** from the alcohol **24** prior to formation of the oxocene ring was initially attempted under modified Hooz conditions.[33d,e,37] However, under these conditions the alcohol was converted into the desired bromide **46** along with a second component tentatively assigned to the bromide **50** as a 1:1.4 mixture (by 500 MHz ^{1}H NMR) in 80% yield (Scheme 6).

Scheme 6. Bromination Studies[a]



[a]Reagents and conditions: (a) cat. **48**, CH_2Cl_2, 40 °C, 2 h, then DMSO, rt, 12 h, 84%; (b) CBr_4, Oct_3P, $BnEt_3NBr$, toluene, 70 °C, 9 h, 54%, **23**:**49** = 1:1; (c) CBr_4, Oct_3P, 1-methyl-1-cyclohexene, toluene, 70 °C, 2 h, 80%, **46**:**50** = 1:1.4,

These unsatisfactory results led us to develop an efficient two-step procedure. Ultimately, we found that activation of the alcohol **24** as the chloromesylate **44** followed by displacement of the sulfonate ester with bromide with inversion of configuration gave the bromoamide **46** (Scheme 5).[53] This two-step procedure was practically straightforward to conduct, and we were able to prepare gram quantities of the diastereomerically pure bromide **46** with relative ease.

Having secured an efficient synthesis of the medium-ring amide **23**, we next proceeded to address the synthesis of the crucial oxocene corresponding to **22** which would allow the key electrophile-induced biomimetic rearrangement to be inves-

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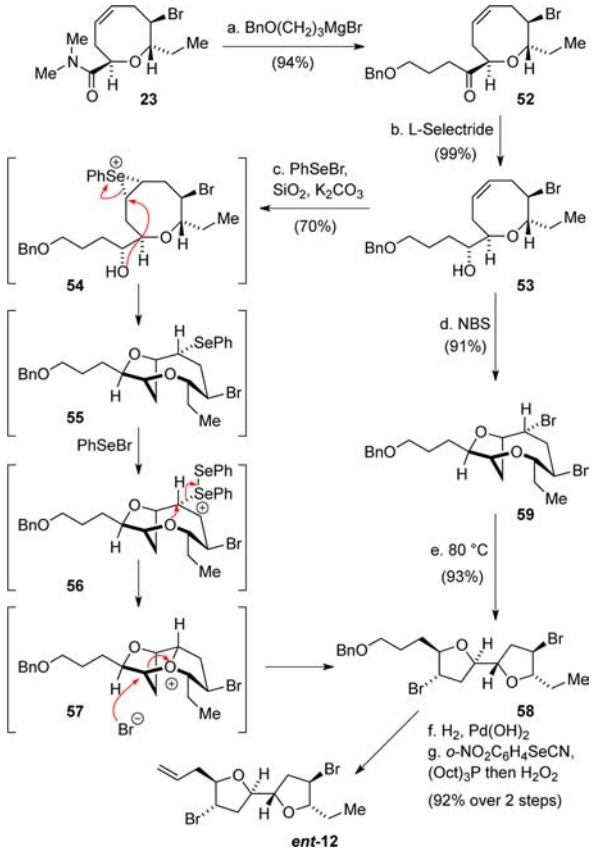
tigated. Application of our direct ketone synthesis protocol to the amide **23** with 3-benzyloxypropylmagnesium bromide followed by Felkin-Anh L-Selectride reduction of the resultant ketone **52**, provided the requisite alcohol **53** as a single stereoisomer in 93% overall yield (Scheme 7).[23a,33b−e,58] Upon exposure to PhSeBr and activated silica gel in the presence of potassium carbonate, the oxocene **53** gave the dibrominated 2,2′-bifuranyl **58** in 70% yield. This complex biomimetic rearrangement is likely initiated by selenonium ion formation (**54**) followed by seleno ether formation giving **55**.[23] Subsequent activation of the phenylselenyl group in **55** by PhSeBr followed by displacement of the nucleofuge by transannular attack of the oxocane oxygen would give the dioxatricyclic oxonium ion **57**. Regioselective opening of the oxonium ion **57** by bromide with inversion of configuration gives the dibrominated 2,2′-bifuranyl **58**. This transformation could be indirectly achieved by initial treatment of the oxocene **53** with NBS, resulting in the formation of the dioxabicyclic dibromide **59** which on heating at 80 °C gave the dibrominated 2,2′-bifuranyl **58** in 85% overall yield. The 2,2′-bifuranyl **58** was readily converted into the allyl-substituted 2,2′-bifuranyl ***ent*-12** using Grieco's method as a key step.[59] The allyl-substituted 2,2′-bifuranyls **12** and ***ent*-12** had identical spectroscopic properties and equal and opposite optical rotations (see Supporting Information).

Scheme 7. Biomimetic Route to the 2,2′-Bifuranyl *ent*-12[a]

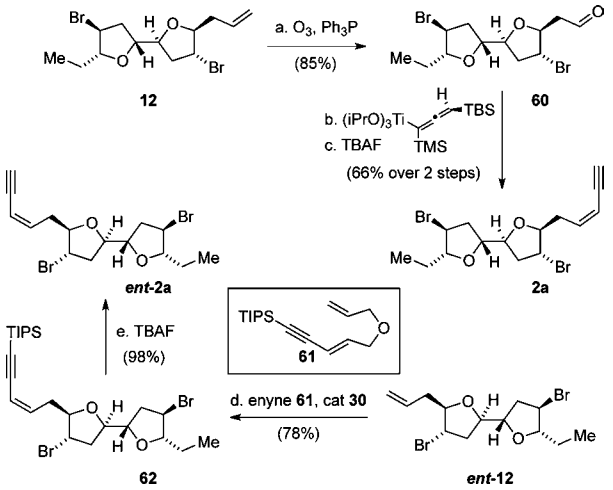


[a]Reagents and conditions: (a) $BnO(CH_2)_3MgBr$, THF, rt, 1 h, 94%; (b) L-Selectride, THF, −78 °C, 1 h, 99%; (c) PhSeBr, SiO_2, K_2CO_3, CH_2Cl_2, rt, 20 h, 70%; (d) NBS, CH_2Cl_2, rt, 2 h, 91%; (e) CH_3CN (0.005 M), 80 °C, 10 h, 93%; (f) H_2, $Pd(OH)_2$, THF, 10 min, rt, 95%; (g) *o*-nitrophenylselenocyanide, $(Oct)_3P$, THF, rt, 30 min, then 30% H_2O_2, rt, 12 h, 97%.

COMPLETION OF THE SYNTHESIS

Having secured efficient syntheses of the allyl-substituted dibromo 2,2′-bifuranyls **12** and ***ent*-12**, all that remained for the completion of the synthesis of elatenyne, was the installation of the (*Z*)-enyne. The Oxford group has previous experience with the use of the Yamamoto−Peterson reaction[10] for the installation of the (*Z*)-enyne, whereas the Seoul group had developed a metathesis strategy for (*Z*)-enyne introduction.[30] Accordingly, ozonolysis of the alkene in **12** followed by a reductive workup delivered the aldehyde **60**. Yamamoto−Peterson reaction[60] using the aldehyde **60** gave the corresponding (*Z*)-enyne as the major product in 83% yield (>30:1, *Z*:*E*, Scheme 8). Removal of the acetylene protecting group gave elatenyne **2a** in 80% yield. Alternatively, (*Z*)-selective cross metathesis of enyne **61** with the alkene ***ent*-12**, in the presence of the Grubbs−Hoveyda second-generation catalyst[39] **30** gave the (*Z*)-enyne **62** as the major product in a combined yield of 78% (4.6:1, *Z*:*E*).[30] Removal of the acetylene protecting group gave elatenyne ***ent*-2a** in 98% yield. The original ^1H NMR spectrum of elatenyne (200 MHz, C_6D_6)[61] and that of the synthetic molecules **2a** and ***ent*-2a** (200 MHz, C_6D_6) were in excellent agreement, in addition the ^{13}C NMR (125 MHz, C_6D_6) spectra were in excellent agreement with the listed resonances in the original isolation paper [^{13}C NMR (50 MHz, C_6D_6)] and confirm that the stereostructure of elatenyne is as represented by **2a**/***ent*-2a**. Unfortunately, we were unable to assign the absolute configuration of elatenyne as the optical rotations measured on the sodium 'D' line of both the Oxford and Seoul samples were close to zero and differed significantly from that reported for the natural product.[7,61] The optical rotations of the synthetic materials recorded with a mercury lamp at 365 nm were equal and opposite in sign.[62]

Scheme 8. Completion of the Synthesis[a]



[a]Reagents and conditions: (a) O_3/O_2, CH_2Cl_2, −78 °C, 2 min, then Ph_3P, −78 °C to rt, 15 h, 85%; (b) TMSC≡CCH_2TBS, *t*BuLi, THF, −78 °C 1 h, then $Ti(OiPr)_4$, 10 min, then **60**, −78 °C, 30 min, rt, 30 min, 83%, *Z*:*E* > 30:1; (c) TBAF, THF, −20 °C, 5 min, 80%; (d) enyne **61**, Grubbs−Hoveyda II **30**, benzene, 70 °C, 6 h, 78%, *Z*:*E* = 4.6:1; (e) TBAF, THF, 0 °C, 30 min, 98%.

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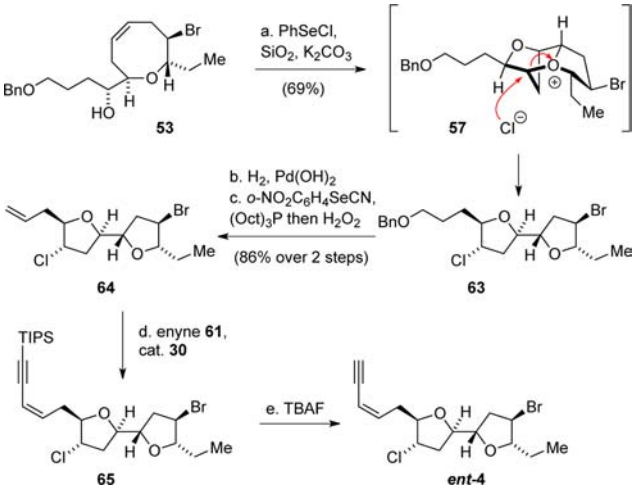
In 2007, Wang and co-workers reported the isolation of an inseparable 1:1 mixture of dihalogenated C_{15} natural products from *L. decumbens* which were ultimately assigned as 2,2′-bifuranyls,[9a,b] structurally related to notoryne[14b] and the reassigned gross structure of elatenyne.[10] The ^{13}C NMR spectra of this mixture of natural products matched closely to the ^{13}C NMR spectrum of elatenyne, although the ^{1}H NMR in $CDCl_3$ had significant differences to the ^{1}H NMR (200 MHz, $CDCl_3$) resonances listed in the original isolation paper,[7,63] and it therefore appeared that the relative configuration of these natural products was probably diastereomeric to elatenyne.[9b] The ^{1}H and ^{13}C NMR spectra, in $CDCl_3$, of synthetic elatenyne prepared above matched the ^{1}H and ^{13}C NMR spectra of Wang and co-workers and, as with Wang's data, showed some differences with the listed resonances (200 MHz, $CDCl_3$) for the ^{1}H NMR spectrum of elatenyne from those in the original isolation paper.[7,64] We concluded that Wang and co-workers had indeed isolated elatenyne (and the bromo−chloro analogue of elatenyne, laurendecumenyne B, **4**). In order to confirm the above, the Seoul group synthesized laurendecumenyne B (Scheme 9). Treatment of the oxocene **53** with PhSeCl gave the corresponding 2,2′-bifuranyl **63** in 69% yield presumably via formation of the tricyclic oxonium ion **57** (Scheme 9).

Scheme 9. Synthesis of Laurendecumenyne B[a]



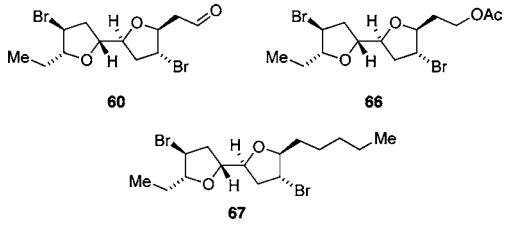
[a]Reagents and conditions: (a) PhSeCl, SiO_2, K_2CO_3, CH_2Cl_2, rt, 3 d, 69%; (b) H_2, $Pd(OH)_2$, THF, 10 min, rt, 94%; (c) *o*-nitrophenylselenocyanide, $(Oct)_3P$, THF, rt, 30 min, then 30% H_2O_2, rt, 12 h, 92%; (d) enyne **61**, Grubbs−Hoveyda II **30**, benzene, 70 °C, 6 h, 77%, *Z*:*E* 3.8:1; (e) TBAF, THF, 0 °C, 20 min, 95%.

Hydrogenolysis of the benzyl group in **63** followed by Grieco elimination[59] delivered the terminal alkene **64** which was converted into laurendecumenyne B ***ent*-4** using the metathesis route analogous to that discussed for the synthesis of **62**. The ^{1}H and ^{13}C NMR spectra of synthetic laurendecumenyne B were an excellent match with the spectra published by Wang[9a,65] and confirm the 2,2′-bifuranyl structure and the relative configuration of laurendecumenyne B as **4**; laurendecumenyne B **4** is thus a diastereomer of notoryne.[14b] Furthermore, the presence of a chlorine atom at C-7 of laurendecumenyne **4** coupled with the transformations described in Schemes 7 and 9, lend weight to the proposed biosynthesis of these 2,2′-bifuranyl halogenated marine natural products (Scheme 1).[14b] Thus, laurendecumenyne B would be derived from the oxonium ion **10** by attack of chloride anion with inversion of configuration at C-7.

With the relative stereochemistry of elatenyne secured, we reasoned that preparation of the (*Z*)- and (*E*)-chloro and -bromofucins (**10** and **11**) would allow their absolute configuration to be confirmed and allow us to propose the absolute configuration of elatenyne. We have successfully synthesized the (*Z*)- and (*E*)-chloro and -bromofucins (**9** and **11**) from the *γ*,*δ*-unsaturated oxocene alcohol *ent*-**53** using haloetherification reactions analogous to the conversion of **53** into **59** depicted in Scheme 7. Comparison of the optical rotations of the synthetic halofucins with the natural product data demonstrated that the absolute configurations of the bromofucins and chlorofucins are represented by structures **9** and **11**, respectively, thus confirming the original absolute configuration assignment of (*E*)-chlorofucin.[26a,66] The likely absolute configuration of elatenyne is therefore represented by **2a**.

Synthesis of Derivatives. In the original isolation paper, Hall and Reiss prepared a number of derivatives of elatenyne including the aldehyde **60**, the acetate **66** and the perhydroderivative **67**. As part of the synthesis of elatenyne **2a** we had already prepared the aldehyde **60**. The ^{13}C NMR spectrum of the synthetic aldehyde **60** was in excellent agreement with the listed data reported by Hall and Reiss.[7,61,67] Reduction of the aldehyde with sodium borohydride followed by acetylation gave the acetate **66**. The ^{1}H NMR of the acetate **66** (200 MHz, C_6D_6) was an excellent match with the corresponding ^{1}H NMR spectrum reported by Hall and Reiss.[61,68] Hydrogenation of a small sample of synthetic elatenyne **2a** gave the perhydroderivative **67** which again showed excellent agreement of the ^{13}C NMR data between the data for the synthetic and natural samples.[7,67]

Chart 2



Synthesis of (*E*)-Elatenyne. In 1989 Erickson and coworkers reported the isolation and partial structure determination of a dibrominated 2,2′-bifuranyl from *L. majuscula*.[13] There are striking similarities between the ^{13}C NMR resonances of elatenyne and the Erickson enyne that led us to propose that the Erickson enyne and elatenyne might be double bond isomers.[10b] The synthesis of the dibrominated 2,2′-bifuranyls **12**/***ent*-12** presented us with an excellent opportunity to test this proposal. Thus, addition of the ylide derived from (3-trimethylsilyl-2-propynyl)-triphenylphosphonium bromide to a cold solution of the aldehyde **60** gave the (*E*)-enyne **68** as an 8:1 mixture of (*E*):(*Z*) geometrical isomers (Scheme 10).[10] Removal of the acetylene protecting group gave (*E*)-elatenyne **3** in 81% yield. Alternatively, using our previously developed, efficient methodology for (*E*)-enyne synthesis,[23a,30a] the allyl substituted 2,2′-bifurnyl ***ent*-12** underwent cross metathesis with crotonaldehyde in the presence of the Grubbs−Hoveyda second-generation catalyst to give exclusively the (*E*)-*α*,*β*-unsaturated

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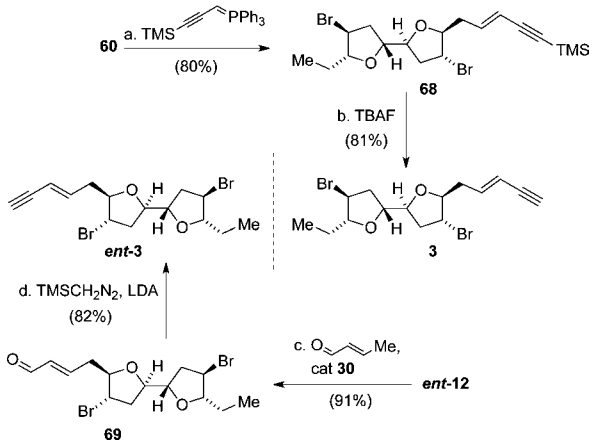
Scheme 10. Synthesis of (*E*)-Elatenyne[a]



[a]Reagents and conditions: (a) TMSC≡CCH_2PPh_3Br, BuLi, THF, −40 °C, 30 min, then **60**, −78 °C to rt, 2 h, 80%, *E*:*Z*, 8:1; (b) TBAF, THF, −20 °C, 5 min, 81%; (c) crotonaldehyde, Grubbs−Hoveyda II **30**, CH_2Cl_2, 40 °C, 1.5 h, then DMSO, rt, 12 h, 91%; (d) $TMSCH_2N_2$, LDA, THF −78 to 0 °C, 1.5 h, 82%.

aldehyde **69** in 91% yield. Colvin−Ohira homologation gave (*E*)-elatenyne ***ent*-3** in 82% yield. The ^1H and ^{13}C NMR spectra of (*E*)-elatenyne **3**/***ent*-3** were in excellent agreement with the resonances listed by Erickson and co-workers, confirming that Erickson had isolated the geometrical isomer of elatenyne. Impressively, Erickson had correctly assigned the relative intra-ring configuration of each THF ring in **3**/***ent*-3** on the basis of ^1H and ^{13}C NMR *J*-value analysis.[69] Our synthesis of both enantiomers of **3**/***ent*-3** will allow the absolute configuration of (*E*)-elatenyne to be determined should a pure sample be isolated again from natural sources.

CONCLUSION

In conclusion we have completed the first total syntheses of both enantiomers of the marine natural product elatenyne **2**/***ent*-2**, as well its double bond isomer (*E*)-elatenyne **3**/***ent*-3**. Additionally, we have synthesized laurendecumenyne B ***ent*-4** and three derivatives of elatenyne **2a**. This work has not only allowed the full structure determination of all of these natural products but also provides excellent supporting evidence for their proposed biogenesis. The total synthesis of elatenyne demonstrates that DFT calculations of GIAO ^{13}C NMR chemical shifts coupled with biosynthetic postulates is a very useful method for distinguishing among large numbers of highly flexible, closely related molecules. Efforts are underway to test and extend the generality of the computational method.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures; spectroscopic and analytical data for all new compounds including copies of NMR spectra; X-ray crystallographic data for **23**. 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.

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(65) There was also an excellent match between the natural ^{13}C NMR spectrum of a 1:1 mixture of elatenyne and laurendecumenyne B reported by Wang and the sum of the ^{13}C NMR spectra of synthetic elatenyne and laurendecumenyne B.

(66) The full synthesis of the halofucins will be reported in due course; Kim, B. Ph.D. Thesis, Seoul National University, Seoul, Korea, 2011.

(67) The ^{1}H NMR data were a reasonable match with the listed resonances reported by Hall and Reiss; see ref 61.

(68) The ^{13}C NMR data were a reasonable match with the listed resonances reported by Hall and Reiss.

(69) We were unable to determine the absolute configuration of natural (*E*)-elatenyne as no optical rotation data were reported in the original isolation paper. Additionally, we have been unable to obtain copies of the proton and carbon NMR data of natural (*E*)-elatenyne.