Pure Appl. Chem., Vol. 85, No. 6, pp. 1175–1184, 2013.
http://dx.doi.org/10.1351/PAC-CON-12-10-25

Oxidative cyclization for the synthesis of complex tetrahydrofuran-containing natural products*

Robert D. C. Pullin†, Radosław M. Lipiński†, and Timothy J. Donohoe‡

Department of Chemistry, University of Oxford, Chemistry Research Laboratory, Mansfield Road, Oxford, OX1 3TA, UK

Abstract: The osmium-catalyzed oxidative cyclization of vicinal diols onto proximal olefins to generate 2,5-*cis*-substituted tetrahydrofurans (THFs) has been exploited as the key step for the construction of several complex THF-containing natural products, namely, the annonaceous acetogenins *cis*-sylvaticin, sylvaticin, and the excitatory amino acid neodysiherbaine A. Recently modified conditions that employ a Lewis acid enable the cyclization to proceed under milder conditions, providing greater tolerance to acid-sensitive functional groups, as demonstrated in two of the syntheses. Flexibility for the construction of 2,5-*trans*-THFs was demonstrated in the synthesis of sylvaticin by utilization of an intramolecular hydride-shift sequence.

Keywords: hydride shift; organic synthesis; osmium; oxidation; transition metals.

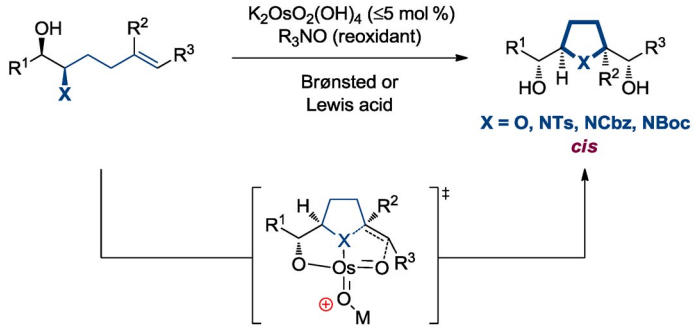
INTRODUCTION

Tetrahydrofuran (THF)-containing natural products widely occur in several important families of biologically active compounds, such as the annonaceous acetogenins [1] and polyether antibiotics isolated from *Streptomyces* organisms (ionomycin, lonomycins A–C, or monensin) [2]. Given the large number and variety of THF motifs in natural products, we are engaged in the development of new methods designed to prepare these important heterocycles, crucially with control over all aspects of stereo- and regiochemistry. In this regard, we have recently developed a general method for the catalytic oxidative cyclization of vicinal diols onto proximal olefins to produce *cis*-2,5-disubstituted THF rings. This article provides an overview of some of our recent accomplishments in the field of synthesis of THF-containing natural products by employing an osmium-mediated oxidative cyclization.

The oxidative cyclization of 1,5-dienes to generate the corresponding 2,5-*cis*-THFs has been known for nearly 50 years. In 1965 Klein and Rojahn discovered that the treatment of 1,5-hexadiene with stoichiometric $KMnO_4$ resulted in the formation of *cis*-THFs flanked with two hydroxymethyl groups [3]. The reaction is particularly useful, as it proceeds with complete stereoselectivity with respect to the formation of 2,5-*cis*-THFs, as well as being *syn*-stereospecific with respect to the addition across both alkenes, as later demonstrated by Baldwin [4]. Since the initial report by Klein and Rojahn a variety of other metal-oxo species have been shown to accomplish this transformation with

Pure Appl. Chem.* **85, 1079–1239 (2013). A collection of invited papers based on presentations at the 19th International Conference on Organic Synthesis (ICOS-19), Melbourne, Australia, 1–6 July 2012.
‡Corresponding author: Tel.: +44 (0) 1865 275649; E-mail: timothy.donohoe@chem.ox.ac.uk
†Equal contribution provided to this article.

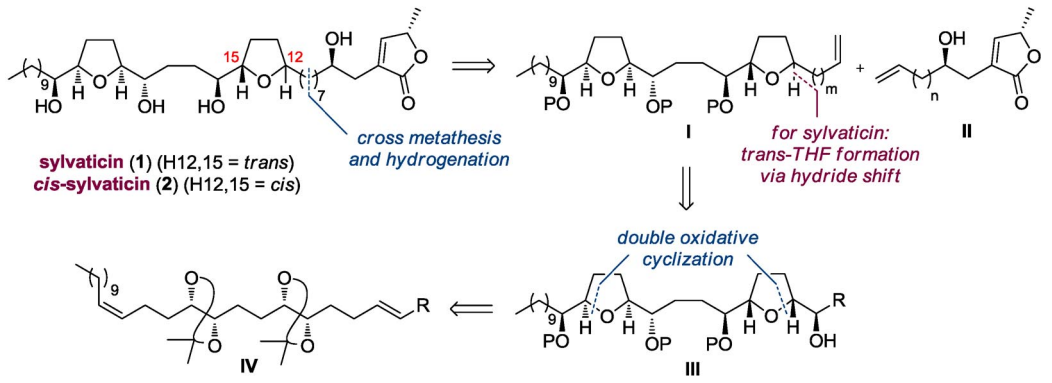
varying degrees of competency [5–7]. We have reported the development of the oxidative cyclization of 1,5-dienes, through the employment of catalytic Os(VI) under acidic conditions [8], in the presence of a tertiary amine *N*-oxide [for the reoxidation of Os(IV) to Os(VI)], to form exclusively *cis*-THFs in high yields [9]. During further investigations we have disclosed a significant improvement to the original methodology with the realization that vicinal diols, possessing a pendent olefin moiety, will form the THF products when subjected to oxidative cyclization conditions (Scheme 1) [10]. This strategy has the major advantage of allowing enantiopure vicinal diols to generate THFs as single enantiomers. Furthermore, this development has allowed an extension of the cyclization reaction of analogous vicinal amino alcohols to form pyrrolidines [11]. We have demonstrated that a range of mono-, di-, and trisubstituted alkenes, of either (*E*)- or (*Z*)-geometry, cyclize with a variety of initiators, including vicinal diols, 1,3-diols, vicinal amino alcohols or α-hydroxy amides, to deliver exclusively *cis*-2,5-disubstituted heterocycles [12]. As part of a program of our research aimed at developing new catalytic methods for the formation of heterocycles with subsequent applications to the synthesis of complex molecules [13], we have selected several natural products as targets on which to test this recently developed methodology. Herein we discuss the utility of the osmium-catalyzed oxidative cyclization in the context of complex natural product synthesis.



Scheme 1 Osmium-catalyzed oxidative cyclization for the diastereoselective synthesis of *cis*-THFs and pyrrolidines.

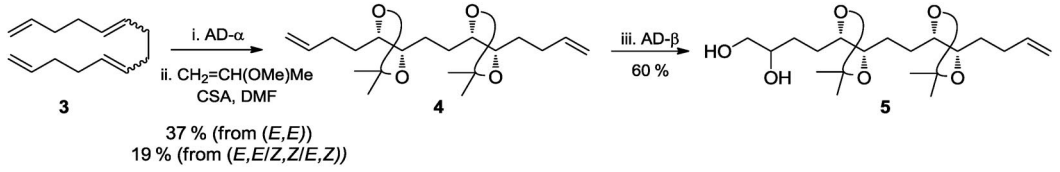
SYLVATICIN AND *cis*-SYLVATICIN

Sylvaticin (**1**) and its C12 epimer, *cis*-sylvaticin (**2**), belong to the class of annonaceous acetogenin natural products. The family exhibits wide-ranging biological activities [14]; indeed, both sylvaticin and *cis*-sylvaticin display potent antitumor activity and exhibit cytotoxicity toward certain solid tumor cell lines (human lung and pancreas carcinomas). Sylvaticin was first isolated in 1990 by McLaughlin from the dried fruits of *Rollina sylvatica* St. Hil. (Anonaceae) [15]. Subsequent isolations were reported in 1993 from *Annona purpurea* [16], and in 1995 from the leaf extracts of *Rollinia mucosa* (Jacq.) Baill. [17], when it was isolated together with *cis*-sylvaticin. Within the acetogenins, members that contain non-adjacent THF rings have been much less studied. Examination of sylvaticin and *cis*-sylvaticin reveals that both contain two non-adjacent THF rings, with sylvaticin bearing one *trans*-THF ring. We sought to develop a common strategy to both targets (Scheme 2); we believed that both bis-THF fragments could be prepared by intramolecular oxidative cyclization methodology, although this would necessitate a novel double oxidative cyclization onto two pendant alkenes of a functionalized linear precursor. Access to the *trans*-THF moiety of sylvaticin was imagined via our recently developed intramolecular hydride shift methodology, involving transformation of one of the *cis*-THFs after oxidative cyclization. In both cases we anticipated that the bis-THF fragments could be joined to the butenolide portions by cross-metathesis (CM) to allow completion of the syntheses.



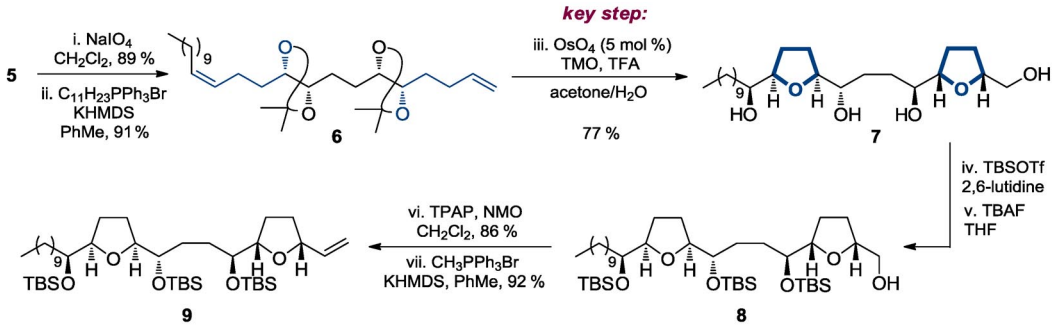
Scheme 2 Retrosynthetic analysis of sylvaticin (**1**) and *cis*-sylvaticin (**2**).

Our syntheses [18,19] began with commercially available tetradecatetraene (**3**) (Scheme 3). After separation of the pure (*E*,*E*)-isomer by chromatography on silica gel doped with $AgNO_3$ (**3** is supplied as a mixture of the three possible geometric isomers), the disubstituted alkenes were selectively dihydroxylated under asymmetric dihydroxylation (AD) conditions to provide a tetraol (>98 % ee), which was subsequently protected as bisacetonide **4** [37 %, two steps from (*E*,*E*)-**3**; maximum theoretical yield 45 %]. The preferential rate of oxidation of 1,2-*trans*-alkenes under AD conditions (over both mono- and *cis*-di-substituted alkenes) [20], allowed us to perform a selective dihydroxylation on the commercial isomeric mixture of tetraene **3** to afford the desired tetraol [**4** in 19 %, two steps from the (*E*,*E*/*Z*,*Z*/*E*,*Z*)-**3** mixture]. We next sought to desymmetrize C_2-symmetric **4**. This was achieved via dihydroxylation under AD conditions to afford diol **5** (60 %) (along with 29 % of the corresponding tetraol, which could be recycled back to **5** in a two-step procedure). Diol **5** served as our common precursor for both syntheses.



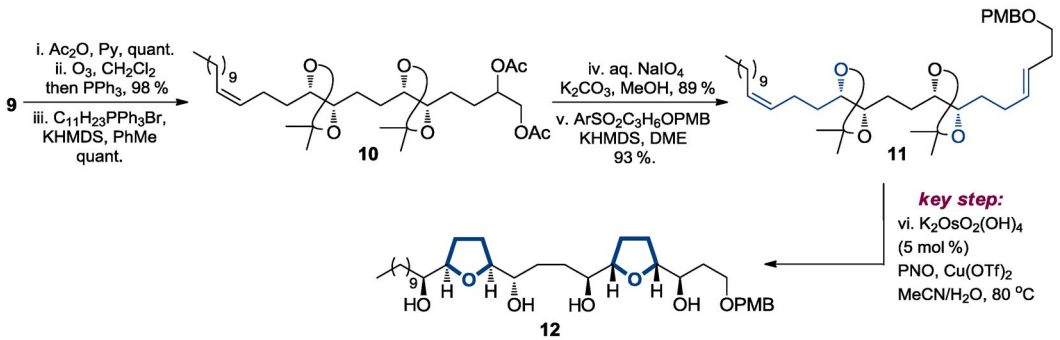
Scheme 3 Preparation of the common intermediate, diol **5**, via selective AD of tetradecatetraene (**3**).

The synthesis of the oxidative cyclization precursor for *cis*-sylvaticin then proceeded via oxidative cleavage of **5** with $NaIO_4$ and subsequent Wittig olefination to provide *cis*-alkene **6** (Scheme 4). The pivotal double oxidative cyclization could then be investigated. Pleasingly, upon subjection of diene **6** to catalytic OsO_4, trifluoroacetic acid (TFA), and trimethylamine *N*-oxide (TMO) (TFA and TMO were utilized in our earlier studies) [10], following in situ acetonide deprotection, bis-*cis*-THF **7** was obtained in good yield (77 %) and as a single diastereoisomer. In preparation for the later CM, bis-THF **7** was then manipulated in four steps to alkene **9**. This involved global *tert*-butyldimethylsilyl (TBS) protection and selective deprotection of the primary silyl ether to afford **8**, followed by oxidation and Wittig olefination, providing terminal alkene **9**.



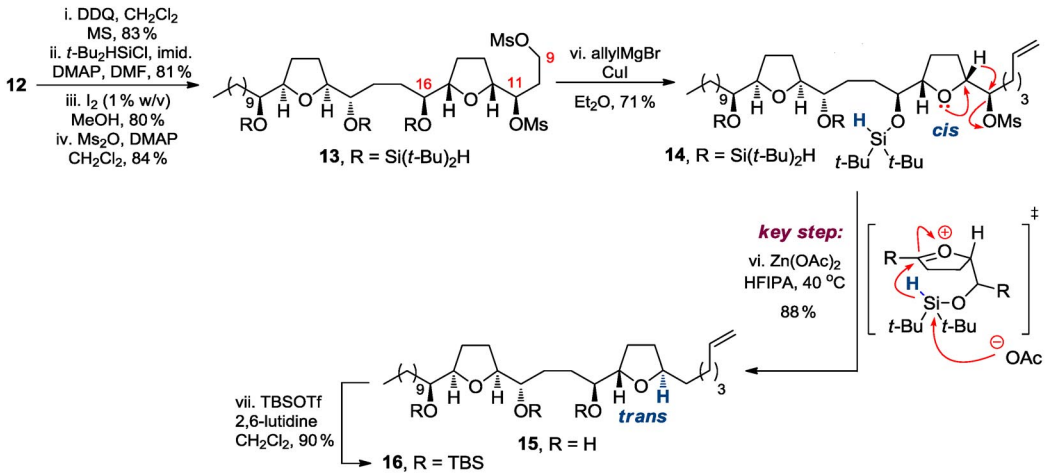
Scheme 4 Double oxidative cyclization of **6** for the synthesis of *cis*-sylvaticin and preparation of metathesis precursor **9**.

For the synthesis of sylvaticin, common intermediate diol **5** was protected as a bisacetate to allow cleavage of the remaining alkene, via ozonolysis, and subsequent Wittig olefination to afford *cis*-alkene **10** (Scheme 5). Functionalization of the other end of the molecule then ensued. Hydrolysis of the bisacetate, with basic $NaIO_4$, gave an aldehyde that was subjected to a Julia–Kocienski olefination, affording *trans*-alkene **11**, the precursor for the key double oxidative cyclization. Exposure of diene **11** to newly developed oxidative cyclization conditions that employ a Lewis acid in place of the Brønsted acid [using catalytic $K_2OsO_2(OH)_4$, $Cu(OTf)_2$ and pyridine *N*-oxide (PNO)] [21] gratifyingly provided doubly cyclized bis-*cis*-THF **12** in good yield (76 %), as a single diastereomer, and without acid-mediated deprotection of the *p*-methoxybenzyl (PMB) group.



Scheme 5 Double oxidative cyclization of **11** for the synthesis of sylvaticin.

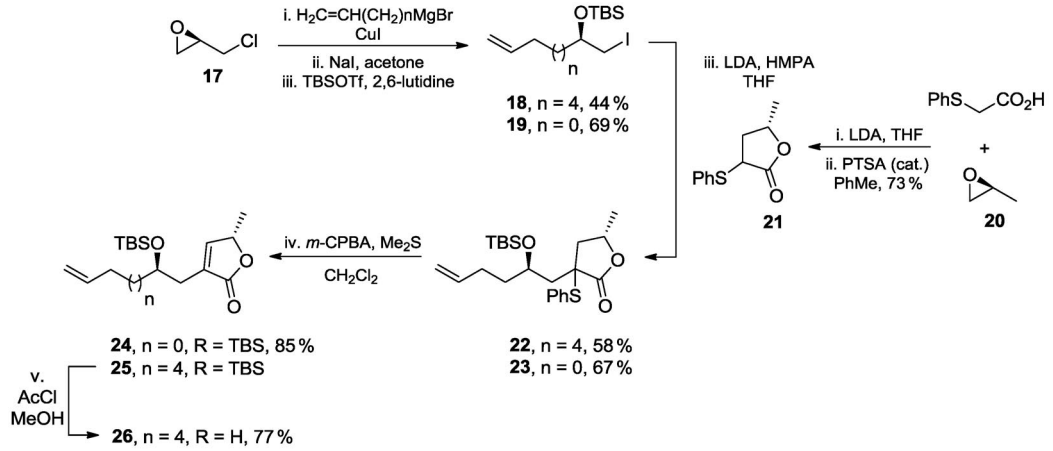
The next sequence was aimed at formation of the *trans*-THF ring of sylvaticin (Scheme 6). This relied on the in situ formation of an oxo-carbenium ion, generated via a 1,2-hydride shift to remove one of the exocyclic hydroxyl groups (activated as a suitable leaving group). We had previously demonstrated that treatment of *cis*-THFs, where one hydroxyl is activated as a mesylate, with the other bearing a silicon hydride to act as an intramolecular nucleophile, generated exclusively the *trans*-THF upon treatment with $Zn(OAc)_2$ [22]. In order to apply this chemistry to sylvaticin, bis-THF **12** was functionalized in four steps to furnish **13**, which bore a silicon-hydride silyl ether at C16, with the hydroxyls at C11 and C9 each activated as their mesylate. At this stage the primary mesylate (C9) was used to chain extend the carbon skeleton, by treatment with a cuprate derived from allylmagnesium bromide in the presence of catalytic CuI, to afford **14**; this would later allow its attachment to the butenolide fragment via CM. Compound **14**, bearing the secondary mesylate (C11), could now be utilized to form the *trans*-



Scheme 6 Hydride shift-intramolecular trapping for the synthesis of the *trans*-THF ring of sylvaticin.

THF. Pleasingly, and in accordance with the previously developed methodology, subjection of **14** to $Zn(OAc)_2$, in hexafluoroisopropyl alcohol (HFIPA), initiated the hydride shift-mesylate expulsion sequence to generate an oxo-carbenium ion, which was trapped intramolecularly by the proximal silicon hydride to form **15**, with the desired *trans*-THF ring of sylvaticin, in excellent yield (88 %). Since the transformation gave small amounts of desilylated material, we elected to conduct this transformation with an extended reaction time so as to remove all three silyl groups; as such subsequent re-silylation using *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) was undertaken to provide **16**.

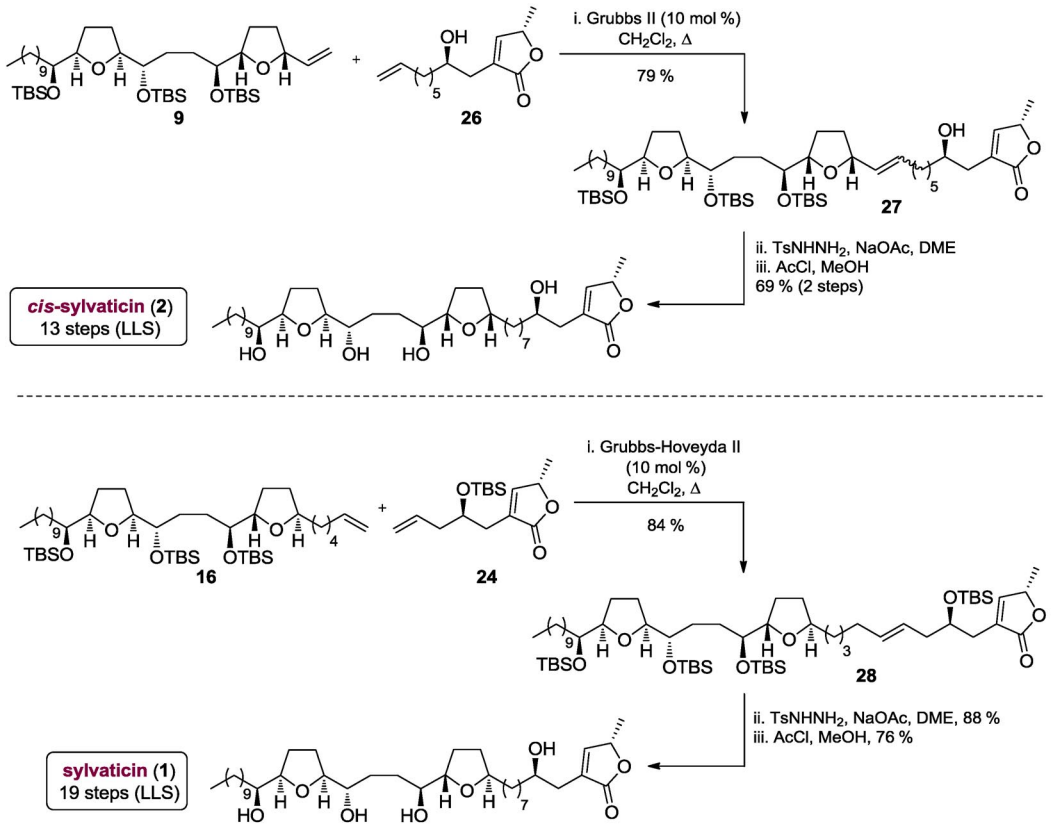
The butenolide fragments for each synthesis (**26** for *cis*-sylvaticin and **24** for sylvaticin) were prepared by following the general strategy originally reported by Lee (Scheme 7) [23]. As such, (*S*)-propylene oxide (**20**) was opened with the dianion of (phenylthio)acetic acid to provide lactone **21** in good yield (73 %), as an inconsequential 1:1 mixture of diastereomers. The lactone was then treated with terminal iodides **18** and **19** [themselves prepared in three steps from (–)-epichlorohydrin (**17**)], via treatment with lithium diisopropylamide (LDA), to afford **22** and **23**, respectively (as an inconsequential 3:1 mixture of diastereomers). Oxidation and regioselective elimination then provided butenolides **24** and



Scheme 7 Synthesis of the butenolide fragments: **26** for *cis*-sylvaticin and **24** for sylvaticin.

25. Necessary removal of the TBS group of **25** was then undertaken, by treatment with AcCl in MeOH, to afford **26**.

The end-game for the syntheses involved the union of the bis-THF and butenolide fragments, which in each case was achieved by CM (Scheme 8). For *cis*-sylvaticin, CM of bis-THF **9**, using Grubbs II catalyst with 4 equiv of **26** (in order to avoid homodimerization of **9**; the homodimer of **26** could be recovered and recycled into the reaction), gave the desired CM product **27** in good yield (79 %). The synthesis was completed in two final steps via diimide reduction of the disubstituted alkene and global removal of the three silyl protecting groups, thus completing the first total synthesis of *cis*-sylvaticin (**2**) in only 13 linear steps [24]. In a similar manner, for sylvaticin, CM of **16**, using Grubbs–Hoveyda II and **24** (4 equiv), gave the CM product **28** in good yield (84 %). Conclusion of the synthesis, in line with that shown for *cis*-sylvaticin, gave sylvaticin (**1**), which again completed the first synthesis of the natural product via a 19-step linear sequence. In both cases the synthesis confirmed the structure of the natural products as originally reported by McLaughlin.



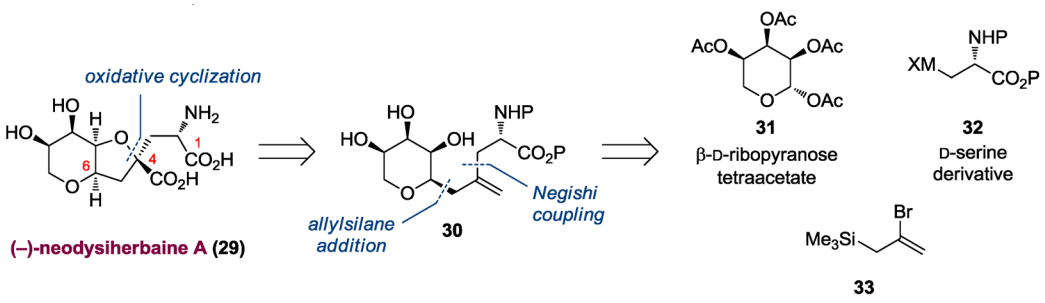
Scheme 8 Completion of the syntheses of *cis*-sylvaticin (**2**) and sylvaticin (**1**) (LLS = longest linear sequence).

NEODYSIHERBAINE A

Neodysiherbaine A (**29**) is an excitatory amino acid, first isolated in 2001 by Sakai and co-workers from the Micronesian marine sponge *Dysidea herbacea* [25]. Neodysiherbaine A was found to be a potent convulsant and a highly selective agonist for kainate (KA) and α-amino-3-hydroxy-5-methyl-4-isoxazole propionate (AMPA) glutamate receptors [26]. The first total synthesis was accomplished by Sakai in 26 steps [25], and three subsequent syntheses have been reported, which ranged between 15 to 23

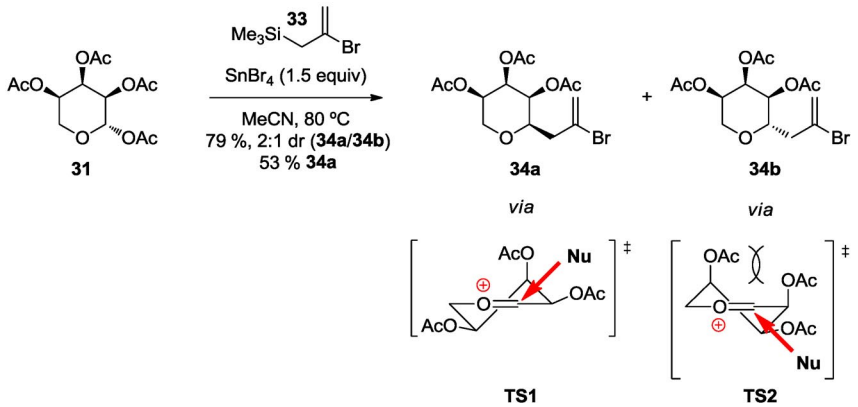
steps [27–29]. We envisioned that the highly functionalized *cis*-THF core embedded within this natural product would pose an interesting challenge for the oxidative cyclization methodology, with the presented strategy providing an expeditious route to this amino acid [30].

Our key disconnections are depicted in Scheme 9. As mentioned earlier, the *cis*-THF core of neodysiherbaine A was envisaged be formed with complete stereochemical control over the C4 center via an osmium-mediated oxidative cyclization. Further disconnection of oxidative cyclization precursor **30** revealed the amino acid side chain, which could be installed by exploiting a Negishi coupling of suitably protected D-serine derivative **32** with an appropriate vinyl halide, which could in turn be assembled from D-ribose derivative **31** and allylsilane **33**.



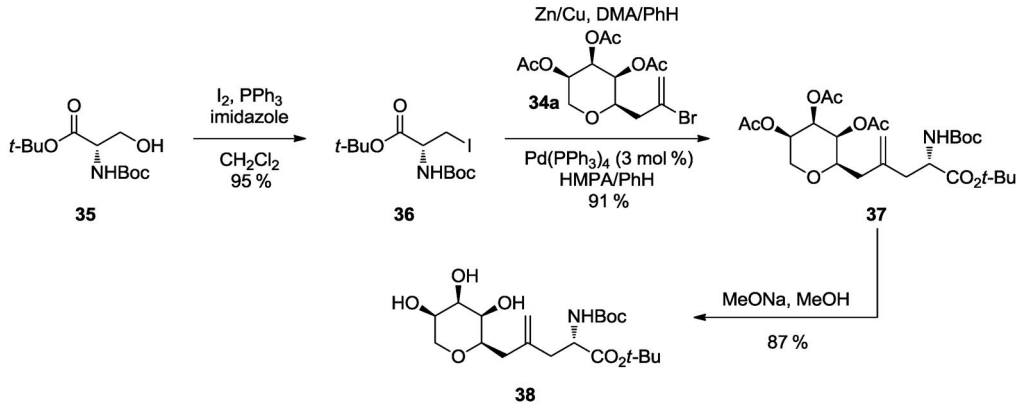
Scheme 9 Retrosynthetic analysis of neodysiherbaine A (**29**).

Our synthesis began with commercially available β-D-ribopyranose tetraacetate (**31**). Compound **31** was treated with commercially available bromoallylsilane **33** in the presence of a Lewis acid in order to install the bromoallyl group at the C1 position of the pyranose ring (Scheme 10). This reaction resulted in the formation of compound **34** with the desired *syn*-selectivity in a good yield of 79 % (2:1 mixture of diastereoisomers), of which the desired diastereoisomer was isolated in 53 % yield. Selectivity in this transformation can be rationalized by a model proposed by Woerpel and co-workers, with axial nucleophilic attack occurring on an oxo-carbenium ion [31]. It is proposed that the formation of the desired product via a chair-like transition state proceeded through structure **TS1**, whereas the minor diastereoisomer arose from transition structure **TS2**, destabilized by 1,3-diaxial interactions.



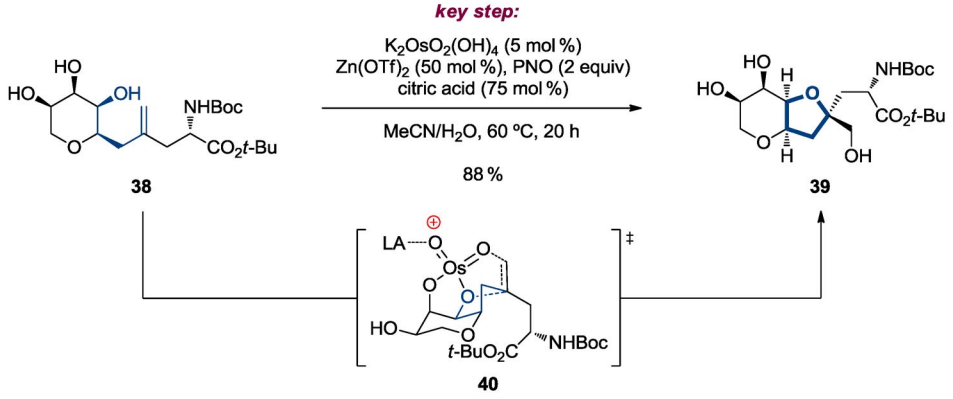
Scheme 10 Installation of the vinyl bromide side chain of **34**.

Subsequent Negishi coupling of vinyl bromide **34a** with iodo serine derivative **36**, which was prepared from Boc-Ser-O*t*-Bu (**35**) via an Appel-type reaction, afforded the desired product in 91 % yield (Scheme 11). Exposure of the coupled product to catalytic sodium methoxide in methanol resulted in removal of the acetate groups and generated the key intermediate, cyclization precursor **38**.



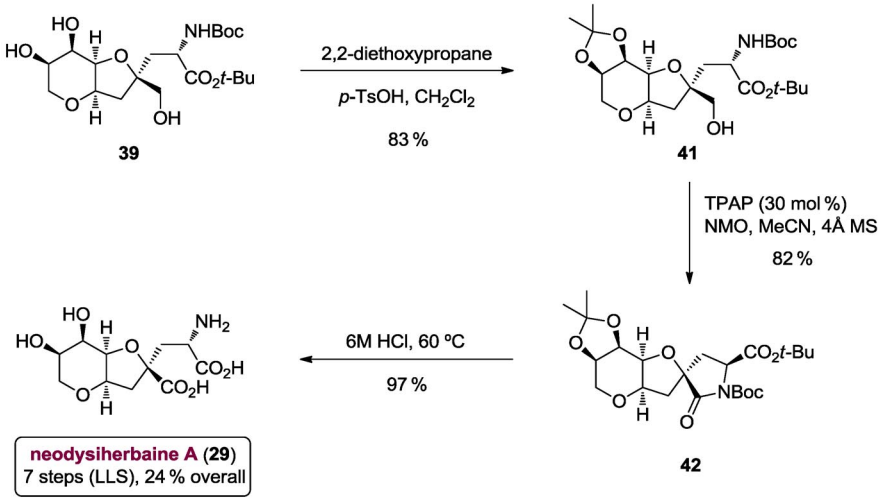
Scheme 11 Construction of the carbon skeleton via Negishi coupling.

The proposed oxidative cyclization of triol **38** represented a difficult test for this methodology. Whilst it was anticipated that utilization of the recently developed Lewis acidic conditions would provide the necessary tolerance of the acid-sensitive functional groups present in **38**, compound **38** bore a 1,2,3-triol moiety, rather than a diol, which could be capable of binding strongly to osmium in a non-productive manner, slowing the rate of reaction or even preventing cyclization from occurring. Moreover, a cyclization of **38** would construct a bicyclic ring in the process, which has previously not been demonstrated using the methodology. Consequently, **38** was subjected to oxidative cyclization conditions that use a Lewis acid (zinc or copper triflate) in place of the Brønsted acid. Use of the Lewis acid allows tolerance a range of acid-sensitive *N*- and *O*- protecting groups, such as Boc, MOM, or TBS, and was crucial in this case for the integrity of the acid labile *N*-Boc and *tert*-butyl ester functionalities. Pleasingly, the use of catalytic $K_2OsO_2(OH)_4$ and pyridine *N*-oxide as the reoxidant, in the presence of $Zn(OTf)_2$ [21] and citric acid [32], delivered the desired bicyclic *cis*-THF **39** in an excellent yield of 88 % (Scheme 12).



Scheme 12 Formation of the bicyclic core of neodysiherbaine A via oxidative cyclization.

In order to complete the synthesis of neodysiherbaine A, cyclized product **39** required oxidation of the primary hydroxyl group to the corresponding carboxylic acid (Scheme 13). This was accomplished by selective protection of the vicinal diol with 2,2-diethoxypropane to yield isopropylidene acetal **41**, which was subsequently oxidized by the action of catalytic tetrapropylammonium perruthenate (TPAP) and *N*-methylmorpholine *N*-oxide (NMO) to form lactam **42** in 82 % yield (via the intermediacy of a hemiaminal). Finally, exposure of **42** to aqueous HCl led to hydrolysis of the lactam and removal of the acetal, ester, and carbamate protecting groups to afford neodysiherbaine A (**29**); the overall sequence constituting a concise seven-step synthesis, in 24 % overall yield, representing the shortest synthesis of this natural product to date.



Scheme 13 Completion of the synthesis of neodysiherbaine A (**29**).

CONCLUSIONS

To conclude, we have reported efficient and concise routes to three complex natural products. The key step in our sequence to both sylvaticin and *cis*-sylvaticin was the double oxidative cyclization of a protected tetraol onto a diene unit that formed two nonadjacent THF rings with complete stereoselectivity. Moreover access to the *trans*-2,5-THF fragment of sylvaticin was prepared by utilizing a one-pot hydride shift/intramolecular oxo-carbenium ion reduction protocol. Finally, the versatility of the oxidative cyclization methodology was verified by application to the synthesis of the highly functionalized bicyclic THF-containing natural product neodysiherbaine A.

ACKNOWLEDGMENTS

We thank the EPSRC (RDCP) and the Dulverton Trust (RML) for funding.

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