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Synthesis of (+)-Didemniserinolipid B: Application of a 2-Allyl-4-fluorophenyl Auxiliary for Relay Ring-Closing Metathesis

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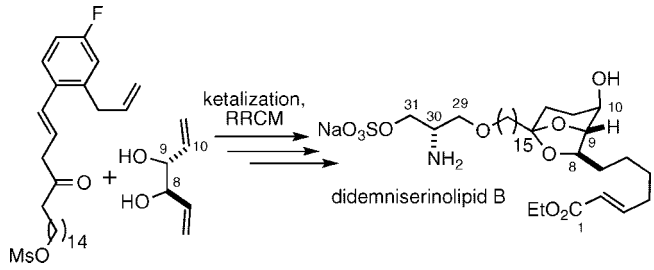

The synthesis of didemniserinolipid B utilizing a ketalization/ring-closing metathesis (K/RCM) strategy is described. In the course of this work, a novel 2-allyl-4-fluorophenyl auxiliary for relay ring-closing metathesis (RRCM) was developed, which increased the yield of the RCM. The resulting 6,8-dioxabicyclo[3.2.1]octene core was selectively functionalized by complimentary dihydroxylation and epoxidation routes to install the C10 axial alcohol. This bicyclic ketal core was further functionalized by etherification and an alkene cross metathesis with an unsaturated α-phenylselenyl ester en route to completing the total synthesis.

Introduction

Didemniserinolipids A−C (**1**−**3**, Figure 1) were isolated in 1999 by Jiménez and co-workers from the methanol extracts of marine tunicate *Didemnum* sp.[1] These structurally interesting molecules possess a central 6,8-dioxabicyclo[3.2.1]octane core with two appended alkyl chains, one of which terminates in a 2-aminopropane 1,3-diol ether, and the other in an α,β-unsaturated acid (or ester). Whereas the initial extract containing these molecules was found to be potently cytotoxic ($IC_{50} = 0.25$ μg/mL against P388, A549, and HT29 tumor cell lines), after further purification and isolation, none of the individual didemniserinolipids were found to be cytotoxic in the same assays.

Despite the lack of known biological activity for the individual didemniserinolipids, many varied natural product structures containing the 6,8-dioxabicyclo[3.2.1]octane moiety have been reported to be biologically active.[2] For example, the closely related cyclodidemniserinol trisulfate, isolated from *Didemnum guttatum*, is an inhibitor of HIV-1 integrase.[3] The large structural diversity among 6,8-dioxabicyclo[3.2.1]octane containing natural products suggests that development of a modular and efficient route to general structures of this type could be valuable in the context of diversity-oriented synthesis.[4] Ley and co-workers have recently demonstrated this concept with their discovery of novel biologically active compounds based on this scaffold.[5]

In addition to the intriguing dioxabicyclo[3.2.1]octane core, didemniserinolipids A−C display two side chains: a relatively short 7-carbon chain featuring an α,β-unsaturated acid (**1**, **3**) or ester (**2**), and an otherwise unfunctionalized 15-carbon chain terminating with a serinol-derived ether. The stereochemistry at the serinol C30 carbon could not be unambiguously assigned

(1) Gonzalez, N.; Rodriguez, J.; Jimenez, C. *J. Org. Chem.* **1999**, *64*, 5705–5707.

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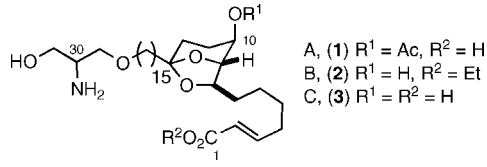

FIGURE 1. Didemniserinolipids A−C, proposed structures.

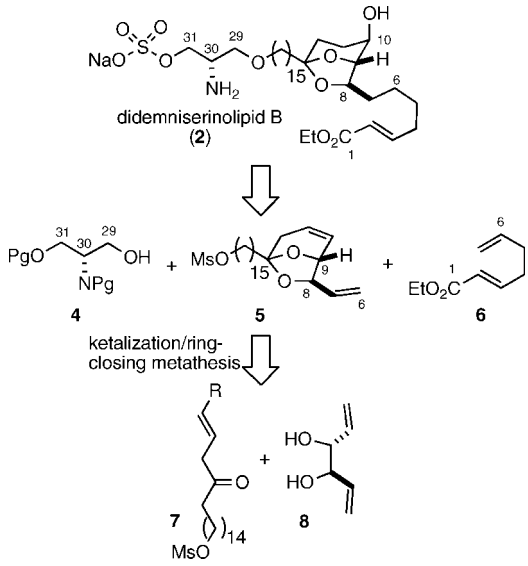

FIGURE 2. Revised didemniserinolipid B structure and K/RCM retrosynthesis.

upon isolation but was elucidated for didemniserinolipid B (**2**) after its first total synthesis by Ley (Figure 2).[6] Ley's pioneering synthesis also resulted in a structural revision for didemniserinolipid B, as the presence of a C31 *O*-sulfate was identified. The structures of didemniserinolipids A and C have yet to be unambiguously determined.

In recent years, our laboratory has explored a novel and efficient synthetic strategy to access bicyclic ketals and acetals such as the 6,8-dioxabicyclo[3.2.1]octane moiety.[7] Traditional routes to such bicyclic ketals generally involve *inter*molecular carbon−carbon bond formation followed by *intra*molecular ketalization via dehydration of a keto diol. Our strategy exploits a bimolecular ketalization to unite a ketone fragment with a C_2-symmetric diene diol, followed by intramolecular ring-closing metathesis to form a carbon−carbon bond and close the bicyclic ketal.[8] This ketalization/ring-closing metathesis (K/RCM) strategy avoids cumbersome protection/deprotection sequences often necessary in traditional approaches to these moieties. Used with C_2-symmetric diene diols, K/RCM serves to effectively desymmetrize the diol fragment, differentiating the alkenes to enable their chemoselective manipulation. The resulting rigid, facially biased dioxabicyclic templates can be manipulated stereoselectively to install additional functional groups. In the context of didemniserinolipid B, we felt that construction of the bicyclic ketal core via K/RCM would enable an efficient and modular synthesis, amenable to varying the side chains for potential analogue preparation.

Our K/RCM retrosynthesis of didemniserinolipid B is shown in Figure 2. We foresaw installation of the C1−C6 α,β-unsaturated side chain via an alkene cross metathesis (CM) with an unsaturated ester such as **6**, followed by chemoselective hydrogenation of the isolated C6−C7 double bond. The C10 axial alcohol would arise from a substrate-controlled epoxidation of the endocyclic alkene in **5**,[9] followed by *trans*-diaxial epoxide opening with hydride.[10] Williamson etherification between a suitable serinol derivative, represented in protected form by **4**, and mesylate **5** would introduce the serinol fragment. The requisite bicyclic ketal **5** would be directly provided by a K/RCM sequence involving a ketone such as **7** and known C_2-symmetric diene diol **8**.[11] In addition to providing a rapid and convenient route to **5**, K/RCM has the benefit of desymmetrizing **8** and leaving one vinyl group unreacted and available for later CM with **6** (or its equivalent).

We have recently disclosed a communication of our didemniserinolipid B synthesis using this strategy.[7h] In this publication we describe the synthesis and application of a novel relay ring-closing metathesis tail to improve the isolated yield of our key K/RCM product and describe an alternative means to install the C10 axial alcohol.

Results and Discussion

From our previous experience, we were wary of the β,γ-alkene migrating into conjugation with the ketone during acid-catalyzed ketalization. Whereas the problem had been avoided in previous K/RCM applications by elimination of a terminal halide as a separate step to install the unsaturation after ketalization,[7a−e] we expected that a phenyl ring substituent on the this alkene (i.e., **12**) would attenuate β,γ-alkene migration during ketalization. Ketone **12** (Scheme 1) was thereby prepared over 3 steps from commercially available 16-hexadecanolide **9**. Macrolactone **9** was opened with lithiated dimethyl methylphosphonate to generate β-ketophosphonate **10**. The crude product **10** was used in a Horner−Wadsworth−Emmons reaction with phenylacetaldehyde and K_2CO_3 in refluxing aqueous methanol to provide **11**, which was activated as mesylate **12** without purification. The presence of the γ-phenyl ring promoted isomerization of the double bond from the α,β- to the β,γ-position (5:1 ratio) during the HWE reaction, as required for our planned RCM. The mesylate group in **12** would strategically play two roles; it would serve as a protecting group to ensure clean ketalization and later be a reactive leaving group for etherification. Azeotropic removal of water successfully drove the ketalization between keto mesylate **12** and (*R,R*)-diene diol **8** to completion, providing a 9:1 mixture of **13** and **14**.

Ketal **13** underwent RCM upon exposure to 10.5 mol% of Grubbs' first generation metathesis catalyst (**G1**) to afford the

(6) Kiyota, H.; Dixon, D. J.; Luscombe, C. K.; Hettstedt, S.; Ley, S. V. *Org. Lett.* **2002**, *4*, 3223–3226.

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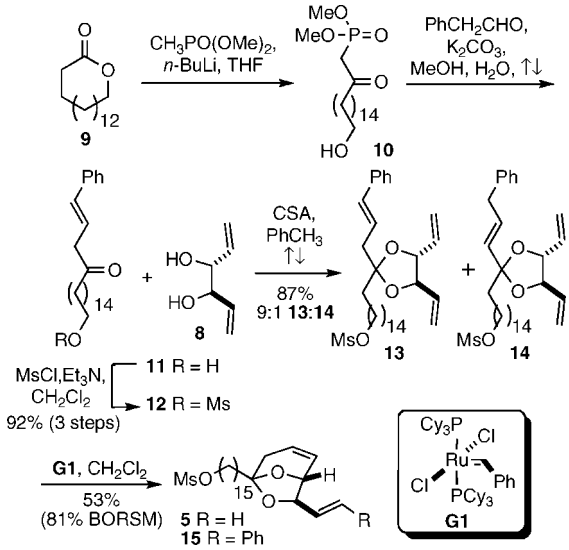
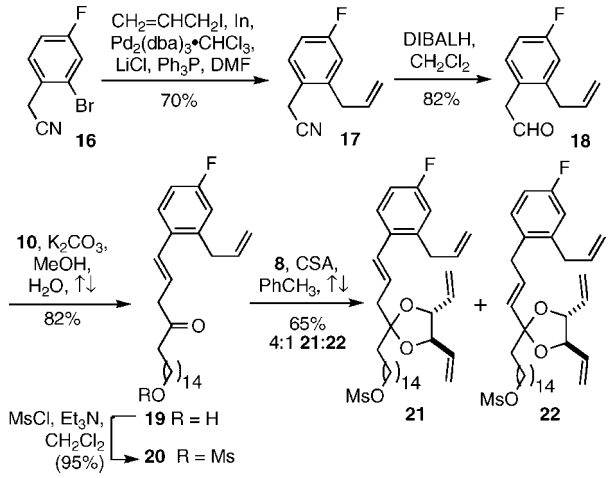
SCHEME 1. Synthesis of Bicyclic Ketal 5



SCHEME 2. Synthesis of the Relay-RCM Group



desired bicyclic ketal **5** (53% isolated yield, 81% yield based on recovered starting material). This reaction was stopped early, as prolonged reaction times led to decreased isolated yields due to formation of significant amounts of **15**. While the phenyl ring had served a convenient role in minimizing alkene migration, its presence proved detrimental during metathesis. The stoichiometric styrene released during RCM underwent CM with **5**, providing **15** as its concentration increased during the progression of this reaction.

Although stopping the RCM of **13** at approximately 50% conversion was a practical solution to minimize the formation of **15**, we sought a more elegant solution to this problem. In addition to the obvious factor of the competing CM with styrene leading to the decreased yield of **5**, we suspected that the initiation site of the RCM was problematic. Pseudo-C_2-symmetric ketal **13** contains three distinct alkenes that can interact with the Grubbs' catalyst. As reaction at the phenyl-substituted alkene is expected to be slow, initiation of metathesis is anticipated to occur at one of two diastereotopic vinyl groups. The diastereotopic relationship between these vinyl groups dictates that the ruthenium catalyst has essentially equal opportunity to initiate at a productive site leading to RCM, or at an unproductive site leading to cross metathesis or dimerization (Figure 3).

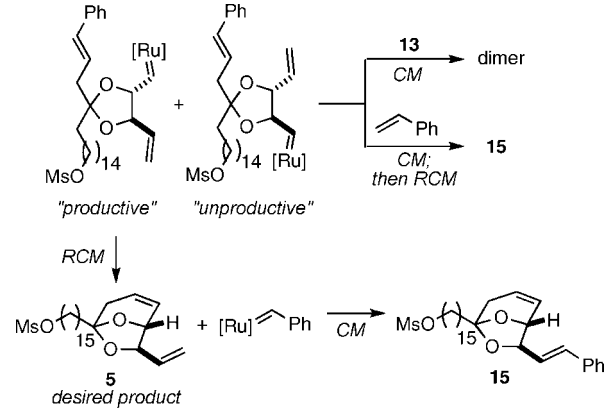


FIGURE 3. Potential metathesis pathways.

Relay-ring closing metathesis (RRCM) has found increasing application in cases where RCM fails to compete with CM dimerization pathways wherein one of two alkenes reacts slowly due to electronic or steric reasons.[12] We were intrigued by the prospect of appending an *ortho*-allyl substituent to the phenyl ring of **13**, to provide a novel group for RRCM that would direct the course of the metathesis to bicyclic ketal **5**. In addition to directing the initiation site for the ruthenium alkylidene and controlling the path of our RCM, this relay tail would release an indene ring upon RCM, which was expected to slow down competing CM pathways by being less reactive than styrene.

Scheme 2 details the straightforward synthesis of ketone **21** possessing the requisite relay group from commercially available aryl fluoro bromide **16**. Following palladium-mediated cross-coupling of **16** with allyl indium to provide **17**,[13] DIBALH reduction of the nitrile and hydrolytic workup gave aldehyde **18**. The starting material **16** was chosen as it strategically positioned a fluorine atom *para*- to the acetaldehyde group in **18**. The electron-withdrawing nature of this group contributed to the use of β-keto phosphonate **10** for a Horner-Wadsworth-Emmons reaction by facilitating isomerization of the newly produced alkene into conjugation with the aryl ring. Without the *p*-fluoro substituent, little isomerization was observed. Mesylation of **19** occurred in nearly quantitative yield to provide **20**. Ketalization with diene diol **8** as described previously gave **21** and **22** as an inseparable mixture in a 4:1 ratio. The decreased yield for this ketalization is due in part to isomerization of the *ortho*-allyl group.[14]

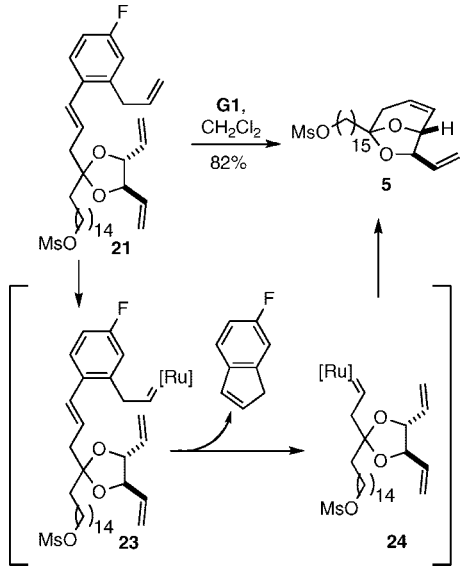
To our delight, bicyclic ketal **5** was isolated in 82% yield upon treatment of this mixture with the first generation Grubbs' catalyst **G1** at room temperature (Scheme 3). Presumably, the catalyst initiates at the unhindered allyl group on the aryl ring to provide ruthenium alkylidene **23**. Subsequent ring-closure releases 6-fluoroindene and produces ruthenium alkylidene **24** followed by RCM to produce bicyclic ketal **5**.

(12) Review: (a) Debra, J. W. *Angew. Chem., Int. Ed.* **2005**, *44*, 1912–1915. Also see: (b) Sato, D.; Fujiwara, K.; Kawai, H.; Suzuki, T. *Tetrahedron Lett.* **2008**, *49*, 1514–1517. (c) Roethle, P. A.; Chen, I. T.; Trauner, D. *J. Am. Chem. Soc.* **2007**, *129*, 8960–8961. (d) Hansen, E. P.; Lee, D. *Org. Lett.* **2004**, *6*, 2035–2038. (e) Hoye, T. R.; Jeffrey, C. S.; Tennakoon, M. A.; Wang, J.; Zhao, H. *J. Am. Chem. Soc.* **2004**, *126*, 10210–10211. (f) Wang, X.; Bowman, E. J.; Bowman, B. J.; Porco, J. A., Jr. *Angew. Chem., Int. Ed.* **2004**, *43*, 3601–3605. (g) Robinson, J.; Piscopio, A. D.; Zhu, L. *Abstracts of Papers*; 226th National Meeting of the American Chemical Society, New York; American Chemical Society: Washington, DC; ORGN-118.

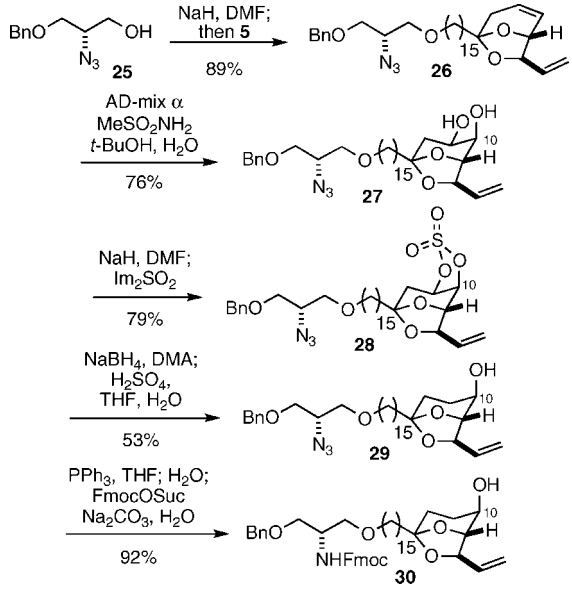
(13) (a) Lee, P. H.; Sung, S.-Y.; Lee, K. *Org. Lett.* **2001**, *3*, 3201–3204. (b) Lee, K.; Lee, J.; Lee, P. H. *J. Org. Chem.* **2002**, *67*, 8265–8268.

(14) This reaction was not optimized to the extent of the ketalization of **12** and **8**.

SCHEME 3. Relay-RCM Sequence

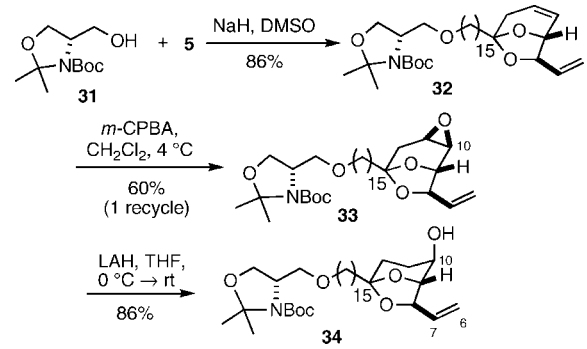


SCHEME 4. Installation of the C10 Alcohol via Dihydroxylation/Cyclic Sulfate Opening



With reliable and high-yielding routes to bicyclic mesylate **5** in hand, an appropriately protected serinol derivative was needed. Azido alcohol **25** (Scheme 4) appeared to be a suitable choice,[15] and after deprotonation with sodium hydride, the alkoxide reacted with mesylate **5** to give azido ether **26** in 89% yield.[16] To install the C10 axial alcohol, the more electron-rich endocyclic double bond was first selectively dihydroxylated using Sharpless's asymmetric dihydroxylation conditions.[7b,e,17] While the stereochemistry of the resulting diol was controlled by the bridged bicyclic ketal, AD-mix α proved to be the matched chiral reagent, since AD-mix β gave the same product

SCHEME 5. Epoxidation Route to Install the C10 Alcohol



at a much slower rate in a similar system.[7a,e] To remove the unnecessary C11 hydroxyl, cyclic sulfate **28** was prepared in 79% yield using 1,1′-sulfonyldiimidazole and sodium hydride in DMF. Reductive opening of cyclic sulfate **28** with sodium borohydride (5 equiv.) in dimethylacetamide, followed by hydrolysis of the resultant sulfate in aqueous sulfuric acid in THF provided axial alcohol **29** in 53% yield (2 steps). The azido group was subsequently reduced and protected in one-pot via Staudinger reduction[18] and reaction with *N*-(9-fluorenylmethoxycarbonyloxy)succinimide to give Fmoc-protected amine **30** in excellent yield.

Due to the relatively low overall yield and the multistep nature of the sequence to install the C10 alcohol (32% over 4 steps), we became interested in an alternative strategy to install this functional group (Scheme 5). Concurrent with this modification to our route, we reconsidered the protecting strategy for the serinol fragment. By using known serinol derivative **31**,[19] we would not need to reduce the azide and would thereby further shorten our synthesis by making it more convergent. Furthermore, replacement of the benzyl ether in **25** with an acid-labile group would provide for a more straightforward endgame. After some optimization, Williamson etherification of **5** with the sodium alkoxide of **31** proceeded cleanly to afford **32** with only trace amounts (~3%) of the elimination byproduct. The more electron-rich endocyclic olefin of bicyclic diene **32** underwent chemo- and stereoselective epoxidation with 1 equiv of *m*-CPBA at 4 °C.[9] This protocol gave 60% yield of epoxide **33** after one recycle of recovered starting material **32**. The isolated yield of **33** suffers from competitive epoxidation of the vinyl group (the other possible epoxides are produced in 15% combined yield). Reductive *trans*-diaxial opening of epoxide **33** was accomplished by treatment with LAH in THF to give C10 alcohol **34** in 86% yield. This epoxidation/LAH reduction provided a more practical protocol for the installation of the C10 alcohol (52% from **32**).

Completion of didemniserinolipid B required elaboration of the C6−C7 alkene to the C1−C7 enoate-containing side chain. Whereas we originally pursued the cross metathesis of **34** with known diene **6**,[20] attempts to selectively hydrogenate the C6−C7 alkene were stymied by either over-reduction of the α,β-unsaturated ester or no reaction.[21] Successful installation of the remaining C1−C7 side chain is shown in Scheme 6. Cross metathesis of **34** and known racemic selenide **35**[22] in refluxing dichloromethane with Grubbs' second generation catalyst **G2**

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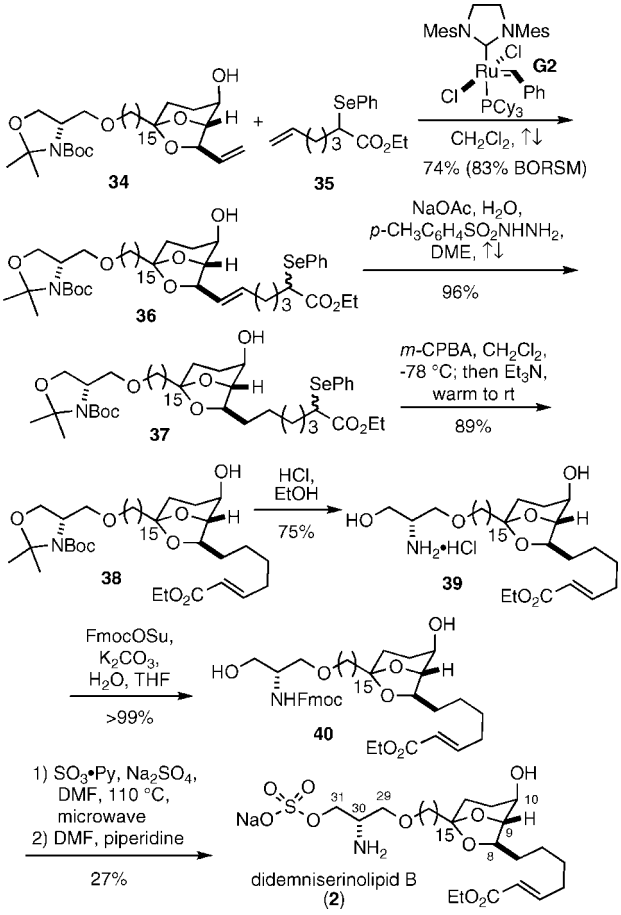
(20) Marshall, J. A.; Sabatini, J. J. *Org. Lett.* **2005**, *7*, 4819–4822.

SCHEME 6. Completion of Didemniserinolipid B



gave exclusively the *E* isomer of **35** in 74% as an inconsequential 1:1 mixture of diastereomers. Whereas the selective reduction of the $\Delta^{6,7}$ alkene in **36** was unsuccessful with Pd/C and 1 atm of hydrogen, use of diimide reduction conditions successfully provided **37** in near quantitative yield.[23] Oxidation of the phenylselenide with *m*-CPBA established the necessary α,β-unsaturated ester in **38** via selenoxide elimination.[24]

Unsaturated ester **38** was converted to didemniserinolipid B in four steps. The acetonide and Boc protecting groups were removed by heating **38** in a 5:1 mixture of ethanol and 1 N HCl at 50 °C. The bicyclic ketal and ethyl ester both survive these conditions, with the amino alcohol obtained in 75% yield. Use of FmocOSu resulted in quantitative conversion of **39** to Fmoc-protected amine **40**. The final two steps follow the sequence described in Ley's didemniserinolipid B synthesis.[6] The monosulfate was prepared by treatment of **40** with 1 equiv of SO_3•Py at 110 °C for 1 h using microwave irradiation.[25] The Fmoc-protecting group was then removed upon dilution of the reaction mixture with DMF and addition of piperidine to provide (+)-didemniserinolipid B (**2**).[26] Synthetic **2** thus obtained was identical to the natural product by comparison to published ^{1}H and ^{13}C NMR, MS, IR, and optical rotation data.[27]

In summary, didemniserinolipid B has been prepared in 2.6% overall yield via a concise route with a longest linear sequence (LLS) of 12 steps from ketone **12** and diene diol **8** (15 step LLS from commercially available materials). In addition to the use of a K/RCM sequence to establish the bicyclic ketal core, an alternative route using a relay-ring closing metathesis has been developed which improves the efficiency of the RCM process. This novel RRCM group avoids unproductive dimerization and cross metathesis pathways via the extrusion of an indene ring that does not participate in alkene metathesis with either the substrate or the desired product under these conditions. The resulting bicyclic ketal template enabled a chemo- and stereoselective epoxidation sequence to install the C10 axial alcohol, and facilitated modular appendage of both the serinol and C1−C7 side chains. This versatile route could potentially be applied to the synthesis of the remaining didemniserinolipids or to the HIV-1 integrase inhibitor cyclodidemniserinol trisulfate.[1,8] Production of (+)-didemniserinolipid B further showcases the merits of the K/RCM strategy in the rapid construction of bicyclic ketals and their conversion to complex natural products.

Experimental Section[28]

Relay Ring-Closing Metathesis Preparation of 5. Ketal **21** (30.5 mg, 0.050 mmol) was dissolved in 9 mL CH_2Cl_2. This reaction was gently refluxed and Grubbs' catalyst **G1** (4 mg, 0.005 mmol) was added as a solution in 1 mL of CH_2Cl_2 over 2 h. The reaction was refluxed for an additional hour after the addition of Grubbs' catalyst was complete. It was then cooled and stirred open to air overnight. The resulting brown solution was concentrated *in vacuo*. Flash column chromatography (20−40% ether:hexanes) provided bicyclic ketal **5** as a white solid (18 mg, 0.0407 mmol, 82% yield). ^{1}H NMR ($CDCl_3$) δ 6.08 (1H, app ddt, J = 9.5, 4.5, 2 Hz), 5.86 (1H, ddd, J = 17, 10, 7.5 Hz), 5.74 (1H, ddd, J = 10, 4, 3 Hz), 5.23 (1H, ddd, J = 17, 1.5, 1 Hz), 5.12 (1H, ddd, J = 10, 1.5, 1 Hz), 4.46 (1H, br d, J = 7.5 Hz), 4.37 (1H, d, J = 4.5 Hz), 4.22 (2H, t, J = 6.5 Hz), 3.00 (3H, s), 2.44 (1H, ap dt, J = 18, 2.5 Hz), 2.12 (1H, ddd, J = 18, 4, 2 Hz), 1.9−1.6 (4H, m), 1.6−1.2 (24H, m); ^{13}C NMR ($CDCl_3$) δ 138.1 (CH), 128.4 (CH), 125.5 (CH), 116.3 (CH_2), 108.6 (C), 85.9 (CH), 76.5 (CH), 70.1 (CH_2), 38.1 (CH_2), 37.3 (CH_3), 36.9 (CH_2), 29.8−28.9 (CH_2 × 11), 25.3 (CH_2), 23.3 (CH_2); IR (thin film) 3041, 2919, 2849 cm^{-1}; HRMS (ESI) calcd for $C_{24}H_{42}O_5SNa$ ($M+Na^+$) 465.2651, found 465.2672; $[\alpha]^{24}_D$ +27 (*c* 1.0, $CHCl_3$); mp 47−49 °C.

Serinol Ether 32. Known serinol acetonide **31** (691.3 mg, 2.99 mmol) was dissolved in dry DMSO (3 mL). Sodium hydride (124.3 mg, 60% dispersion in mineral oil, 3.1 mmol) and mesylate **5** (666.7 mg, 1.50 mmol) were added sequentially. The reaction immediately changed color from nearly colorless to deep red. The reaction was stirred at room temperature for 16 h, and was then quenched by addition of saturated aqueous NH_4Cl (20 mL) and diluted with CH_2Cl_2 (20 mL). These layers were separated and the aqueous layer extracted with CH_2Cl_2 (5 × 15 mL). The combined ether layers were dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash

(21) Hydrogenation using H_2 (1 atm), 10% Pd/C, in THF or diimide conditions (NaOAc, $TsNHNH_2$, DME, reflux) gave over reduction to the completely saturated derivative. Poisoning 10% Pd/C with Et_3N under 1 atm H_2 or using Lindlar's catalyst gave only recovered starting material. Marvin, C. C. Ph.D. Thesis, University of Wisconsin-Madison, 2008.

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(26) Ley and co-workers obtained a 49% yield for this sequence, see ref 6. In addition to didemniserinolipid B, we observed amino alcohol **39**, which suggests the sulfonation step is not going to completion.

(27) See the Supporting Information.

(28) For general procedures and syntheses of **10**−**21**, **26**−**30**, **33**, **34**, **39**, **40** and **2**, see the Supporting Information.

column chromatography (20%-40% ether:hexanes) yielded serinol ether **32** (0.75 g, 1.29 mmol, 86% yield) as a colorless oil. R_f = 0.40 (20% EtOAc:hexanes); **^{1}H NMR** ($CDCl_3$) δ 6.08 (1H, ddt, J = 10, 5, 2 Hz), 5.87 (1H, ddd, J = 17, 10, 7 Hz), 5.74 (1H, ddd, J = 10, 4, 3 Hz), 5.24 (1H, ddd, J = 17, 1.5, 1.3 Hz), 5.13 (1H, ddd, J = 10, 1.5, 1.3 Hz), 4.47 (1H, d, J = 8 Hz), 4.37 (1H, d, J = 5 Hz), 4.1−4.05 (1H, m), 4.05−3.9 (2H, m), 3.61−3.26 (4H, m), 2.45 (1H, dt, J = 18, 2.5 Hz), 2.13 (1H, ddd, J = 18, 4, 2 Hz), 1.82−1.77 (2H, m), 1.57−1.44 (17H, m), 1.40−1.26 (24H, m); **^{13}C NMR** ($CDCl_3$) δ 151.7 (C), 138.2 (CH), 128.5 (CH), 125.6 (CH), 116.4 (CH_2), 108.7 (C), 93.7 (C) rotamer A, 93.2 (C) rotamer B, 85.9 (CH), 79.7 (C) rotamer, 76.6 (CH), 71.4 (CH_2), 70.0 (CH_2) rotamer A, 69.3 (CH_2) rotamer B, 65.7 (CH_2) rotamer A, 65.4 (CH_2) rotamer B, 56.5 (CH) rotamer A, 56.4 (CH) rotamer B, 38.1 (CH_2), 37.0 (CH_2), 29.9−29.3 (CH_2 × 12), 28.4 (CH_3 × 3), 27.5 (CH_3) rotamer A, 26.7 (CH_3) rotamer B, 26.1 (CH_2), 24.4 (CH_3) rotamer A, 23.4 (CH_2), 23.1 (CH_3) rotamer B; **IR** (thin film) 2975, 2937, 2857, 1702 cm^{-1}; **HRMS** (ESI) calcd for $C_{34}H_{59}NO_6Na$ (M+Na$^+$) 600.4240, found 600.4232; **[α]$^{25}_D$** +57.1 (*c* 1.195 $CHCl_3$).

Alkenyl Selinide 36. Axial alcohol **34** (610 mg, 1.02 mmol) and alkene **35**[28] (4.45 g, 14.3 mmol) were dissolved in CH_2Cl_2 (30 mL). Grubbs' second generation catalyst **G2** was added in one portion, the reaction was heated to 45 °C and stirred for 16 h. NMO (120.6 mg) was added and the solvent was removed *in vacuo*. Purification by flash column chromatography (40−80% ether/hexanes) provided recovered alcohol **33** (69.1 mg, 0.12 mmol, 11% recovered yield), and alkenyl selenide **36** (664 mg, 0.755 mmol, 74% yield) as a yellow oil. R_f = 0.25 (40% EtOAc:hexanes); ^{1}H NMR ($CDCl_3$) δ 7.61−7.58 (2H, m), 7.34−7.26 (3H, m), 5.63 (1H, dt, J = 15, 6 Hz), 5.45 (1H, dd, J = 15, 7 Hz), 4.28 (1H, d, J = 8 Hz), 4.09 (2H, q, J = 7 Hz), 4.20−3.90 (4H, m), 3.68 (1H, br s), 3.59 (1H, dd, J = 8.5, 6.5 Hz), 3.6−3.25 (4H, m), 2.47 (1H, br s), 2.09−1.22 (24H, m), 1.16 (3H, t, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 172.8 (C), 135.6 (CH) diastereomer A, 135.5 (CH) diastereomer B, 133.0 (CH) diastereomer A, 132.6 (CH) diastereomer B, 130.2 (CH) diastereomer A, 130.2 (CH), 130.0 (CH) diastereomer B, 128.9 (CH), 128.5 (CH), 128.4 (CH), 128.0 (C), 109.9 (C), 93.7 (C) rotamer A, 93.2 (C) rotamer B, 83.3 (CH), 79.6 (C) rotamer A, 78.9 (CH) diastereomer A, 78.8 (CH) diastereomer B, 78.6 (CH) rotamer B, 71.3 (CH_2), 70.0 (CH_2) rotamer A, 69.3 (CH_2) rotamer B, 66.0 (CH), 65.7 (CH_2) rotamer A, 65.4 (CH_2) rotamer B, 60.9 (CH_2), 60.2 (CH_2), 56.4 (CH) rotamer A, 56.3 (CH) rotamer B, 43.4 (CH), 37.7 (CH_2), 34.1 (CH_2) diastereomer A, 31.6 (CH_2) diastereomer B, 31.4 (CH_2), 31.3 (CH_2), 30.9 (CH_2) diastereomer A, 30.3 (CH_2) diastereomer B, 29.8−29.4 (CH_2 × 9), 28.4 (CH_3 × 3), 27.5 (CH_3) rotamer A, 27.4 (CH_2) diastereomer A, 26.7 (CH_3) rotamer B, 26.1 (CH_2), 24.9 (CH_2), 24.4 (br CH_3) rotamers A, 23.2 (CH_2), 23.2 (CH_3) rotamer B, 14.2 (CH_3) diastereomer A, 14.0 (CH_3) diastereomer B; IR (thin film) 3480 (br), 2926, 2854, 1729, 1700 cm^{-1}; HRMS (ESI) calcd for $C_{47}H_{77}NO_9SeNa$ (M + Na$^+$) 896.4721 (monoisotopic), found 896.4758; [α]$^{25}_D$ +33.5 (*c* 1.08, $CHCl_3$).

Alkyl Selenide 37. Alkenyl selenide **36** (482 mg, 0.548 mmol) was dissolved in 1,2-dimethoxyethane (40 mL). *p*-Toluenesulfonyl hydrazide (4.95 g, 26.6 mmol) was added, and this solution was heated to reflux (oil bath temperature 85 °C). A solution of NaOAc (2.24 g, 27.3 mmol) in H_2O (40 mL) was added via syringe pump over 3 h. The reaction was stirred for an additional 2 h, and then cooled to rt. The reaction mixture was extracted exhaustively with CH_2Cl_2 (75 mL portions). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification by flash column chromatography (60−80% ether/hexanes) provided alkyl selenide **37** (466.5 mg, 0.529 mmol, 96% yield) as a colorless oil. R_f = 0.62 (100% ether); ^{1}H NMR ($CDCl_3$) δ 7.61−7.58 (2H, m), 7.36−7.26 (3H, m), 4.17−3.85 (7H, m), 3.61 (1H, br s), 3.59 (1H, dd, J = 9, 6.5 Hz), 3.52−3.27 (4H, m), 2.29 (1H, t, J = 7.5 Hz), 2.04−1.23 (60H, m), 1.17 (3H, t, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 173.0 (C), 135.5 (CH × 2), 128.9 (CH × 2), 128.3 (CH), 128.1 (C), 109.5 (C), 82.3 (CH), 80.2 (C) rotamer A, 79.7 (C) rotamer B, 77.8 (CH), 71.4 (CH_2), 70.0 (CH_2) rotamer A, 69.2 (CH_2) rotamer B, 66.3 (CH), 65.7 (CH_2) rotamer A, 65.4 (CH_2) rotamer B, 60.8 (CH_2), 60.1 (CH_2) rotamer A (2nd rotamer did not resolve from noise), 56.4 (br CH), 43.6 (CH), 37.5 (CH_2), 35.1 (CH_2) diastereomer A, 35.1 (CH_2), 34.3 (CH_2) diastereomer B, 31.7 (CH_2), 30.1 (CH_2), 29.8−29.4 (CH_2 × 8), 29.0 (CH_2) diastereomers A and B, 28.9 (CH_2), 28.4 (CH_3 × 3), 28.0 (CH_2), 27.5 (CH_3) rotamer A, 26.7 (CH_3) rotamer B, 26.1 (CH_2), 25.3 (CH_2) diastereomer A, 25.2 (CH_2), 25.0 (CH_2), 24.8 (CH_2) diastereomer B, 24.4 (CH_3) rotamer A, 23.0 (CH_3) rotamer B, 22.9 (CH_2), 14.0 (CH_3); IR ($CHCl_3$ soln) 3010, 2929, 2856, 1721, 1691 cm^{-1}; HRMS (ESI) calcd for $C_{47}H_{79}NO_9SeNa$ (M + Na$^+$) 898.4872 (monoisotopic), found 898.4863; [α]$^{25}_D$ +32.6 (*c* 1.18, $CHCl_3$).

α,β-Unsaturated Ester 38. Alkyl selenide **37** (62.7 mg, 0.0712 mmol) was dissolved in CH_2Cl_2 (5 mL) and cooled to −78 °C. A CH_2Cl_2 (5 mL) solution of *m*-CPBA (21.1 mg, <77% purity, 0.094 mmol) was added dropwise via cannula. After 2 h, Hünig's base (0.05 mL) was added and the cold bath was removed. After an additional 2 h at rt, the reaction was concentrated *in vacuo*. Flash column chromatography (60−80% ether/hexanes, then 100% ether) provided α,β-unsaturated ester **38** (46 mg, 0.064 mmol, 89% yield) as a colorless oil. R_f = 0.52 (100% ether); ^{1}H NMR ($CDCl_3$) δ 6.94 (1H, dt, J = 15.5, 7 Hz), 5.81 (1H, d, J = 15.5 Hz), 4.18 (2H, q, J = 7 Hz), 4.05 (1H, br s), 4.00−3.86 (4H, m), 3.65−3.25 (5H, m), 2.44 (1H, br d, J = 9 Hz), 2.21 (2H, q, J = 6.5 Hz), 1.96 (1H, m), 1.84−1.26 (55H, m); ^{13}C NMR ($CDCl_3$) δ 166.6 (C), 148.8 (CH), 121.5 (CH), 109.6 (C), 93.8 (C) rotamer A, 93.7 (C) rotamer B, 82.4 (CH), 80.2 (C) rotamer A, 79.7 (C) rotamer B, 77.7 (CH), 71.3 (CH_2), 70.0 (CH_2) rotamer A, 69.3 (CH_2) rotamer B, 66.2 (CH), 65.7 (CH_2) rotamer A, 65.4 (CH_2) rotamer B, 60.1 (CH_2), 56.5 (CH) rotamer A, 56.4 (CH) rotamer B, 37.5 (CH_2), 35.0 (CH_2), 32.0 (CH_2), 30.1 (CH_2), 29.7−29.4 (CH_2 × 13), 28.4 (CH_3 × 3), 27.8 (CH_2), 27.5 (CH_3) rotamer A, 26.7 (CH_3) rotamer B, 26.1 (CH_2), 25.1 (CH_2), 24.4 (CH_3) rotamer A, 23.1 (CH_3) rotamer B, 23.0 (CH_2), 14.3 (CH_3); IR ($CHCl_3$ soln) 3010, 2929, 2856, 1693 (br) cm^{-1}; HRMS (ESI) calcd for $C_{41}H_{73}NO_9$ (M + Na$^+$) 746.5178, found 746.5159; [α]$^{25}_D$ +37.6 (*c* 0.98, $CHCl_3$).

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Supporting Information Available: Experimental procedures and ^{1}H and ^{13}C NMR spectra for all new compounds and a comparison of **2** with literature data are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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