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Formal Total Synthesis of the Polyketide Macrolactone Narbonolide

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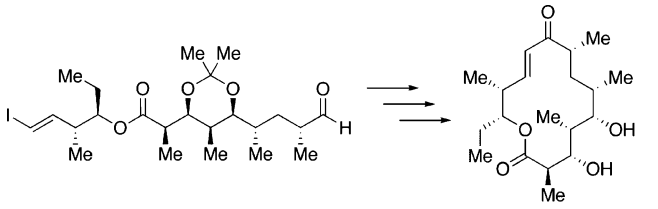
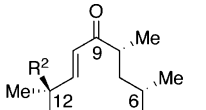


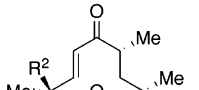
An improved synthesis of (3*S*)-3-dihydronarbonolide is reported that constitutes a formal total synthesis of the 14-membered macrolactone antibiotic narbonolide. The key step was an intramolecular Nozaki−Hiyama−Kishi coupling to accomplish macrocyclization in improved yield. The high level of convergence will also allow us to rapidly synthesize narbonolide analogues for the study of enzymes in the pikromycin biosynthetic pathway.

Introduction

Narbonolide (**1**) is a 14-membered polyketide macrolactone biosynthesized by the pikromycin polyketide synthase (PKS) system of *Streptomyces venezuelae* ATCC 15439 and undergoes further post-PKS C5-glycosylation to narbomycin (**2**) followed by C12-oxidation to pikromycin (**3**).[1,2] Pikronolide (**4**), the pikromycin aglycon, has been isolated from *S. venezuelae* MCRL-0376.[3] The pikromycin PKS system of *S. venezuelae* ATCC 15439 also biosynthesizes the 12-membered macrolactone 10-deoxymethynolide (**5**), which is a metabolic precursor to YC-17 (**6**) and methymycin (**7**).[1,2] The inherent substrate tolerance of the pikromycin PKS system is interesting for the study of its mechanism of regulating the size of macrolactone ring formation and for its potential utility in combinatorial biosynthesis. To complement our efforts in studying the late stages of the pikromycin PKS with its natural chain elongation intermediates,[4,5] we sought convenient synthetic access to narbonolide and its structural analogues for the study of the post-PKS glycosylation and oxidation enzymes DesVII and PikC. Narbonolide and related derivatives are also of potential therapeutic interest due to their structural similarity to ketolide antibacterials such as telithromycin and cethromycin.



narbonolide (**1**), R^1 = H, R^2 = H
narbomycin (**2**),
R^1 = desosaminyl, R^2 = H
pikromycin (**3**),
R^1 = desosaminyl, R^2 = OH
pikronolide (**4**), R^1 = H, R^2 = OH



10-deoxymethynolide (**5**),
R^1 = H, R^2 = H
YC-17 (**6**),
R^1 = desosaminyl, R^2 = H
methymycin (**7**),
R^1 = desosaminyl, R^2 = OH

A total synthesis of narbonolide (**1**) has been reported by Masamune and co-workers; however, cyclization by

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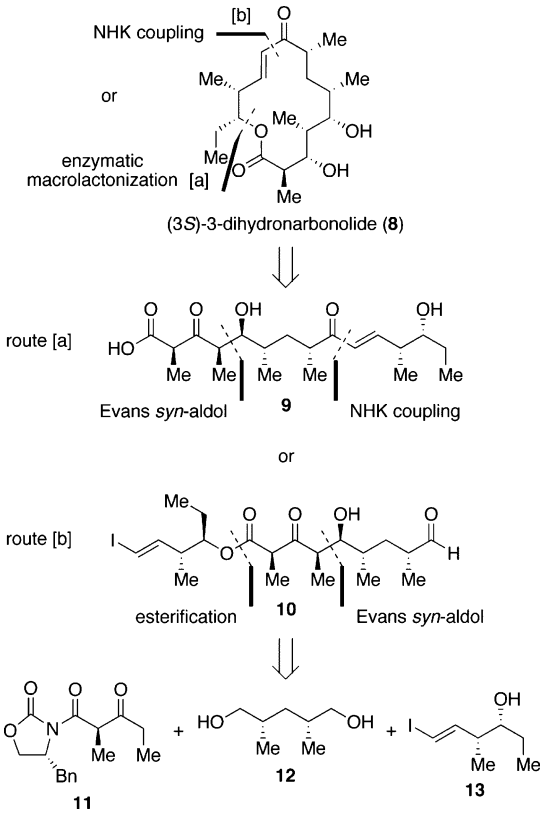
macrolactonization proceeded in only 32% yield and was complicated by formation of a dimeric product in 25% yield.[6] Yonemitsu and co-workers have reported two total syntheses of pikronolide (**4**), which both use an intramolecular Horner−Wadsworth−Emmons (HWE) macrocyclization.[7−9] The yields for these intramolecular HWE reactions were sensitive to the nature of the protecting groups at the intermediate C3- and C5-alcohols. When the C3- and C5-alcohols were protected as their PMB and DMPM ethers, respectively, HWE cyclization proceeded in high yield (89%);[7,8] however, protection of the C3- and C5-alcohols as an isopropylidene ketal led to moderate yield (55%) of the HWE cyclization with formation of a dimeric product (18% yield).[9]

We envisioned a highly convergent route to narbonolide that would utilize an alternate macrocyclization strategy and one that would be readily amenable to the synthesis of analogues that could not be readily prepared by semisynthesis for substrate specificity studies of DesVII and PikC. Two macrocyclization strategies were considered: an enzymatic macrolactonization with the isolated pikromycin thioesterase (Pik TE) domain[10] from the pikromycin biosynthetic pathway[1,2] and an intramolecular Nozaki−Hiyama−Kishi (NHK) coupling. We have recently used Pik TE as a macrolactonization catalyst in the total synthesis of 10-deoxymethynolide (**5**).[5] The intramolecular NHK coupling has been utilized in macrocyclization toward many natural products,[11] including macrolides such as the 12-membered 10-deoxymethynolide (**5**),[12] the 13-membered brefeldin C,[13] and the 16-membered spiramycin aglycone.[14] To the best of our knowledge, these macrocyclization strategies have not been reported for 14-membered macrolides. We report here the total synthesis of (3*S*)-3-dihydronarbonolide highlighted by an intramolecular NHK coupling that constitutes a formal total synthesis of narbonolide.

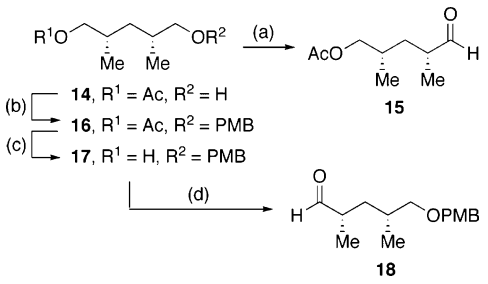
Results and Discussion

Retrosynthesis of (3*S*)-3-dihydronarbonolide (**8**) by enzymatic macrolactonization (route a) or NHK (route b) disconnections leads to acid **9** and aldehyde **10**, respectively (Scheme 1). Further retrosynthetic analysis of acid **9** and aldehyde **10** leads to three fragments of similar size and complexity: Evans' β-keto imide (**11**),[15] representing C1−C4; *meso*-diol **12**,[16] corresponding to C5−C9; and vinyl iodide **13**,[12] representing C10−C15. The use of common fragments for both approaches to macrocyclization will permit the evaluation of these routes in a complementary, parallel manner. Additionally, the structural simplicity and ready availability of fragments **11**−**13** will enable us to modify them for rapid incorporation into the synthesis of narbonolide analogues.

SCHEME 1. Retrosynthesis of (3*S*)-3-Dihydronarbonolide



SCHEME 2. Synthesis of C5−C9 Fragments 15 and 18[a]



[a] Key: (a) Dess−Martin, $NaHCO_3$, 75%; (b) $Cl_3CC(NH)OPMB$, CSA, 93%; (c) $LiAlH_4$, 84%; (d) Dess−Martin, pyr., 83%.

Synthesis of two C5−C9 fragments commenced with monoacetate **14**,[16] prepared by the lipase-mediated desymmetrization of *meso*-diol **12** (Scheme 2). Oxidation to aldehyde **15** provided a C5−C9 fragment suitable for NHK coupling and synthesis of a protected form of acid **9** for enzymatic macrolactonization. Alternatively, a C5−C9 fragment suitable for elaboration to aldehyde **10** for intramolecular NHK coupling was also synthesized. Protection of the alcohol of acetate **14** as PMB ether **16** was followed by reductive removal of the acetate to alcohol **17**. Dess−Martin oxidation of alcohol **17** afforded the C5−C9 fragment as aldehyde **18**.

We chose to initially examine the use of aldehyde **15** in synthesizing a protected form of acid **9** for enzymatic

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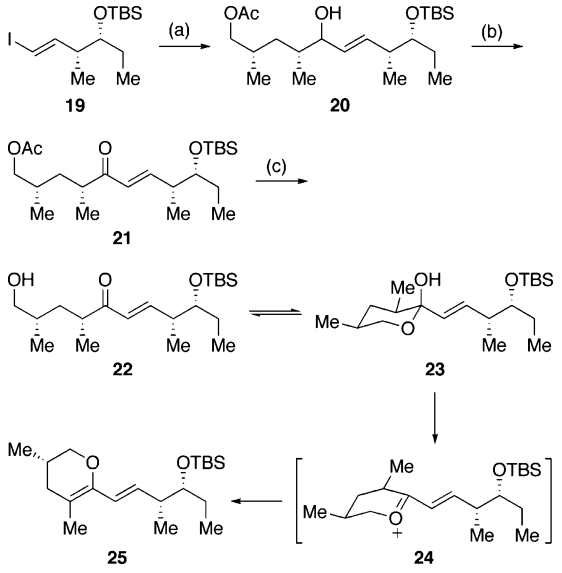
SCHEME 3. Attempted Synthesis of C5−C15 Fragment 22[a]

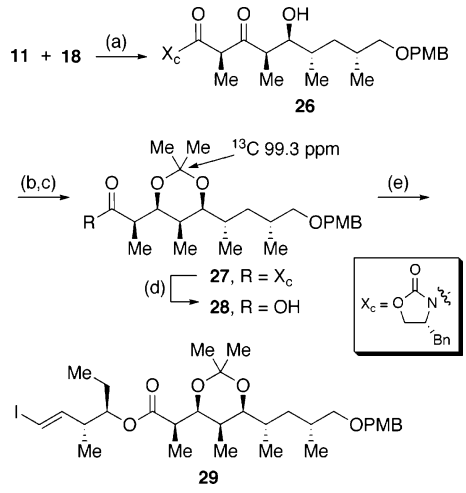


[a] Key: (a) **15**, $CrCl_2$, Ni(acac)$_2$, 67%; (b) Dess−Martin, $NaHCO_3$, 79%; (c) K_2CO_3 (0.25 equiv), anhydrous MeOH, 15%.

macrolactonization with Pik TE. Thus, NHK coupling of aldehyde **15** and vinyl iodide **19**[12] afforded allylic alcohol **20**, which was oxidized to enone **21** (Scheme 3). Attempted saponification of the acetate of **21** with K_2CO_3 (8 equiv) yielded a complex mixture of products that indicated elimination of the siloxy group had taken place. The acetate of enone **21** was successfully saponified with catalytic K_2CO_3; however, we were unable to isolate the desired alcohol **22**. Rather, dihydropyran **25** was isolated after chromatography in 15% yield in addition to numerous unidentified products and unreacted starting material (14%). The tautomeric hemiketal **23** that is in equilibrium with the initially formed alcohol **22** underwent dehydration to dihydropyran **25** via intermediate oxocarbenium ion **24** that is stabilized by the adjacent double bond. We then sought to avoid the sensitivity of ketone **22** by replacing the acetate function with a PMB ether that could be deprotected under neutral conditions; however, this approach also ultimately led to the isolation of dihydropyran **25** (35% isolated yield).[5]

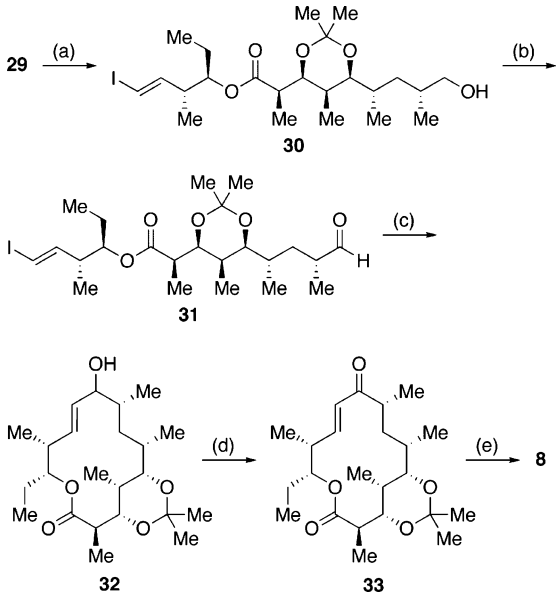
Given the unexpected difficulties due to the instability of enone **22**, we chose to complete the synthesis using the intramolecular NHK coupling. Assembly of the entire C1−C15 carbon skeleton began with the chiral auxiliary-mediated *syn*-aldol reaction between Evans' β-keto imide (**11**)[15] and aldehyde **18** to give the C1−C9 fragment, alcohol **26** (Scheme 4). Attempts to protect the C5-alcohol as a PMB ether were unsuccessful, so we elected to reduce the C3-ketone and simultaneously protect the resulting 1,3-diol as an isopropylidene ketal. Directed reduction of **26** with $Zn(BH_4)_2$ was immediately followed by protection of the *syn*-1,3-diol as acetonide **27**. The ^{13}C NMR acetonide analysis was used to confirm the presence of the *syn*-acetonide and the diastereoselectivity of the $Zn(BH_4)_2$ reduction.[17] Removal of the chiral auxiliary to acid **28** and esterification with C10−C15 fragment **13**[12]

SCHEME 4. Synthesis of C1−C15 Intermediate 29[a]



[a] Key: (a) $TiCl_4$, *i*-Pr_2NEt, 74%; (b) $Zn(BH_4)_2$; (c) $Me_2C(OMe)_2$, CSA, 96% (two steps); (d) LiOH, H_2O_2, 90%; (e) **13**, 2,4,6-$Cl_3C_6H_2COCl$, Et_3N, 90%.

SCHEME 5. Completion of Synthesis of 8[a]



[a] Key: (a) DDQ, 87%; (b) Swern, 89%; (c) $CrCl_2$, $NiCl_2$, 58%; (d) Dess−Martin, pyr., 82%; (e) TFA, 89%.

completed the synthesis of the C1−C15 framework (compound **29**).

With the entire C1−C15 skeleton assembled, completion of the synthesis began with deprotection of compound **29** to primary alcohol **30**, followed by Swern oxidation to aldehyde **31** (Scheme 5). Initial attempts to cyclize aldehyde **31** by an intramolecular NHK coupling in DMF failed; however, macrocyclization proceeded smoothly in DMSO to allylic alcohol **32**. Failure of this reaction in DMF was unexpected since it is the preferred solvent for NHK couplings.[18] It is possible that the DMF used in this reaction contained trace impurities that are known to complex Cr(II).[11] As expected, this macrocyclization was also concentration dependent. Macrocyclization proceeded in moderate yield at dilute concen-

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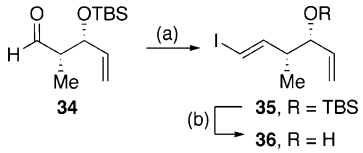
SCHEME 6. Synthesis of a C10−15 Fragment Analogue[a]



[a] Key: (a) CHI_3, $CrCl_2$, 61%; (b) 48% HF, 95%.

tration (0.0008 M); however, a sole dimeric product was isolated at higher concentration (0.01 M). In contrast to the previous synthesis of narbonolide,[6] we observed no dimeric side products when the macrocyclization was carried out at dilute concentration. Oxidation of allylic alcohol **32** to enone **33**[6] successfully completed the formal total synthesis of narbonolide. Removal of the acetonide protecting group afforded (3*S*)-3-dihydronarbonolide (**8**), which has previously been converted to narbonolide (**1**).[6] Still unresolved is a method to selectively oxidize the C3-alcohol in the presence of the C5-alcohol to directly convert (3*S*)-3-dihydronarbonolide (**8**) to narbonolide (**1**). Masamune and co-workers reported an indirect solution to this problem by a nonselective oxidation that led to a roughly 1:1 mixture of the desired C3-ketone (narbonolide) and the C5-ketone.[6] The undesired C5-ketone was recycled by reduction back to (3*S*)-3-dihydronarbonolide (**8**) and reoxidation to the C3- and C5-ketone mixture.[6] Selective PMB protection of the C5-alcohol in a total synthesis of pikronolide (**4**) proceeded in only 35% yield.[9] Methods to convert (3*S*)-3-dihydronarbonolide by microbial transformation to narbomycin and pikromycin are currently under investigation by us, and results will be reported in due course.

We are also interested in using this synthetic strategy to synthesize narbonolide analogues that will be useful for studying the substrate specificity of the post-PKS enzymes DesVII and PikC and to gain access to novel derivatives of potential therapeutic use. To demonstrate the utility of this synthetic approach, we have synthesized an analogue of the C10−C15 fragment **13**. Aldehyde **34**[19] (synthesized in four steps) was easily converted to vinyl iodide **36** in two steps (Scheme 6). Aldehyde **34** was reacted to give compound **35**, which was followed by deprotection to **36**. Vinyl iodide **36** could then be used in place of vinyl iodide **13** to install the C10−C15 fragment at a late stage of the macrolide synthesis (Scheme 4). Placement of a terminal vinyl group at C13 in a macrolide analogue has the added advantage of serving as a point of chemical diversification for future macrolide derivatives.

Conclusion

As shown here, the intramolecular NHK coupling can be successfully applied to the synthesis of 14-membered macrolides such as narbonolide (**1**). Our synthesis of (3*S*)-3-dihydronarbonolide utilized an intramolecular NHK coupling for macrocyclization of this 14-membered macrolide. In this way we were able to successfully avoid significant side product formation that limited its previous synthesis. The convergence of this synthetic route will enable us to readily synthesize narbonolide analogues for future biochemical experiments with post-PKS enzymes in the pikromycin biosynthetic pathway.

Experimental Section

(2*S*,4*R*,5*R*/*S*,6*E*,8*R*,9*R*)-9-(*tert*-Butyldimethylsilyloxy)-5-hydroxy-2,4,8-trimethylundec-6-enyl Acetate (20). To a solution of aldehyde **15** (106 mg, 0.62 mmol, 1.0 equiv), vinyl iodide **19**[12] (270 mg, 0.76 mmol, 1.22 equiv), and $Ni(acac)_2$ (0.8 mg, 0.003 mmol, 0.005 equiv) in degassed DMF (3 mL) was added $CrCl_2$ (185 mg, 1.5 mmol, 3.0 equiv) via a Schlenk addition flask. The reaction was stirred at room temperature for 8 h, quenched with aqueous EDTA (0.5*M*, pH 8.0, 5 mL), and diluted with EtOAc (10 mL). The resulting deep purple solution was stirred for 15 min, and the layers were separated. The aqueous layer was extracted with EtOAc (2 × 15 mL), and the combined organic layers were washed with H_2O (2 × 20 mL) and saturated aqueous NaCl (20 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (10% EtOAc/hexanes) afforded the title compound (153 mg, 67% yield) as a colorless oil. Additionally, a symmetrical diene (42 mg, 24% yield) due to homocoupling of vinyl iodide **19** was isolated: $R_f = 0.39$ (15% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.57−5.70 (m, 1H), 5.39−5.48 (m, 1H), 3.78−4.00 (m, 3H), 3.38−3.48 (m, 1H), 2.32 (pent, $J = 6.6$ Hz, 1H), 2.05 (s, 3H), 1.82−1.96 (m, 1H), 1.62−1.76 (m, 1H), 1.31−1.54 (m, 4H), 0.83−1.01 (m, 22H), 0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.1, 135.8, 135.5, 130.5, 129.6, 68.9, 41.3, 36.8, 36.7, 36.2, 30.0, 26.6, 26.5, 26.0, 21.1, 18.3, 18.2, 16.0, 15.6, 15.1, 9.6, 9.4, −4.2, −4.3 (C1 and C5 obscured by $CDCl_3$ signal); IR (thin film) 3468 (br), 2959, 2930, 2857, 1740, 1249 cm^{-1}; HRMS calcd for ($C_{22}H_{44}O_4Si + Na^+$) 423.2901, found 423.2924.

((3*R*,4*R*,*E*)-6-((*S*)-5,6-Dihydro-3,5-dimethyl-4*H*-pyran-2-yl)-4-methylhex-5-en-3-yloxy)(*tert*-butyl)dimethylsilane (25). To a solution of enone **21** (43 mg, 0.10 mmol) in anhydrous MeOH (10 mL) at room temperature was added K_2CO_3 (3.5 mg, 0.025 mmol, 0.25 equiv), and the reaction was stirred for 16 h. The reaction was concentrated under reduced pressure, and purification by flash chromatography (10% EtOAc/hexanes) afforded the title compound (5.6 mg, 15% yield) as a colorless oil whose spectral data corresponded to those reported.[5] Additionally, unreacted **21** (6.1 mg, 14%) was recovered.

(*R*)-3-((2*R*,4*R*,5*S*,6*S*,8*R*)-9-(4-Methoxybenzyloxy)-5-hydroxy-2,4,6,8-tetramethyl-3-oxononanoyl)-4-benzyloxazolidin-2-one (26). To a solution of β-ketoimide **11**[15] (5.46 g, 18.9 mmol) in CH_2Cl_2 (40 mL) at −5 °C was added $TiCl_4$ (1.0 M solution in PhMe, 20.77 mL, 20.77 mmol, 1.1 equiv) followed by *i*-Pr_2NEt (3.59 mL, 20.77 mmol, 1.1 equiv). The dark brown solution was stirred at −5 °C for 1 h and then cooled to −78 °C. To this solution was added a solution of aldehyde **18** (4.72 g, 18.9 mmol, 1.0 equiv) in CH_2Cl_2 (15 + 5 mL), and the reaction was stirred at −78 °C for 30 min, slowly warmed to −50 °C, and stirred for an additional 12 h. The reaction was quenched by the addition of pH 7 phosphate buffer (1 M, 100 mL) and slowly warmed to room temperature with vigorous stirring. The mixture was diluted with CH_2Cl_2 (100 mL); the layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (20 mL) and saturated aqueous NaCl (10 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification by flash chromatography (30% EtOAc/hexanes) afforded the title compound (7.50 g, 74% yield) as a colorless oil: $R_f = 0.48$ (30% EtOAc/hexanes); $[\alpha]_D^{23} = -102.7$ ($c = 0.94$, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.18−7.74 (m, 7H), 6.86 (d, $J = 9.0$ Hz, 2H), 4.86 (q, $J = 7.2$ Hz, 1H), 4.70−4.80 (m, 1H), 4.42 (ABq, $J = 12.0$, 18.3 Hz, 2H), 4.16−4.29 (m, 2H), 3.74−3.81 (m, 4H), 3.39 (dd, $J = 4.8$, 9.0 Hz, 1H), 3.28 (dd, $J = 3.0$, 13.2 Hz, 1H),

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3.18 (dd, J = 7.2, 9.0 Hz, 1H), 2.94−3.04 (m, 1H), 2.72−2.84 (m, 2H), 1.76−1.98 (m, 2H), 1.54−1.72 (m, 1H), 1.46 (d, J = 7.5 Hz, 3H), 1.08 (d, J = 6.6 Hz, 3H), 0.94−1.02 (ovlp m, 4H), 0.87 (d, J = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 211.8, 170.4, 159.1, 154.2, 135.2, 131.1, 129.6, 129.3, 129.2, 127.7, 113.9, 75.8, 75.6, 72.9, 66.9, 55.7, 55.6, 51.8, 46.7, 38.9, 38.3, 34.1, 31.7, 19.7, 16.8, 13.6, 8.7; IR (thin film) 3345 (br), 1775, 1715 cm^{-1}; HRMS calcd for ($C_{31}H_{41}NO_7$ + Na^+): 562.2781, found 562.2808.

(*R*)-3-((*R*)-2-((4*S*,5*R*,6*S*)-6-((2*S*,4*R*)-5-(4-Methoxybenzyloxy)-4-methylpentan-2-yl)-2,2,5-trimethyl-1,3-dioxan-4-yl)propanoyl)-4-benzyloxazolidin-2-one (27). To a solution of the alcohol **26** (3.66 g, 6.78 mmol) in CH_2Cl_2 (30 mL) at −78 °C was added a solution of $Zn(BH_4)_2$ in Et_2O (0.145 M, 70.1 mL, 10.2 mmol, 1.5 equiv), and the reaction was stirred for 30 min. The reaction was quenched by the addition of saturated aqueous NH_4Cl (100 mL) and stirred vigorously as it was warmed to room temperature. After 15 min, the mixture was diluted with CH_2Cl_2 (100 mL). The layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with saturated aqueous NaCl (15 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure to a foamy solid and used as such for the next reaction. The crude 1,3-diol was dissolved in 2,2-dimethoxypropane (30 mL) at room temperature, and a catalytic amount of CSA (0.10 g) was added. The solution was stirred for 6 h, and the reaction was quenched by the addition of Et_3N (2 mL). The mixture was concentrated under reduced pressure, and the residue was purified by flash chromatography (20% EtOAc/hexanes) to afford the title compound (3.80 g, 96% yield) as a white foam: R_f = 0.42 (20% EtOAc/hexanes); $[\alpha]_D^{23}$ = −69.2 (c = 1.25, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.22−7.35 (m, 7H), 6.88 (d, J = 9.0 Hz, 2H), 4.64−4.72 (m, 1H), 4.44 (AB system, J = 11.5, $\Delta\upsilon$ = 34.5 Hz, 2H), 4.14−4.24 (ovlp m, 2H), 4.09 (dd, J = 2.0, 9.5 Hz, 1H), 3.86−3.94 (m, 1H), 3.81 (s, 3H), 3.32−3.38 (ovlp m, 2H), 3.25 (dd, J = 3.5, 13.0 Hz, 1H), 3.15 (dd, J = 7.5, 9.0 Hz, 1H), 2.76 (dd, J = 9.5, 13.5 Hz, 1H), 1.82−1.92 (m, 1H), 1.66−1.74 (m, 1H), 1.55−1.66 (m, 2H), 1.41 (s, 3H), 1.38 (s, 3H), 1.32 (d, J = 7.0 Hz, 3H), 0.98 (d, J = 9.0 Hz, 3H), 0.76−0.84 (m, 1H), 0.78 (d, J = 7.0 Hz, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.3, 159.1, 152.8, 135.3, 131.3, 129.6, 129.19, 129.16, 127.6, 113.9, 99.3, 78.3, 75.6, 75.1, 72.8, 66.3, 55.6, 55.4, 40.3, 38.9, 38.1, 32.6, 31.6, 31.2, 30.4, 20.0, 19.7, 16.3, 15.3, 6.0; IR (thin film) 1782, 1694 cm^{-1}; HRMS calcd for ($C_{34}H_{47}NO_7$ + Na^+) 604.3250, found 604.3253.

(*R*)-((3*R*,4*R*,*E*)-6-Iodo-4-methylhex-5-en-3-yl) 2-((4*S*,5*R*,6*S*)-6-((2*S*,4*R*)-5-(4-Methoxybenzyloxy)-4-methylpentan-2-yl)-2,2,5-trimethyl-1,3-dioxan-4-yl)propanoate (29). To a solution of acid **28** (0.21 g, 0.50 mmol) in THF (5 mL) at room temperature were added 2,4,6-trichlorobenzoyl chloride (0.105 mL, 0.675 mmol, 1.35 equiv) and Et_3N (0.087 mL, 0.625 mmol, 1.25 equiv). After the mixture was stirred for 2 h, the solids were filtered and washed with hexanes. The solvents were removed under reduced pressure, and the residue was dissolved in benzene (5 mL). To this solution was added vinyliodide **13**[12] (0.144 g, 0.600 mmol, 1.20 equiv) in benzene (5 mL) followed by DMAP (0.0825 g, 0.675 mmol, 1.35 equiv), and the reaction was stirred at room temperature for 24 h. The reaction was diluted with Et_2O (100 mL), washed with saturated aqueous $NaHCO_3$ (15 mL) and saturated aqueous NaCl (10 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (10% EtOAc/hexanes) afforded the title compound (0.29 g, 90% yield) as a colorless oil: R_f = 0.58 (10% EtOAc/hexanes); $[\alpha]_D^{23}$ = +10.1 (c = 0.90, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.28 (d, J = 7.5 Hz, 2H), 6.88 (d, J = 8.5 Hz, 2H), 6.45 (dd, J = 8.0, 14.5 Hz, 1H), 6.10 (d, J = 14.5 Hz, 1H), 4.72−4.80 (m, 1H), 4.44 (AB system, J = 11.5, $\Delta\upsilon$ = 34.0 Hz, 2H), 3.84 (dd, J = 1.5, 10.0 Hz, 1H), 3.81 (s, 3H), 3.38 (dd, J = 5.0, 9.0 Hz, 1H), 3.34 (dd, J = 1.5, 10.0 Hz, 1H), 3.15 (dd, J = 7.5, 9.0 Hz, 1H), 2.58−2.70 (m, 1H), 2.40−2.56 (m, 1H), 1.80−1.96 (m, 1H), 1.64−1.76 (m, 1H), 1.46−1.62 (m, 4H), 1.39 (s, 3H), 1.38 (s, 3H), 1.24 (d, J = 6.5 Hz, 3H), 1.03 (d, J = 7.0 Hz, 3H), 0.97 (d, J = 6.5 Hz, 3H), 0.77−0.92 (ovlp m, 7H), 0.76 (d, J = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 174.5, 159.1, 147.4, 131.2, 129.2, 113.9, 99.4, 78.6, 77.3, 76.4, 75.6, 75.4, 72.8, 55.6, 44.0, 43.1, 38.8, 32.4, 31.9, 31.5, 30.3, 24.6, 19.9, 19.6, 15.9, 15.3, 15.1, 10.3, 5.6; IR (thin film) 2970, 2935, 2877, 1729, 1612 cm^{-1}; HRMS calcd for ($C_{31}H_{49}IO_6$ + Na^+) 667.2492, found 667.2471.

(1*S*,2*R*,5*R*,6*R*,9*R*/*S*,10*R*,12*S*,13*S*,17*R*,*E*)-5-Ethyl-9-hydroxy-2,6,10,12,15,15,17-heptamethyl-4,14,16-trioxabicyclo[11.3.1]heptadec-7-en-3-one (32). To a solution of aldehyde **31** (0.075 g, 0.15 mmol) in DMSO (190 mL) at room temperature were added $CrCl_2$ (0.362 g, 2.94 mmol, 20 equiv) and $NiCl_2$ (0.0018 g, 0.0147 mmol, 0.1 equiv). The reaction mixture was stirred for 48 h and then quenched by the addition of H_2O (40 mL). The mixture was diluted with EtOAc (500 mL), and the layers were separated. The organic layer was washed with H_2O (3 × 30 mL) and saturated aqueous NaCl (30 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification by flash chromatography (25% EtOAc/hexanes) afforded the title compound (0.034 g, 58% yield) as a colorless oil: R_f = 0.49 (25% EtOAc/hexanes); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.47−5.68 (m, 2H), 4.78−4.82 (m, 0.5 H), 4.61−4.67 (m, 0.5 H), 4.16−4.20 (m, 0.5 H), 3.78−3.86 (m, 1.5 H), 3.27−3.37 (m, 1H), 2.41−2.68 (m, 2H), 2.08−2.24 (m, 1H), 1.46−1.85 (m, 6H), 1.19−1.39 (m, 10H), 1.00−1.03 (m, 3H), 0.68−0.93 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 175.2, 175.1, 134.1, 132.6, 131.6, 130.0, 99.7, 99.5, 79.6, 79.1, 78.1, 77.6, 75.8, 75.6, 72.1, 42.9, 42.7, 39.7, 38.7, 38.1, 37.4, 36.9, 36.8, 32.2, 31.8, 31.5, 30.2, 24.6, 22.5, 20.1, 19.9, 17.1, 16.1, 16.0, 15.9, 15.0, 14.9, 14.5, 13.8, 10.7, 10.6, 5.8, 5.6; IR (thin film) 3483 (br), 2970, 2937, 1727, 1180 cm^{-1}; HRMS calcd for ($C_{23}H_{40}O_5$ + Na^+) 419.2773, found 419.2788.

(1*S*,2*R*,5*R*,6*R*,10*R*,12*S*,13*S*,17*R*,*E*)-5-Ethyl-2,6,10,12,15,15,17-heptamethyl-4,14,16-trioxa-bicyclo[11.3.1]-heptadec-7-ene-3,9-dione (33). To a solution of alcohol **32** (18.4 mg, 0.067 mmol) in CH_2Cl_2 (10 mL) at room temperature were added the Dess−Martin periodinane (158 mg, 0.374 mmol, 8.0 equiv) and pyridine (0.11 mL, 1.40 mmol, 30 equiv). The reaction was stirred for 12 h and diluted with EtOAc (25 mL). The mixture was washed with saturated aqueous $NaHCO_3$ (5 mL), 1 M aqueous Na_2SO_3 (5 mL), and saturated aqueous NaCl (5 mL), dried (Na_2SO_4), filtered, and concentrated under reduced pressure. Purification by flash chromatography (20% EtOAc/hexanes) afforded the title compound (15 mg, 82% yield) as a wet solid: R_f = 0.51 (20% EtOAc/hexanes); $[\alpha]_D^{23}$ = +6.1 (c = 0.28, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.67 (dd, J = 5.7, 16.5 Hz, 1H), 6.04 (dd, J = 1.8, 16.5 Hz, 1H), 5.08−5.14 (m, 1H), 3.96 (dd, J = 1.8, 6.6 Hz, 1H), 3.76 (dd, J = 1.5, 10.5 Hz, 1H), 2.84−2.90 (m, 1H), 2.71−2.79 (m, 2H), 2.07−2.17 (m, 1H), 1.86 (q, J = 6.6 Hz, 1H), 1.53−1.66 (m, 3H), 1.44 (s, 3H), 1.43 (s, 3H), 1.20−1.24 (m, 1H), 1.17 (d, J = 6.6 Hz, 3H), 1.14 (d, J = 7.2 Hz, 3H), 1.08 (d, J = 6.3 Hz, 3H), 0.97 (d, J = 6.6 Hz, 3H) 0.96 (d, J = 7.2 Hz, 3H), 0.90 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 204.9, 175.2, 147.3, 130.7, 100.4, 77.9, 77.1, 73.5, 41.5, 39.8, 38.8, 37.8, 33.9, 33.1, 30.1, 24.7, 20.2, 16.8, 14.6, 14.0, 13.7, 10.8 8.1; IR (thin film) 2972, 2937, 1730, 1695, 1626, 1200 cm^{-1}; HRMS calcd for ($C_{23}H_{38}O_5$ + Na^+) 417.2617, found 417.2630.

(3*S*)-3-Dihydronarbonolide (8). To a solution of acetonide **33** (14 mg, 0.0381 mmol) in MeCN/H_2O (1:1, 2 mL) at 0 °C was added TFA (15 drops). After the reaction was stirred for 1.5 h, it was diluted with Et_2O (30 mL). The mixture was washed with saturated aqueous $NaHCO_3$ (3 mL), H_2O (3 mL), and saturated aqueous NaCl (5 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (50% EtOAc/hexanes) afforded the title compound (12 mg, 89% yield) as a wet solid: R_f = 0.46 (50% EtOAc/hexanes); $[\alpha]_D^{23}$ = +13.4 (c = 0.50, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 6.95 (dd, J = 4.8, 16.8 Hz, 1H), 6.09 (dd, J = 1.8, 16.8 Hz, 1H), 5.14−5.19 (m, 1H), 3.64−3.66 (m, 1H), 3.50 (br s, 1H), 2.82−2.88 (m, 1H),

2.60−2.66 (m, 1H), 2.50−2.58 (m, 1H), 2.01 (br s, 2H), 1.52−1.88 (m, 4H), 1.36−1.44 (m, 1H), 1.25−1.27 (m, 1H), 1.23 (d, J = 6.6 Hz, 3H), 1.10 (d, J = 6.6 Hz, 3H), 1.09 (d, J = 7.2 Hz, 3H), 0.99 (d, J = 7.2 Hz, 3H), 0.93 (d, J = 6.6 Hz, 3H), 0.90 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 204.9, 176.2, 150.4, 126.8, 76.9, 76.5, 75.4, 44.1, 42.4, 40.9, 39.4, 36.1, 35.7, 25.7, 19.7, 18.4, 15.3, 10.8, 10.7, 8.3; IR (thin film) 3425 (br), 2935, 1719, 1687, 1620 cm^{-1}; HRMS calcd for ($C_{20}H_{34}O_5$ + Na^+) 377.2304, found 377.2306.

(3*R*,4*R*,*E*)-3-(*tert*-Butyldimethylsilyloxy)-6-iodo-4-methylhexa-1,5-diene (35). To a suspension of $CrCl_2$ (3.10 g, 24.0 mmol, 6 equiv) in THF (25 mL) at 0 °C were added CHI_3 (3.15 g, 8.0 mmol, 2 equiv) and a solution of aldehyde **34**[19] (0.91 g, 4.0 mmol) in THF (10 mL). The reaction was stirred for 2 h and quenched with H_2O (10 mL). The mixture was diluted with Et_2O (100 mL); the layers were separated, and the aqueous layer was extracted with Et_2O (3 × 25 mL). The combined organic layers were washed with H_2O (2 × 10 mL) and saturated aqueous NaCl (10 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Purification by flash chromatography (hexanes) afforded the title compound (0.86 g, 61% yield) as an oil: R_f = 0.43 (hexanes); $[\alpha]_D^{23}$ = +23.7 (c = 1.33, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.51 (dd, J = 4.8, 8.7 Hz, 1H), 5.97 (d, J = 9.0 Hz, 1H), 5.67−5.79 (m, 1H), 5.07−5.17 (m, 2H), 3.95−3.99 (m, 1H), 2.28 (sext, J = 3.9 Hz, 1H), 0.95 (d, J = 4.2 Hz, 3H), 0.88 (s, 9H), 0.23 (s, 3H), 0.01 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 149.1, 139.2, 115.7, 76.8, 75.3, 47.2, 26.2, 18.6, 14.1, −3.9, −4.4; IR (thin film) 2956, 2856, 1600 cm^{-1}; HRMS calcd for ($C_{13}H_{25}IOSi$ + NH_4^+) 370.1058, found 370.1078.

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Supporting Information Available: General experimental procedures, experimental procedures and spectral data for compounds **15**−**18**, **21**, **28**, **30**, **31**, and **36**, and ^{1}H and ^{13}C spectra for compounds **8**, **15**−**18**, **20**, **21**, **26**−**33**, **35**, and **36**. This material is available free of charge via the Internet at http://pubs.acs.org.

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