Tetrahedron 69 (2013) 5205–5220

Contents lists available at SciVerse ScienceDirect

Tetrahedron

journal homepage: www.elsevier.com/locate/tet

Total syntheses of the squalene-derived halogenated polyethers *ent*-dioxepandehydrothyrsiferol and armatol A via bromonium- and Lewis acid-initiated epoxide-opening cascades

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ARTICLE INFO

Article history:
Received 5 February 2013
Received in revised form 8 April 2013
Accepted 11 April 2013
Available online 15 April 2013

Keywords:
Natural products
Total synthesis
Structure elucidation
Terpenoids
Epoxidation

ABSTRACT

Herein we describe in full our investigations leading to the first total syntheses of *ent*-dioxepandehydrothyrsiferol and armatol A. Discovery of a bromonium-initiated epoxide-opening cascade enabled novel tactics for constructing key fragments found in both natural products and have led us to revise the proposed biogeneses. Other common features found in the routes include convergent fragment coupling strategies to assemble the natural products' backbones and the use of epoxide-opening cascades for rapid constructions of the fused polyether subunits. Through de novo synthesis of armatol A, we elucidate the absolute and relative configuration of this natural product.

1. Introduction

Halogenated squalene-derived terpenoid polyethers comprise a class of structurally intriguing natural products bearing various sizes of oxygen heterocycles and stereochemical relationships by which they are connected (Fig. 1).[1] Dioxepandehydrothyrsiferol (**1**),[2] along with venustatriol (**2**),[3] thyrsiferol (**3**),[4] and enshuol (**4**)[5] was isolated from red algae of the genus *Laurencia*. A common feature found in these natural products is the presence of a secondary neopentyl bromide moiety within a bromo-oxane or bromo-oxepane ring. In **1**, the bromo-oxepane ring is part of a fused tricycle with a unique *trans-anti-trans* ring connectivity. A direct and efficient construction of such a substructure was unknown prior to this study and hence served as a motivation to undertake the total synthesis of *ent*-**1**.[6] This account will outline approaches that eventually led to the successful first total synthesis of this natural product.[7]

In contrast, armatols A–F (**5**–**10**) are derived from a related alga of the genus *Chondria* and generally possess a *trans-syn-trans* topography on the fused tricyclic portion of the molecule (Fig. 1).[8] In particular, armatol A (**5**) is the only natural product among the oxasqualenoid polyethers that contains a 7,7,6-fused tricycle in

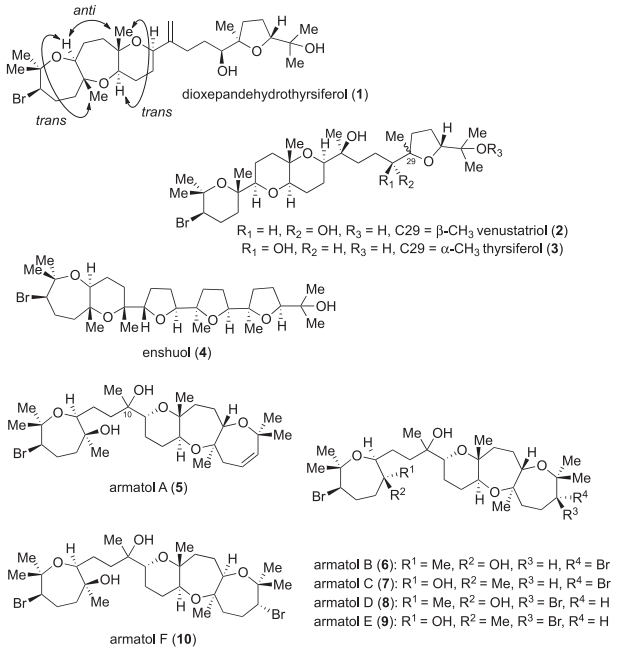

Fig. 1. Representative examples of the halogenated squalene-derived terpenoid polyethers.

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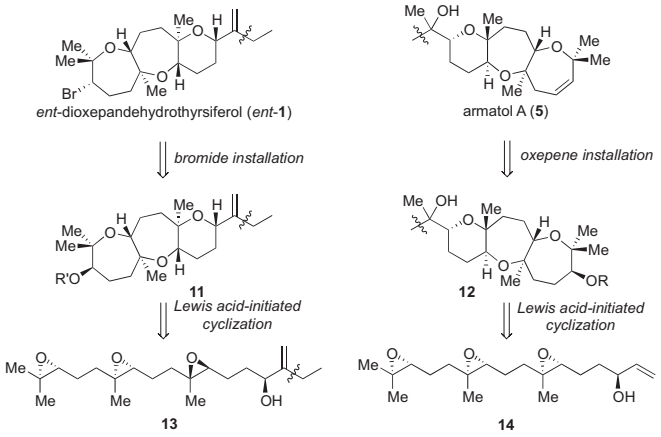
0040-4020/$ – see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.tet.2013.04.041

which one of the rings is an oxepene. Our interest in this family of natural products is bolstered by a lack of absolute and complete relative stereochemical assignment, either by advanced spectroscopic techniques or synthetic studies.

In line with the ongoing program in our group to access polyether natural products through epoxide-opening cascades,[9] we embarked on the syntheses of *ent*-**1** and **5** using such an approach. While a cascade cyclization of a polyepoxide precursor has been proposed in the biosynthesis of **1**,[2] no biogenetic proposal has been put forth for the armatol natural products. Given the structural similarities between **1** and **5**–**10** (the 7,7,6-fused polyether fragments and bromo-oxepanes; either as part of a fused tricycle or by itself), we hypothesize that the two classes of natural products share unified biogenetic mechanisms.

A universal strategy utilized at the beginning of our study involved Lewis acid-initiated epoxide-opening cascades to construct the fused tricycles found in both natural products (Scheme 1). Both of these cascades would rely on Me groups to direct the desired regioselectivity in the epoxide-opening events.[10] The *trans-anti-trans* ring connectivity in *ent*-**1** could retrosynthetically be traced to polyepoxide **13**, bearing epoxides of both *R* and *S* configurations. A bromide installation would follow this cyclization. On the other hand, the *trans-syn-trans* ring connectivity in **5** would come from **14**, and an oxepene installation via elimination of an activated alcohol moiety would follow this cascade. The initial strategy employed an allylic alcohol as a trapping nucleophile in both cascades. This functional group is found in the backbone of *ent*-**1** and would also allow for elaboration toward fragment coupling to eventually access **5** (vide infra).



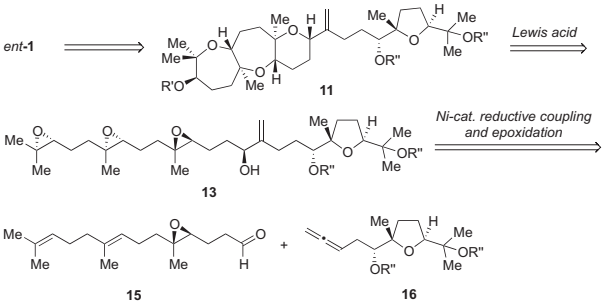
Scheme 1. A unified approach toward the tricyclic fragments of *ent*-**1** and **5**.

2. Results and discussion

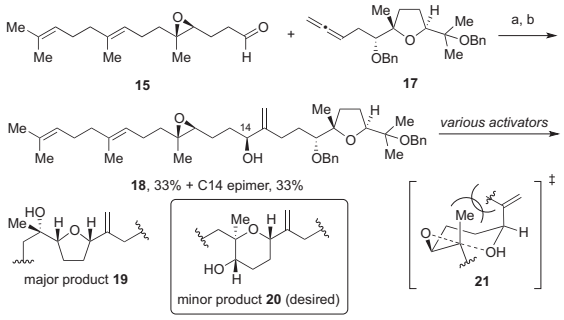
2.1. Synthetic studies toward *ent*-dioxepandehydrothyrsiferol

Our first approach toward *ent*-**1** is delineated in Scheme 2. We planned to access the natural product from an intermediate such as **11**,[11] which would be obtained via a Lewis acid-initiated epoxide-opening cascade of triepoxide **13**. The allylic alcohol moiety in the backbone of this intermediate could be prepared by Ni-catalyzed reductive coupling of aldehyde **15** and allene **16**, as previously described by our group.[12]

Toward this end, **15** and **17** were coupled in the presence of stoichiometric $Ni(cod)_2$ and *t*-$BuMe_2SiH$ to provide the desired allylic ether as a 1:1 mixture of diastereomers at C14 (Scheme 3).[13] After desilylation, allylic alcohols **18** (as a mixture of diastereomers) were obtained for cyclization studies. We felt that these substrates were appropriate model systems to explore the



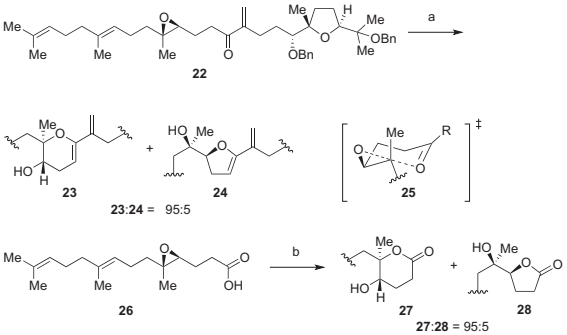
Scheme 2. First-generation retrosynthetic analysis of *ent*-**1**.



Scheme 3. Reductive coupling to access **18** and cyclization studies. Reagents and conditions: (a) $Ni(cod)_2$, Cyp_3P, *t*-$BuMe_2SiH$, THF, rt, 67%, 1:1 dr; (b) TBAF, THF, rt.

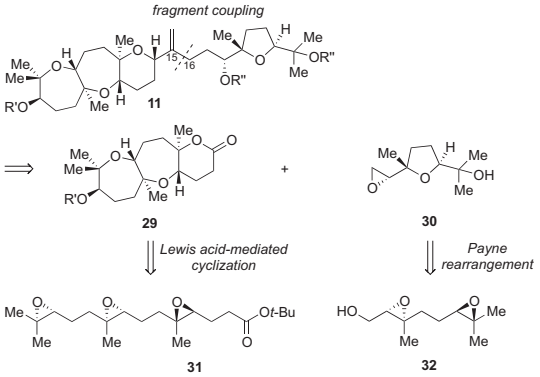
feasibility of formation of the tetrahydropyran (THP) ring in the fused tricyclic portion of *ent*-**1**. However, cyclization of the desired stereoisomer of **18** under thermal, Lewis acidic, or BrØnsted acidic conditions gave predominantly the undesired tetrahydrofuran (THF) product **19** instead of the desired THP product **20** (Scheme 3). This result could be accounted for using a chair transition state model (**21**) to form the THP product, which has also been suggested by Forsyth.[14] This produces an unfavorable 1,3-diaxial interaction between the Me group of the epoxide and alkenyl group of the allylic alcohol.

We postulated that a way to remove the unfavorable interaction in the transition state leading to the desired six-membered ring product was to use a trapping nucleophile attached to an sp^2-hybridized carbon to give a transition state such as **25** (Scheme 4). As a proof of principle, after oxidation of **18** to enone **22**, exposure to Amberlyst 15 gave dihydropyran **23** as the sole product over dihydrofuran **24**. Alternatively, oxidation of aldehyde **15** to carboxylic acid **26** (used crude in the cyclization reaction) also provided a substrate capable of selective δ-lactone **27** formation over γ-lactone **28** under $BF_3{\cdot}OEt_2$-promotion.



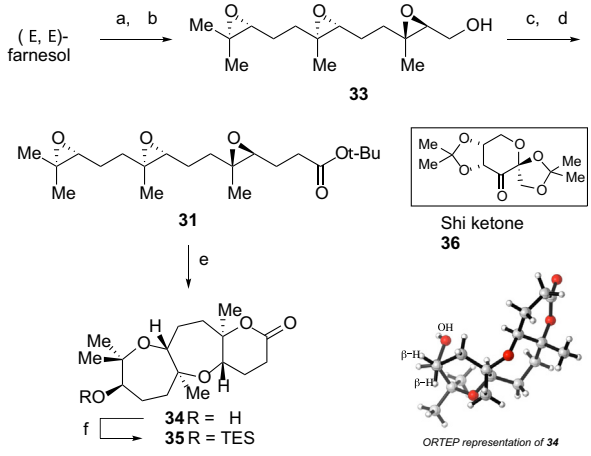
Scheme 4. Successful six-membered ring formations using nucleophiles attached to sp^2-hybridized carbons. Reagents and conditions: (a) Amberlyst 15, CH_2Cl_2, rt; (b) $BF_3{\cdot}OEt_2$, CH_2Cl_2, −78 °C to −50 °C, 73% from **15**.

This discovery led to a revised strategy toward **11** (Scheme 5). In this new route, cyclization to form the tricyclic portion of the molecule would precede fragment coupling along the C15–C16 bond. A Lewis acid-initiated cyclization of triepoxide **31** with a *t*-Bu ester trapping nucleophile attached would give **29**.[10a,b] The other fragment of the molecule would come from diepoxide **32**,[15] which could undergo a Payne rearrangement to give **30**.[16]



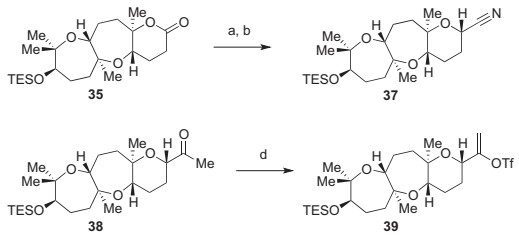
Scheme 5. A new retrosynthetic disconnection toward **11**.

Triepoxide **31** was synthesized in four steps from commercially available material as outlined in Scheme 6. Starting from (*E*,*E*)-farnesol, Sharpless asymmetric epoxidation followed by a Shi epoxidation gave triepoxy alcohol **33**.[6] Conversion of the alcohol to an iodide and displacement with an enolate derived from *tert*-butyl acetate provided **31**. Upon exposure of this substrate to $BF_3 \cdot OEt_2$, the desired tricyclic lactone **35** was obtained in up to 25% over two steps after TES protection of the resultant secondary alcohol. Analysis of the X-ray crystal structure confirmed structure of tricyclic alcohol **34**.



Scheme 6. Synthesis and cyclization of triepoxide **31**. Reagents and conditions: (a) L-(+)-DET, Ti(O*i*-Pr)$_4$, *t*-BuOOH, 4 Å MS, CH_2Cl_2, −50 °C to −40 °C, 95%, 87% ee; (b) Shi ketone (**36**), oxone, *n*-Bu_4NHSO_4, aq K_2CO_3, $Na_2B_4O_7$ buffer, pH 10.5, $(CH_3O)_2CH_2$/CH_3CN/H_2O, 0 °C, 88%; (c) I_2, PPh_3, imidazole, CH_2Cl_2, 0 °C to rt, 87%; (d) *t*-BuOAc, LDA, HMPA, THF, −78 °C, 88%; (e) $BF_3 \cdot OEt_2$, 1,2,3-$(MeO)_3$–C_6H_3, CH_2Cl_2, −78 °C; (f) TESCl, imid, DMF, 45 °C, 25% from **31**.

With lactone **35** in hand, we envisioned forming the C15–C16 bond of *ent*-**1** via a Suzuki–Miyaura fragment coupling. Toward this goal, **35** was elaborated to alkenyl triflate **39** as delineated in Scheme 7: first a DIBAL-H reduction gave a lactol, which underwent TMSCN displacement to give nitrile **37**.[17] This was then followed by a MeMgBr addition to furnish methyl ketone **38**. Conversion to alkenyl triflate **39** (used without purification in the coupling

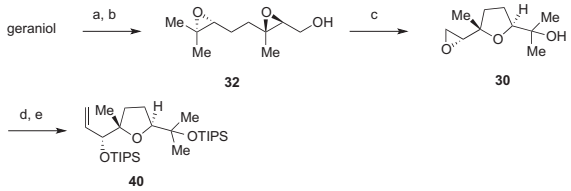


Scheme 7. Synthesis of alkenyl triflate **39**. Reagents and conditions: (a) DIBAL-H, toluene, −78 °C; (b) TMSCN, $BF_3 \cdot OEt_2$, −12 °C to −5 °C, 51% from **35**, 78:22 dr; (c) $Ni(acac)_2$, MeMgBr, toluene, −15 °C to −8 °C, 50%, 93:7 dr; (d) $(SO_2CF_3)_2NC_5H_3NCl$, LHMDS, THF, −78 °C to 0 °C.

reaction) was achieved through reaction with Comins' reagent in the presence of LHMDS.[18]

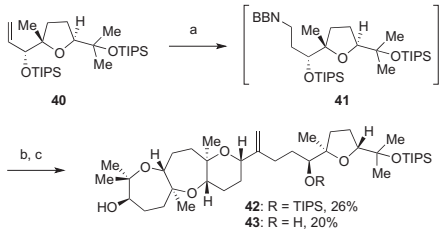
Access to the other coupling partner started with geraniol, which was exposed to a Sharpless asymmetric epoxidation followed by a Shi epoxidation to give **32** (Scheme 8).[15] The diepoxide was then subjected to NaOH in THF/H_2O to effect a Payne rearrangement, giving **30**. Reaction with an ylide derived from trimethylsulfonium iodide followed by bis-TIPS protection gave **40**.[19]

The Suzuki–Miyaura fragment coupling commenced with



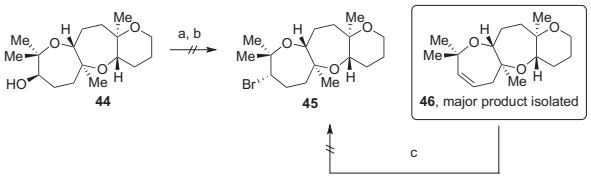
Scheme 8. Synthesis of α-olefin **40**. Reagents and conditions: (a) L-(+)-DET, Ti(O*i*-Pr)$_4$, *t*-BuOOH, 4 Å MS, CH_2Cl_2, −50 °C to −40 °C, 84% ee; (b) (i) Shi ketone (**36**), oxone, *n*-Bu_4NHSO_4, aq K_2CO_3, $Na_2B_4O_7$ buffer, pH 10.5, $(CH_3O)_2CH_2$/CH_3CN/H_2O, 0 °C, 83% (from geraniol); (ii) *p*-NO_2BzCl, Et_3N, CH_2Cl_2, rt,; (iii) 1 M NaOH, THF/H_2O, rt, 95:5 dr, 95% ee (after recrystallization of the *p*-NO_2benzoate derivative); (c) NaOH, THF/H_2O, rt, 59%; (d) (i) $(CH_3)_3SI$, *n*-BuLi, THF, −15 °C to rt; (ii) TIPSCl; (e) TIPSOTf, Et_3N, CH_2Cl_2, 45 °C, 64% from **30**.

hydroboration of **40**–**41**; treatment with aq Cs_2CO_3, $Pd(dppf)Cl_2$, and crude alkenyl triflate **39** at 55 °C provided the desired coupled product (Scheme 9). Deprotection with TBAF gave a mixture of **42** and **43** in approximately 46% combined yield over two steps from **39**, providing the full carbon skeleton of *ent*-**1**.



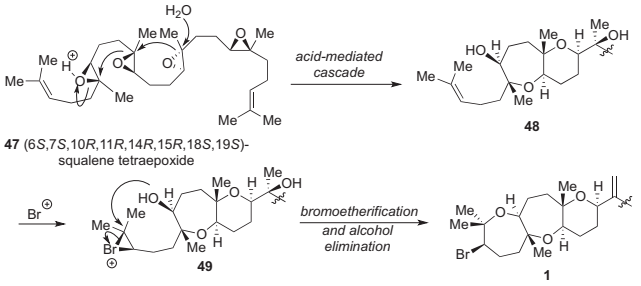
Scheme 9. Suzuki cross-coupling to access the carbon skeleton of *ent*-**1**. Reagents and conditions: (a) 9-BBN dimer, THF, 55 °C; (b) **39**, $PdCl_2(dppf)$, aq Cs_2CO_3, THF/DMF/H_2O, 55 °C; (c) TBAF, THF, rt, 26% **42** and 20% **43** from **39**.

Model system **44** was used to investigate the next key transformation, installation of the neopentyl bromide moiety (Scheme 10).[13] Oxepene **46** was often the main product observed upon conversion of the alcohol to a good leaving group followed by treatment with various bromide sources. Examination of X-ray structural data of **34** (Scheme 6, might be representative of **44**) showed a β-hydrogen antiperiplanar to the alcohol, hence allowing facile elimination to occur. Attempts to convert oxepene **46** to the desired bromide **45** under acidic conditions led only to decomposition.



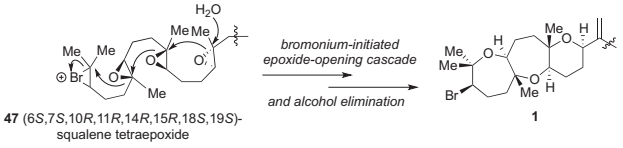
Scheme 10. Representative bromine installation studies. Reagents and conditions: (a) $ClCH_2SO_2Cl$, pyr, DMAP; (b) LiBr, DMPU; (c) HBr, AcOH or PBr_3, SiO_2.

A new strategy was necessary to prepare *ent*-**1** and we turned to the current proposed biosynthesis of **1** for inspiration (Scheme 11).[2] Starting from (6*S*,7*S*,10*R*,11*R*,14*R*,15*R*,18*S*,19*S*)-squalene tetraepoxide **47**, the proposed bioprecursor to **1**, an acid-initiated epoxide-opening cascade could give bicyclic intermediate **48**. This is followed by a discrete bromoetherification step to complete the fused tricyclic portion of **1** bearing a bromo-oxepane. Support for this mechanism comes from the isolation of predehydrovenustatriol acetate, a metabolite containing the entire carbon skeleton of venustatriol (**2**), but lacking the bromo-oxane ring.[2] Bromoetherification to form a single bromo-oxane or bromo-oxepane ring has been used widely in the syntheses of various bromotriterpenes.[20]



Scheme 11. Current proposed biosynthesis of **1**.

A biogenesis in which an epoxide-opening cascade is initiated by formation of a bromonium ion has been proposed for thyrsiferol,[20b] venustatriol,[3] and enshuol,[5] but yet to be demonstrated chemically. McDonald[21] and Holton[22] demonstrated that an epoxide-opening event can be initiated by electrophilic activation of an alkene (using a bromenium or phenylselenium ion, respectively) to afford two rings simultaneously. We surmised that a bromonium-initiated cascade involving a multiepoxide chain likely to be operative in the biosynthesis of **1** (Scheme 12) and decided to pursue such a strategy to construct *ent*-**1**.

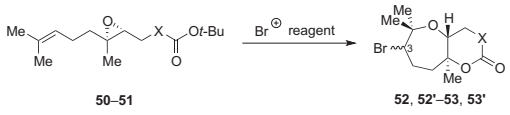


Scheme 12. A bromonium-initiated epoxide-opening cascade to access **1**.

2.2. Model studies of the bromonium-initiated cyclizations

Initial cyclization studies were conducted using monoepoxide model system **50** with a *t*-Bu ester trapping nucleophile (Table 1).[13] Using the conditions reported by McDonald et al. (using $Br(coll)_2ClO_4$ in CH_2Cl_2),[21] no desired product was obtained (entry 1). However, using the highly polar non-nucleophilic solvent 1,1,1,3,3,3-hexafluoro-*iso*-propanol (HFIP),[22,23] the desired bicyclic lactones **52** and **52′** were obtained in 73–76% combined yield (as a 1:1 mixture of C3 diastereomers, entry 2). This transformation could be conducted using either NBS or $Br(coll)_2ClO_4$ as the reagent for presumed bromonium formation. When the new conditions

Table 1
Bromonium-initiated cyclization studies using monoepoxide model systems



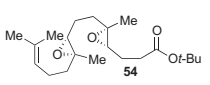
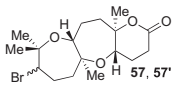
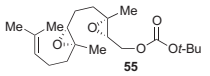
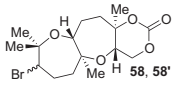
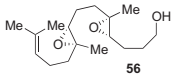
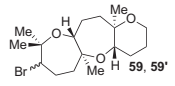
Entry	Substrate	X	Solvent	Product	Yield[a] (%)	
					NBS	$Br(coll)_2ClO_4$
1	**50**	CH_2	CH_2Cl_2	**52**, **52′**	na	—
2	**50**	CH_2	HFIP	**52**, **52′**	76	73
3	**51**	O	HFIP	**53**, **53′**	91	99

[a] Isolated as a 1:1 mixture of diastereomers in all cases.

were applied to monoepoxide substrate **51** bearing a *t*-Bu carbonate trapping nucleophile, carbonates **53** and **53′** were obtained in nearly quantitative yields, significantly improved from the previously reported value (entry 3).[21]

Encouraged by this result, we applied the method to diepoxide substrates containing a *t*-Bu ester, carbonate, or alcohol trapping nucleophiles (Table 2, **54**–**56**).[7] Generally, yields of desired products did not depend significantly on the reagent used for bromonium formation. A trapping nucleophile attached to an sp^2-hybridized carbon usually gave higher yields than that attached to an sp^3-hybridized carbon.

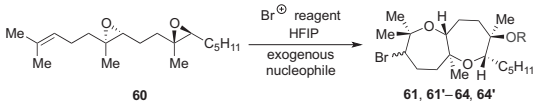
Table 2
Bromonium-initiated cyclization studies using diepoxide model systems

Substrate	Product	Yield[a] (%)	
		NBS	$Br(coll)_2ClO_4$
 **54**	 **57**, **57′**	73	61
 **55**	 **58**, **58′**	66	65
 **56**	 **59**, **59′**	58	52

[a] Isolated as a 1:1 mixture of diastereomers in all cases.

The bromonium-initiated epoxide-opening cascades could also incorporate *intermolecular* trapping nucleophiles when a substrate lacking an intramolecular nucleophile such as **60** was used (Table 3).[13] Potentially, this could enable an approach to the fused tricyclic portion of *ent*-**1** closer to the proposed biogenesis, through incorporation of a water molecule (Scheme 12). As shown in Table

Table 3
Incorporation of exogenous trapping nucleophiles

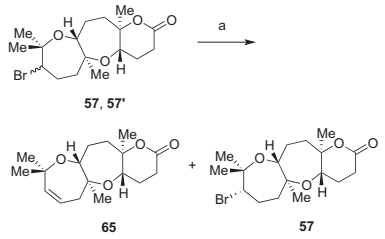


Entry	Nucleophile (equiv)	R	Product	Yield[a] (%)
1	Bu_4NOAc (1.5)	Ac	**61**, **61′**	74[b]
2	EtOH (56)	Et	**62**, **62′**	56[c]
3	H_2O (125)	H	**63**, **63′**	41[b]
4	—	$CH(CF_3)_2$	**64**, **64′**	33[c]
5	$CsOH·H_2O$ (1.5)	H	**63**, **63′**	45[b,d]

[a] Isolated as a 1:1 mixture of diastereomers in all cases.
[b] NBS used.
[c] $Br(coll)_2ClO_4$ used.
[d] 19% of **64**, **64′** also isolated.

3, an ester (entry 1), primary alcohol (entry 2), or even water (entry 3) afforded bicyclic products **61**, **61′**–**63**, **63′** in good yields. If no exogenous nucleophiles were added, HFIP itself was incorporated to form **64**, **64′** (entry 4). Use of a hydroxide base gave both alcohols **63**, **63′** and hexafluorinated products **64**, **64′**, perhaps arising from initial deprotonation of the solvent (entry 5).

Though a 1:1 mixture of diastereomers was isolated in each of these cyclizations, when one such mixture (**57**, **57′**) was subjected to base, the diastereomer with relative configuration found in *ent*-**1** (**57**) was more resistant toward E2 elimination (Scheme 13). Unsurprisingly, the diastereomer that underwent facile elimination (**57′**) was of the same relative configuration as model system **44** (Scheme 10). Observation of the three-dimensional structures of **57** and **57′** explained the differential aptitudes of these intermediates toward E2 elimination.[24] As shown in Fig. 2, there was a β-hydrogen antiperiplanar to the bromine in **57′**, which was not found in **57**. Hence, we have shown that elimination of either a bromide (**57′**) or an alcohol derivative (Scheme 10) could give rise to an oxepene, which is found in the related natural product armatol A (**5**, Fig. 1).



Scheme 13. Differential aptitudes of diastereomers **57** and **57′** toward E2 elimination. Reagents and conditions: (a) DBU, DMSO, 80 °C.

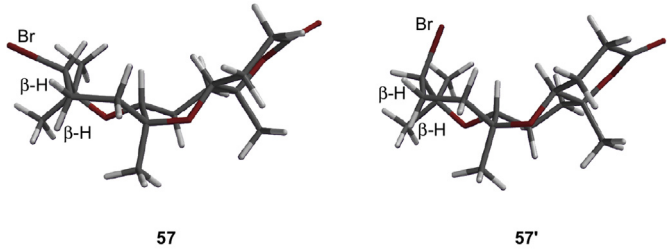
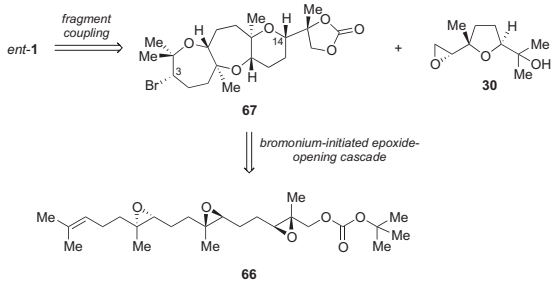


Fig. 2. Computed three-dimensional structures of **57** and **57′** (Spartan, HF/6-31G*).

2.3. A new cascade to construct the tricyclic fragment of ent-1

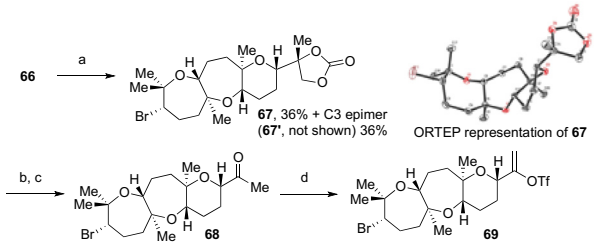
Though **57** could potentially be carried forward to complete the synthesis (Scheme 7), we proposed a new cascade to construct the tricyclic portion of *ent*-**1**: utilizing triepoxide **66** to give tetracycle **67** (Scheme 14).[7] An advantage to this new strategy would be construction of the C14 stereocenter in the cascade, which was previously unattainable (Scheme 3) and required a number of steps to construct (Scheme 7). A *t*-Bu carbonate was chosen as the intramolecular trapping nucleophile in place of a *t*-Bu ester



Scheme 14. A new cascade for the construction of the tricyclic fragment of *ent*-**1**.

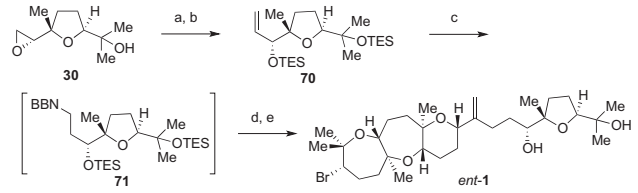
previously used in **31**, for more straightforward elaboration toward fragment coupling (vide infra).[10a,b] The fragment coupling partner **30** would be constructed using our previous strategy (Scheme 8).

Upon exposure of **66** to NBS in HFIP at 0 °C for 15 min, tetracycles **67** and **67′** were obtained in 72% combined yield as a 1:1 mixture of C3 epimers (Scheme 15).[7] After chromatographic separation, basic hydrolysis of the cyclic carbonate moiety of **67** was followed by diol cleavage with $NaIO_4$ to give methyl ketone **68**. This was converted to alkenyl triflate **69** using Comins' reagent and LHMDS as before.



Scheme 15. Access to the tricyclic fragment of *ent*-**1**. Reagents and conditions: (a) NBS, 4 Å MS, HFIP, 0 °C, 36% (+C3 epimer, 36%); (b) NaOH, MeOH, rt, 83%; (c) $NaIO_4$, THF/H_2O, rt, 96%; (d) $(SO_2CF_3)_2NC_5H_3NCl$, LHMDS, THF, −78 °C, quant.

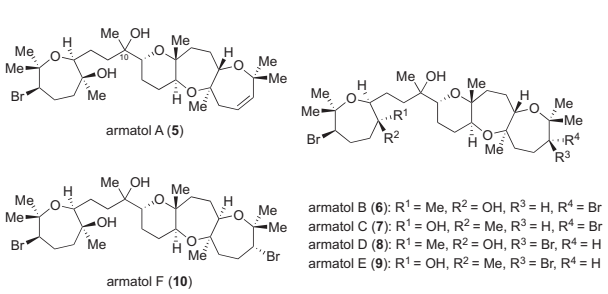
Compared to the previous condition, the Suzuki–Miyaura fragment coupling utilizing **69** was carried out at a lower temperature to avoid complications involving the sp^3 C–Br atom (Scheme 16). Smaller silyl groups on α-olefin **70** facilitated the final deprotection step using TBAF. This concluded the first total synthesis of *ent*-dioxepandehydrothyrsiferol (*ent*-**1**). Discovery of a bromonium-initiated epoxide-opening cascade enabled construction of the unique *trans-anti-trans* 7,7,6-fused polyether framework containing a bromo-oxepane in a single step.[7]



Scheme 16. Completion of the synthesis of *ent*-**1**. Reagents and conditions: (a) $(CH_3)_3SI$, *n*-BuLi, THF, −13 °C to 5 °C, 73%; (b) TESCl, imid, DMF, rt, 95%; (c) 9-BBN dimer, THF, 60 °C; (d) **69**, $PdCl_2$(dppf), aq Cs_2CO_3, THF/DMF/H_2O, 40 °C, 78%; (e) TBAF, THF, rt, 83%.

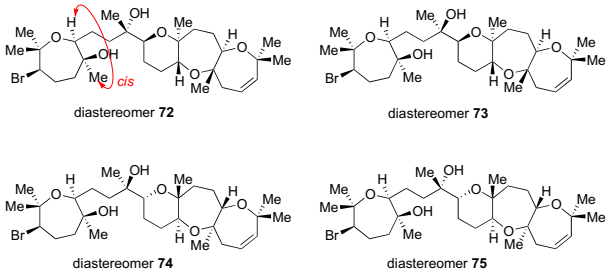
2.4. Total synthesis and structural elucidation of armatol A

The armatol family of natural products was isolated in 2000 Scheme 17,[8] and there have been only two synthetic studies reported toward a single member of this class, armatol F.[25] In these communications, the authors reported approaches toward the proposed structure of the natural product.[8] However, the absolute and relative configurations of armatols A–F had actually never been determined, and such was our goal through de novo synthesis.



Scheme 17. The armatols family of natural products (proposed structures).

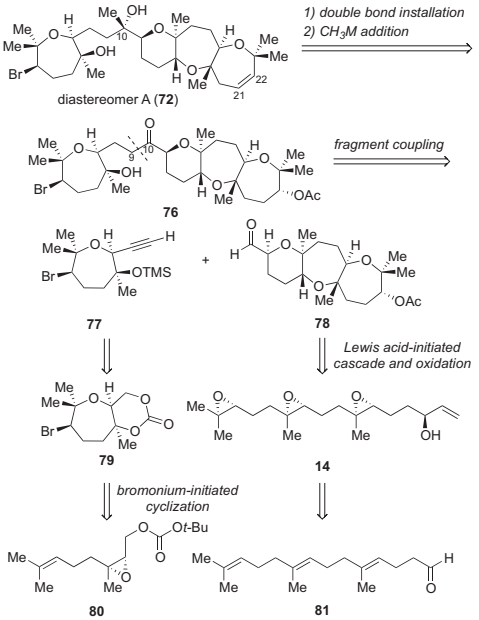
Though the absolute stereochemistry of the lone bromo-oxepane ring has been deduced by degradation studies followed by Mosher analysis,[8,26] the absolute stereochemistry of the C10 tetrasubstituted center had yet to be determined. In addition, though the relative stereochemistry of the 6,7,7-fused tricycle was known to be *trans-syn-trans* (deduced from NOE, NOESY, and other NMR techniques),[8] the absolute stereochemistry of this fragment relative to the rest of the molecule was unknown. Hence, four possible diastereomers (**72**–**75**) were consistent with the published data (Scheme 18).



Scheme 18. The four possible diastereomers of armatol A.

Another intriguing feature found in armatols A, B, D, and F is the cis relationship between the H and Me groups found on the lone bromo-oxepane moiety (Scheme 18, shown for **72**), as opposed to the more common trans relationship.

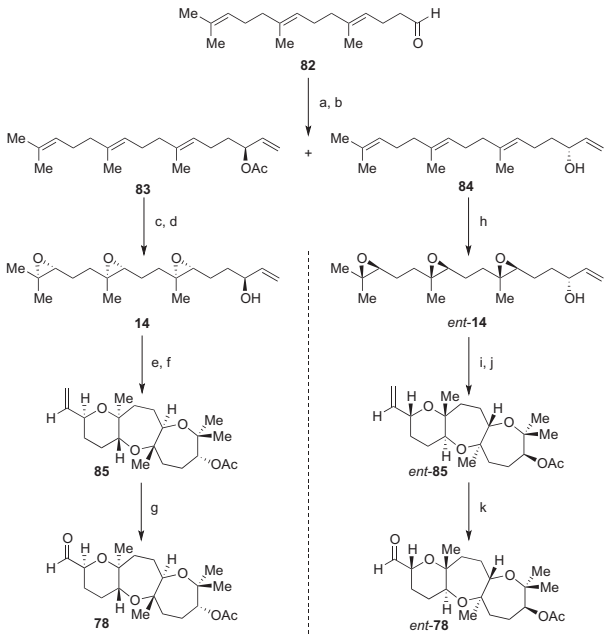
In order to determine the absolute and relative configuration of armatol A, a convergent approach to access diastereomers **72**–**75** was devised (Scheme 19, shown for **72**). Key features of the route included: (1) installation of the C21–C22 olefin via elimination of a suitably activated alcohol and (2) late-stage installation of the C10 stereocenter via methylmetal addition to a ketone such as **76**. Lastly, (3) the C9–C10 bond could be formed from alkyne **77** and tricyclic aldehyde **78**.



Scheme 19. Retrosynthetic disconnection of one possible diastereomer of armatol A (**72**).

Based on our study with model system **51** (Table 1), *cis*-fused bicyclic carbonate **79** could be derived from nerol derivative **80** via a bromonium-initiated 7-*endo*-*trig* cyclization. The fused *trans-syn-trans* tricycle **78** could be accessed by a Lewis acid-initiated epoxide-opening cascade of triepoxide **14**. Since both enantiomers of fragment **14** would be readily accessible, this approach could provide **72**–**75** in a rapid and convergent manner.

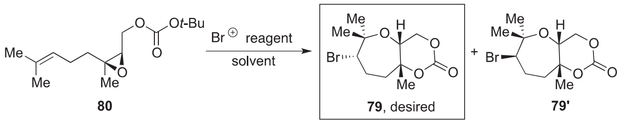
Access to each enantiomer of the key-fused tricyclic fragment is shown in Scheme 20. From aldehyde **82**,[27] vinylmetal addition followed by enzymatic resolution provided tetraenes **83** and **84** with high enantioselectivities.[28] Shi asymmetric epoxidation was followed by deacetylation to give triepoxide **14**. Exposure to $BF_3 \cdot OEt_2$ gave the *trans-syn-trans* tricycle **85** in 18% yield (two steps from **14** after acetylation). Notably, an allylic alcohol trapping nucleophile was tolerated in this case, as opposed to our previous observation in Scheme 3. This is perhaps due to the absence of any unfavorable diaxial interactions in the transition state of this diastereomer. Ozonolysis of α-olefin **85** gave **78**, ready for fragment coupling. Tetraene **84**, on the other hand, was exposed to *ent*-Shi catalyst (*ent*-**36**) under a similar epoxidation condition to give *ent*-**14**.[29] Cyclization as before provided *ent*-**85**, which was oxidized to *ent*-**78**.



Scheme 20. Syntheses of fused tricycles **78** and *ent*-**78**. Reagents and conditions: (a) $CH_2CHMgBr$, THF, −10 °C to rt, 73%; (b) Novozyme 435, vinyl acetate, Et_2O, 4 °C, 40%, 99% ee (for **83**), 33%, 98% ee (for **84**); (c) Shi ketone (**36**), oxone, *n*-Bu_4NHSO_4, aq K_2CO_3, $Na_2B_4O_7$ buffer, pH 10.5, $(CH_3O)_2CH_2/CH_3CN/H_2O$, rt, 88%, 3.5:1 dr; (d) LiOH, THF/MeOH/H_2O, 0 °C, 93%; (e) $BF_3 \cdot OEt_2$, CH_2Cl_2, −78 °C; (f) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 18% from **14**; (g) (i) O_3, $NaHCO_3$, CH_2Cl_2/MeOH, −78 °C; (ii) PPh_3, −78 °C to rt, 65%; (h) *ent*-Shi ketone (*ent*-**36**), oxone, *n*-Bu_4NHSO_4, aq K_2CO_3, $Na_2B_4O_7$ buffer, pH 10.5, $(CH_3O)_2CH_2/CH_3CN/H_2O$, rt, 61%, 3.5:1 dr; (i) $BF_3 \cdot OEt_2$, CH_2Cl_2, −78 °C; (j) Ac_2O, Et_3N, DMAP, CH_2Cl_2, rt, 25% from *ent*-**14**; (k) (i) O_3, $NaHCO_3$, CH_2Cl_2/MeOH, −78 °C; (ii) PPh_3, −78 °C to rt, 74%.

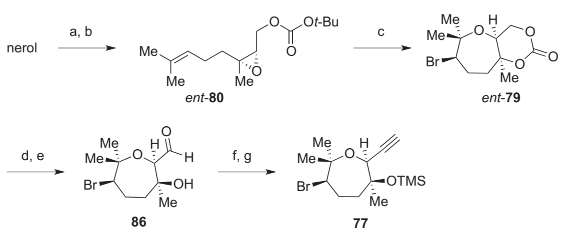
Studies toward formation of the bromo-oxepane fragment of the natural product started with **80** (Table 4).[13] As with *trans* analog **51**, cyclization under literature condition using $Br(coll)_2ClO_4$ in CH_2Cl_2 resulted in a modest combined yield (25%) of diastereomers **79** and **79′** in a 2:3 ratio (Table 4, entry 1).[21] Consistent with our earlier findings, employing the polar non-nucleophilic solvent HFIP significantly increased the yield (entry 2). Altering the counterion of the reagent and performing the cyclization in $MeNO_2$ were found to give comparable yields (entries 3 and 4). Bromodiethylsulfonium bromopentachloroantimonate (BDSB), a reagent recently reported by Snyder et al., also provided similar yields for this cyclization (entries 5 and 6).[30] The decreased yields, as compared to **51**, may result from a non-optimal positioning of the carbonate trapping nucleophile. Hence, the unstable epoxonium ion intermediate would be prone to undergo undesirable side reactions more readily.[31]

Table 4
Cyclization studies of nerol-derived carbonate **80**



Entry	Bromonium source	Solvent	*T* (°C)	Yield **79** (%)	Yield **79′** (%)
1	$Br(coll)_2ClO_4$	CH_3CN	−40	10	15
2	$Br(coll)_2ClO_4$	HFIP	0	18	32
3	$Br(coll)_2BF_4$	HFIP	0	17	31
4	$Br(coll)_2BF_4$	$MeNO_2$	0	22	36
5	$BrSEt_2SbCl_5$	$MeNO_2$	0	22	34
6	$BrSEt_2SbCl_5$	HFIP	0	23	36

With the optimum cyclization conditions in hand, access to the bromo-oxepane fragment of **5** proceeded as shown in Scheme 21. Starting from nerol, Sharpless asymmetric epoxidation installed the epoxide in a modest enantioselectivity. This could be enhanced by enzymatic resolution,[32] which was then followed by installation of the *t*-Bu carbonate group to give *ent*-**80**. The bromonium-initiated cyclization was conducted using $Br(coll)_2BF_4$ in $MeNO_2$ to give the desired diastereomer *ent*-**79** in 22% yield. Hydrolysis under basic condition followed by oxidation provided aldehyde **86**, which was converted via Seyferth–Gilbert homologation to alkyne **77** after TMS protection.[33]

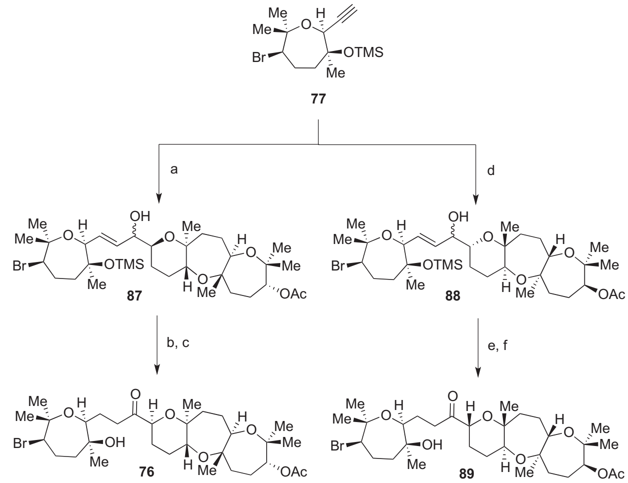


Scheme 21. Elaboration of the bromo-oxepane moiety for fragment coupling. Reagents and conditions: (a) (i) L-(+)-DET, Ti(O*i*-Pr)$_4$, *t*-BuOOH, 4 Å MS, CH_2Cl_2, −23 °C; (ii) Amano lipase-PS, vinyl acetate, Et_2O, 0 °C, 99% ee, 41% from nerol; (iii) K_2CO_3, MeOH, rt, 99%; (b) Boc_2O, 1-Meimid, 0 °C to rt, 77%; (c) $Br(coll)_2BF_4$, 4 Å MS, $MeNO_2$, 0 °C, 22%; (d) NaOH, MeOH, rt; (e) SO_3·pyr, DMSO, Et_3N, CH_2Cl_2, 0 °C to rt; 74% (two steps from *ent*-**79**); (f) dimethyl-1-diazo-2-oxopropylphosphate, K_2CO_3, MeOH, rt; (g) TMSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 59% (two steps from **86**).

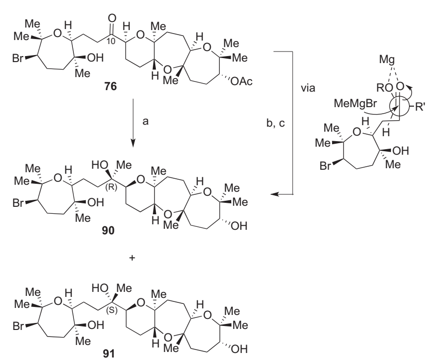
With an ample supply of both coupling partners in hand, we turned our attention to the backbone of armatol A, as shown in Scheme 22. Alkyne **77** was treated with $Cp_2Zr(H)Cl$, followed by transmetalation to the organozinc intermediate, and subsequently treated with aldehyde **78** to give allylic alcohol **87**.[34] Hydrogenation in EtOH gave the saturated alkane with concomitant TMS ether cleavage. Finally, oxidation to ketone **76** was accomplished using TPAP and NMO. An analogous sequence of steps carried out with **77** and *ent*-**78** led to ketone **89**. Starting with ketones **76** and **89**, all four possible diastereomers of armatol A (**72**–**75**) could be accessed.

Treatment of **76** with methyllithium at −78 °C in THF led to a 1:1 ratio of C10 epimers (**90** and **91**, Scheme 23). The relative configuration of each product was assigned after reaction of **76** with methylmagnesium bromide in THF, which gave the (*R*)-diastereomer **90** selectively after acetate deprotection. This is due to addition of MeMgBr to the less hindered face of the chelate formed between the ketone and the oxygen of the THP ring.[35]

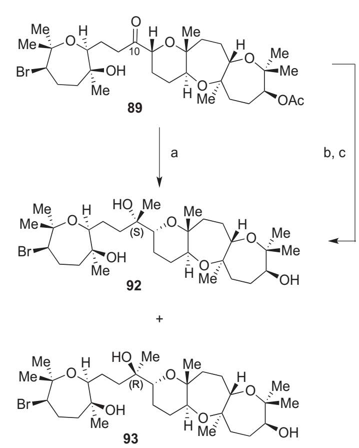
Similarly, reaction of **89** with MeLi yielded **92** and **93**, whilst reaction with MeMgBr gave **92** only after deacetylation (Scheme 24). Gratifyingly, no Br or acetate elimination was observed under these conditions.



Scheme 22. Fragment coupling to access the backbone of armatol A. Reagents and conditions: (a) (i) $[Cp_2Zr(H)Cl]$, CH_2Cl_2, rt; (ii) Me_2Zn, CH_2Cl_2, −78 °C; (iii) **78**, CH_2Cl_2, −78 °C to rt, 64%; (b) H_2 (1 atm), Pd/C, EtOH, rt; (c) TPAP, NMO, 4 Å MS, CH_2Cl_2, 0 °C to rt, 53% (from **87**); (d) (i) $[Cp_2Zr(H)Cl]$, CH_2Cl_2, rt; (ii) Me_2Zn, CH_2Cl_2, −78 °C; (iii) *ent*-**78**, CH_2Cl_2, −78 °C to rt; (e) H_2 (1 atm), Pd/C, EtOH, rt, 52% (from *ent*-**78**); (f) TPAP, NMO, 4 Å MS, CH_2Cl_2, 0 °C to rt, 90%.



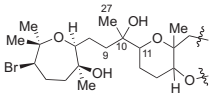
Scheme 23. Access to two diastereomeric carbon skeletons of armatol A. Reagents and conditions: (a) MeLi, THF, −78 °C, 84%, 1:1 dr; (b) MeMgBr, THF, −78 °C to 0 °C; (c) K_2CO_3, MeOH, rt, 67%.



Scheme 24. Access to the remaining diastereomeric carbon skeletons of armatol A. Reagents and conditions: (a) MeLi, THF, −78 °C, 75%, 1:1 dr; (b) MeMgBr, THF, −78 °C, 64%; (c) K_2CO_3, MeOH, rt.

At this point, the ^{13}C NMR shifts between the four diastereomers **90**–**93** and natural armatol A were compared (Table 5).[8] It was observed that the three carbons directly attached to the C10 stereocenter (C9, C11, and C27) in **90** and **92** were much closer to the assigned carbon shifts of the natural product (within 0.4 ppm).

Table 5
Comparison of ^{13}C NMR shifts of **90**–**93** against natural armatol A[8]

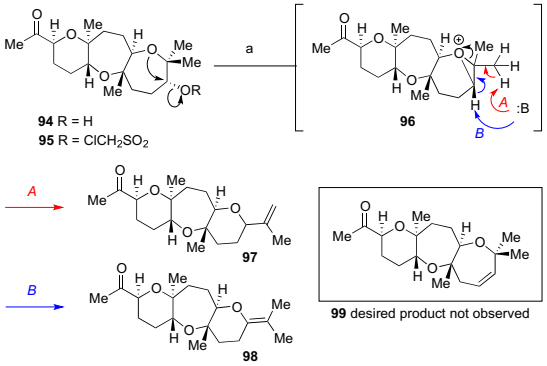


Position	δ **90**[a]	δ **91**[a]	δ **92**[a]	δ **93**[a]	δ Natural **5**[a,8]
9	34.4	36.8[b]	34.7	36.8[b]	34.5
10	73.3	73.4	73.3	73.4	73.4
11	76.3	74.4[b]	76.3	75.4[b]	76.1
27	24.0	23.0[b]	24.3	21.7[b]	23.9

[a] ^{13}C NMR data taken in C_6D_6, referenced to 128.0 ppm.
[b] $|\delta|>0.4$ ppm relative to natural **5**.

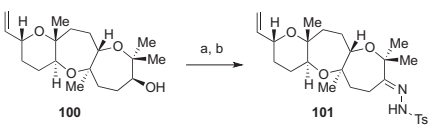
Conversely, the ^{13}C NMR shifts of **91** and **93** differ by as much as 2.3 ppm from the reported data, allowing us to rule out **91** and **93** as potential structures leading to armatol A.

The final challenge involved elimination of the neopentyl alcohol moiety to install the oxepene, which was studied using model system **94**. Standard elimination conditions (Martin's sulfurane, Grieco's protocol, and Burgess's reagent) all failed to provide the desired alkene.[36] Conversion to the activated chloromesylate **95** followed by heating with base led to ring contraction products **97** and **98** (Scheme 25). These outcomes were unexpected, given our previous experience with model system **44** (Scheme 10). Products **97** and **98** could arise from an intermediate such as **96**, which resulted from anchimeric assistance of one of the oxepane's oxygen in displacing the leaving group. The desired oxepene **99** was not observed.



Scheme 25. Oxepene installation studies using model system **94**. Reagents and conditions: (a) DBU, THF, reflux.

An alternative strategy was needed for oxepene installation. Using model system **100**, oxidation of either diastereomer of the secondary alcohol with Dess–Martin periodinane gave the desired ketone in 64% yield (Scheme 26). This could be converted to hydrazone **101** using H_2NNHTs in MeOH in 43% yield.



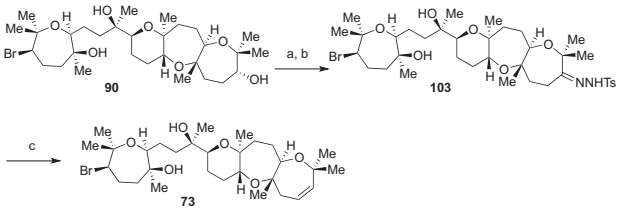
Scheme 26. Elaboration to hydrazone **101**. Reagents and conditions: (a) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 0 °C to rt, 64%; (b) H_2NNHTs, MeOH, 40 °C, 43%.

After hydrazone formation, **101** was subjected to an array of conditions as shown in Table 6.[37] Only sodium hydride in toluene or THF led to the desired olefin **102** in up to 16% yield.[38] With a method to form the oxepene in hand, we were poised to complete the synthesis and assign the absolute configuration of armatol A.

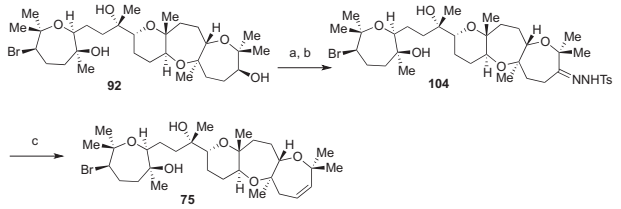
Table 6
Model studies for oxepene installation from hydrazone **101**

Entry	Base	*T* (°C)	Solvent	Result
1	MeLi	−78 °C to rt	THF	NR
2	*n*-BuLi	−78 °C to rt	THF	Decomp.
3	LHMDS	−78 °C to rt	THF	NR
4	NaH	Reflux	THF	12% yield
5	NaH	90 °C	PhMe	16% yield

The oxidation–elimination strategy was applied to late-stage intermediate **90**. Ley oxidation followed by condensation with $TsNHNH_2$ led to hydrazone **103** in a good yield (Scheme 27). Treatment with sodium hydride in THF at 80–100 °C led to the desired alkene **73** in 6% yield. A similar sequence carried out with **92** gave alkene **75** (Scheme 28).



Scheme 27. Access to a possible diastereomer of **5**. Reagents and conditions: (a) TPAP, NMO, 4 Å MS, CH_2Cl_2, 0 °C to rt, 82%; (b) H_2NNHTs, MeOH, 45 °C, 63%; (c) NaH, THF, 90–110 °C, 6%.



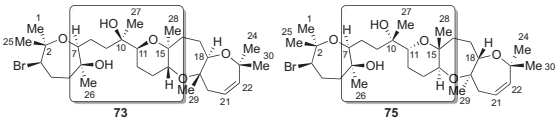
Scheme 28. Access to alkene **75**. Reagents and conditions: (a) TPAP, NMO, 4 Å MS, CH_2Cl_2, 0 °C to rt, 97%; (b) H_2NNHTs, MeOH, 45 °C, 63%; (c) NaH, THF, 100 °C, 6%.

Table 7 summarizes selected ^{13}C NMR data for **73** and **75** compared to natural armatol A.[8] All signals in **73** are within 0.1 ppm of the reported data, with the exception of C11 (in C_6D_6), which differs by 0.2 ppm. Hydrogen bonding of the tertiary alcohol with the adjacent THP ring might account for this difference. Conversely, ^{13}C NMR data for **75** in C_6D_6 differ by at least 0.2 ppm, specifically in the C7–C13 portion of the molecule. Even more significantly, the optical rotation of **73** in $CHCl_3$ is +33.9, while that of **75** is −17.9. The reported optical rotation of armatol A in $CHCl_3$ is +43.4. Taken together, these data confirm the correct structure of armatol A (**5**) as **73**.

Upon completion of this synthesis, comparisons were made for ^{13}C and ^{1}H NMR data of structure **73** against the reported data for armatols B–F (**6**–**10**, Table 8).[8]

The data is consistent with the hypothesis that the natural products share identical quaternary stereochemistry at C10. We believe this also applies to armatol D, despite the marked difference in the ^{13}C NMR shift at C27 of this natural product as

Table 7
Tabulation of ^{13}C NMR data of diastereomers **73** and **75** as compared to natural armatol A[8]



Position	δ **73**[a]	δ **75**[a]	δ Natural **5**[a,8]	Position	δ **73**[b]	δ **75**[b]	δ Natural **5**[b,8]
7	76.4	76.0[c]	76.4	7	76.6	76.1[c]	76.6
8	23.4	23.7[c]	23.4	8	23.9	24.0[c]	23.7
9	33.4	33.4	33.4	9	34.1	34.3[c]	34.1
10	73.1	73.0	73.1	10	73.1	72.8	73.0
11	74.9	75.0	74.9	11	75.5	75.4[c]	75.7
12	27.0	27.1	26.9	12	25.6	25.8	25.6
13	27.2	27.2	27.3	13	27.5	27.6[c]	27.3
14	73.5	73.5	73.5	14	74.2	74.2	74.1
15	77.2	77.2	77.2	15	77.4	77.4	77.4
26	26.0	25.5[c]	25.9	26	25.3	25.2	25.2
27	23.4	23.8[c]	23.4	27	23.5	24.1[c]	23.5
28	26.0	25.0[c]	25.9	28	17.5	17.5	17.5
29	18.0	18.0	18.0	29	18.1	18.2	18.1
30	29.4	29.4	29.3	30	29.5	29.5	29.5

[a] ^{13}C NMR data taken in $CDCl_3$, referenced to 77.0 ppm.
[b] ^{13}C NMR data taken in C_6D_6, referenced to 128.0 ppm.
[c] $|\delta|>0.2$ ppm.

Table 8
Select tabulation of NMR data of **73** compared to the reported data for armatols B–F (**6**–**10**)[8]

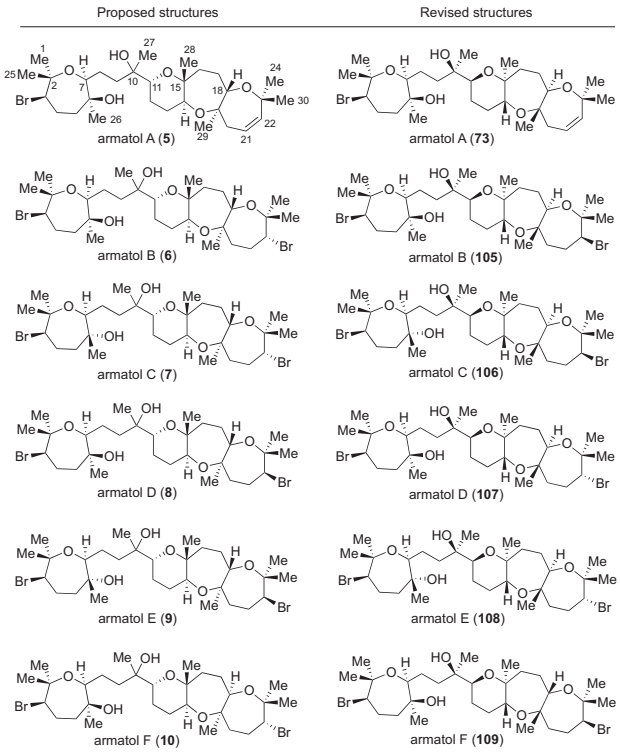
Position	δ **73**[a,b]	δ **6**[b,8]	δ **7**[b,8]	δ **8**[b,8]	δ **9**[b,8]	δ **10**[b,8]
C9	33.4	33.5	33.4	34.0[c]	33.7	33.1
C10	73.1	73.2	73.4	73.7[c]	73.7[c]	72.9
C11	74.9	75.4[c]	75.5[c]	75.7[c]	75.3	76.6[c]
C27	23.4	23.5	23.5	25.5[c]	23.5	23.4
H27	1.09	1.09	1.09	1.09	1.10	1.10

[a] Synthetic data for armatol A.
[b] ^{13}C NMR data taken in $CDCl_3$ referenced to 77.0 ppm. ^1H NMR data taken in $CDCl_3$, referenced to 7.26 ppm.
[c] $|\delta|>0.4$ ppm relative to **73**.

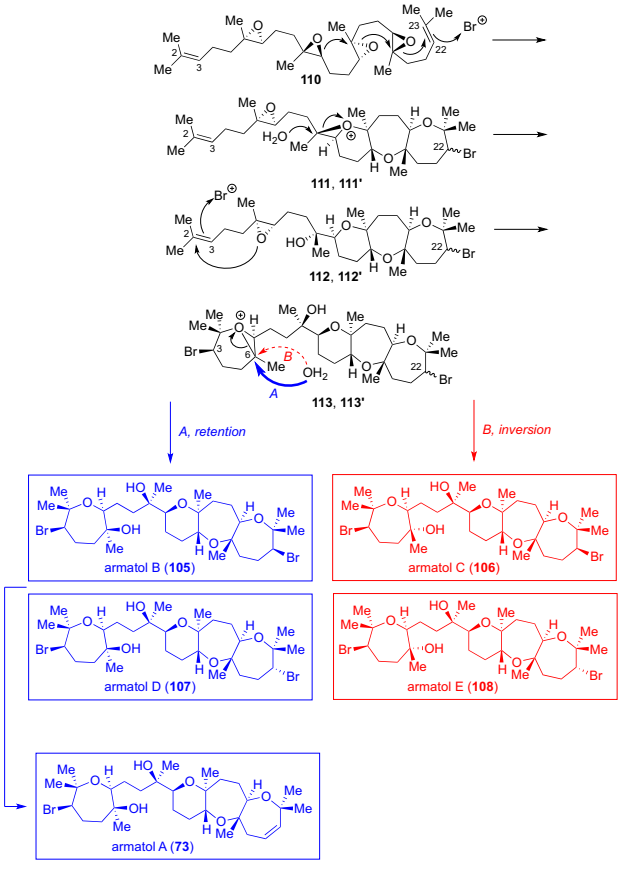
compared to **73**. We have shown the absolute stereochemistry of armatol A (**73**) through de novo synthesis and have supported that our proposed structure might apply for the remaining members of the armatol family to give structures **105**–**109** (Scheme 29).

2.5. Proposed biogenesis for the armatol family of natural products

Our proposed biogenesis for the armatol natural products (**73** and **105**–**108**) is shown in Scheme 30. In line with our previous proposal for dioxepandehydrothyrsiferol (**1**), a bromonium-initiated epoxide-opening cascade of a polyepoxide precursor such as **110** could give tricycles **112** and **112′**, common intermediates to the natural products. Bromonium formation at C22–C23 alkene would not have to be facially-selective, as both C22 diastereomers are found in nature. A stereoselective bromonium formation at the C2–C3 alkene could initiate a cyclization event with the remaining epoxide. Opening of this epoxonium at C6 by a water molecule with inversion would give armatol C (**106**) and E (**108**) while opening with retention would give armatol B (**105**) and D (**107**). Armatol A (**73**) could then arise from elimination of an HBr equivalent from **105** or **107**. A different polyepoxide precursor might give rise to **109**, given the unique cis ring junction between two fused oxepanes found in this natural product.



Scheme 29. Proposed structures of armatols A–F.



Scheme 30. Proposed biogenesis for **73** and **105**–**108**.

3. Conclusion

In summary, we have completed the first total syntheses of *ent*-dioxepandehydrothyrsiferol (*ent*-**1**) and armatol A (**73**). Through our studies of *ent*-**1**, we have discovered a biomimetic bromonium-initiated epoxide-opening cascade that proceeded optimally in a polar non-nucleophilic solvent. This methodology was used to construct the fused *trans-anti-trans* tricyclic portion of *ent*-**1**, bearing a bromo-oxepane in one step from a polyepoxide precursor, previously unattainable utilizing the corresponding Lewis acid-initiated epoxide-opening cascade. The bromo-oxepane moiety in **73** was also constructed using this method from a nerol derivative, representing one of the first examples of such a transformation utilizing a *cis* epoxide.

The convergent route developed toward armatol A allowed rapid access to all four possible diastereomers of this natural product (**72**–**75**). A Lewis acid-initiated epoxide-opening cascade constructed both enantiomers of the fused *trans-syn-trans* tricycle. After fragment coupling and installation of the C10 quaternary center, a Bamford–Stevens reaction constructed the oxepene (as part of the tricycle) and confirmed the relative and absolute configuration of armatol A (**73**). It is also possible that the structure we propose applies to the other members of the armatol family. Finally, through our work with *ent*-**1** and the discovery of the bromonium-initiated epoxide-opening cascade, we have proposed a unified biogenesis for this natural product as well as members of the armatol family.

4. Experimental

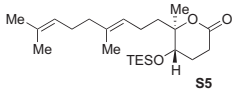
4.1. General

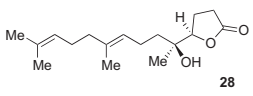
Experimental procedures and characterization data for selected compounds are included in this text. Additional experimental procedures, characterization data, and spectra for all new compounds can be found in the Supplementary data submitted along with this manuscript and the Supplementary data of a previous communication.[7]

Unless otherwise noted, all reactions were performed under an oxygen-free atmosphere of argon with rigid exclusion of moisture from reagents and glassware. Teflon stir bars were oven or flame-dried prior to use. Except where noted, all solvents and triethylamine used in the reactions were purified via an SG Water USA solvent column system. 1,1,1,3,3,3-Hexafluoro-2-propanol (HFIP) (≥99%) was purchased from Aldrich Chemical Company and was used without further purification. Nitromethane was dried at 90 °C overnight with CaH_2 before being distilled into and stored in an airtight Schlenk tube. 4 Å MS was activated by flame drying under high vacuum three times (with cooling in between) immediately before use. HN(*i*-Pr)$_2$, hexamethylphosphoramide (HMPA), and 1,3-dimethyltetrahydropyrimin-2(1*H*)-one (DMPU) were distilled from CaH_2 before use. $BF_3\cdot OEt_2$ and Ti(O*i*-Pr)$_4$ were distilled from CaH_2 before use. EtOH was distilled from 4 Å MS before use. Solvents for the Suzuki cross-coupling reaction were rigorously degassed through freeze–pump–thaw cycles within a week before use and kept in an airtight Schlenck tube. Cs_2CO_3 used in the Suzuki cross-coupling reaction was pumped on under high vacuum overnight, kept and used inside a glovebox. 9-Borabicyclo[3.3.1]nonane (9-BBN) dimer was pumped on under high vacuum overnight, kept and used inside a glovebox. CuI and the CH_2Cl_2 adduct of $PdCl_2$(dppf) were purchased from Strem chemical company and kept and used inside a glovebox. Bis(cyclooctadienyl)nickel(0) (Ni(cod)$_2$) and tricyclopentylphosphine (Cyp$_3$P) were purchased from Strem Chemicals, Inc., stored under nitrogen atmosphere and used without further purification. Tetrabutylammonium acetate was pumped under vacuum overnight, kept and used inside a glovebox. Trimethylsulfonium iodide was azeotropically dried from toluene three times before use. $SO_3\cdot$pyr and $(CH_3)_3N\cdot HCl$ were pumped on under high vacuum overnight before use. $NaIO_4$ adsorbed on SiO_2 was made as follows: 2.57 g of $NaIO_4$ was dissolved in 5 mL of H_2O at 70–80 °C. It was then poured into 10.0 g of silica. The resulting mixture was stirred well for 30 min until homogenous.[39] Shi ketone **36** was prepared from D-fructose according to the procedure of Vidal-Ferran and co-workers and was used without recrystallization.[40] *t*-BuOOH was purchased from Fluka as a ~5.5 M solution in decane stored over activated 4 Å MS. MsCl was distilled from calcium hydride before use. $[(Ph_3P)CuH]_6$ was purchased from Fluka (brick red powder), pumped on under high vacuum overnight, kept and used inside a glovebox. *N*-Bromosuccinimide (NBS) was recrystallized from H_2O before use and kept at 0 °C in the absence of light. Br(coll)$_2ClO_4$ was prepared according to the previously reported procedure,[41] and kept at 0 °C in the absence of light.

Analytical thin layer chromatography was performed using EM Science silica gel 60 F_{254} plates. The developed chromatogram was analyzed by UV lamp (254 nm) and Ceric Ammonium Molybdate (CAM) or ethanolic phosphomolybdic acid (PMA) solution. Liquid chromatography was performed using flash chromatography of the indicated solvent system on Silicycle Silica Gel (230–400 mesh). Alternatively, flash chromatography was also performed on the Biotage Isolera™ automated purification unit with SNAP columns™. Analytical HPLC was performed on the column phase indicated on a Hewlett–Packard 1100 Series HPLC. ^{1}H and ^{13}C NMR spectra were recorded on a Varian Inova-500 MHz, Bruker AVANCE-400 MHz, or Bruker AVANCE-600 MHz spectrometer in $CDCl_3$ or C_6D_6. Chemical shifts in ^{1}H NMR spectra are reported in parts per million (ppm) on the δ scale from an internal standard of residual $CHCl_3$ in $CDCl_3$ (7.27 ppm) or residual C_6HD_5 in C_6D_6 (7.16 ppm). Data are reported as follows: chemical shift, multiplicity (app=apparent, br=broad, s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet), coupling constant in hertz (Hz), and integration. Chemical shifts of ^{13}C NMR spectra are reported in parts per million from the central peak of $CDCl_3$ (77.23 ppm) or residual C_6D_6 (128.39 ppm) on the δ scale. ^{19}F NMR spectra were recorded on a Varian Inova-300 MHz or Bruker AVANCE-400 MHz spectrometer in C_6D_6 using either CF_3CH_2OH (at −77.8 ppm) or C_6F_6 (at −164.9 ppm) as a reference. Infrared (IR) spectra were recorded on a Perkin–Elmer 2000 FT-IR. High-resolution mass spectra (HRMS) were obtained on a Bruker Daltonics APEXIV 4.7 T Fourier Transform Ion Cyclotron Resonance Mass Spectrometer by Li Li of the Massachusetts Institute of Technology, Department of Chemistry Instrumentation Facility. Optical rotations were measured on a Jasco Model 1010 polarimeter at 589 nm.

4.2. Preparation of lactones S5 and 28



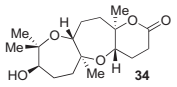


Aldehyde **15**[13] (600 mg, 2.27 mmol, 100 mol %) was dissolved in 2-methyl-2-butene (60 mL, ~25 mL/mmol of aldehyde) at room temperature in a 250 mL Erlenmeyer flask. *tert*-Butyl alcohol (60 mL) and water (30 mL) were added. $NaH_2PO_4\cdot H_2O$ (1.252 g, 9.076 mmol, 400 mol %) was added and the mixture was stirred vigorously at rt for 5 min until the mixture became homogeneous. Sodium chlorite (1.23 g, 13.6 mmol, 600 mol %) was added in one portion. The mixture was stirred vigorously at rt for 1 h. The mixture was poured into 5% aq NaH_2PO_4 solution (200 mL) and extracted twice with diethylether (100 mL then 150 mL). The organic fraction was dried with $MgSO_4$. NMR of the crude reaction mixture showed the desired acid **26**. The crude mixture was used directly in the next step.

Crude acid **26** (~2.27 mmol, 100 mol %, used directly without purification) was dissolved in dichloromethane (45 mL). The solution was cooled to −78 °C. $BF_3{\cdot}OEt_2$ was diluted in dichloromethane (5 mL) and added to the reaction mixture over 2 min. Temperature of the cold bath was maintained under −70 °C for 8 h. Acetone was added to the cold bath to warm the bath to −50 °C over 5 min. The reaction was quenched with saturated $NaHCO_3$ (20 mL). The flask was removed from the cold bath and warmed to room temperature. The mixture was extracted with dichloromethane. The organic layer was dried with $MgSO_4$. ^1H NMR of the crude mixture indicated δ-lactone **27**/γ-lactone **28** ratio of 95:5. Column chromatography isolated γ-lactone **28**. ^1H NMR (400 MHz, C_6D_6): δ 5.23 (t, J=6.7 Hz, 1H), 5.17 (t, J=7.0 Hz, 1H), 3.68 (t, J=7.4 Hz, 1H), 2.20–1.70 (m, 8H), 1.68 (s, 3H), 1.58 (s, 3H), 1.57 (s, 3H), 1.45–1.10 (m, 4H), 1.08 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6): δ 176.8, 135.8, 131.7, 125.1, 125.0, 85.5, 72.8, 40.5, 37.8, 29.1, 27.5, 26.2, 23.5, 22.5, 22.1, 18.1, 16.4.

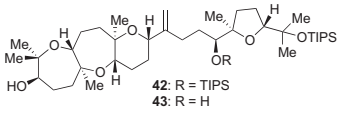
δ-Lactone **27** and imidazole (232 mg, 3.40 mmol, 150 mol %) were dissolved in *N*,*N*-dimethylformamide (12 mL). Under argon, chlorotriethylsilane (0.460 mL, 2.72 mmol, 120 mol %) was added in one portion at room temperature. The solution was heated at 50 °C for 4 h. The reaction mixture was removed from the oil bath and cooled to rt. The reaction was quenched with water (5 mL, exothermic). The mixture was diluted with diethylether (100 mL) and washed twice with saturated NH_4Cl. The organic fraction was dried with $MgSO_4$. Column chromatography isolated 658 mg of silylated δ-lactone **S5** (73% yield over three steps from aldehyde **15**). $[\alpha]_D^{20}$ +18.0 (*c* 2.8, CH_2Cl_2); IR (NaCl, thin film): 2957, 2914, 2877, 1738, 1457, 1378, 1239, 1098, 1006, 745 cm^{-1}; ^1H NMR (400 MHz, C_6D_6): δ 5.23 (t, J=6.8 Hz, 1H), 5.20 (t, J=7.1 Hz, 1H), 3.51 (dd, J=4.6, 7.2 Hz, 1H), 2.42 (dt, J=7.3, 18.0 Hz, 1H), 2.30–2.00 (m, 7H), 1.68 (s, 3H), 1.60 (s, 3H), 1.57 (s, 3H), 1.60–1.40 (m, 4H), 1.21 (s, 3H), 0.89 (t, J=8.0 Hz, 9H), 0.44 (q, J=7.8 Hz, 6H); ^{13}C NMR (100 MHz, C_6D_6): δ 168.8, 136.1, 131.6, 125.2, 124.5, 85.2, 69.6, 40.52, 40.49, 27.5, 27.1, 26.2, 25.7, 22.6, 21.3, 18.1, 16.4, 7.4, 5.6; HRMS (ESI) m/z calcd for $C_{23}H_{42}O_3Si$ $[M+Na]^+$: 417.2795, found 417.2802.

4.3. Lewis acid-mediated cyclization to prepare 34



Ester **31**[13] (5.15 g, 14.0 mmol, 100 mol %) and 1,2,3-trimethoxybenzene (4.70 mg, 27.0 mmol, 200 mol %) were dissolved in CH_2Cl_2 (280 mL). The mixture was cooled under argon to −78 °C. $BF_3{\cdot}OEt_2$ (1.77 mL, 14.0 mmol, 100 mol %) was added. The mixture was stirred at −78 °C for 1 h and quenched with saturated $NaHCO_3$ (50 mL) at −78 °C. The cold bath was removed and the mixture was warmed to rt. Layers were separated and the aqueous layer was extracted two times with CH_2Cl_2 (2×100 mL). The extract was dried with $MgSO_4$. Column chromatography isolated cyclization product **34** in a concentrated CH_2Cl_2 solution (~3–5 mL) and carried on directly to the next step. $[\alpha]_D^{20}$ −3.1 (*c* 1.3, CH_2Cl_2); IR (NaCl, thin film): 3470, 2976, 2941, 1722, 1381, 1273, 1206, 1083 cm^{-1}; ^1H NMR (400 MHz, C_6D_6): δ 4.14 (d, J=8.9 Hz, 1H), 3.64 (dd, J=5.1, 11.7 Hz, 1H), 3.40 (t, J=5.1 Hz, 1H), 2.27 (dt, J=3.5, 12.8 Hz, 1H), 2.16–2.00 (m, 2H), 1.90–1.45 (m, 10H), 1.26 (s, 3H), 1.20 (s, 3H), 1.13 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6): δ 169.3, 84.8, 80.5, 78.4, 76.7, 76.5, 68.7, 42.1, 31.9, 29.2, 29.1, 28.8, 26.1, 25.4, 22.9, 20.9, 20.7; HRMS (ESI) m/z calcd for $C_{17}H_{28}O_5$ $[M+Na]^+$: 335.1829, found 335.1833.

4.4. Suzuki–Miyaura fragment coupling to prepare 42 and 43

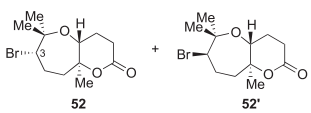


9-BBN dimer (24.4 mg, 0.100 mmol, 110 mol %) was placed in a Schlenk tube. Alkene **40**[13] (51.3 mg, 0.100 mmol, 110 mol %) in THF (1 mL) was added under argon at rt. More THF (0.2 mL) was used for rinsing. The Schlenk tube was closed and the mixture was heated at 55 °C for 20 h. After the mixture was cooled to rt, cesium carbonate solution (0.20 mL, 0.20 mmol, 220 mol %, 1 M in H_2O, saturated with nitrogen) was added under argon. Bubbling occurred immediately. The mixture was stirred at rt for 15 min. Crude alkenyl triflate **39**[13] (~0.0884 mmol, 100 mol %) in THF (1 mL) was added. $Pd(dppf)Cl_2$ (8 mg, 0.01 mmol, 10 mol %) in DMF (1 mL) was added. The Schlenk tube was closed and the mixture was heated at 55 °C for 18 h. The reaction mixture was cooled to room temperature. The crude was diluted with Et_2O, washed with 0.5 M HCl and brine, and dried with $MgSO_4$. Column chromatography isolated cross-coupling products. The mixture of products was dissolved in THF (5 mL) and TBAF (80 μL, 0.08 mmol, 1 M THF) was added at rt. The reaction mixture was stirred for 1.25 h. The mixture was diluted with Et_2O and washed with H_2O. Column chromatography isolated TES deprotected cross-coupling product **42** (19 mg, 26%) and also cross-coupling product that has both TES and 2° TIPS group deprotected (**43**) (12 mg, 20%). Data for **42**: IR (NaCl, thin film): 3451, 2943, 2866, 1463, 1380, 1082, 883 cm^{-1}; ^1H NMR (600 MHz, C_6D_6): δ 4.96 (s, 1H), 4.93 (s, 1H), 4.24 (m, 2H), 3.93 (t, J=5.2 Hz, 1H), 3.89 (dd, J=6.4, 9.0 Hz, 1H), 3.81 (dd, J=4.3, 11.5 Hz, 1H), 3.20 (d, J=6.3 Hz, 1H), 2.54 (m, 2H), 2.34 (t, J=12.8 Hz, 1H), 2.24 (q, J=10.4 Hz, 1H), 2.15–1.50 (m, 16H), 1.45 (s, 3H), 1.37 (s, 3H), 1.35 (s, 3H), 1.30 (s, 3H), 1.27 (s, 3H), 1.21 (m, 21H), 1.16 (m, 21H), 1.09 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6): δ 152.9, 109.2, 87.8, 87.1, 80.1, 78.9, 78.7, 78.0, 77.2, 76.8, 74.9, 71.7, 70.8, 42.4, 36.0, 34.3, 32.4, 30.6, 29.9, 29.3, 29.0, 27.6, 27.5, 26.2, 25.42, 25.35, 23.1, 22.6, 21.1, 20.1, 19.11, 19.05, 14.12, 14.08; HRMS (ESI) m/z calcd for $C_{48}H_{92}O_7Si_2$ $[M+Na]^+$: 859.6274, found 859.6277.

4.5. Model studies of the bromonium-initiated cyclization using monoepoxides 50 and 51

4.5.1. Representative procedure for the bromonium-initiated cyclization in HFIP. 4 Å MS was activated as described in the General Experimental Methods. The substrate was added to HFIP. Either NBS or $Br(coll)_2ClO_4$ was added in one portion under Ar at the specified temperature. The reaction mixture was stirred in the absence of light. It was then filtered through Celite, eluting with Et_2O. After concentrating the filtrate, the residue was repartitioned between Et_2O and H_2O. The aqueous layer was extracted with Et_2O (2×) and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Column chromatography (25% EtOAc in hexanes) isolated the products together as a 1:1 mixture of C3 epimers as colorless oils. In few cases, second column chromatography (50–60% Et_2O in hexanes) was performed to separate the two diastereomers for characterization purposes. Relative configurations of the diastereomers were determined by NOE studies.

*4.5.2. Preparation of **52** and **52'** using NBS as the bromenium source.*



The general procedure was followed with ester **50**[13] (25.4 mg, 0.0946 mmol, 100 mol %), 4 Å MS (234 mg, unactivated mass), HFIP (1.8 mL), and NBS (50.5 mg, 0.284 mmol, 300 mol %). The reaction

was performed at 0 °C for 1 h. Lactones **52**, **52′** were isolated together as a 1:1 mixture of C3 epimers (20.9 mg, 0.0718 mmol, 76%) as a colorless oil, which was further separated using column chromatography with a Et_2O/hexanes solvent system.

*4.5.3. Preparation of **52** and **52′** using Br(coll)$_2$ClO$_4$ as the bromenium source.* The general procedure was followed with ester **50**[13] (50.0 mg, 0.187 mmol, 100 mol%), 4 Å MS, HFIP (3.7 mL), and Br(coll)$_2$ClO$_4$ (236 mg, 0.560 mmol, 300 mol%). The reaction was performed at rt for 15 min. Lactones **52**, **52′** were isolated together as a 1:1 mixture of C3 epimers (39.6 mg, 0.136 mmol, 73%) as a colorless oil. Data for **52**: $[\alpha]_D^{22}$ −7.6 (*c* 0.085, $CHCl_3$); IR (thin film, NaCl): 2977, 2936, 1773, 1734, 1700, 1457, 1384, 1263, 1208, 1134, 1077 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 4.09–4.07 (m, 1H), 3.66 (dd, *J*=11.8, 5.2 Hz, 1H), 2.71 (ddd, *J*=18.7, 7.5, 1.8 Hz, 1H), 2.59 (dd, *J*=11.4, 8.2 Hz, 1H), 2.19–2.16 (m, 2H), 2.03–1.99 (m, 1H), 1.96–1.92 (m, 1H), 1.85–1.80 (m, 1H), 1.79–1.75 (m, 1H), 1.40 (s, 3H), 1.39 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.1, 84.4, 79.1, 69.5, 59.3, 43.8, 31.4, 29.3, 26.3, 25.2, 24.9, 20.9; HRMS (ESI) *m*/*z* calcd for $C_{12}H_{19}BrO_3$ $[M+H]^+$: 291.0590, found 291.0593. Data for **52′**: $[\alpha]_D^{22}$ +1.7 (*c* 0.23, $CHCl_3$); IR (thin film, NaCl): 2979, 2937, 1773, 1734, 1701, 1457, 1269, 1242, 1193, 1150, 1100, 1084 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 4.43 (dd, *J*=6.2, 2.6 Hz, 1H), 4.11 (dd, *J*=11.9, 5.3 Hz, 1H), 2.71 (ddd, *J*=18.8, 7.7, 2.1 Hz, 1H), 2.63 (dd, *J*=11.0, 8.3 Hz, 1H), 2.43 (ddd, *J*=14.5, 9.6, 4.9 Hz, 1H), 2.10–2.07 (m, 2H), 1.91–1.85 (m, 2H), 1.83–1.81 (m, 1H), 1.46 (s, 3H), 1.41 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.7, 84.9, 78.3, 69.5, 64.7, 38.9, 30.7, 29.3, 28.7, 27.5, 24.8, 21.8; HRMS (ESI) *m*/*z* calcd for $C_{12}H_{19}BrO_3$ $[M+H]^+$: 291.0590, found 291.0597.

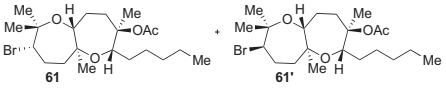
*4.5.4. Preparation of **53** and **53′** using NBS as the bromenium source.* The general procedure was followed with carbonate **51** (35.1 mg, 0.130 mmol, 100 mol%), 4 Å MS (241 mg, unactivated mass), HFIP (1.9 mL), and NBS (69.2 mg, 0.390 mmol, 300 mol%). The reaction was performed at 0 °C for 1 h. Lactones **53**, **53′** were isolated together as a 1:1 mixture of C3 epimers (34.5 mg, 0.118 mmol, 91%) as a colorless oil.[42]

*4.5.5. Preparation of **53** and **53′** using Br(coll)$_2$ClO$_4$ as the bromenium source.* The general procedure was followed with carbonate **51** (25.5 mg, 0.0944 mmol, 100 mol%), 4 Å MS, HFIP (1.5 mL), and Br(coll)$_2$ClO$_4$ (117.0 mg, 0.277 mmol, 300 mol%). The reaction was performed from 0 °C to rt for 3 h. Lactones **53**, **53′** were isolated together as a 1:1 mixture of C3 epimers (27.3 mg, 0.0931 mmol, 99%) as a colorless oil.[42]

4.6. Model studies of the bromonium-initiated cyclization using diepoxide 60

4.6.1. Representative procedure for the bromonium-initiated cyclization in HFIP. To diepoxide **60**[13] was added the specified amount of trapping nucleophile in HFIP. Either NBS or Br(coll)$_2$ClO$_4$ was added in one portion under Ar at the specified temperature. The reaction mixture was stirred in the absence of light. It was then quenched by the addition of saturated aq $Na_2S_2O_3$ and filtered through Celite, eluting with Et_2O. After concentrating the filtrate, the residue was repartitioned between Et_2O and a 1:1 mixture of saturated aq $Na_2S_2O_3$/NaCl. The aqueous layer was extracted with Et_2O (2×). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Column chromatography isolated the products.

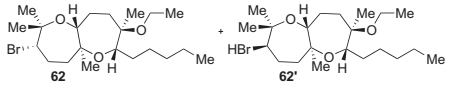
*4.6.2. Preparation of **61** and **61′**.*



ca. 1:1 mixture of diastereomers obtained

The general procedure was followed with **60**[13] (50.0 mg, 0.170 mmol, 100 mol%), 4 Å MS (250 mg, activated mass), *n*-$Bu_4NOCOMe$ (76.9 mg, 0.301 mmol, 175 mol%), HFIP (2.5 mL), and NBS (60.5 mg, 0.340 mmol, 200 mol%). The reaction was performed at 0 °C for 15 min. Column chromatography (10–20% Et_2O in hexanes) isolated the following as colorless oils: dioxepane **61** (21.8 mg), **61′** (23.9 mg), and a mixture of the two (9.00 mg) for a total of 0.126 mmol (74% yield) of products. Relative configurations of the diastereomers were determined by NOE studies. Data for **61**: $[\alpha]_D^{22}$ −25.3 (*c* 0.91, $CHCl_3$); IR (thin film, NaCl): 2930, 2858, 1734, 1700, 1653, 1559, 1457, 1379 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6): δ 4.06 (dd, *J*=10.0, 1.5 Hz, 1H), 3.76 (dd, *J*=10.5, 1.7 Hz, 1H), 3.28 (d, *J*=10.5 Hz, 1H), 2.15 (td, *J*=13.5, 3.1 Hz, 1H), 2.06 (ddd, *J*=13.0, 5.5, 2.6 Hz, 1H), 2.02–1.89 (m, 2H), 1.87–1.79 (m, 1H), 1.69 (s, 3H), 1.67–1.49 (m, 6H), 1.43 (s, 3H), 1.41–1.27 (m, 8H), 1.16 (s, 6H), 0.95 (t, *J*=7.0 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6): δ 169.9, 86.6, 78.8, 78.0, 76.6, 73.9, 60.3, 41.0, 37.6, 33.0, 32.3, 30.8, 29.1, 27.2, 26.2, 24.9, 23.5, 22.4, 21.4, 19.5, 14.7; HRMS (ESI) *m*/*z* calcd for $C_{21}H_{37}BrO_4$ $[M+Na]^+$: 455.1767, found 455.1752. Data for **61′**: $[\alpha]_D^{22}$ −24.5 (*c* 0.89, $CHCl_3$); IR (thin film, NaCl): 2932, 2860, 1734, 1718, 1653, 1559, 1457, 1377 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6): δ 4.39 (dd, *J*=10.0, 1.5 Hz, 1H), 4.29 (dd, *J*=10.5, 1.1 Hz, 1H), 4.04 (dd, *J*=6, 2.2 Hz, 1H), 2.62 (m, 1H), 2.31–2.23 (m, 1H), 1.94–1.86 (m, 1H), 1.78–1.72 (m, 2H), 1.70–1.64 (m, 6H), 1.54–1.46 (m, 6H), 1.40–1.32 (m, 7H), 1.28 (s, 3H), 1.18–1.12 (m, 1H), 0.94 (t, *J*=7.0 Hz, 3H), 0.90 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6): δ 169.7, 86.4, 79.3, 76.7, 76.3, 74.3, 66.6, 38.0, 36.0, 32.8, 30.9, 29.9, 29.3, 28.7, 28.5, 27.1, 23.5, 22.4, 21.8, 19.4, 14.8; HRMS (ESI) *m*/*z* calcd for $C_{21}H_{37}BrO_4$ $[M+Na]^+$: 455.1767, found 455.1748.

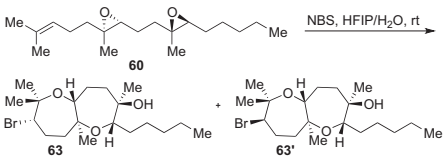
*4.6.3. Preparation of **62** and **62′**.*



ca. 1:1 mixture of diastereomers obtained

The general procedure was followed with **60**[13] (25.2 mg, 0.0856 mmol, 100 mol%), EtOH (0.28 mL), HFIP (1.4 mL), and Br(coll)$_2$ClO$_4$ (72.2 mg, 0.171 mmol, 200 mol%). The reaction was performed at 0 °C for 17 h. Column chromatography (5–10% Et_2O in hexanes) isolated bicycle **62** (10.0 mg) and **62′** (10.0 mg) for a total of 0.0479 mmol (56% yield) of products. Relative configurations of the diastereomers were determined by NOE studies. Data for **62**: $[\alpha]_D^{22}$ −29.8 (*c* 0.17, $CHCl_3$); IR (thin film, NaCl): 2929, 2856, 1457, 1377, 1139, 1116, 1105, 1064 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 4.13–4.11 (m, 1H), 3.48–3.44 (m, 2H), 3.42–3.36 (m, 2H), 2.18–2.16 (m, 2H), 1.93 (ddd, *J*=13.2, 6.0, 2.4 Hz, 1H), 1.86–1.79 (m, 1H), 1.78–1.72 (m, 2H), 1.63–1.59 (m, 8H), 1.57 (dd, *J*=12.6, 2.4 Hz, 1H), 1.54–1.49 (m, 1H), 1.47–1.43 (m, 1H), 1.37 (s, 6H), 1.35–1.30 (m, 2H), 1.16 (s, 3H), 1.14 (s, 3H), 0.92 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 79.1, 78.6, 78.3, 77.0, 76.6, 60.5, 57.1, 41.1, 39.3, 32.9, 32.4, 30.7, 29.0, 27.5, 26.2, 25.3, 23.4, 21.5, 17.8, 16.9, 14.8; HRMS (ESI) *m*/*z* calcd for $C_{21}H_{39}BrO_3$ $[M+H]^+$: 419.2155, found 419.2155. Data for **62′**: $[\alpha]_D^{22}$ −21.7 (*c* 0.15, $CHCl_3$); IR (thin film, NaCl): 2929, 2858, 1457, 1378, 1117, 1073, 1063 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ 4.56 (d, *J*=6.0 Hz, 1H), 4.05 (d, *J*=10.2 Hz, 1H), 3.56 (d, *J*=10.2 Hz, 1H), 3.48 (pentet, *J*=6.6 Hz, 1H), 3.39 (pentet, *J*=7.2 Hz, 1H), 2.42 (td, *J*=12.6, 3.6 Hz, 1H), 2.07–2.00 (m, 2H), 1.86 (ddd, *J*=12.6, 5.4, 1.8 Hz, 1H), 1.82–1.74 (m, 2H), 1.66 (dd, *J*=13.2, 2.4 Hz, 1H), 1.56–1.53 (m, 2H), 1.45 (s, 3H), 1.39–1.33 (m, 5H), 1.29 (s, 3H), 1.28–1.26 (m, 5H), 1.20 (s, 3H), 1.15 (s, 3H), 0.92 (t, *J*=7.2 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 79.2, 79.1, 77.1, 76.7, 76.2, 67.0, 57.0, 39.0, 35.8, 32.9, 30.6, 30.5, 29.2, 29.0, 28.8, 27.2, 23.5, 21.8, 18.2, 17.0, 14.9; HRMS (ESI) *m*/*z* calcd for $C_{21}H_{39}BrO_3$ $[M+H]^+$: 419.2155, found 419.2165.

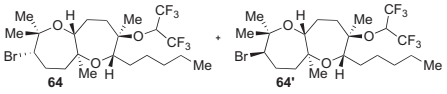
*4.6.4. Preparation of **63** and **63′**.*



ca. 1:1 mixture of diastereomers obtained

The general procedure was followed with **60**[13] (36.8 mg, 0.125 mmol, 100 mol %), H_2O (0.28 mL), HFIP (0.42 mL), and NBS (44.5 mg, 0.250 mmol, 200 mol %). The reaction was performed at rt for 22 h. Column chromatography (20–30% Et_2O in hexanes) isolated bicycle **63** (8.80 mg), **63′** (8.60 mg), and a mixture of the two (2.80 mg) for a total of 0.0513 mmol (41% yield) of products. Relative configurations of the diastereomers were determined after deacetylation of bicycles **61** and **61′** (DIBAL-H, CH_2Cl_2, −30 °C). Data for **63**: $[\alpha]_D^{22}$ −31.0 (*c* 0.29, $CHCl_3$); IR (thin film, NaCl): 3420, 2927, 2856, 1653, 1559, 1457, 1437, 1378 cm^{-1}; ^1H NMR (500 MHz, C_6D_6): δ 3.80 (dd, *J*=10.5, 2.0 Hz, 1H), 3.03 (dd, *J*=10.0, 1.8 Hz, 1H), 3.02 (d, *J*=10.0 Hz, 1H), 2.03–1.91 (m, 2H), 1.84–1.74 (m, 2H), 1.68–1.59 (m, 1H), 1.55 (ddd, *J*=12.5, 4.9, 1.9 Hz, 1H), 1.45–1.28 (m, 12H), 1.27–1.20 (m, 1H), 1.18 (s, 3H), 1.16 (s, 3H), 1.07 (s, 3H), 0.97 (t, *J*=7.0 Hz, 3H); ^{13}C NMR (100 MHz, C_6D_6): δ 78.5, 77.9, 77.0, 76.9, 74.4, 60.4, 44.3, 41.0, 33.1, 32.3, 30.5, 29.3, 27.5, 26.1, 25.0, 23.5, 21.9, 21.5, 14.8; HRMS (ESI) *m*/*z* calcd for $C_{19}H_{35}BrO_3$ $[M+Na]^+$: 413.1662, found 413.1657. Data for **63′**: $[\alpha]_D^{22}$ −33.4 (*c* 0.42, $CHCl_3$); IR (thin film, NaCl): 3395, 2930, 2858, 1457, 1653, 1559, 1540, 1507, 1378 cm^{-1}; ^1H NMR (500 MHz, C_6D_6); δ 4.13 (d, *J*=10.5 Hz, 1H), 4.06 (dd, *J*=6.0, 2.1 Hz, 1H), 3.51 (dd, *J*=10.0, 1.8 Hz, 1H), 2.59–2.53 (m, 1H), 1.92–1.82 (m, 2H), 1.80–1.24 (m, 1H), 1.71–1.61 (m, 3H), 1.54–1.33 (m, 12H), 1.28 (s, 3H), 1.15 (s, 3H), 0.95 (t, *J*=7.0 Hz, 3H), 0.90 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6): δ 79.0, 77.4, 76.9, 76.6, 74.5, 67.2, 44.8, 36.1, 32.9, 30.6, 29.9, 29.7, 28.9, 28.6, 27.4, 23.5, 21.9, 21.7, 14.8; HRMS (ESI) *m*/*z* calcd for $C_{19}H_{35}BrO_3$ $[M+Na]^+$: 413.1662, found 413.1653.

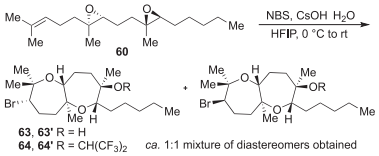
*4.6.5. Preparation of **64** and **64′**.*



ca. 1:1 mixture of diastereomers obtained

The general procedure was followed with **60**[13] (20.8 mg, 0.0706 mmol, 100 mol %), HFIP (1.1 mL), and $Br(coll)_2ClO_4$ (59.5 mg, 0.141 mmol, 200 mol %). The reaction was performed at 0 °C for 20 h. Column chromatography (packed with 2% Et_3N in hexanes, flushed with hexanes, then 2–10% Et_2O in hexanes) isolated bicycle **64** (6.00 mg) and **64′** (6.50 mg) for a total of 0.0233 mmol (33% yield) of products. Relative configurations of the diastereomers were determined by NOE studies. Data for **64**: $[\alpha]_D^{22}$ −23.1 (*c* 0.15, $CHCl_3$); IR (thin film, NaCl): 2956, 2927, 2857, 1653, 1559, 1457, 1383, 1355, 1284, 1227, 1196 cm^{-1}; ^1H NMR (500 MHz, C_6D_6): δ 3.91 (septet, *J*=6.0 Hz, 1H), 3.63 (dd, *J*=10.0, 3.3 Hz, 1H), 3.22 (dd, *J*=10.0, 2.0 Hz, 1H), 2.92 (d, *J*=10.5 Hz, 1H), 1.98–1.88 (m, 3H), 1.60–1.52 (m, 2H), 1.41–1.33 (m, 7H), 1.32–1.25 (m, 7H), 1.11 (s, 3H), 1.10 (s, 3H), 0.94 (t, *J*=7.0 Hz, 3H), 0.92 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6): δ 85.8, 78.8, 78.1, 76.6, 75.9, 70.2 (t, *J*=31.3 Hz), 59.9, 40.6, 39.7, 32.9, 32.1, 30.4, 28.7, 27.2, 26.0, 25.0, 23.5, 21.3, 16.1, 14.7; ^{19}F NMR (300 MHz, C_6D_6): δ −70.9 (q, *J*=6.9 Hz), −70.8 (q, *J*=6.6 Hz, 6F). (Referenced with C_6F_6 at −164.9 ppm). Data for **64′**: $[\alpha]_D^{22}$ −13.7 (*c* 0.25, $CHCl_3$); IR (thin film, NaCl): 2956, 2930, 2859, 1653, 1559, 1465, 1457, 1437, 1385, 1356, 1284 cm^{-1}; ^1H NMR (500 MHz, C_6D_6): δ 4.14 (dd, *J*=10.5, 1.1 Hz, 1H), 3.97 (septet, *J*=6.0 Hz, 1H), 3.97 (d, *J*=6.0 Hz, 1H), 3.73 (dd, *J*=10.0, 1.8 Hz, 1H), 2.49 (ddd, *J*=14.0, 11.0, 4.3 Hz, 1H), 2.05–2.00 (m, 1H), 1.73–1.58 (m, 5H), 1.48–1.44 (m, 2H), 1.42–1.28 (m, 12H), 1.24 (s, 3H), 1.02 (s, 3H), 0.90 (t, *J*=7.0 Hz, 3H), 0.89 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6): δ 85.7, 79.3, 76.8, 76.4, 76.3, 70.3 (t, *J*=32.5 Hz), 66.2, 40.0, 35.8, 32.7, 30.6, 29.8, 29.0, 28.8, 28.4, 27.1, 23.5, 21.8, 16.6, 14.7; ^{19}F NMR (300 MHz, C_6D_6): δ −71.0 (q, *J*=6.6 Hz), −70.9 (q, *J*=6.6 Hz, 6F). (Referenced with C_6F_6 at −164.9 ppm).

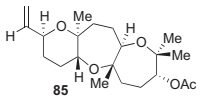
*4.6.6. Preparation of **63**, **63′**–**64**, **64′** using reaction of **60** with $CsOH \cdot H_2O$.*



ca. 1:1 mixture of diastereomers obtained

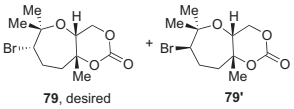
The general procedure was followed with **60**[13] (26.8 mg, 0.0910 mmol, 100 mol %), $CsOH \cdot H_2O$ (24.5 mg, 0.146 mmol, 150 mol %), HFIP (1.4 mL), and NBS (34.7 mg, 0.195 mmol, 200 mol %). The reaction was performed at 0 °C while warming to rt over 15 h. Column chromatography (5–50% Et_2O in hexanes) isolated **63**, **63′** (16.0 mg total, 0.0409 mmol, 45%) and **64**, **64′** (9.20 mg, 0.0170 mmol, 19%) as colorless oils.

4.7. Preparation of tricycle 85



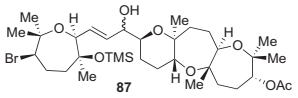
To a flame-dried 100 mL round-bottom flask equipped with a stir bar was added triepoxide **14**[13] (1.56 g, 4.81 mmol) in 100 mL of dichloromethane and cooled to −78 °C. $BF_3 \cdot OEt_2$ (210 μL, 1.70 mmol) was added dropwise and the reaction mixture was stirred at the same temperature for 15 min. Saturated NH_4Cl was added to quench the reaction and it was warmed to room temperature. The reaction mixture was poured into a separatory funnel and extracted with CH_2Cl_2 (3×) from brine. The organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude reaction mixture was dissolved in 50 mL of dichloromethane in a 100 mL flame-dried round-bottom flask equipped with a stir bar. Acetic anhydride (950 μL, 10.0 mmol), triethylamine (2.80 mL, 20.1 mmol), and DMAP (59.8 mg, 0.490 mmol) were all added and the reaction mixture was stirred at room temperature overnight. Saturated NH_4Cl was added and the reaction mixture was transferred to a separatory funnel and extracted with CH_2Cl_2 (3×). The organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. Column chromatography provided colorless oil **85** (325 mg, 0.886 mmol, 18.4% yield). $[\alpha]_D^{24}$ +22.9 (*c* 0.06, $CHCl_3$); IR (NaCl, thin film): 2936, 2361, 2339, 1734, 1653, 1540, 1457, 1241, 1078 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 5.84–5.77 (m, 1H), 5.21 (dt, *J*=17.3, 1.4 Hz, 1H), 5.09 (ddd, *J*=10.5, 1.6, 1.1 Hz, 1H), 4.92 (d, *J*=6.7 Hz, 1H), 4.01–3.97 (m, 1H), 3.62 (dd, *J*=11.1, 5.0 Hz, 1H), 3.46 (dd, *J*=11.5, 2.5 Hz, 1H), 2.12 (s, 3H), 2.10–2.04 (m, 2H), 2.00–1.81 (m, 3H), 1.81–1.61 (m, 5H), 1.54–1.43 (m, 2H), 1.30 (s, 3H), 1.26 (s, 3H), 1.16 (s, 3H), 1.14 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 208.5, 139.6, 115.3, 78.8, 78.6, 78.4, 77.4, 77.1, 71.1, 70.2, 40.8, 36.8, 32.1, 29.2, 28.9, 27.8, 23.2, 21.8, 21.3, 20.1, 16.4; HRMS (ESI) *m*/*z* calcd for $C_{21}H_{34}O_5$ $[M+Na]^+$: 389.2298, found 389.2290.

4.8. Representative procedure for the bromonium-initiated cyclization of 80 in HFIP using $Br(coll)_2BF_4$ to prepare 79 and 79′



To a 500 mL round-bottom flask equipped with a stir bar was added 4 Å molecular sieves (27 g) followed by carbonate **80**[13] (3.87 g, 14.3 mmol) and 278 mL of HFIP. The reaction mixture was cooled to 0 °C and $Br(coll)_2BF_4$ (17.6 g, 43.0 mmol) was added in one portion and the reaction mixture was stirred for 30 min. The mixture was filtered through Celite and then added to 150 mL of brine and 150 mL of saturated $Na_2S_2O_3$. The aqueous layer was extracted with CH_2Cl_2 (3×) and then the organic layers were dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude solid was purified by column chromatography (20–50–100% EtOAc in hexanes) to furnish **79** (1.31 g, 4.48 mmol, 31% yield) and **79′** (693 mg, 2.36 mmol, 17% yield) as white solids. Data for **79**: $[\alpha]_D^{24}$ −23.0 (*c* 0.1, $CHCl_3$); IR (NaCl, thin film): 2937, 1732, 1159, 1540, 1457, 1298, 1208, 1120, 1086, 1040 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 4.52 (dd, *J*=11.5, 2.9 Hz, 1H), 4.22 (dd, *J*=11.4, 1.8 Hz, 1H), 3.88 (dd, *J*=10.6, 1.9 Hz, 1H), 3.77 (dd, *J*=2.7, 1.9 Hz, 1H), 2.50 (dtd, *J*=14.5, 10.6, 3.6 Hz, 1H), 2.20 (ddd, *J*=15.0, 6.9, 3.3 Hz, 1H), 2.03–1.99 (m, 1H), 1.72–1.67 (m, 1H), 1.43 (s, 3H), 1.42 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 149.2, 83.7, 79.2, 71.2, 66.8, 57.1, 39.9, 30.3, 25.7, 25.5, 24.4; HRMS (ESI) *m*/*z* calcd for $C_{11}H_{17}O_4Br$ $[M+Na]^+$: 315.0202, found 315.0214. Data for **79′**: $[\alpha]_D^{24}$ −9.7 (*c* 1.2, $CHCl_3$); IR (NaCl, thin film): 2981, 1750, 1457, 1388, 1292, 1247, 1218, 1122, 1091, 1042 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): 4.46 (dd, *J*=11.6, 2.8 Hz, 1H), 4.18 (dd, *J*=11.6, 2.2 Hz, 1H), 4.13 (dd, *J*=10.3, 2.5 Hz, 1H), 3.94 (t, *J*=2.5 Hz, 1H), 2.35 (ddt, *J*=14.9, 10.2, 2.2 Hz, 1H), 2.14 (ddd, *J*=14.8, 10.1, 1.5 Hz, 1H), 2.03–1.99 (m, 1H), 1.86–1.80 (m, 1H), 1.46 (s, 3H), 1.43 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): 149.4, 86.6, 79.5, 70.4, 67.8, 61.9, 38.4, 30.4, 29.2, 25.8, 22.4; HRMS (ESI) *m*/*z* calcd for $C_{11}H_{17}O_4Br$ $[M+H]^+$: 293.0389, found 293.0374.

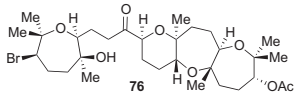
4.9. Fragment coupling to access 87



87

To a 25 mL round-bottom flask equipped with a stir bar was added $[Cp_2Zr(H)Cl]$ (256 mg, 0.990 mmol) and alkyne **77**[13] (321 mg, 96.0 mmol) and placed under nitrogen in the dark. 9.6 mL of CH_2Cl_2 was added and stirred for 30 min at room temperature. The flask was then cooled to −78 °C and Me_2Zn (2.0 M in toluene, 505 μL, 1.01 mmol) was added dropwise. After stirring for 15 min, a solution of aldehyde **78**[13] (306 mg, 0.830 mmol) in 8 mL of CH_2Cl_2 was added and the reaction mixture was allowed to slowly warm to room temperature overnight. A saturated solution of NH_4Cl was added and a white solid formed. The aqueous layer was extracted with CH_2Cl_2 (3×) and then the organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo to provide a colorless oil. The crude mixture was purified by column chromatography (5–50% EtOAc in hexanes) to provide allylic alcohol **87** (373 mg, 0.530 mmol, 64% yield) as a colorless oil. $[\alpha]_D^{24}$ +28.2 (*c* 0.4, $CHCl_3$); IR (NaCl, thin film): 3583, 2939, 1739, 1442, 1379, 1248, 1067, 840, 753 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 5.85 (dd, *J*=15.6, 7.5 Hz, 1H), 5.50 (dd, *J*=15.6, 6.7 Hz, 1H), 4.91 (d, *J*=6.8 Hz, 1H), 3.96 (d, *J*=10.4 Hz, 1H), 3.86–3.84 (m, 1H), 3.63 (t, *J*=6.8 Hz, 1H), 3.58 (dd, *J*=9.7, 6.1 Hz, 1H), 3.45 (dd, *J*=11.3, 2.0 Hz, 1H), 3.34 (ddd, *J*=11.8, 7.2, 1.9 Hz, 1H), 2.69 (d, *J*=2.4 Hz, 1H), 2.54 (td, *J*=12.9, 10.1 Hz, 1H), 2.12 (s, 3H), 2.08–2.01 (m, 2H), 1.94–1.86 (m, 4H), 1.79 (dd, *J*=14.4, 13.6 Hz, 2H), 1.70 (t, *J*=14.0 Hz, 1H), 1.62 (dt, *J*=6.8, 3.1 Hz, 2H), 1.52–1.44 (m, 4H), 1.41 (s, 3H), 1.33 (s, 3H), 1.25 (s, 3H), 1.24 (s, 3H), 1.16 (s, 3H), 1.15 (s, 3H), 1.06 (s, 3H), 0.11 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 170.3, 131.6, 131.0, 78.8, 78.6, 78.3, 78.3, 77.7, 77.6, 77.4, 75.9, 75.5, 73.2, 70.3, 60.8, 44.2, 40.6, 36.8, 31.0, 29.1, 28.9, 28.1, 27.8, 27.4, 26.2, 24.4, 23.2, 21.8, 21.3, 20.1, 16.4, 2.8.

4.10. Preparation of 76

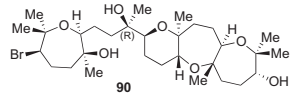


76

To a 25 mL round-bottom flask equipped with a stir bar was added allylic alcohol **87** (373 mg, 0.530 mmol) and 5.2 mL of EtOH. Palladium on carbon (218 mg, 10% by weight) was added and placed under vacuum. Hydrogen gas was added and the reaction mixture was stirred at room temperature for 90 min. The solution was filtered through Celite (eluted with EtOAc) to remove the palladium. The crude reaction mixture was purified by the Biotage purification system to provide the intermediate alcohol (223 mg, 0.352 mmol, 66% yield) as a colorless oil.

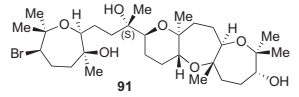
To a 10 mL round-bottom flask equipped with a stir bar were added 4 Å molecular sieves (194 mg) followed by alcohol from the previous step (223 mg, 0.352 mmol) in 3.5 mL of CH_2Cl_2. *N*-Methylmorpholine-*N*-oxide (131 mg, 1.12 mmol) was added and the reaction mixture was cooled to 0 °C. Tetrapropylammonium perruthenate (29.0 mg, 82.5 mmol) was added and the reaction mixture was allowed to warm to room temperature over 2 h. The crude reaction mixture was filtered through Celite using a CH_2Cl_2 and EtOAc wash and concentrated in vacuo. The reaction was purified by the Biotage purification system to provide **76** (180 mg, 0.285 mmol, 81% yield) as a colorless oil. $[\alpha]_D^{24}$ −4.8 (*c* 0.24, $CHCl_3$); IR (NaCl, thin film): 3584, 2976, 2938, 1736, 1445, 1379, 1243, 1138, 109, 1069, 1029 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 4.92 (d, *J*=6.6 Hz, 1H), 3.89 (td, *J*=7.5, 4.0 Hz, 2H), 3.60 (dd, *J*=13.8, 7.0 Hz, 1H), 3.47 (dd, *J*=11.4, 2.3 Hz, 1H), 3.41 (dd, *J*=10.3, 2.8 Hz, 1H), 2.96 (s, 1H), 2.69–2.67 (m, 2H), 2.33 (qd, *J*=13.0, 1.6 Hz, 1H), 2.12 (s, 3H), 2.04–1.60 (m, 13H), 1.53–1.46 (m, 4H), 1.41 (s, 3H), 1.31 (s, 3H), 1.26 (s, 3H), 1.25 (s, 3H), 1.17 (s, 3H), 1.15 (s, 3H), 1.14 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 212.1, 170.2, 78.9, 78.6, 78.2, 78.0, 77.8, 77.4, 75.8, 74.6, 72.3, 69.8, 68.1, 59.1, 44.5, 43.0, 40.5, 36.7, 34.1, 30.5, 30.4, 28.9, 25.8, 25.7, 25.6, 25.0, 24.5, 23.2, 21.8, 21.3, 19.6, 16.4.

4.11. Preparation of 90 and 91 by the addition of MeLi to 76



90

+



91

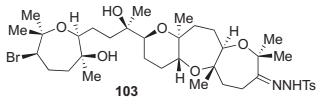
To a 20 mL vial with stir bar was added ketone **76** (180 mg, 0.285 mmol) and 3.5 mL of THF and the reaction mixture was cooled to −78 °C. MeLi (950 μL, 1.60 M in Et_2O, 1.52 mmol) was added dropwise and the reaction mixture was stirred for 1 h. The reaction mixture solidified and eventually stirring ceased. Saturated NH_4Cl was added, and the reaction mixture was allowed to warm to rt. The aqueous layer was extracted with Et_2O (3×), dried over Na_2SO_4, filtered, and the solvent was removed in vacuo. The crude was redissolved in 10 mL of THF and cooled to −78 °C. MeLi (1.0 mL, 1.6 M in Et_2O, 1.6 mmol) was added dropwise and the reaction mixture was stirred at this temperature for 1 h. The reaction mixture stayed in solution and went to completion by TLC. Saturated NH_4Cl was added and allowed to warm to rt. The aqueous layer was extracted with Et_2O (3×) and then the organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by careful column chromatography (0.1–2% MeOH in Et_2O) on the Biotage purification system to provide clean alcohol **91** (29.7 mg, 49.3 mmol, 17% yield) and the

remaining material as a mixture of alcohol **91** and alcohol **90** (117 mg, 0.192 mmol, 67% yield). Data for **90**: $[\alpha]_D^{24}$ +40.9 (*c* 0.2, $CHCl_3$). For reference, *ent*-**90**: $[\alpha]_D^{24}$ −41.7 (*c* 0.1, $CHCl_3$); IR (NaCl, thin film): 3583, 3452, 2932, 1659, 1641, 1462, 1451, 1378, 1137, 1071, 891 cm^{-1}; ^1H NMR (500 MHz, C_6D_6): δ 3.81 (dd, *J*=11.4, 2.4 Hz, 1H), 3.65 (dd, *J*=10.6, 5.4 Hz, 1H), 3.51 (d, *J*=11.1 Hz, 1H), 3.23 (td, *J*=8.5, 3.5 Hz, 2H), 2.92 (s, 1H), 2.78 (dd, *J*=9.9, 3.0 Hz, 1H), 2.24 (s, *J*=5.2 Hz, 1H), 2.24–2.14 (m, 3H), 1.95–1.43 (m, 17H), 1.34 (s, 3H), 1.33 (s, 3H), 1.25 (s, 6H), 1.14 (s, 6H), 1.01 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (125 MHz, C_6D_6): δ 79.6, 78.2, 78.1, 78.0, 77.9, 76.9, 76.7, 76.3, 73.4, 72.4, 71.2, 59.7, 44.7, 41.1, 36.8, 34.4, 31.0, 30.0, 29.4, 28.3, 26.3, 26.1, 26.0, 25.7, 25.6, 24.1, 24.0, 22.1, 20.2, 17.1; HRMS (ESI) *m*/*z* calcd for $C_{30}H_{53}BrO_7$ $[M+H]^+$: 605.3047, found 605.3059. Data for **91**: ^1H NMR (400 MHz, C_6D_6): δ 3.80 (dd, *J*=11.4, 2.3 Hz, 1H), 3.62 (dd, *J*=10.2, 6.0 Hz, 1H), 3.50 (d, *J*=11.0 Hz, 1H), 3.29–3.19 (m, 2H), 2.90 (br s, 1H), 2.78 (dd, *J*=9.3, 3.2 Hz, 1H), 2.30 (br s, 1H), 2.27–2.12 (m, 3H), 1.92–1.75 (m, 4H), 1.72–1.53 (m, 8H), 1.53–1.40 (m, 5H), 1.33 (s, 6H), 1.25 (s, 3H), 1.24 (s, 3H), 1.13 (s, 3H), 1.10 (s, 3H), 1.02 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (100 MHz, C_6D_6): δ 79.6, 78.1, 78.1, 77.9, 77.9, 76.7, 76.6, 74.4, 73.4, 72.4, 71.0, 59.8, 44.7, 41.1, 36.9, 36.8, 31.0, 30.1, 29.4, 28.3, 26.3, 26.1, 25.9, 25.6, 25.6, 24.7, 23.0, 22.0, 20.3, 17.1; HRMS (ESI) *m*/*z* calcd for $C_{30}H_{53}BrO_7$ $[M+H]^+$: 605.3047, found 605.3051.

4.12. Preparation of 90 by the addition of MeMgBr to 76 and deacetylation

To a 5 mL round-bottom flask equipped with a stir bar was added ketone **76** (65.2 mg, 103 μmol) and 1.6 mL of THF. The reaction mixture was cooled to −78 °C and MeMgBr (200 μL, 3.0 M in Et_2O, 600 μmol) was added and the reaction mixture was allowed to warm to 0 °C over 1 h. The reaction was quenched with saturated NH_4Cl and the aqueous layer was extracted with Et_2O (3×). The organic layer was dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude oil was purified by column chromatography (20–50% EtOAc in hexanes) to provide the acetate intermediate (19.6 mg, 30.3 μmol, 29% yield) and alcohol **90** (9.60 mg, 15.9 μmol, 15% yield) along with recovered ketone **76** (35.0 mg, 55.4 μmol, 54% yield). The recovered starting material was redissolved in 3.2 mL of THF and MeMgBr (200 μL, 3.0 M in Et_2O, 600 μmol) was added at −78 °C and allowed to stir for 1 h. The reaction mixture was quenched with saturated NH_4Cl and extracted with Et_2O (3×). The organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude residue, along with the acetate intermediate (19.6 mg, 30.3 μmol) was dissolved in 3.4 mL of MeOH and K_2CO_3 (18.3 mg, 132 μmol) was added and stirred at room temperature for 4 h. The reaction mixture was then quenched with saturated NH_4Cl and extracted with Et_2O (5×). The organic layers were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude was purified by column chromatography (50% EtOAc in hexanes) to provide alcohol **90** (34.6 mg, 57.1 μmol, 67% yield) as a colorless oil.

4.13. Preparation of 103

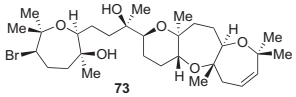


103

To a 5 mL round-bottom flask equipped with a stir bar was added 15 mg of 4 Å MS and heated under vacuum for 5 min. The flask was cooled to 0 °C and alcohol **90** (18.0 mg, 0.0298 mmol) was added in 2 mL of CH_2Cl_2. NMO (15.0 mg, 0.128 mmol) was added and then TPAP (~2 mg, 0.006 mmol) was added and the reaction mixture was allowed to slowly warm to room temperature for 2 h. The crude material was purified by the Biotage purification system to furnish the intermediate ketone (14.7 mg, 0.0244 mmol, 82% yield).

To a 5 mL flask equipped with a stir bar was added ketone from the previous step (25.8 mg, 42.7 μmol) and tosyl hydrazone (19.3 mg, 0.104 mmol) in 300 μL of MeOH. The reaction mixture was heated to 45 °C with a reflux condenser for 18 h. The reaction mixture was cooled to room temperature and concentrated in vacuo and loaded directly onto a silica gel column. The crude was purified by column chromatography (50–100% EtOAc in hexanes) to furnish hydrazone **103** (20.7 mg, 26.8 μmol, 63% yield) as a white solid. $[\alpha]_D^{24}$ −15.4 (*c* 1.0, $CHCl_3$); IR (NaCl, thin film): 3535, 3220, 2977, 2937, 1644, 1598, 1463, 1381, 1342, 1262, 1169, 1088, 1031, 814, 756 cm^{-1}; ^1H NMR (600 MHz, C_6D_6): δ 8.02 (d, *J*=8.2 Hz, 2H), 6.79 (d, *J*=8.2 Hz, 2H), 3.54 (d, *J*=11.1 Hz, 2H), 3.50 (t, *J*=8.0 Hz, 2H), 3.28 (dd, *J*=11.7, 2.2 Hz, 1H), 2.96 (s, 1H), 2.75 (dd, *J*=9.4, 2.9 Hz, 1H), 2.54 (dd, *J*=11.3, 2.1 Hz, 1H), 2.24–2.17 (m, 1H), 2.13–2.05 (m, 2H), 2.02–1.97 (m, 1H), 1.92 (s, 3H), 1.91–1.80 (m, 6H), 1.65–1.57 (m, 4H), 1.53–1.48 (m, 3H), 1.48–1.38 (m, 4H), 1.35 (s, 3H), 1.29 (s, 3H), 1.25 (s, 3H), 1.17 (s, 3H), 1.12 (s, 3H), 1.05 (s, 3H), 1.01 (s, 3H), 0.99 (s, 3H); ^{13}C NMR (150 MHz, C_6D_6): δ 164.1, 143.9, 136.8, 129.9, 128.8, 80.8, 80.2, 78.1, 78.0, 77.4, 76.3, 76.20, 73.3, 72.4, 71.1, 59.7, 44.7, 41.2, 40.8, 37.1, 34.7, 31.0, 29.5, 27.4, 26.1, 26.0, 25.56, 25.5, 24.4, 24.3, 23.3, 21.7, 20.0, 16.2; HRMS (ESI) *m*/*z* calcd for $C_{37}H_{59}BrSN_2O_8$ $[M+H]^+$: 771.3248, found 771.3245.

4.14. Preparation of 73



73

To a 500 μL sealed tube equipped with a stir bar was added sodium hydride (6.50 mg, 0.285 mmol, 95% in mineral oil) in the glovebox and then transferred to the hood under nitrogen. The reaction was purged while a solution of hydrazone **103** (16.6 mg, 21.5 μmol) in 500 μL of THF was added by syringe. The reaction mixture was sealed and heated to 90 °C for 100 min then to 110 °C for 70 min. The reaction mixture turned brown and was then cooled to room temperature. H_2O was added to quench remaining sodium hydride, followed by addition of 1 mL of saturated NH_4Cl. The aqueous layer was extracted with Et_2O (5×) and then dried over Na_2SO_4, filtered, and concentrated in vacuo. Careful column chromatography (20–50% HPLC-grade EtOAc in hexanes) provided a small amount of analytically clean **73** (0.8 mg, 1.3 μmol, 6% yield) as colorless oil. $[\alpha]_D^{24}$ +33.9 (*c* 0.04, $CHCl_3$); IR (NaCl, thin film): 3432, 2922, 2851, 1727, 1463, 1378, 1261, 1088 cm^{-1}; ^1H NMR (600 MHz, C_6D_6): δ 5.46–5.42 (m, 4H), 5.21 (d, *J*=11.7 Hz, 1H), 3.85 (dd, *J*=11.4, 4.6 Hz, 1H), 3.53 (d, *J*=11.0 Hz, 1H), 3.48 (dd, *J*=11.5, 4.5 Hz, 1H), 3.26 (dd, *J*=7.7, 4.3 Hz, 1H), 3.22 (dd, *J*=10.9, 3.2 Hz, 1H), 2.89 (d, *J*=0.5 Hz, 1H), 2.81 (dt, *J*=6.4, 3.4 Hz, 1H), 2.58 (ddd, *J*=15.4, 5.7, 1.7 Hz, 1H), 2.25–2.14 (m, 2H), 2.14–2.10 (m, 1H), 2.03 (t, *J*=7.5 Hz, 1H), 2.01–1.95 (m, 1H), 1.84–1.67 (m, 5H), 1.65–1.46 (m, 6H), 1.34 (s, 3H), 1.29 (s, 3H), 1.25 (s, 6H), 1.22 (s, 3H), 1.15 (s, 3H), 1.10 (s, 3H), 1.02 (s, 3H), 0.96–0.90 (m, 1H); ^{13}C NMR (125 MHz, C_6D_6): δ 137.0, 122.8, 80.7, 78.3, 77.9, 77.8, 77.0, 76.9, 75.8, 74.5, 73.4, 72.4, 59.7, 44.7, 42.6, 39.1, 34.4, 31.0, 29.9, 28.1, 27.9, 26.5, 26.1, 26.0, 25.6, 25.4, 24.1, 23.9, 18.5, 17.9; HRMS (ESI) *m*/*z* calcd for $C_{30}H_{51}O_6Br$ $[M+H]^+$: 587.2942, found 587.2930.

Acknowledgements

This work was supported by the NIGMS (GM-72566). We thank Dr. Jeffrey H. Simpson for helpful discussions regarding NMR experiments, Li Li for mass spectrometry data, and Dr. Peter Müller for the crystal structures of **34** and **67**. J.T. would like to thank Novartis and Amgen for graduate fellowships.

Supplementary data

Experimental procedures and characterization data for compounds **14**–**15**, *ent*-**14**, **17**–**18**, **20**, **22**, **26**, **31**, **33**, **35**, **37**–**40**, **44**, **46**, **50**, **60**, **75**, **78**, *ent*-**79**, **80**, *ent*-**80**, **83**–**84**, **89**, **92**–**93**, and **101**–**102** are provided. Crystallographic data (excluding structure factors) for the structures in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers 931730 (tricycle **34**) and 755014 (tetracycle **67**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.Uk). Experimental procedures and characterization data for compounds **30**, **32**, **54**–**56**, **57**–**59**, **66**–**67**, **67′**, **68**–**70**, and *ent*-**1** can be found in the Supplementary data of a previous communication.[7] Supplementary data associated with this article can be found in the online version, at http://dx.doi.org/10.1016/j.tet.2013.04.041.

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