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Stereoselective Synthesis of Erythronolide A via Nitrile Oxide Cycloadditions and Related Studies

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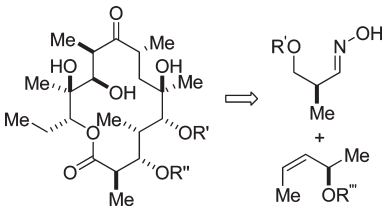
Received August 23, 2009



An expeditious synthesis of erythronolide A is documented. Key steps of the approach include two magnesium-mediated nitrile oxide cycloadditions, a chelation-controlled Grignard reaction, and a Sharpless asymmetric dihydroxylation.

Introduction

There is hardly a class of molecules that has attracted more attention than erythromycin A (**1a**) and B (**1b**) and especially their aglycons, erythronolide A (**1c**) and B (**1d**) in the history of synthetic organic chemistry. Erythromycin A, first isolated in 1952 by McGuire and co-workers at Lilly Research Laboratories from the actinomycete *Sacharopolyspora erythraea*,[1] consists of a 14-membered lactone ring with 10 stereogenic centers and two unusual sugars, L-cladinose at the C3 position and D-desosamine at the C5 position (Figure 1). The 14-membered polyketide has attracted the attention of many synthetic organic chemists and resulted in more than 15 total syntheses of erythromycin A and its derivatives.[2,3] The starting signal for exploring this molecule was given by Woodward in his famous statement in 1956: "*Erythromycin, with all our advantages, looks at present quite hopelessly complex, particularly in view of its plethora of asymmetric centers.*"[4] The efforts in developing new methodology for polyketide synthesis in the 1960s and 1970s culminated in the first total synthesis of erythronolide B (**1d**) in 1978 by Corey and co-workers.[5] This accomplishment still remains a milestone in synthetic organic chemistry. Woodward and co-workers then published in 1981 the first total synthesis of erythromycin A (**1a**),[6] which remained the only one that involved the attachment of the two sugar moieties until the mid-1990s, when Toshima and Kinoshita reported another synthesis of erythromycin A (**1a**),[7] and Martin accomplished the total synthesis of erythromycin B (**1b**).[3b] The erythronolides have become the molecules of choice to demonstrate new methodologies of stereoselective synthesis for polyketide building blocks. Thus, the history of the development of methods in stereoselective synthesis of

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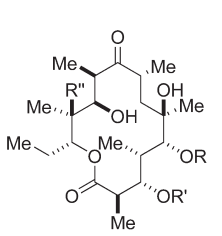
DOI: 10.1021/jo901817b Published on Web 10/19/2009



Erythromycin A (**1a**): R = D-desosamine; R' = L-cladinose; R" = OH
Erythromycin B (**1b**): R = D-desosamine; R' = L-cladinose; R" = H
Erythronolide A (**1c**): R = H; R' = H; R" = OH
Erythronolide B (**1d**): R = H; R' = H; R" = H

FIGURE 1. Structures of the erythromycins and erythronolides.

polyketides can be traced from the synthesis of erythronolides.

We now report the total synthesis of erythronolide A (**1c**) by taking advantage of the Kanemasa hydroxy-directed nitrile oxide cycloaddition,[8] as well as a full account of our studies and observations, leading to a short and expedient synthesis.

Synthetic Planning

Erythronolide A (**1c**) is ideally suited for the application and extension of methods involving magnesium-mediated nitrile oxide cycloaddition reactions, which we have studied in detail.[9] As the isoxazolines can serve as protected β-hydroxy ketone surrogates, the N−O bond reduction and hydrolysis can be effected at a late stage of the synthesis. Macrocyclization was intended to proceed by lactonization of an ω-hydroxy acid **3**. We envisioned that *seco*-acid **3** would be formed by a nitrile oxide cycloaddition. Oxime **4**, a nitrile oxide precursor, is derived from ketone **5** and bromide **6** and assembled by a Grignard coupling. Ketone **5** is accessible from oxime **7** and allylic alcohol **8** by cycloaddition followed by oxidation.

Results and Discussion

The synthesis of erythronolide A started with the preparation of oxime **11** and allylic alcohol **14** (Scheme 1). Oxime **11** was easily prepared via a high-yielding three-step sequence from Roche ester **9**. Protection of the primary hydroxyl group furnished the corresponding TBS ether, which was reduced to aldehyde **10** by careful addition of DIBAl-H to a solution of the ester in Et_2O at −78 °C.[10] Conversion of aldehyde **10** to the corresponding oxime **11** with hydroxylamine hydrochloride in py/EtOH occurred smoothly in 70% yield over three steps.

The preparation of enantiomerically enriched allylic alcohol **14** started with the addition of acetaldehyde to commercially available propynylmagnesium bromide (Aldrich, 0.5 M in THF). The reaction afforded the propargylic alcohol in 93% yield. Ketone **12** was obtained in 73% yield after oxidation, using Ley's TPAP/NMO procedure.[11] To access enantioenriched propargylic alcohol, we decided to employ Noyori's transfer hydrogenation protocol (79% yield, 92% ee, as determined by GC analysis).[12] For the *Z*-selective reduction of the triple bond, we followed a modified procedure previously reported by Hamed,[13] using Lindlar's catalyst[14] and pentane as solvent. The target (*R*)-allylic alcohol **14** was obtained in 73% yield after distillation.

To initiate the cycloaddition sequence, oxime **11** was treated with *tert*-butylhypochlorite[15] at −78 °C to form the hydroximoyl chloride in situ, which was slowly added to a solution of allylic alcohol **14**, 2-PrOH, and EtMgBr at 0 °C, providing the desired cycloadduct **15** in 86% yield as a single diastereomer (^{1}H NMR) (Scheme 2). Oxidation to the corresponding ketone **16** proceeded smoothly using NMO and catalytic TPAP (82% yield). With ketone **16** in hand, the first substrate for the Grignard coupling was generated. Bromide **18**, the second reaction partner, was prepared in three steps from Roche ester **9**.[16] Protection of the primary hydroxyl group as *p*-methoxybenzyl ether was achieved under acidic conditions with PMB-imidate and catalytic amounts of CSA (10 mol %) in 86% yield. The methyl ester was reduced to the corresponding alcohol **17** with DIBAl-H (84% yield), and subsequent reaction with Br_2, PPh_3, and imidazole provided bromide **18** in 89% yield.

The Grignard coupling reagent was generated from **18** through a transmetalation sequence by treatment of a solution of bromide **18** (1.3 equiv) in Et_2O with *t*-BuLi (1.7 M in pentane, 2.7 equiv) and subsequently with $MgBr_2$ (1 M in Et_2O/PhH, 1.5 equiv) at −78 °C (Scheme 3).[17] The off-white suspension was treated with a solution of ketone **16** (1 equiv) in THF. After stirring for 1 h at −78 °C, the colorless solution was quenched with satd aq NH_4Cl and 65% of the coupling product **19** was isolated as a 20:1 mixture of diastereomers as assayed by ^{1}H NMR (98% yield based on recovered ketone). In order to determine the configuration at C6, the corresponding substituted tetrahydrofuran **21** was formed; this sequence is initiated by cleavage of the PMB-ether in **19**, mesylation, and subsequent ring formation. Analysis of the NOE spectrum revealed a through-space interaction between the methyl group at C6 and the C8-H, indicating a chelation-controlled addition for the Grignard coupling and thereby the desired configuration of the C6-stereocenter.

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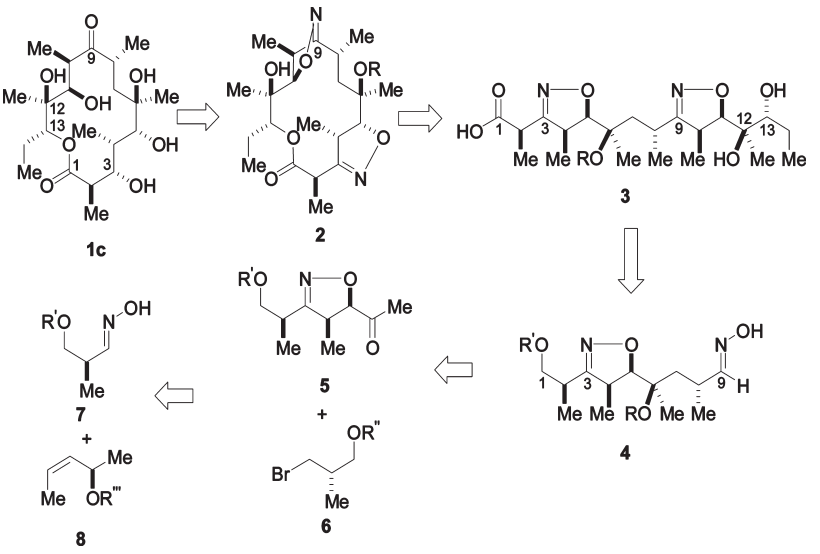
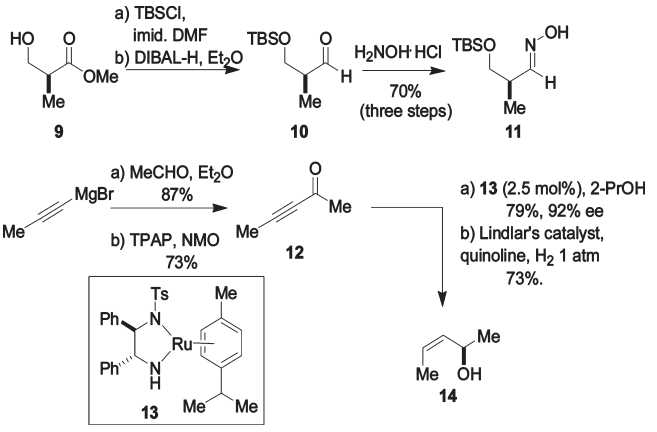


FIGURE 2. Retrosynthetic analysis.

SCHEME 1



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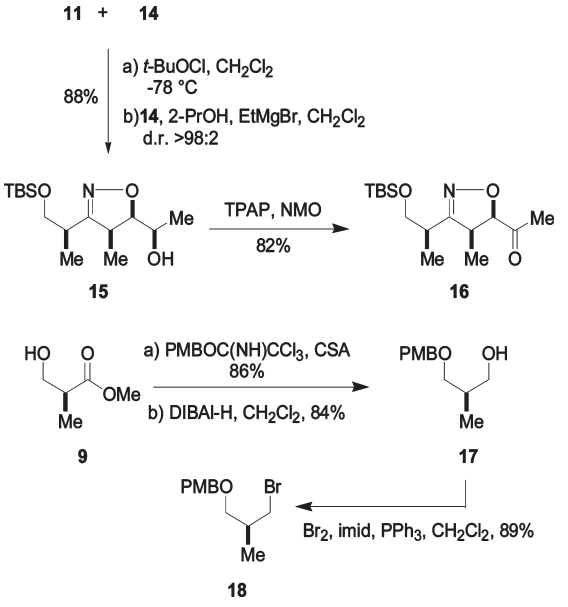

Protection of the tertiary hydroxyl group of **19** as a triethylsilyl ether was accomplished under standard conditions with TESOTf and 2,6-lutidine (93% yield) (Scheme 4). Oxidative cleavage of the PMB-ether (DDQ, pH 7 buffer) of **22** afforded **23**. To our surprise, a dimeric byproduct was formed, whose NMR spectrum was consistent with **25** (51%). Under acidic conditions (10 mol % CSA, MeOH), it could easily be converted to the desired product **23** (85% yield). Oxidation of the alcohol to the aldehyde was achieved under TEMPO/NaOCl conditions and pH 8.6 buffer.[18] The previously used Ley oxidation procedure[11] was not suitable for this substrate because epimerization of the C8-stereocenter was detected. Conversion to oxime **24** was performed with $H_2NOH \cdot HCl$/pyridine in 81% yield over 2 steps.

The preparation of oxime **24** sets the stage for a second Mg-mediated 1,3-dipolar cycloaddition reaction to enjoin the C(1)−C(9) and the C(10)−C(15) fragments and assemble the entire carbon skeleton. Treatment of oxime **24** with *t*-BuOCl leads to its oxidation to the corresponding hydroxymoyl chloride, which was then in turn treated with a preformed solution of methylene chloride including allylic alcohol **14** under standard reaction conditions (EtMgBr, *i*-PrOH) (Scheme 5). Cycloadduct isoxazoline **26** was isolated in 86% yield, as a single diastereomer as assayed by ^{1}H NMR spectroscopy. Subsequent oxidation of the secondary alcohol (TEMPO/NaOCl)[18] furnished ketone **27** in 77% yield, which upon exposure to $PrPPh_3Br$ (*t*-BuLi, THF) provided olefin **28** in 71% yield as a 30:1 mixture of *Z* and *E* isomers (^{1}H NMR). The installation of the remaining diol was effected through application of the asymmetric dihydroxylation reaction of Sharpless.[19] Treatment of **28** with

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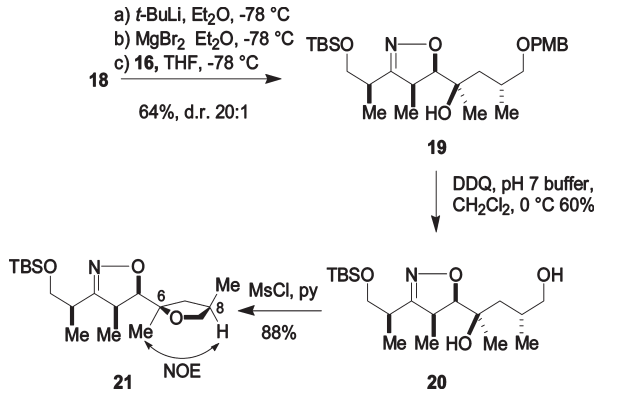
SCHEME 3



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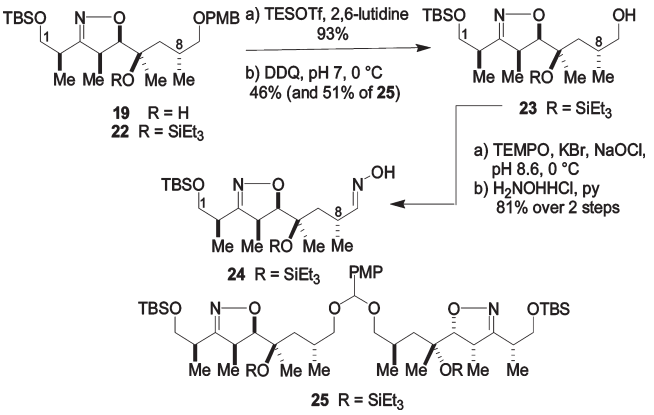

$(DHQD)_2PHAL$ (0.1 equiv), $K_3Fe(CN)_6$ (3 equiv), K_2CO_3 (3 equiv), methanesulfonamide (3 equiv), and $K_2OsO_4 \cdot 2H_2O$ (0.04 equiv) gave diol **29** in 82% as a single diastereomer. Exposure of **29** to HF·pyridine/pyridine (1:3) led to selective deprotection of the primary *tert*-butyldimethylsilyl ether (83% yield).[20]

The simple transformation of alcohol **30** to the corresponding aldehyde turned out to play a crucial role in the continuation of the synthesis. Several protocols for selective oxidation of primary alcohols over secondary ones were examined,[21] and the previously employed TEMPO-catalyzed procedure should have been well-suited for such a problem.[18] However, these reaction conditions were unsuccessful, and only methyl ketone byproduct **32** could be isolated. Similar results were obtained for Ley's TPAP procedure. Several other well-established oxidation procedures were examined but did not lead to any success. Either no reaction (DMSO, NEt_3, cyanuric acid;[22] Pt black, O_2;[23] DMS, NCS, NEt_3[24]), formation of methyl ketone **32** (PDC;[25] H_2SO_4, CrO_3[26]), or decomposition (IBX, NHS, DMSO;[27] bisacetoxyiodobenzene, TEMPO;[28] DMSO, $(COCl)_2$, NEt_3[29]) occurred. Fortunately, successful results were observed with Dess–Martin periodinane (DMP).[30] Under conditions excluding H_2O, a solution of alcohol **30** in CH_2Cl_2 was treated with 4 equiv of DMP (Scheme 6). After 1 h at 0 °C, the solvent was removed under vacuum and the unstable aldehyde was immediately subjected to Lindgren oxidation,[31] providing the *seco*-acid **31** in 65% yield without affecting the secondary alcohol.

The stage was set to investigate whether bisisoxazoline *seco*-acid **31** would undergo cyclization to afford the targeted macrocycle. The idiosyncracies of ring closure in the formation of macrolactones have been appreciated since the classic work of Woodward involving the cyclization of erythromycin A *seco*-acids.[6] Analysis of simple models convinced us that the isoxazolines bridging C3–C5 and C9–C11 would lead to conformations enabling macrolactonization. In the event through the use of a modified Yamaguchi protocol,[32] desired macrolactone **33** was isolated in 55% yield (Scheme 7).

With macrolactone **33** in hand, we were at a stage to finish erythronolide A (**1c**) in 3 steps: reductive cleavage of the isoxazolines, reduction of the ketone at C3, and deprotection of the triethylsilyl ether. However, isoxazoline opening already proved challenging. Under standard conditions described by Curran, employing Raney Ni, boric acid, and hydrogen, no conversion was observed.[33] Under similar conditions, using acetic acid instead of boric acid, no product was formed.[34] Stirring for several days slowly led to decomposition of the starting material. The use of different palladium[35] and rhodium sources[36] for hydrogenation did not lead to satisfactory results, and only starting material could be isolated. Homogeneous conditions such as SmI_2 in THF,[37] SmI_2/HMPA in THF, and $Mo(CO)_6$ in CH_3CN/H_2O[38] were unsuccessful. The SmI_2-procedures led to the recovery of **33**, the latter led only to deprotection of the triethylsilyl ether, and the diketone **34** was never obtained. With these unsatisfactory results a revision of the route had to be considered. An early reduction of the isoxazoline at C3–C5 to the 1,3-diol and subsequent protection might bring the necessary flexibility to the 14-membered

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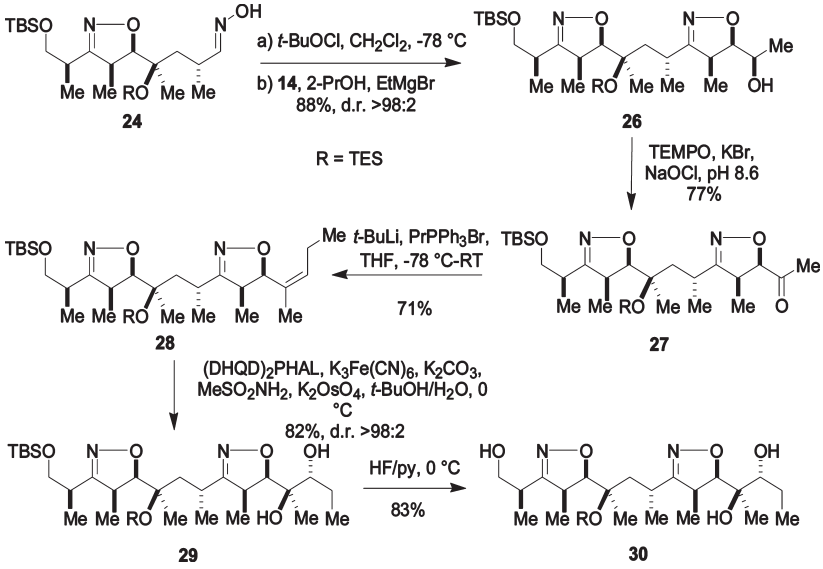
SCHEME 5



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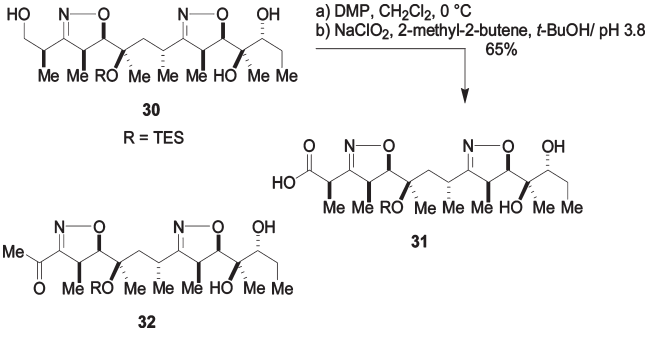
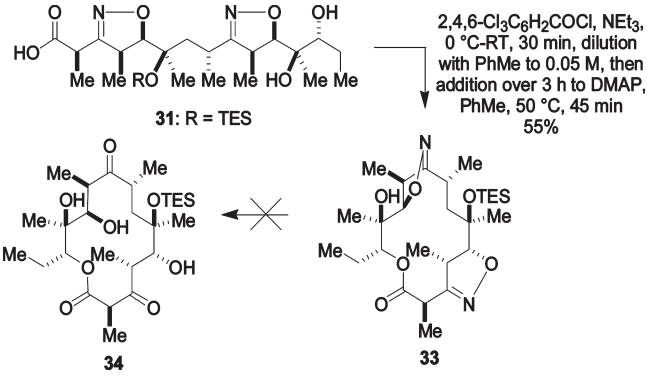


SCHEME 7

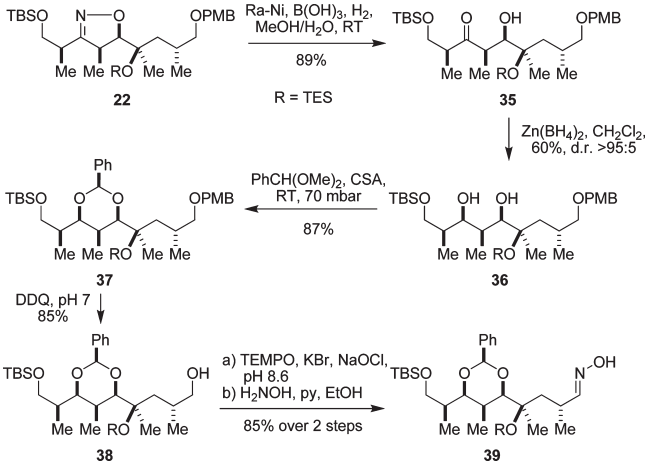


macrocycle for a successful late-stage opening of the second isoxazoline at C9−C11.

Final Route to Erythronolide A

Reductive opening of the isoxazoline **22** to the β-hydroxy ketone was accomplished with Raney Ni, $B(OH)_3$ in 89% (Scheme 8).[33] Reduction of β-hydroxy ketone **35** with

SCHEME 8



$Zn(BH_4)_2$ afforded the *syn*-1,3-diol in 60% yield and a diastereomeric ratio greater than 95:5 (by ^{1}H NMR).[39] Other reduction procedures such as Prasad's conditions[40] or DIBAl-H[41] led to significantly decreased selectivities. The diol was protected as its benzylidene acetal **37** ($PhCH(OMe)_2$, CSA, 87% yield). The PMB ether was removed with DDQ at 0 °C (85% yield) and then oxidized to the aldehyde under TEMPO/NaOCl conditions.[18] Subsequent conversion to oxime **39** was accomplished with $H_2NOH\cdot$HCl/py in 85% yield (over 2 steps).

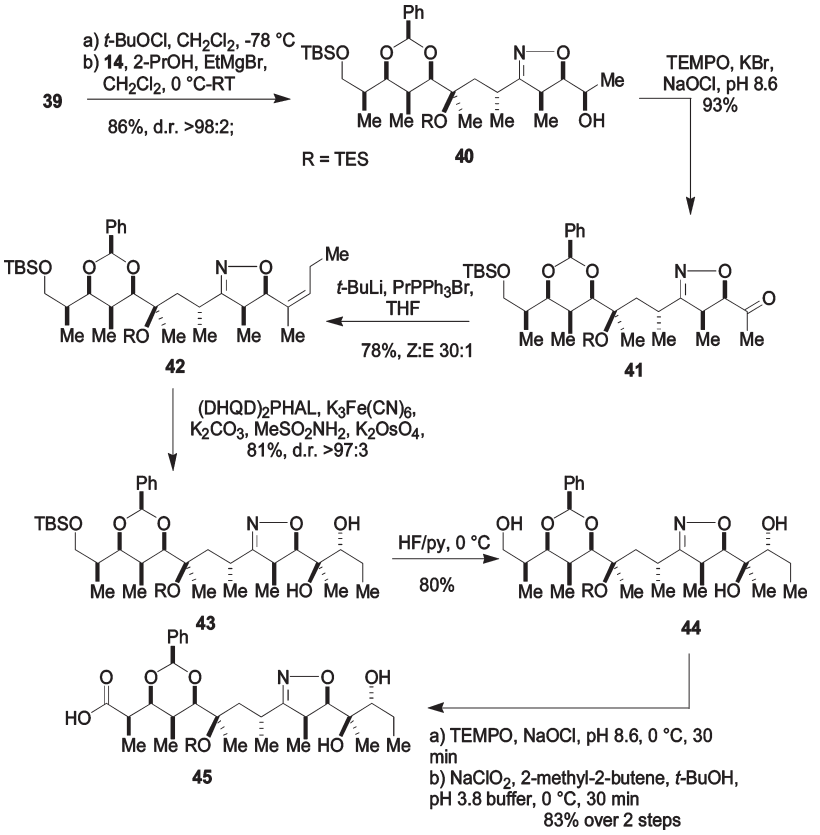
The cycloaddition afforded **40** in 86% yield as single diastereomer (determined by ^{1}H NMR) (Scheme 9). Oxidation of the secondary alcohol under TEMPO/NaOCl conditions (93% yield), and Wittig reaction provided olefin **42** in 78% yield and a 33:1 *Z*:*E* diastereoselectivity. Sharpless asymmetric dihydroxylation to **43** (81% yield, dr > 97:3, determined by ^{1}H NMR) and selective deprotection

(39) Ito, Y.; Yamaguchi, M. *Tetrahedron Lett.* **1983**, *24*, 5385–5386.

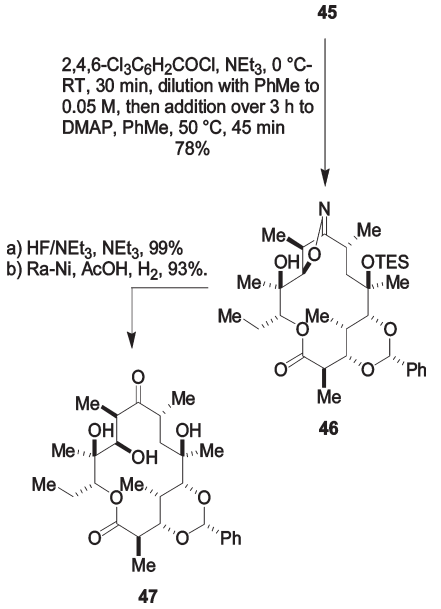
(40) Chen, K.-M.; Gunderson, K. G.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. *Chem. Lett.* **1987**, *16*, 1923–1926.

(41) Kiyooka, S.; Kuroda, H.; Shimasaki, Y. *Tetrahedron Lett.* **1986**, *27*, 3009–3012.

SCHEME 9



SCHEME 10



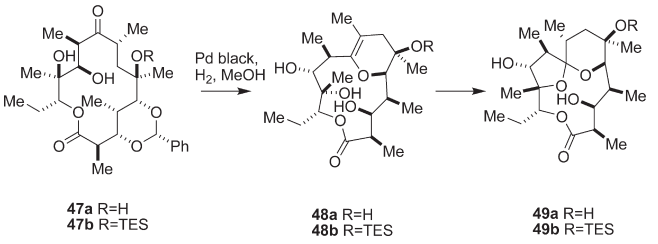
of the *tert*-butyldimethylsilyl ether, using HF·py/py (1:3) furnished the primary alcohol in 80% yield. *seco*-Acid **45** was obtained in 83% yield by formation of the aldehyde, using TEMPO/NaOCl, followed by Lindgren oxidation.[31]

With the benzylidene acetal protecting group at the C3/C5 position, the yield of the macrolactonization significantly improved. Using the same conditions as for the previously described macrolactonizations, lactone **46** was formed in 78% yield (Scheme 10). Then careful deprotection of the triethylsilyl ether with HF·NEt_3 and NEt_3[42] at 30 °C over 3 days was necessary. Smooth reductive opening of the isoxazoline in 10 min, using Raney Ni and AcOH in EtOH, provided macrolactone **47** in 93% yield. The completion of the synthesis of **47** represents a formal total synthesis of erythronolide A.

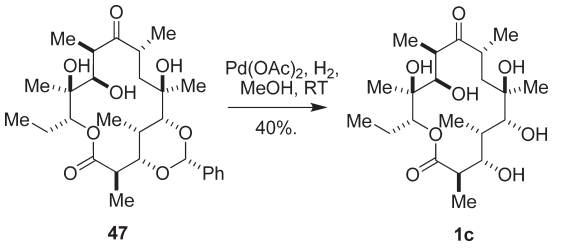
Buoyed by Kinoshita's report on the deprotection of the benzylidene acetal using Pd black/H_2 in MeOH over 30 min to give erythronolide A in 85% yield, we set out to reproduce this result.[43] After stirring substrate **47** for 30 min in a mixture of Pd black in MeOH under an atmosphere of H_2, only starting material was observed. After prolonged stirring, a new product was formed. Isolation of this product showed successful removal of the benzylidene acetal, but comparison of the ^{1}H NMR spectrum with Kinoshita's analysis revealed none of the expected erythronolide A. Examination of the mass spectrum indicated loss of water, and no signal at 220 ppm was detected by ^{13}C NMR spectroscopic analysis, indicating the absence of the ketone at C9. Instead, unexpected signals at 151 and 102 ppm revealed the formation of a cyclic enol ether. Further analysis by COSY, HSQC, and HMBC suggested the formation of the six-membered cyclic enol ether **48a** (Scheme 11). After stirring the reaction mixture for 15 h,

(42) Bode, J. W. Ph.D. thesis, Diss. ETH No. 14115, **2001**, ETH, Zürich.
(43) (a) Kinoshita, M.; Arai, M.; Ohsawa, N.; Nakata, M. *Tetrahedron Lett.* **1986**, *27*, 1815–1818. (b) *Bull. Chem. Soc. Jpn.* **1989**, *62*, 2618−2635.

SCHEME 11



SCHEME 12



the formation of a second byproduct could be detected. Isolation of this compound and analysis of the ^{1}H NMR and ^{13}C NMR spectra provided evidence for the generation of bicyclic acetal **49a**, which was confirmed by COSY, HSQC, and HMBC analysis.[44] Similar results were also obtained with the triethylsilyl protecting group still in place.

The desired effect could not be achieved by raising the pressure of H_2 up to 6 bar. To our surprise, by changing the palladium source to Pd/C (10%) or $Pd(OH)_2$/C (10%), the reaction rate could be significantly enhanced, but the desired product was not detected. However, in situ preparation of Pd black from $Pd(OAc)_2$ led to the desired result. Erythronolide A (**1c**) could be isolated in 40% yield by treating **47** with H_2, excess $Pd(OAc)_2$, MeOH, and catalytic amounts of water (Scheme 12). The material accessed by the described route was identical in all respects to that reported for previous syntheses and the natural product.

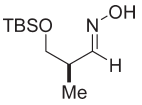
Conclusion

In summary, a synthesis of erythronolide A is documented that relies on the implementation of tactics involving the dipolar cycloaddition reaction of nitrile oxides and allylic alcohols. The successful use of two Mg(II)-mediated nitrile oxide cycloaddition reactions results in a synthesis of erythronolide A that is the shortest to date, proceeding in 21 linear steps and 4% overall yield. The work we have delineated establishes the nitrile oxide cycloaddition reaction with allylic alcohols as a means of joining complex fragments and thus as a salient, powerful tactic for the synthesis of polyketide-derived natural products. The derived isoxazoline cycloadducts can function as β-hydroxyketone surrogates that can be unmasked late in a synthesis within a densely functionalized structure.

(44) Corey already described the acid sensitivity of erythronolide A and the subsequent formation of a tricyclic ketal: Schomburg, D.; Hopkins, P. B.; Lipscomb, W. N; Corey, E. J. *J. Org. Chem.* **1980**, *43*, 1544–1546.

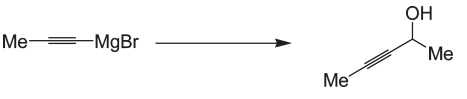
Experimental Section

(2*R*)-3-{[*tert*-Butyl(dimethyl)silyl]oxy}-2-methylpropanal Oxime (11).



To a solution of imidazole (15.4 g, 226 mmol, 2.50 equiv) and TBSCl (16.3 g, 108 mmol, 1.20 equiv) in dry DMF (15.0 mL) was added dropwise a solution of (*R*)-methyl 3-hydroxy-2-methylpropionate (**9**)(10.0 mL, 90.2 mmol, 1.00 equiv) in DMF (15 mL). The mixture was stirred for 6 h at rt, before Et_2O (250 mL) and H_2O (60.0 mL) were added. The layers were separated, and the organic phase was washed with H_2O (3 × 60 mL) and brine, dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the intermediate TBS ether. The resulting colorless oil was used without further purification. Neat DIBAl-H (48.2 mL, 271 mmol, 3.00 equiv) was added dropwise to the unpurified TBS ether in CH_2Cl_2 (600 mL) at −78 °C. The mixture was stirred for 90 min at −78 °C and was then quenched carefully by addition of MeOH (10 mL). After stirring for 10 min, saturated, aqueous sodium potassium tartrate (300 mL) was added. The mixture was treated with Et_2O (600 mL), allowed to warm to rt, and stirred for 12 h. The two layers were separated, and the aqueous layer was extracted with Et_2O (2 × 300 mL). The combined organic solutions were dried over anhydrous Na_2SO_4, filtered, and concentrated under reduced pressure to give the intermediate primary alcohol, which was used without further purification. To the unpurified alcohol in CH_2Cl_2 (400 mL) at rt were added NMO (15.9 g, 135 mmol, 1.50 equiv) and 4 Å M.S. (45.0 g), and the slurry was stirred for 30 min at rt before TPAP (0.984 g, 2.80 mmol, 3.00 mol %) was slowly added as a solid at rt. The mixture was stirred at rt for 30 min. Pentane (400 mL) was added, and the mixture filtered over a short column of silica gel, eluting with 2:1 pentane/Et_2O (1000 mL). Concentration provided the intermediate aldehyde **10** as a slightly yellow liquid that was used immediately without further purification.[45] To a solution of unpurified aldehyde **10** in EtOH (800 mL) at rt was added $NH_2OH \cdot HCl$ (9.41 g, 135 mmol, 1.50 equiv) in pyridine (110 mL). The mixture was stirred at rt for 14 h and subsequently concentrated under reduced pressure. To the resulting residue were added EtOAc (600 mL) and H_2O (200 mL), and the organic layer was washed with H_2O (2 × 200 mL) and brine, and dried over anhydrous Na_2SO_4. The pyridine was removed by azetropical coevaporation with cyclohexane (6 × 200 mL). Purification by chromatography on silica gel (hexane/EtOAc 10:1) gave oxime **11** as colorless oil (10.7 g, 55% yield over 4 steps from (*R*)-methyl 3-hydroxy-2-methylpropionate). $[\alpha]^{20.0}_D$ (*c* 1.100, $CHCl_3$) = −5.7°. ^{1}H NMR (300 MHz, $CDCl_3$, * denotes minor *cis*/*trans* isomeric peak) δ: 7.41 (d, 1 H, J = 6.2 Hz), 6.66* (d, 1 H, J = 7.2 Hz), 3.66−3.56 (m, 2 H), 3.32−3.19* (m, 1 H), 2.62−2.48 (m, 1 H), 1.09 (d, 3 H, J = 6.9 Hz), 1.08* (d, 3 H, J = 6.9 Hz), 0.89 (s, 9 H), 0.05 (s, 3 H), 0.04 (s, 3 H). ^{13}C NMR (75 MHz, $CDCl_3$, * denotes minor *cis*/*trans* isomeric peak) δ: 155.1*, 154.5, 66.0, 65.2*, 37.3, 25.8, 18.3, 14.2, 13.9*, −5.4. IR (thin film) 3306, 2956, 2930, 2885, 2858, 1472, 1462, 1389, 1362, 1257, 1104, 1032, 1007 (cm^{-1}). Anal. Calcd for $C_{10}H_{23}NO_2Si$: C, 55.25; H, 10.66; N, 6.44. Found: C, 55.43; H, 10.64; N, 6.47.

3-Pentyn-2-ol.

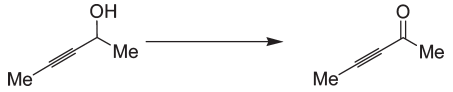


Propynylmagnesium bromide (0.5 M in THF, 800 mL, 400 mmol, 1.00 equiv) was concentrated to 400 mL and treated with

(45) This aldehyde was described earlier: Gaucher, A.; Ollivier, J.; Marguerite, J.; Paugam, R.; Salaün, J. *Can. J. Chem.* **1994**, *72*, 1312–1327.

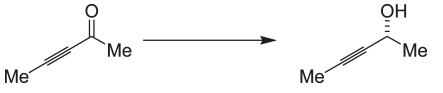
Et_2O (400 mL). A solution of acetaldehyde (45.0 mL, 800 mmol, 2.00 equiv) in Et_2O (400 mL) was added at 0 °C. The brown solution was warmed to rt and stirred for 5 h. The reaction solution was quenched with satd aq NH_4Cl (400 mL), washed with brine (200 mL), dried over anhydrous Na_2SO_4, and concentrated at 40 °C/700 mbar. The remaining brown liquid was distilled under reduced pressure (50 mbar, 90 °C) to give the racemic title alcohol (29.1 g, 87% yield) as a clear, colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.49 (m, 1H), 1.84 (d, 3H, J = 2.07 Hz), 1.42 (d, 3H, J = 6.4 Hz). The spectral data were identical with those previously reported.[46]

3-Pentyn-2-one (12).



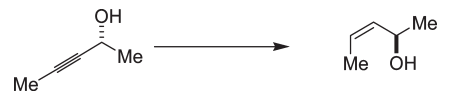
To a suspension of 3-pentyn-2-ol (15.0 g, 178 mmol, 1.00 equiv), NMO (31.3 g, 232 mmol, 1.30 equiv), and 4 Å M.S. (90.0 g) in CH_2Cl_2 (350 mL) was added TPAP (1.88 g, 5.35 mmol, 0.03 equiv) over a period of 30 min. After 2 h of stirring at ambient temperature, pentane (400 mL) was added. The dark brown mixture was filtered over a plaque of silica gel (pentane/Et_2O 1:1). The solvent was evaporated at 900 mbar, 40 °C. The liquid was purified by fractionated distillation (70 mbar, 80 °C) to afford 3-pentyn-2-one (**12**) (10.9 g, 73% yield) as a clear, colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 2.31 (s, 3H), 2.01 (s, 3H). The spectral data were identical with those previously reported.[46]

(*R*)-(+)-3-pentyn-2-ol.



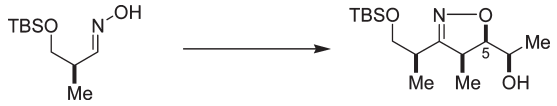
A mixture of 3-pentyn-2-one (9.9 g, 0.12 mol, 1.0 equiv) and Ru[(1*R*,2*R*)-*p*-TsNCH(C_6H_5)CH(C_6H_5)NH] (η^6-*p*-cymene) (**13**)[11] (0.36 g, 0.60 mmol, 0.0050 equiv) in 2-propanol (250 mL) was stirred under nitrogen at 25 °C for 1 day before more catalyst (0.36 g, 0.60 mmol, 0.0050 equiv) was added. Another addition of catalyst was carried out after 2 days (0.72 g, 1.2 mmol, 0.010 equiv) and 4 days (0.36 g, 0.60 mmol, 0.0050 equiv). After 6 days, distillation of the crude reaction mixture at 80 °C at 50 mbar provided (*R*)-(+)-3-pentyn-2-ol (8.0 g, 79% yield). The enantiomeric excess of the alcohol was determined to be 92% by chiral capillary GC analysis using a Supelco-Beta-Dex 120 column (50 °C isotherm). t_R (*R* enantiomer): 7.54 min. t_R (*S* enantiomer): 8.48 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.49 (m, 1H), 1.84 (d, 3H, J = 2.07 Hz), 1.42 (d, 3H, J = 6.4 Hz). The spectral data were identical with those previously reported.[46]

(*R*)-(−)-(*Z*)-3-Penten-2-ol (14).



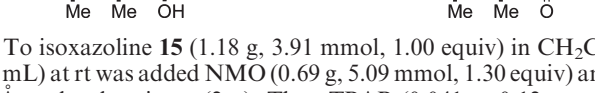
To a solution of (*R*)-(+)-3-pentyn-2-ol (7.70 g, 91.5 mmol, 1.00 equiv) in pentane (25 mL) were added Pd on $CaCO_3$ with Pb (Lindlar catalyst)[14] and quinoline (0.4 mL). The gray mixture was purged with H_2 and stirred for 5 days. The suspension was filtered over Celite, and the solvent was removed at 800 mbar, 40 °C. Distillation of the liquid (75 mbar, 63 °C) provided (*R*)-(−)-(*Z*)-3-penten-2-ol (**14**) (5.67 g, 72% yield) as a clear, colorless liquid. The enantiomeric excess of the alcohol was determined to be 91% by chiral capillary GC analysis using a Supelco-Beta-Dex 120 column (50 °C isotherm). t_R (*R* enantiomer): 3.88 min. t_R (*S* enantiomer): 4.16 min. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.56−5.40 (m, 2H), 4.73−4.64 (m, 1H), 1.68 (d, 3H, J = 6.4 Hz), 1.24 (d, 3H, J = 6.3 Hz). The spectral data were identical with those previously reported.[46]

(1*R*)-1-[(4*S*,5*R*)-3-((1*R*)-2-{[*tert*-Butyl-(dimethyl)-silyl]oxy}-1-methylethyl)-4-methyl-4,5-dihydroisoxazol-5-yl]ethanol (15).



To a solution of (*R*)-(−)-(*Z*)-3-penten-2-ol (**14**) (0.475 g, 5.52 mmol, 1.20 equiv) and 2-propanol (1.17 mL, 15.2 mmol, 3.30 equiv) in CH_2Cl_2 (250 mL) at 0 °C was added EtMgBr (3 M in Et_2O, 4.60 mL, 13.8 mmol, 3.00 equiv). The reaction mixture turned momentarily cloudy, becoming clear and colorless upon stirring at 0 °C for 30 min. At this time, the hydroxymoyl chloride, prepared by addition of *t*-BuOCl (0.580 mL, 5.06 mmol, 1.10 equiv) to a solution of oxime (−)-**11** (1.00 g, 4.60 mmol, 1.00 equiv) in CH_2Cl_2 (46 mL) at −78 °C and stirring for 1.5 h, was added dropwise via cannula to the reaction to give a slightly yellow solution. It was allowed to warm to rt and stirred for 16 h. The reaction was quenched by the addition of satd aq NH_4Cl (200 mL), and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic solutions were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification by chromatography on silica gel (hexane/EtOAc 3:1) provided isoxazoline **15** (1.20 g, 86% yield) as a clear colorless oil. No other diastereoisomer could be detected, as determined by examination of the diastereotopic signals of the proton at C5 (4.0 −4.2 ppm) of **15** in the ^{1}H NMR spectrum of the crude material. R_f = 0.21 (3:1 hexane/EtOAc). $[\alpha]^{25.0}_D$ (c 1.060, $CHCl_3$) = −13°. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.16 (dd, 1H, J = 9.3, 5.3 Hz), 3.98−3.90 (m, 1H), 3.66−3.58 (m, 2H), 3.31−3.23 (m, 1H), 2.67−2.60 (m, 1H), 2.06 (d(br), 1H, J = 6.2 Hz), 1.25 (d, 3H, J = 6.5 Hz), 1.19 (d, 3H, J = 6.9 Hz), 1.17 (d, 3H, J = 7.2 Hz), 0.87 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.6, 85.9, 67.1, 66.1, 45.3, 34.7, 25.9, 20.3, 18.3, 14.6, 10.7, −5.4. IR Spectroscopy (thin film) 3408, 2930, 2857, 1462, 1389, 1255, 1091, 900, 837, 776 (cm^{-1}). EI-MS (m/z): 300.3 ($[M]^+$), 244.1(20), 240.1(12), 172.1, (17), 142.0(31), 122.0(13), 115.0(31), 96.0(16), 84.0(23), 75.0(100), 73.0(30). Anal. Calcd for $C_{15}H_{31}NO_3Si$: C, 59.76; H, 10.36. Found: C, 59.69; H, 10.48.

(1*R*)-1-[(4*S*,5*R*)-3-((1*R*)-2-{[*tert*-Butyl-(dimethyl)-silyl]oxy}-1-methylethyl)-4-methyl-4,5-dihydroisoxazol-5-yl]ethanone (16).

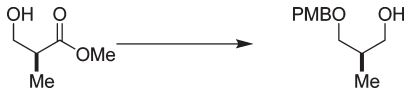


To isoxazoline **15** (1.18 g, 3.91 mmol, 1.00 equiv) in CH_2Cl_2 (8 mL) at rt was added NMO (0.69 g, 5.09 mmol, 1.30 equiv) and 4 Å molecular sieves (2 g). Then TPAP (0.041 g, 0.12 mmol, 0.030 equiv) was added as a solid in two portions to give a green mixture. After 10 min, the reaction had become dark red, and after 20 min, more TPAP (0.020 g, 0.057 mmol, 0.015 equiv) was added. After stirring for 1.5 h at rt, the dark red mixture was diluted with pentane (8 mL) and filtered over a plug of silica gel, eluting with 3:2 pentane/ether. The solution was concentrated and a green oil was obtained. Purification by chromatography on silica gel (hexane/EtOAc 5:1) provided ketone **16** (0.96 g, 82% yield) as a clear, colorless oil. R_f = 0.44 (3:1 hexane/EtOAc). $[\alpha]^{28.7}_D$ (c 0.950, $CHCl_3$) = +51°. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.76 (d, 1H, J = 10.9 Hz), 3.71−3.58 (m, 3H), 2.72−2.61 (m, 1H), 2.26 (s, 3H), 1.23 (d, 3H, J = 7.2 Hz), 1.08 (d, 3 Hz, J = 7.5 Hz), 0.88 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 208.2, 165.0, 87.0, 67.0, 47.7, 34.7, 28.4, 25.9, 18.3, 14.5, 12.1, −5.4. IR (thin film) 2955, 2931, 2858, 1716, 1463, 1359, 1255, 1136, 1095, 1007, 970, 838, 777

(46) Hamed, O.; Henry, P. M. *Organometallics* **1997**, *16*, 4903–4909.

(cm^{-1}). EI-MS (m/z): 300.1 ($[M + H]^+$), 243.1(19), 240.1(26), 142.0(67), 115.0(50), 112.0(18). Anal. Calcd for $C_{15}H_{29}NO_3Si$: C, 60.16; H, 9.76. Found: C, 60.10; H, 9.60.

(2*R*)-3-(4-Methoxyphenoxy)-2-methylpropan-1-ol (17).

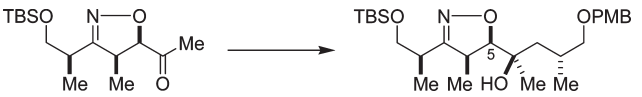


p-Methoxybenzylalcohol (14.4 mL, 116 mmol, 1.00 equiv) was slowly added to a suspension of NaH (0.278 g, 11.5 mmol, 0.100 equiv) in Et_2O (45 mL). After stirring for 30 min, the reaction mixture was cooled to 0 °C, and trichloroacetonitrile (11.6 mL, 116 mmol, 1.00 equiv) was added. The reaction was allowed to warm to rt and stirred for another 4 h. After evaporation of the solvent, the residue was dissolved in MeOH (1 mL) and hexane (40 mL). The suspension was filtered over Celite and concentrated under reduced pressure. The crude imidate was used without further purification. To a solution of (*R*)-methyl 3-hydroxy-2-methylpropionate (4.00 g, 33.9 mmol, 1.00 equiv) in CH_2Cl_2 (70.0 mL) were added PMB-imidate (14.4 g, 50.8 mmol, 1.50 equiv) and CSA (0.787 g, 3.39 mmol, 0.100 equiv). The light brown solution was stirred for 15 h and quenched with H_2O (30 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organics were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification by chromatography on silica gel (hexane/EtOAc 3:1) provided the product (6.97 g, 86% yield) as a clear, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.23 (d, 2H, J = 8.5 Hz), 6.87 (d, 2H, J = 8.7 Hz), 4.45 (s, 2H), 3.80 (s, 3H), 3.69 (s, 3H), 3.63 (dd, 1H, J = 9.2, 7.4 Hz), 3.45 (dd, 1H, J = 9.1, 5.9 Hz), 2.80−2.73 (m, 1H), 1.17 (d, 3H, J = 7.0 Hz). The spectral data were identical with those previously reported.[47] At −78 °C, DIBAl-H (20.4 mL, 113 mmol, 2.20 equiv) was added to a solution of the PMB ester (12.2 g, 51.2 mmol, 1.00 equiv) in CH_2Cl_2 (100 mL). The clear solution was warmed to 0 °C and quenched after 30 min by the addition of ethyl formate (5 mL). The mixture was cooled to −78 °C and diluted with ether (150 mL). Saturated, aqueous Na/K-tartrate (200 mL) was added, and the solution was vigorously stirred at ambient temperature for 15 h. The two layers were separated, and the aqueous phase was extracted with Et_2O (3 × 50 mL). The combined organic solutions were washed with H_2O (50 mL) and brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification by chromatography on silica gel (hexane/EtOAc 3:1 to 1:1) afforded alcohol **17** (9.00 g, 84% yield) as a clear, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.25 (d, 2H, J = 7.7 Hz), 6.88 (d, 2H, J = 8.6 Hz), 4.45 (s, 2H), 3.81 (s, 3H), 3.63−3.57 (m, 1H), 3.53 (dd, 1H, J = 9.0, 4.6 Hz), 3.39 (m, 1H), 2.57 (dd, 1H, J = 7.0, 4.4 Hz), 2.10−2.01 (m, 1H), 0.87 (d, 3H, J = 6.9 Hz). The spectral data were identical with those previously reported.[48]

1-{[(2*S*)-3-Bromo-2-methylpropyl]oxy}-4-methoxybenzene (18).

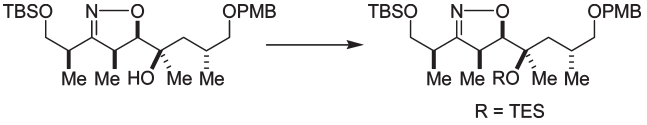
To a solution of PPh_3 (23.0 g, 87.7 mmol, 1.50 equiv) and imidazole (11.9 g, 175 mmol, 3.00 equiv) in CH_2Cl_2 (250 mL) was added bromine (4.21 mL, 81.9 mmol, 1.40 equivl) at 0 °C. After 15 min of stirring, alcohol **17** (12.3 g, 58.5 mmol, 1.00 equiv) was added, and the stirring was maintained for 30 min at 0 °C before additional triphenylphosphine (7.00 g, 26.7 mmol, 0.456 equiv) and bromine (1.2 mL, 23.3 mmol, 0.398 equiv) had to be added. The light brown suspension was quenched with H_2O_2 (3% in H_2O, 50 mL). The organic layer was washed with brine, dried over anhydrous Na_2SO_4, and concentrated in vacuo. The light brown mixture was filtered over a plaque of silica gel (pentane/Et_2O 4:1) and concentrated under reduced pressure to afford bromide **18** (14.2 g, 89% yield) as a clear, colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.27 (d, 2H, J = 8.8 Hz), 6.89 (d, 2H, J = 8.7 Hz), 4.45 (s, 2H), 3.81 (s, 3H), 3.55−3.45 (m, 2H), 3.43−3.34 (m, 2H), 2.17−2.07 (m, 1H), 1.03 (d, 3H, J = 6.8 Hz). The spectral data were identical with those previously reported.[49]

(2*R*,4*R*)-2-[(4*S*,5*R*)-3-((1*R*)-2-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-methylethyl)-4-methyl-4,5-dihydroisoxazol-5-yl]-5-[(4-methoxybenzyl)oxy]-4-methylpentan-2-ol (19).



To a solution of bromide **18** (0.24 g, 0.87 mmol, 1.3 equiv) in Et_2O (4.8 mL) at −78 °C was added *t*-BuLi (1.76 M solution in pentane, 1.0 mL, 1.8 mmol, 2.7 equiv). The colorless suspension was stirred for 20 min at −78 °C before $MgBr_2$ (1.0 M solution in ether/benzene (3:1), 1.00 mL, 1.0 mmol, 1.50 equiv) was added. The colorless reaction mixture was stirred for 10 min and treated with a solution of ketone **16** (0.20 g, 0.67 mmol, 1.0 equiv) in THF (3.4 mL). After stirring for 1 h at −78 °C, the colorless suspension was quenched with satd aq NH_4Cl (5 mL) and extracted with EtOAc (3 × 10 mL). The organic solution was washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Analysis of the signals of the proton at C5 (4.0−4.2 ppm) in the ^{1}H NMR spectrum of the crude material indicated a 20:1 ratio of diastereomers. Purification by chromatography on silica gel (hexane/EtOAc 5:1 to 3:1) provided pure **19** (0.21 g, 64% yield, > 50:1 dr), accompanied with ketone **16** (0.065 g, 33% recovered starting material). R_f = 0.33 (3:1 hexane/EtOAc). $[\alpha]_D^{30.0}$ (c 2.570, $CHCl_3$) = +3.5°. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.26 (d, 2H, J = 8.7 Hz), 6.87 (d, 2H, J = 8.7 Hz), 4.49 (d, 1H, J = 11.5 Hz), 4.43 (d, 1H, J = 11.5 Hz), 4.03 (d, 1H, J = 8.7 Hz), 3.80 (s, 3H), 3.64 (d, 2H, J = 6.5 Hz), 3.46 (s(br), 1H), 3.36 (dd, 1H, J = 8.7, 5.0 Hz), 3.24−3.14 (m, 2H), 2.68−2.59 (m, 1H), 2.10−2.05 (m, 1H), 1.96 (dd, 1H, J = 14.6, 6.9 Hz), 1.44 (dd, 1H, J = 14.3, 3.4 Hz), 1.27 (s, 3H), 1.24 (d, 3H, J = 5.0 Hz), 1.21 (d, 3H, J = 4.4 Hz), 0.95 (d, 3H, J = 6.9 Hz), 0.89 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 167.6, 159.0, 129.9, 129.2, 113.7, 88.5, 76.4, 72.9, 72.2, 67.3, 55.3, 45.5, 34.9, 28.9, 25.9, 23.9, 19.8, 18.3, 14.7, 12.7, −5.3. IR (thin film) 3436, 2954, 2931, 2857, 1613, 1514, 1361, 1301, 1249, 1174, 1089, 1036, 938, 837, 777 (cm^{-1}). HRMS-MALDI (m/z) calcd for $[C_{27}H_{47}NO_5SiNa]^+$, 516.3116; found, 516.3111. Anal. Calcd for $C_{27}H_{47}NO_5Si$: C, 65.68; H, 9.59. Found: C, 65.78; H, 9.57.

(4*S*,5*R*)-3-((1*R*)-2-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-methylethyl)-5-{(1*R*,3*R*)-4-[(4-methoxybenzyl)oxy]-1,3-dimethyl-1-[(triethylsilyl)oxy]butyl}-4-methyl-4,5-dihydroisoxazole (22).



At 0 °C, triethylsilyl triflate (3.20 mL, 14.0 mmol, 1.30 equiv) was added to a solution of alcohol **19** (5.30 g, 10.7 mmol, 1.00 equiv) and 2,6-lutidine (3.80 mL, 32.2 mmol, 3.00 equiv) in CH_2Cl_2 (30 mL). The yellow solution was stirred for 1 h at 0 °C and quenched with water (30 mL). The two layers were

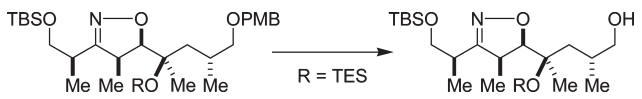
(47) Walkup, R. D.; Kahl, J. D.; Kane, R. K. *J. Org. Chem.* **1998**, *63*, 9113–9116.

(48) Organ, M. G.; Wang, J. *J. Org. Chem.* **2003**, *68*, 5568–5574.

(49) Smith, P. M.; Thomas, E. J. *J. Chem. Soc., Perkin Trans. 1* **1998**, 3541–3556.

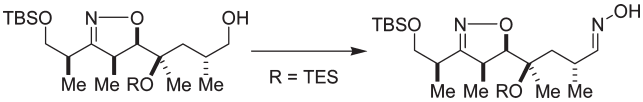
separated, and the aqueous layer was extracted with CH_2Cl_2. The organic solution was washed with 1 N HCl (60 mL) and brine (30 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification by chromatography on silica gel (hexane/EtOAc 6:1) afforded **22** (6.01 g, 93% yield) as a clear, colorless oil. R_f = 0.67 (3:1 hexane/EtOAc). $[\alpha]_D^{30.0}$ (*c* 1.0450, $CHCl_3$) = −4.8°. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.24 (d, 2H, *J* = 8.1 Hz), 6.86 (d, 2H, *J* = 8.4 Hz), 4.41 (s, 2H), 4.12 (d, 1H, *J* = 9.0 Hz), 3.80 (s, 3H), 3.62 (d, 2H, *J* = 6.5 Hz), 3.32 (dd, 1H, *J* = 8.7, 6.2 Hz), 3.21−3.12(m, 2H), 2.63−2.56(m, 1H), 1.95−1.90 (m, 1H), 1.68 (dd, 1H, *J* = 13.9, 4.0 Hz), 1.48 (dd, 1H, *J* = 14.0, 6.5 Hz), 1.34 (s, 3H), 1.20 (d, 3H, *J* = 6.9 Hz), 1.13 (d, 3H, *J* = 7.4 Hz), 1.02 (d, 3H, *J* = 6.7 Hz), 0.94 (t, 9H, *J* = 7.8 Hz), 0.88 (s, 9H), 0.63 (q, 6H, *J* = 7.7 Hz), 0.05 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.9, 158.9, 130.8, 129.0, 113.6, 88.3, 76.6, 76.5, 76.5, 72.6, 67.3, 55.3, 45.3, 43.6, 34.9, 29.8, 25.9, 19.6, 18.3, 14.7, 12.7, 7.4, 6.9, −5.3. IR (thin film) 2953, 2875, 1614, 1514, 1463, 1361, 1301, 1249, 1094, 1008, 838, 776, 741 (cm^{-1}). HRMS-MALDI (*m*/*z*) calcd for $[C_{33}H_{61}NO_5Si_2Na]^+$, 630.3980; found, 630.3975.

(4*S*,5*R*)-3-((1*R*)-2-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-methylethyl)-5-{(1*R*,3*R*)-4-hydroxy]-1,3-dimethyl-1-[(triethylsilyl)oxy]butyl}-4-methyl-4,5-dihydroisoxazole (23).



At 0 °C, DDQ (0.859 g, 3.78 mmol, 1.15 equiv) was added to a solution of **22** (2.00 g, 3.29 mmol, 1.00 equiv) in CH_2Cl_2 (30.0 mL). After addition of pH 7 buffer (0.020 mL), the reaction mixture was stirred for 40 min, and more DDQ (0.400 g, 1.76 mmol, 0.54 equiv) was added. After an additional 1 h at 0 °C, the brown suspension was quenched with satd aq $Na_2S_2O_3$ (20 mL) and satd aq $NaHCO_3$ (30 mL). The biphasic red solution was extracted with CH_2Cl_2. The combined organic solutions were extracted with CH_2Cl_2 (5 × 10 mL), washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification by chromatography on silica gel (hexane/EtOAc 3:1) provided **23** (0.74 g, 46%) as a clear, colorless oil. Dimerized byproduct **25** (0.91 g, 51%) was also isolated. R_f = 0.26 (3:1 hexane/EtOAc). $[\alpha]_D^{28.6}$ (*c* 0.905, $CHCl_3$) = +11°. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.14 (d, 1H, *J* = 8.9 Hz), 3.68−3.58 (m, 2H), 3.51 (dd, 1H, *J* = 10.4, 5.5 Hz), 3.35 (dd, 1H, *J* = 10.3, 6.9 Hz), 3.23−3.13 (m, 1H), 2.65−2.58 (m, 1H), 2.34 (s, 1H), 1.92−1.84 (m, 1H), 1.67 (dd, 1H, *J* = 14.2, 6.0 Hz), 1.49 (dd, 1H, *J* = 14.2, 4.7 Hz), 1.38 (s, 3H), 1.19 (d, 3H, *J* = 8.0 Hz), 1.17 (d, 3H, *J* = 8.6 Hz), 0.96 (d, 3H, *J* = 6.8 Hz), 0.94 (t, 9H, *J* = 7.5 Hz), 0.87 (s, 9H), 0.67 (q, 6H, *J* = 7.8 Hz), 0.04 (s, 3H), 0.03 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 167.5, 88.9, 77.4, 69.0, 67.5, 45.9, 43.4, 35.0, 31.6, 26.0, 25.5, 19.7, 18.4, 14.7, 12.8, 7.4, 6.8, −5.3. IR (thin film) 3436, 2954, 2876, 1460, 1378, 1253, 1135, 1092, 1060, 1007, 837, 777, 742, 668 (cm^{-1}). HRMS-MALDI (*m*/*z*) calcd for $[C_{25}H_{53}NO_4Si_2Na]^+$, 510.3405; found, 510.3402. Anal. Calcd for $C_{25}H_{53}NO_4Si_2$: C, 61.55; H, 10.95. Found: C, 61.55; H, 10.96.

(2*R*,4*R*)-2-[(4*S*,5*R*)-3-((1*R*)-2-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-methylethyl)4-methyl-4,5-dihydroisoxazol-5-yl]-4-[(triethylsilyl)oxy]-2-methylpentanal Oxime (24).



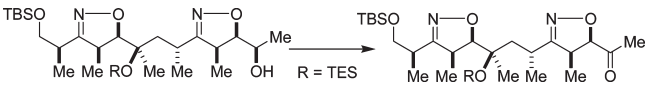
To a biphasic solution of **23** (1.33 g, 2.73 mmol, 1.00 equiv), TEMPO (0.0085 g, 0.054 mmol, 0.020 equiv), and KBr (0.0316 g, 0.273 mmol, 0.100 equiv) in CH_2Cl_2 (14 mL) and pH 8.6 buffer (14 mL) was slowly added NaOCl (0.5 M in H_2O, 11.0 mL, 5.45 mmol, 2.00 equiv) at 0 °C. After 15 min, NaOCl (0.5 M in H_2O, 11.0 mL, 5.45 mmol, 2.00 equiv) had to be added again. After another 10 min, H_2O (10 mL) and CH_2Cl_2 (10 mL) were added. The two layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The organic solution was washed with brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo. The light orange oil was used without further purification. A solution of $H_2NOH\cdot HCl$ (0.380 g, 5.47 mmol, 2.00 equiv) in py (2 mL) was added to a solution of the crude aldehyde (1.33 g, 2.74 mmol, 1.00 equiv) in EtOH (10.0 mL) and stirred for 15 min at rt. The light green solution was quenched with 1 N HCl (30 mL), and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic solutions were washed with brine (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification by chromatography on silica gel (hexane/EtOAc 5:1) provided oxime **24** (1.12 g, 81% yield over two steps) as a mixture of *E*/*Z* isomers (∼2:1). R_f = 0.49 (3:1 hexane/EtOAc). $[\alpha]_D^{23.9}$ (*c* 0.675, $CHCl_3$) = −0.54°. ^{1}H NMR (300 MHz, $CDCl_3$,*denotes minor isomer) δ: 7.30, (d, 1H, *J* = 7.5 Hz), 7.26 (s(br), 1H), 6.60* (d, 1H, *J* = 7.7 Hz) 4.18* (d, 1H, *J* = 9.2 Hz), 4.14 (d, 1H, *J* = 9.2 Hz), 3.63* (d, 2H, *J* = 6.6 Hz), 3.63 (d, 2H, *J* = 6.5 Hz), 3.31−3.26* (m, 1H), 3.25−3.17 (m, 1H), 2.68−2.59 (m, 2H), 1.86−1.63 (m, 2H), 1.33 (s, 3H), 1.32* (s, 3H), 1.23* (d, 3H, *J* = 6.9 Hz), 1.21 (d, 2 × 3H, *J* = 7.0 Hz), 1.10 (d, 3H, *J* = 6.9 Hz), 1.07* (d, 3H, *J* = 6.9 Hz), 0.94 (t, 9H, *J* = 7.9 Hz), 0.89 (s, 9 Hz), 0.63 (q, 6H, *J* = 7.5 Hz), 0.62* (q, 6H, *J* = 7.6 Hz), 0.05 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.7, 158.0*, 157.2, 87.7, 87.6*, 76.3*, 76.2, 67.2, 45.6*, 45.5, 44.9*, 44.7, 34.8, 30.7, 26.4, 26.1*, 25.9, 20.7, 19.1*, 18.3, 14.6, 12.8, 7.3, 6.9, −5.4. IR (thin film) 3306, 2954, 2877, 1461, 1379, 1253, 1091, 107, 941, 837, 777, 724 (cm^{-1}). HRMS-MALDI (*m*/*z*) calcd for $[C_{25}H_{52}N_2O_4Si_2Na]^+$, 523.3358; found, 523.3366. Anal. Calcd for $C_{25}H_{52}N_2O_4Si_2$: C, 59.95; H, 10.46. Found: C, 60.09; H, 10.26.

(1*R*)-1-((4*S*,5*R*)-3-{(1*R*,3*R*)-3-[(4*S*,5*R*))-3-((1*R*)-2-{[*tert*-Butyl-(dimethyl)silyl]oxy}-1-methylethyl)-4-methyl-4,5-dihydroisoxazol-5-yl]-1-methyl-3-[(triethylsilyl)oxy]butyl}-4-methyl-4,5-dihydroisoxazol-5-yl)ethanol (26).

To a solution of (*R*)-(−)-(*Z*)-3-penten-2-ol (**14**) (0.262 g, 3.04 mmol, 1.30 equiv) and 2-propanol (0.594 mL, 7.71 mmol, 3.30 equiv) in CH_2Cl_2 (150 mL) at 0 °C was added EtMgBr (3 M in Et_2O, 2.33 mL, 7.07 mmol, 3.00 equiv). The reaction mixture turned momentarily cloudy, becoming clear and colorless upon stirring at 0 °C for 30 min. At this time, the hydroxymoyl chloride, prepared by addition of *t*-BuOCl (0.280 mL, 2.45 mmol, 1.05 equiv) to a solution of oxime **24** (1.17 g, 2.33 mmol, 1.00 equiv) in CH_2Cl_2 (23 mL) at −78 °C and stirring for 1.5 h, was added dropwise via cannula to the reaction to give a slightly yellow solution. It was allowed to warm to ambient temperature and stirred for 16 h. The reaction was quenched by the addition of satd aq NH_4Cl (100 mL), and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic solutions were washed with brine (50 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification by chromatography on silica gel (hexane/EtOAc 3:1) provided isoxazoline **26** (1.20 g, 88% yield) as a clear, colorless oil. No other diastereoisomer could be detected, as determined by examination of the diastereotopic signals of the proton at C11 (4.0−4.2 ppm) of **26** in the ^{1}H NMR of the crude material. R_f = 0.23 (3:1 hexane/EtOAc). $[\alpha]_D^{31.5}$ (*c* 1.050, $CHCl_3$) = −16°. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.20 (dd, 1H, *J* = 9.7, 5.0 Hz), 4.10 (d, 1H, *J* = 8.9 Hz), 3.96−3.88 (m, 1H), 3.66−3.58 (m, 1H), 3.63 (dd, 1H, *J* = 6.5, 2.9 Hz), 3.33−3.25 (m, 1H), 3.23−3.12 (m, 1H), 2.79−2.73 (m, 1H), 2.65−2.56 (m, 1H),

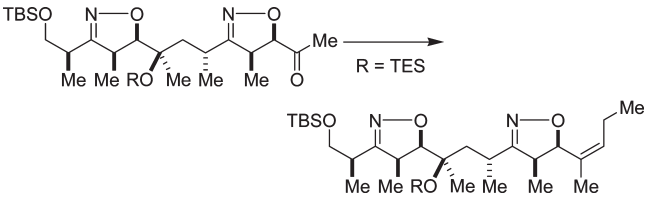
2.32 (dd, 1H, J = 14.2, 6.2 Hz), 1.98 (d, 1H, J = 6.5 Hz), 1.84 (dd, 1H, J = 14.2, 4.5 Hz), 1.33 (s, 3H), 1.27 (d, 3H, J = 6.4 Hz), 1.22 (d, 3H, J = 4.8 Hz), 1.21 (d, 3H, J = 7.0 Hz), 1.20 (d, 3H, J = 5.2 Hz), 1.18 (d, 3H, J = 7.4 Hz), 0.95 (t, 9H, J = 8.0 Hz), 0.89 (s, 9H), 0.64 (q, 6H, J = 7.9 Hz), 0.05 (s, 3H), 0.05 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 167.9, 166.9, 87.8, 85.9, 76.1, 67.1, 66.1, 45.3, 44.1, 43.0, 34.9, 27.8, 26.2, 25.9, 21.5, 20.4, 18.3, 14.7, 12.8, 10.7, 7.3, 6.9, −5.4. IR (thin film) 3436, 2954, 2877, 1612, 1461, 1378, 1254, 1134, 1091, 1007, 900, 838, 776, 742 (cm^{-1}). HRMS-MALDI (m/z) calcd for $[C_{30}H_{60}N_2O_5Si_2Na]^+$, 607.3933; found, 607.3940. Anal. Calcd for $C_{30}H_{60}N_2O_5Si_2$: C, 61.60; H, 10.34; N, 4.79. Found: C, 61.78; H, 10.47; N, 4.86.

1-((4*S*,5*R*)-3-{(1*R*,3*R*)-3-[(4*S*,5*R*))-3-((1*R*)-2-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-methylethyl)-4-methyl-4,5-dihydroisoxazol-5-yl]-1-methyl-3-[(triethylsilyl)oxy]butyl}-4-methyl-4,5-dihydroisoxazol-5-yl)ethanone (27).



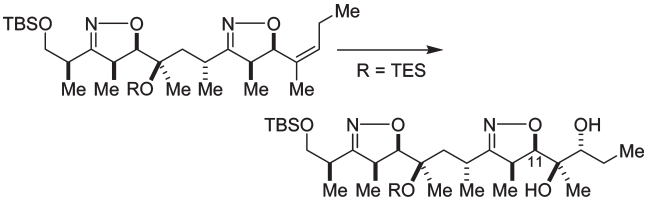
To a biphasic solution of **26** (1.94 g, 3.32 mmol, 1.00 equiv), TEMPO (0.0104 g, 0.0664 mmol, 0.0200 equiv), and KBr (0.0385 g, 0.332 mmol, 0.100 equiv) in CH_2Cl_2 (35.0 mL) and pH 8.6 buffer (35 mL) was slowly added NaOCl (0.5 M in H_2O, 20 mL, 9.95 mmol, 3.00 equiv) at 0 °C. Fifteen minutes and 30 min later, more NaOCl (0.5 M in H_2O, 20 mL, 9.95 mmol, 3.00 equiv (2 ×)) and pH 8.6 buffer (35 mL (2 x)) had to be added. After stirring for another 30 min at 0 °C, the two layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The organic solution was washed with brine (20 mL), dried over Na_2SO_4, and concentrated in vacuo. Purification by chromatography on silica gel (hexane/EtOAc 5:1) afforded **27** (1.49 g, 77% yield) as a clear, colorless oil. R_f = 0.46 (3:1 hexane/EtOAc). $[\alpha]_D^{23.8}$ (c 1.050, $CHCl_3$) = +22°. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.76 (d, 1H, J = 11.1 Hz), 4.10 (d, 1H, J = 8.8 Hz), 3.67−3.56 (m, 1H), 3.62 (d, 2H, J = 6.5 Hz), 3.24−3.13 (m, 1H), 2.87−2.79 (m, 1H), 2.66−2.57 (m, 1H), 2.35 (dd, 1H, J = 14.3, 6.4 Hz), 2.24 (s, 3H), 1.81 (dd, 1H, J = 14.3, 4.6 Hz), 1.36 (s, 3H), 1.22 (d, 3H, J = 7.3 Hz), 1.21 (d, 3H, J = 6.8 Hz), 1.19 (d, 3H, J = 7.8 Hz), 1.10 (d, 3H, J = 7.5 Hz), 0.95 (t, 9H, J = 7.5 Hz), 0.88 (s, 9H), 0.64 (q, 6H, J = 7.5 Hz), 0.05 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 208.3, 166.9, 166.3, 88.0, 87.1, 75.9, 67.1, 46.6, 45.5, 43.2, 34.8, 28.3, 27.6, 26.3, 25.9, 21.4, 18.3, 14.6, 12.7, 11.9, 7.3, 6.8, −5.4. IR (thin film) 2955, 2877, 1716, 1458, 1418, 1379, 1359, 1253, 1167, 1135, 1093, 1006, 974, 941, 838, 777, 741 (cm^{-1}). HRMS-MALDI (m/z) calcd for $[C_{30}H_{58}N_2O_5Si_2Na]^+$, 605.3777; found, 605.3784. Anal. Calcd for $C_{30}H_{58}N_2O_5Si_2$: C, 61.81; H, 10.03; N, 4.81. Found: C, 61.98; H, 10.15; N, 4.98.

(4*S*,5*R*)-3-((1*R*)-2-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-methylethyl)-4-methyl-5-{(1*R*,3*R*)-1-methyl-3-{(4*S*,5*R*)-4-methyl-5-[(1*Z*)-1-methylbut-1-en-1-yl]-4,5-dihydroisoxazol-3-yl}-1-[(triethylsilyl)oxy]butyl}-4,5-dihydroisoxazole (28).



At −78 °C, t-BuLi (1.76 M in pentane, 7.20 mL, 12.7 mmol, 6.00 equiv) was added to a suspension of propyltriphenylphosphonium bromide (5.69 g, 14.8 mmol, 7.00 equiv) in THF (200 mL). The reaction mixture slowly turned red, was allowed to warm to rt, and stirred for 2 h. The dark red suspension was cooled to −78 °C before a solution of ketone **27** (1.23 g, 2.11 mmol, 1.00 equiv) in THF (20 mL) was added dropwise via cannula. The red mixture was slowly warmed to rt and stirred for 15 h. To the orange suspension was added H_2O (50 mL) and Et_2O (100 mL) and the two layers were separated. The aqueous phase was extracted with Et_2O (3 × 30 mL). The combined organics were washed with H_2O_2 (3% in H_2O, 100 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification by chromatography on silica gel (hexane/EtOAc 10:1 to 5:1) provided olefin **28** (0.91 g, 71% yield) as a clear, colorless oil and 30:1 mixture of Z/E diastereomers, accompanied with 0.16 g of recovered ketone **27** (13%). The diastereomeric ratio was determined by examination of the proton at C11 (5.2−5.3 ppm) of **28** in the ^{1}H NMR spectrum of the crude material. R_f = 0.62 (3:1 hexane/EtOAc). $[\alpha]_D^{23.6}$ (c 1.225, $CHCl_3$) = +21°. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.33 (dt, 1H, J = 7.8, 1.2 Hz), 5.30 (d, 1H, J = 10.7 Hz), 4.12 (d, 1H, J = 8.9 Hz), 3.68−3.58 (m, 2H), 3.39−3.29 (m, 1H), 3.23−3.13 (m, 1H), 2.93−2.77 (m, 1H), 2.66−2.59 (m, 1H), 2.32 (dd, 1H, J = 14.2, 5.8 Hz), 2.09−1.88 (m, 2H), 1.84 (dd, 1H, J = 14.2, 5.2 Hz), 1.67 (d, 3H, J = 1.3 Hz), 1.36 (s, 3H), 1.23 (d, 3H, J = 7.1 Hz), 1.23 (d, 3H, J = 6.9 Hz), 1.19 (d, 3H, J = 7.4 Hz), 1.01 (d, 3H, J = 7.5 Hz), 0.97 (t, 3H, J = 7.5 Hz), 0.95 (t, 9H, J = 7.6 Hz), 0.88 (s, 9H), 0.65 (m, 6H), 0.05 (s, 3H), 0.05 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.9, 166.3, 131.0, 130.9, 88.0, 82.2, 76.1, 67.1, 45.5, 45.3, 43.1, 35.0, 28.0, 26.1, 25.9, 21.5, 21.2, 20.3, 18.3, 14.7, 14.4, 12.8, 11.8, 7.3, 6.9, −5.3. IR (thin film) 2956, 2876, 1459, 1378, 1253, 1135, 1095, 1060, 1007, 958, 880, 838, 776, 741 (cm^{-1}). HRMS-MALDI (m/z) calcd for $[C_{33}H_{64}N_2O_4Si_2Na]^+$, 631.4297; found, 631.4304. Anal. Calcd for $C_{33}H_{64}N_2O_4Si_2$: C, 65.08; H, 10.59; N, 4.60. Found: C, 65.05; H, 10.710; N, 4.80.

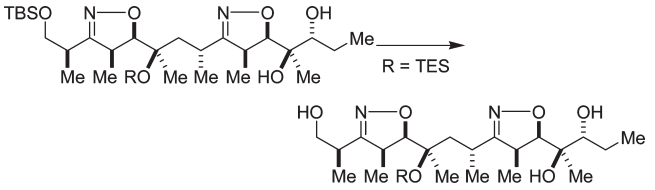
(2*R*,3*R*)-2-((4*S*,5*R*)-3-{(1*R*,3*R*)-3-[(4*S*,5*R*)-3-((1*R*)-2-{[*tert*-Butyl(dimethyl)silyl]oxy}-1-methylethyl)-4-methyl-4,5-dihydroisoxazol-5-yl]-1-methyl-3-[(triethylsilyl)oxy]butyl}-4-methyl-4,5-dihydroisoxazol-5-yl)pentane-2,3-diol (29).



To a solution of olefin **28** (0.880 g, 1.44 mmol, 1.00 equiv) in t-BuOH (7.0 mL) and H_2O (7.0 mL) were added $(DHQD)_2PHAL$ (0.112 g, 0.144 mmol, 0.100 equiv), $K_3Fe(CN)_6$ (1.43 g, 4.33 mmol, 3.00 equiv), K_2CO_3 (0.599 g, 4.33 mmol, 3.00 equiv), and methanesulfonylamide (0.426 g, 4.33 mmol, 3.00 equiv). The biphasic mixture was cooled to 0 °C before $K_2OsO_4 \cdot H_2O$ (0.0106 g, 0.0289 mmol, 0.0200 equiv) was added. The suspension slowly turned brown and was stirred for 3.5 h at 0 °C. Then it was quenched with satd aq $Na_2S_2O_3$ (10 mL) and extracted with EtOAc (4 × 10 mL). The organic solution was washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification by chromatography on silica gel (hexane/EtOAc 4:1) provided diol **29** (0.762 g, 82% yield) as a clear, colorless oil. No other diastereoisomer could be detected, as determined by examination of the proton at C11 (4.0−4.2 ppm) of **29** in the ^{1}H NMR spectrum of the crude material. R_f = 0.25 (3:1 hexane/EtOAc). $[\alpha]_D^{22.5}$ (c 1.030, $CHCl_3$) = +11°. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.26 (d, 1H, J = 8.5 Hz), 4.11 (d, 1H, J = 8.9 Hz), 3.63 (d, 2H, J = 6.4 Hz), 3.27 (s, 1H), 3.24−3.15 (m, 3H), 2.78−2.72 (m, 1H), 2.66−2.60 (m, 1H), 2.34 (dd, 1H, J = 14.1, 5.7 Hz), 2.20 (d, 1H, J = 11.1 Hz), 1.85 (dd, 1H, J = 14.1, 5.0 Hz), 1.72−1.62 (m, 1H), 1.46−1.36 (m, 1H), 1.34 (s, 3H), 1.30 (d, 3H, J = 7.3 Hz), 1.25 (d, 3H, J = 7.6 Hz), 1.23 (s, 3H), 1.22 (d, 3H, J = 6.9 Hz), 1.19 (d, 3H, J = 8.5 Hz), 1.09

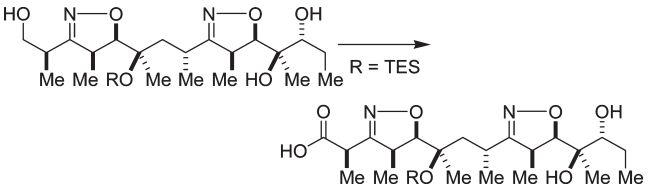
(t, 3H, J = 7.2 Hz), 0.95 (t, 9H, J = 7.8 Hz), 0.88 (s, 9 Hz), 0.65 (q, 6H, J = 7.8 Hz), 0.05 (s, 3H), 0.04 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.9, 167.0, 87.8, 85.9, 82.2, 76.1, 73.6, 67.2, 45.5, 45.4, 42.9, 34.9, 27.9, 26.3, 25.9, 25.4, 22.1, 21.0, 18.3, 14.7, 13.1, 12.8, 11.7, 7.3, 6.9, −5.3. IR (thin film) 3435, 2955, 2877, 1459, 1380, 1253, 1220, 1099, 1007, 976, 940, 738, 775, 742 (cm^{-1}). HRMS-MALDI (m/z) calcd for $[C_{33}H_{66}N_2O_6Si_2Na]^+$, 665.4352; found, 665.4360.

(2*R*,3*R*)-2-((4*S*,5*R*)-3-{(1*R*,3*R*)-3-[(4*S*,5*R*)-3-[(1*R*)-2-Hydroxy-1-methylethyl)-4-methyl-4,5-dihydroisoxazol-5-yl]-1-methyl-3-[(triethylsilyl)oxy]butyl}-4-methyl-4,5-dihydroisoxazol-5-yl)-pentane-2,3-diol (30).



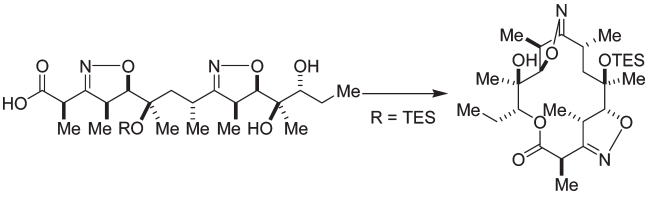
At 0 C, HF·pyridine (3.0 mL) was added to a solution of diol **29** (0.740 g, 1.15 mmol, 1.00 equiv) in pyridine (9.0 mL). The solution was stirred for 3 h at 0 °C and then quenched with H_2O (10 mL) and solid $NaHCO_3$ (5 g) (caution!). The biphasic mixture was extracted with EtOAc (5 × 10 mL). The combined organic solutions were washed with 1 N HCl (100 mL) and brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification by chromatography on silica gel (hexane/EtOAc 1:3) afforded triol **30** (0.510 g, 83% yield) as a clear, colorless oil. R_f = 0.26 (1:3 hexane/EtOAc). $[\alpha]_D^{23.3}$ (c 1.010, $CHCl_3$) = +15°. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.31 (d, 1H, J = 8.8 Hz), 4.11 (d, 1H, J = 8.8 Hz), 3.75 (dd, 1H, J = 10.8, 4.8 Hz), 3.67 (dd, 1H, J = 10.7, 6.4 Hz), 3.43 (s(br), 1H), 3.30−3.16 (m, 3H), 2.86−2.80 (m, 1H), 2.69−2.61 (m, 1H), 2.40 (dd, 1H, J = 14.3, 6.5 Hz), 2.33 (d(br), 1H, J = 10.4 Hz), 2.24 (s(br), 1H), 1.75 (dd, 1H, J = 14.3, 4.0 Hz), 1.69−1.62 (m, 1H), 1.45−1.39 (m, 1H), 1.36 (s, 3H), 1.32 (d, 3H, J = 7.4 Hz), 1.24 (d, 3H, J = 7.0 Hz), 1.22 (d, 3H, J = 7.2 Hz), 1.21 (s, 3H), 1.18 (d, 3H, J = 7.5 Hz), 1.08 (t, 3H, J = 7.3 Hz), 0.96 (t, 9H, J = 7.8 Hz), 0.69−0.61 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 169.5, 166.8, 87.7, 85.8, 82.0, 48.7, 73.7, 66.2, 45.4, 45.1, 43.3, 34.9, 27.2, 26.1, 25.3, 22.3, 20.8, 14.6, 13.0, 12.7, 11.7, 7.3, 6.9. IR (thin film) 3412, 2959, 2877, 1616, 1457, 1414, 1379, 1239, 1167, 1130, 1056, 1009, 977, 939, 885, 742 (cm^{-1}). HRMS-MALDI (m/z) calcd for $[C_{27}H_{52}N_2O_6SiNa]^+$, 551.3487; found, 551.3493.

(2*R*)-2-((4*S*,5*R*)-5-{(1*R*,3*R*)-3-{(4*S*,5*R*)-5-[(1*R*,2*R*)-1,2-Dihydroxy-1-methylbutyl]-4-methyl-4,5-dihydroisoxazol-3-yl}-1-methyl-1-[(triethylsilyl)oxy]butyl}-4-methyl-4,5-dihydroisoxazol-3-yl)propanoic Acid (31).



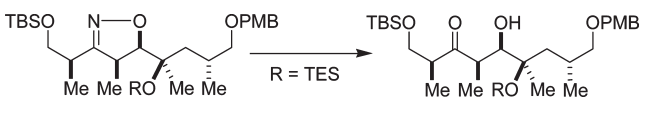
At 0 °C, Dess−Martin periodinane (0.385 g, 0.908 mmol, 4.00 equiv) was added to a solution of triol **30** (0.120 g, 0.227 mmol, 1.00 equiv) in CH_2Cl_2 (4.0 mL). After 2 h of stirring at 0 °C, the solvent was removed under high vacuum. Then a solution of $NaClO_2$ (0.123 g, 1.36 mmol, 6.00 equiv) and 2-methyl-2-butene (0.240 mL, 2.27 mmol, 10.0 equiv) in t-BuOH (7.0 mL) and pH 3.8 buffer (1.4 mL) was added. The light yellow suspension was allowed to warm to rt and stirred for 30 min, before more pH 3.8 buffer (4 mL) was added. The biphasic mixture was extracted with EtOAc (7 × 5 mL). The organic solution was washed with brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification by chromatography on silica gel (hexane/EtOAc 1:3 to 1:3 + 1% AcOH) provided *seco*-acid **31** (0.069 g, 56% yield) as a clear, colorless oil. R_f = 0.17 (1:3 hexane/EtOAc + 1% AcOH). $[\alpha]_D^{22.1}$ (c 1.695, $CHCl_3$) = +2.8°. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.30 (d, 1H, J = 8.8 Hz), 4.09 (d, 1H, J = 8.4 Hz), 3.43 (q, 1H, J = 7.1 Hz), 3.38−3.28 (m, 2H), 3.25−3.18 (m, 1H), 2.96−2.92 (m, 1H), 2.45 (dd, 1H, J = 14.4, 7.3 Hz), 1.69−1.61 (m, 2H), 1.50 (d, 3H, J = 7.4 Hz), 1.47−1.40 (m, 1H), 1.37 (s, 3H), 1.33 (d, 3H, J = 7.4 Hz), 1.22 (s, 3H), 1.18 (d, 3H, J = 7.2 Hz), 1.08 (d, 3H, J = 7.4 Hz), 1.06 (t, 3H, J = 7.2 Hz), 9.53 (t, 9H, J = 7.9 Hz), 0.73−0.58 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 174.9, 169.2, 163.3, 88.6, 85.7, 82.3, 75.6, 73.9, 45.7, 43.9, 43.7, 38.0, 26.6, 26.0, 25.3, 22.8, 21.2, 13.5, 13.1, 12.5, 11.6, 7.3, 6.9. IR (thin film) 3446, 2959, 2877, 1728, 1616, 1458, 1414, 1380, 1295, 1239, 1205, 1131, 1106, 1050, 1009, 977, 940, 908, 825, 745, 666.

(2*R*,4*R*,5*R*,9*R*,12*R*,13*R*,14*R*,17*S*,18*S*)-12-Ethyl-4-13-dihydroxy-2,4,9,13,17,18-hexamethyl-6,11,15-trioxa-7,16-diayatricyclo[12.2.1.1^{5,8}]octadeca-1(16),7-dien-10-one (33).



To a solution of acid **31** (32 mg, 0.059 mmol, 1.0 equiv) in THF (3.0 mL) was added triethylamine (50 μL, 0.35 mmol, 6.0 equiv) and 2,4,6-trichlorobenzoylchloride (46 μL, 0.29 mmol, 5.0 equiv) at 0 °C. The solution turned cloudy and was stirred for 30 min. The colorless suspension was allowed to warm to rt, and toluene (9.0 mL) was added. This cloudy reaction mixture was added to a 50 °C solution of DMAP (72 mg, 0.59 mmol, 10 equiv) in toluene (18 mL) via syringe pump over 3 h. After addition, the colorless suspension was filtered over a plug of silica gel (eluent hexane/EtOAc 1:1). The filtrate was concentrated under reduced pressure and purified by chromatography on silica gel (hexane/EtOAc 10:1 to 6:1 to 3:1) providing macrolactone **33** (17 mg, 55% yield) as a colorless solid. R_f = 0.39 (1:3 hexane/EtOAc); mp = 178−179 °C; $[\alpha]_D^{25.1}$ (c 0.850, $CHCl_3$) = −93°. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 4.84 (dd, 1H, J = 11.2, 2.0 Hz), 4.40 (dd, 1H, J = 10.2, 1.9 Hz), 4.19−3.99 (m, 2H), 3.62−3.53 (m, 1H), 3.50 (q, 1H, J = 7.1 Hz), 3.05−2.95 (m, 1H), 2.47 (dd, 1H, J = 14.4, 9.6 Hz), 2.26−2.10 (m, 1H), 1.67−1.60 (m, 1H), 1.52−1.45 (m, 1H), 1.47 (d, 3H, J = 6.9 Hz), 1.47 (d, 3H, J = 8.4 Hz), 1.37 (s, 3H), 1.23 (s, 3H), 1.06 (d, 3H, J = 7.3 Hz), 1.00 (d, 3H, J = 6.7 Hz), 0.97 (t, 3H, J = 7.4 Hz), 0.94 (t, 9H, J = 7.9 Hz), 0.74−0.56 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 174.4, 166.4, 164.1, 89.4, 84.4, 84.1, 78.4, 75.2, 45.3, 45.2, 43.5, 38.6, 26.1, 26.0, 25.4, 22.7, 21.4, 13.3, 12.1, 11.7, 10.6, 7.5, 6.9. IR (thin film) 3496, 2960, 2876, 1734, 1458, 1378, 1306, 1260, 1206, 1159, 1128, 1075, 1051, 1016, 954, 886, 742 (cm^{-1}). HRMS-MALDI (m/z) calcd for $[C_{27}H_{48}N_2O_6SiNa]^+$, 547.3176; found, 547.3182. Anal. Calcd for $C_{27}H_{48}N_2O_6Si$: C, 61.80; H, 9.22; N, 5.34. Found: C, 61.98; H, 9.00; N, 5.11.

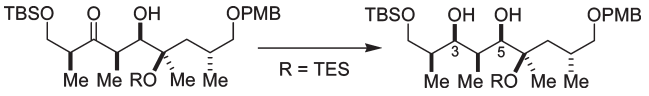
1-*O*-[*tert*-Butyl(dimethyl)silyl]-2,4,7,8-tetradeoxy-9-*O*-(4-methoxybenzyl)-2,4,8-trimethyl-6-*C*-methyl-6-*O*-(triethylsilyl)-L-*glycero*-D-*gulo*-non-3-ulose (35).



After addition of boric acid (0.102 g, 1.65 mmol, 5.00 equiv) and Raney Ni (W2, spatula tip) to a biphasic mixture of **22**

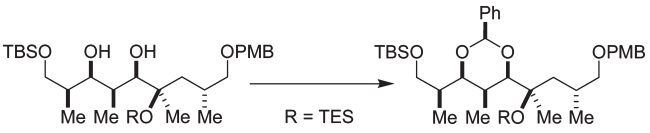
(0.202 g, 0.33 mmol, 1.00 equiv) in MeOH/H_2O (5:1, 4.0 mL), the Schlenk flask was purged several times with H_2. The black suspension was stirred rapidly under an atmosphere of H_2 for 2 h. The black reaction mixture was filtered over Celite and eluted with CH_2Cl_2. The biphasic mixture was washed with H_2O. The organic solution was dried over anhydrous Na_2SO_4 and concentrated in vacuo. Purification by chromatography on silica gel (hexane/EtOAc 7:1) provided β-hydroxyketone **35** (0.181 g, 89% yield) as a clear, colorless oil. R_f = 0.54 (3:1 hexane/EtOAc). $[\alpha]_D^{30.1}$ (*c* 1.530, $CHCl_3$) = +12°. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.25 (d, 2H, *J* = 8.6 Hz), 6.87 (d, 2H, *J* = 8.7 Hz), 4.42 (s, 2H), 3.87−3.83 (m, 1H), 3.81−3.75 (m, 1H), 3.80 (s, 3H), 3.53 (dd, 1H, *J* = 9.7, 5.9 Hz), 3.27−3.16 (m, 2H), 2.99−2.88 (m, 2H), 2.49 (d, 1H, *J* = 7.8 Hz), 1.81−1.76 (m, 1H), 1.66−1.50 (m, 2H), 1.18 (s, 3H), 1.16 (d, 3H, *J* = 7.2 Hz), 1.04 (d, 3H, *J* = 6.8 Hz), 1.01 (d, 3H, *J* = 6.5 Hz), 0.95 (t, 9H, *J* = 8 Hz) 0.87 (s, 9H), 0.61 (q, 6H, *J* = 8 Hz) 0.03 (s, 3H), 0.02 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 216.4, 158.9, 130.7, 129.0, 113.6, 79.2, 76.4, 73.1, 72.6, 65.6, 55.3, 47.1, 47.0, 44.0, 30.0, 26.0, 25.2, 19.4, 18.5, 14.2, 11.2, 7.3, 7.0, −5.3, −5.3. IR (thin film) 3524, 2954, 2876, 1701, 1613, 1587, 1513, 1463, 1361, 1302, 1249, 1172, 1095, 1005, 837, 775, 741, 724, 666 (cm^{-1}). HRMS-MALDI (*m*/*z*) calcd for $[C_{33}H_{62}O_6Si_2Na]^+$, 633.3983; found, 633.3972. Anal. Calcd for $C_{33}H_{62}O_6Si_2$: C, 64.87; H, 10.23. Found: C, 64.69; H, 10.46.

9-*O*-[*tert*-Butyl(dimethyl)silyl]-2,3,6,8-tetradeoxy-1-*O*-(4-methoxybenzyl)-2,6,8-trimethyl-4-*C*-methyl-4-*O*-(triethylsilyl)-L-*threo*-L-*ido*-nonitol (36).



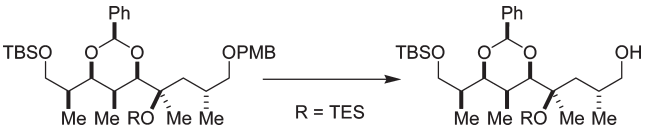
At −78 °C, $Zn(BH_4)_2$ (0.145 M solution in Et_2O, 12.0 mL, 1.73 mmol, 2.50 equiv) was added to a solution of β-hydroxy ketone **35** (0.424 g, 0.694 mmol, 1.00 equiv) in CH_2Cl_2 (35 mL). The clear, colorless solution was stirred at −30 °C for 2 h before more $Zn(BH_4)_2$ (0.145 M solution in Et_2O, 2.40 mL, 0.345 mmol, 0.500 equiv) was added. The solution was stirred for another 30 min before it was quenched with MeOH/H_2O (1:1, 10 mL). The biphasic mixture was stirred for 1 h at rt, and then 1 N HCl (5 mL) was added. The aqueous layer was separated and extracted with CH_2Cl_2 (3 × 10 mL). The combined organics were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification by chromatography on silica gel (hexane/EtOAc 10:1 to 7:1) afforded pure 1,3-diol **36** (0.260 g, 60% yield) as a clear, colorless oil. No other diastereoisomer could be detected, as determined by examination of the diastereotopic signals of the protons at C3 and C5 (3.1−3.7 ppm) of **36** in the ^{1}H NMR spectrum of the crude material. R_f = 0.48 (3:1 hexane/EtOAc). $[\alpha]_D^{27.6}$ (*c* 1.035, $CHCl_3$) = +10°. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.25 (d, 2H, *J* = 7.8 Hz), 6.87 (d, 2H, *J* = 8.7 Hz), 4.42 (s, 2H), 3.81 (s, 3H), 3.74 (s, 1H), 3.67−3.63 (m, 1H), 3.62 (dd, 1H, *J* = 10.0, 4.1 Hz) 3.56−3.49 (m, 2H), 3.25−3.16 (m, 2H) 2.72 (d, 1H, *J* = 9.3 Hz), 1.93−1.87 (m, 1H), 1.81−1.73 (m, 1H), 1.71−1.45 (m, 3H), 1.23 (s, 3H), 1.02−0.97 (m, 9H), 0.95 (t, 9H, *J* = 7.8 Hz), 0.88 (s, 9H), 0.62 (q, 6H, *J* = 7.8 Hz), 0.038 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 158.9, 130.6, 129.0, 113.6, 79.6, 79.2, 77.5, 76.3, 72.6, 67.0, 55.3, 44.6, 37.4, 35.8, 30.3, 26.0, 24.7, 19.4, 18.3, 13.0, 7.5, 7.3, 7.0, −5.4, −5.4. IR (thin film) 3502, 2955, 2876, 1613, 1587, 1514, 1463, 1415, 1389, 1361, 1302, 1249, 1172, 1097, 1004, 972, 837, 776, 742, 668 (cm^{-1}). HRMS-MALDI (*m*/*z*) calcd for $[C_{33}H_{64}O_6Si_2Na]^+$, 635.4139; found, 635.4127. Anal. Calcd for $C_{33}H_{64}O_6Si_2$: C, 64.66; H, 10.52. Found: C, 64.40; H, 10.66.

3,5-*O*-Benzylidene-1-*O*-[*tert*-butyl(dimethyl)silyl]-2,4,7,8-tetradeoxy-9-*O*-(4-methoxybenzyl)-2,4,8-trimethyl-6-*C*-methyl-6-*O*-(triethylsilyl)-L-*threo*-L-*ido*-nonitol (37).



To a solution of **36** (0.580 g, 0.946 mmol, 1.00 equiv) in toluene (10 mL) were added benzaldehyde dimethyl acetal (0.213 mL, 1.42 mmol, 1.50 equiv) and CSA (0.0220 g, 0.0946 mmol, 0.100 equiv). The solution was stirred at rt and 70 mbar for 1.5 h, and then satd aq $NaHCO_3$ (10 mL) and EtOAc (10 mL) were added. The layers were separated, and the aqueous phase was extracted with EtOAc (3 × 10 mL). The combined organic phases were washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. The residue was purified by chromatography on silica gel (hexane/EtOAc 15:1) to provide **37** (0.58 g, 87% yield) as a clear, colorless oil. R_f = 0.64 (3:1 hexane/EtOAc). $[\alpha]_D^{23.6}$ (*c* 1.225, $CHCl_3$) = −1.5°. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.53−7.50 (m, 2H), 7.38−7.31 (m, 3H), 7.27−7.23 (m, 2H), 6.90−6.85 (m, 2H), 5.50 (s, 1H), 4.43 (s, 2H), 3.81 (s, 3H), 3.60 (d, 1H, *J* = 1.9 Hz), 3.55−3.50 (m, 3H), 3.36 (dd, 1H, *J* = 8.71, 5.6 Hz), 3.15 (dd, 1H, *J* = 8.7, 7.5 Hz), 1.96−1.86 (m, 3H), 1.55 (dd, 1H, *J* = 13.7, 4.4 Hz), 1.42 (dd, 1H, *J* = 13.7, 5.9 Hz), 1.29 (s, 3H), 1.05 (d, 3H, *J* = 6.5 Hz), 1.05 (d, 3H, *J* = 6.5 Hz), 1.02 (d, 3H, *J* = 6.9 Hz), 0.90 (s, 9H), 0.86 (t, 9H, *J* = 8.1 Hz) 0.51 (q, 6H, *J* = 8.1 Hz), 0.04 (s, 3H), 0.03 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 158.8, 139.1, 130.9, 128.9, 128.3, 127.8, 126.2, 113.6, 102.1, 87.1, 85.0, 78.0, 76.7, 72.5, 64.1, 55.3, 43.2, 36.3, 31.4, 29.4, 26.0, 24.9, 19.9, 18.3, 14.6, 8.4, 7.3, 6.8, −5.3, −5.4. IR (thin film) 2953, 2874, 1612, 1587, 1514, 1406, 1360, 1302, 1249, 1141, 1101, 1035, 1010, 972, 836, 776, 741, 698 (cm^{-1}). HRMS-MALDI (*m*/*z*) calcd for $[C_{40}H_{68}O_6Si_2Na]^+$, 723.4447; found, 723.4439. Anal. Calcd for $C_{40}H_{68}O_6Si_2$: C, 68.52; H, 9.78. Found: C, 68.44; H, 9.79.

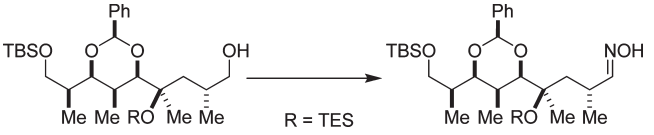
3,5-*O*-Benzylidene-1-*O*-[*tert*-butyl(dimethyl)silyl]-2,4,7,8-tetradeoxy-2,4,8-trimethyl-6-*C*-methyl-6-*O*-(triethylsilyl)-L-*threo*-L-*ido*-nonitol (38).



At 0 °C, a solution of benzylidene acetal **37** (0.650 g, 0.927 mmol, 1.00 equiv) in CH_2Cl_2 (18 mL) was treated with DDQ (0.253 g, 1.11 mmol, 1.2 equiv) and pH 7 buffer (30 μL). The green suspension slowly turned light brown. After stirring for 2 h at 0 °C, the reaction was quenched with satd aq $Na_2S_2O_3$ (5 mL) and satd aq $NaHCO_3$ (60 mL). The two layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The organic solution was washed with brine (20 mL), dried over anhydrous Na_2SO_4, filtered over Na_2SO_4, and concentrated under reduced pressure. The light yellow residue was purified by chromatography on silica gel (hexane/EtOAc 7:1) to afford primary alcohol **38** (0.461 g, 85% yield) as a clear, colorless oil. R_f = 0.51 (3:1 hexane/EtOAc). $[\alpha]_D^{31.4}$ (*c* 1.055, $CHCl_3$) = +8.1°. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.53−7.50 (m, 2H), 7.40−7.33 (m, 3H), 5.51 (s, 1H), 3.67 (d, 1H, *J* = 1.9 Hz), 3.58−3.48 (m, 4H), 3.38−3.30 (m, 1H), 2.44 (t, 1H, *J* = 5.5 Hz), 2.00−1.87 (m, 3H), 1.66 (dd, 1H, *J* = 14.3, 5.91 Hz), 1.41 (dd, 1H, *J* = 14.0, 4.1 Hz), 1.34 (s, 3H), 1.06 (d, 3H, *J* = 6.5 Hz), 1.03 (d, 3H, *J* = 6.5 Hz), 0.98 (d, 3H, *J* = 6.9 Hz),

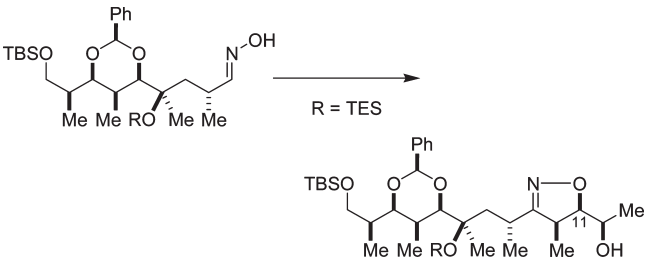
0.90 (s, 9H), 0.86 (t, 9H, J = 7.5 Hz), 0.59−0.51 (m, 6H), 0.05 (s, 3H), 0.05 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 139.2, 128.8, 128.3, 126.7, 102.6, 88.2, 85.5, 78.8, 69.3, 64.5, 43.5, 36.5, 31.7, 31.2, 26.1, 24.4, 20.0, 18.5, 14.7, 8.5, 7.3, 6.6, −5.3, −5.3. IR (thin film) 3436, 2954, 2875, 1947, 1458, 1406, 1376, 1349, 1311, 1253, 1213, 1111, 1065, 1033, 1010, 915, 837, 776, 742, 698, 674 (cm^{-1}). HRMS-MALDI (m/z) calcd for $[C_{32}H_{60}O_5Si_2Na]^+$, 603.3872; found, 603.3870. Anal. Calcd for $C_{32}H_{60}O_5Si_2$: C, 66.15; H, 10.41. Found: C, 66.27; H, 10.58.

5,7-*O*-Benzylidene-9-*O*-[*tert*-butyl(dimethyl)silyl]-2,3,6,8-tetradeoxy-2,6,8-trimethyl-4-*C*-methyl-4-*O*-(triethylsilyl)-L-*threo*-L-*ido*-nonose (39).



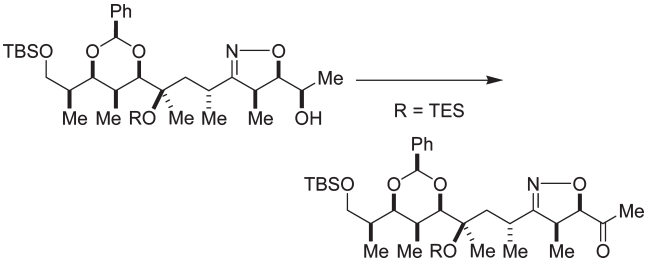
To a biphasic solution of **38** (0.461 g, 0.793 mmol, 1.00 equiv), TEMPO (0.0186 g, 0.119 mmol, 0.150 equiv), and KBr (0.0092 g, 0.079 mmol, 0.100 equiv) in CH_2Cl_2 (8.0 mL) and pH 8.6 buffer (8.0 mL) was slowly added NaOCl (0.5 M in H_2O, 6.35 mL, 3.17 mmol, 4.00 equiv) at 0 °C. After 10 min, H_2O (5 mL) and CH_2Cl_2 (10 mL) were added. The two layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The organic solution was washed with brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo. The light orange oil was used without further purification. R_f = 0.65 (3:1 hexane/EtOAc). ^{1}H NMR (300 MHz, $CDCl_3$) δ: 9.48 (d, 1H, J = 3.1 Hz), 7.52−7.49 (m, 2H), 7.40−7.33 (m, 3H), 5.46 (s, 1H), 3.62 (d, 1H, J = 1.9 Hz), 3.58−3.48 (m, 3H), 2.67−2.61 (m, 1H), 2.15 (dd, 1H, J = 14.0, 9.3 Hz), 1.96−1.87 (m, 2H), 1.45 (dd, 1H, J = 14.3, 3.11 Hz), 1.32, (s, 3H), 1.08 (d, 3H, J = 5.3 Hz), 1.06 (d, 3H, J = 7.16 Hz), 1.04 (d, 3H, J = 7.2 Hz), 0.91 (s, 9H), 0.87 (t, 9H, J = 7.5 Hz), 0.53 (q, 6H, J = 7.5 Hz), 0.05 (s, 3H), 0.05 (s, 3H). A solution of $H_2NOH\cdot HCl$ (0.110 g, 1.59 mmol, 2.00 equiv) in py (1.6 mL) was added to a solution of unpurified aldehyde (0.459 g, 0.793 mmol, 1.00 equiv) in EtOH (8.0 mL), and the mixture was stirred for 20 min at rt. The light green solution was quenched with 1 N HCl (20 mL), and the aqueous layer was extracted with EtOAC (3 × 10 mL). The combined organic solutions were washed with brine (10 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification by chromatography on silica gel (hexane/EtOAc 7:1) provided oxime **39** (0.402 g, 85% yield over 2 steps) as a mixture of E/Z isomers (~1.5:1). R_f = 0.56, 0.51* (3:1 hexane/EtOAc, *denotes minor isomer). $[\alpha]_D^{24.0}$ (c 1.185, $CHCl_3$) = −5.9°. ^{1}H NMR (300 MHz, $CDCl_3$, *denotes minor isomer) δ: 7.53−7.50 (m, 2H), 7.39−7.29 (m, 3H), 6.75* (s(br), 1H), 6.63 (d, 1H, J = 7.8 Hz), 5.53* (s, 1H), 5.51 (s, 1H), 3.68* (d, 1H, J = 1.9 Hz), 3.63 (d, 1H, J = 1.9 Hz), 3.60−3.49 (m, 3H), 3.34−3.30* (m, 1H), 2.70−2.61 (m, 1H), 1.94−1.87 (m, 1H), 1.77−1.71 (m, 1H), 1.68−1.60* (m, 1H), 1.29 (s, 3H), 1.29* (s, 3H), 1.11 (d, 3H, J = 6.9 Hz), 1.07 (d, 3H, J = 6.54 Hz), 1.06* (d, 3H, J = 6.54 Hz), 1.04 (d, 3H, J = 6.5 Hz), 0.91* (s, 9H), 0.91 (s, 9H), 0.88 (t, 9H, J = 7.5 Hz), 0.55 (q, 6H, J = 7.8 Hz), 0.06* (s, 3H), 0.05 (s, 3H), 0.05 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, *denotes minor isomer) δ: 158.5*, 157.6, 139.4*, 139.4, 128.7*, 128.2, 126.5, 102.4, 87.2, 87.1*, 85.4, 64.4, 45.2*, 44.7, 36.6, 36.5*, 31.6, 30.6, 26.1, 26.0, 25.5, 25.2*, 20.9, 19.5, 18.5, 14.6, 8.6, 7.4, 6.9, 6.8*, −5.2, −5.3. IR (thin film) 3255, 3036, 2955, 2875, 1948, 1805, 1662, 1457, 1407, 1377, 1348, 1311, 1252, 1212, 1111, 1068, 1030, 971, 911, 837, 811, 776, 741, 698, 672 (cm^{-1}). HRMS-MALDI (m/z) calcd for $[C_{32}H_{59}NO_5Si_2Na]^+$, 616.3824; found, 616.3823. Anal. Calcd for $C_{32}H_{59}NO_5Si_2$: C, 64.71; H, 10.01. Found: C, 64.48; H, 9.93.

3,5-*O*-Benzylidene-7-*O*-[*tert*-butyl(dimethyl)silyl]-1,4,6-trideoxy-2-*C*-((2*R*)-2-{(4*S*,5*R*)-5-[(1*R*)-1-hydroxyethyl]-4-methyl-4,5-dihydroisoxazol-3-yl}propyl)-4,6-dimethyl-2-*O*-(triethylsilyl)-L-*glycero*-D-*gulo*-heptitol (40).



To a solution of (*R*)-(−)-(*Z*)-3-penten-2-ol (**14**) (0.091 g, 1.1 mmol, 1.3 equiv) and 2-propanol (0.21 mL, 2.7 mmol, 3.3 equiv) in CH_2Cl_2 (40 mL) at 0 °C was added EtMgBr (3 M in Et_2O, 0.81 mL, 2.4 mmol, 3.0 equiv). The reaction mixture turned momentarily cloudy, becoming clear and colorless upon stirring at 0 °C for 30 min. At this time, the hydroxymoyl chloride, prepared by addition of *t*-BuOCl (0.10 mL, 0.89 mmol, 1.1 equiv) to a solution of oxime **39** (0.48 g, 0.81 mmol, 1.0 equiv) in CH_2Cl_2 (8.0 mL) at −78 °C and stirring for 1.5 h, was added dropwise via cannula to the reaction to give a slightly yellow solution. The yellow solution was allowed to warm to rt and stirred for 2 h. The reaction was quenched by the addition of satd aq NH_4Cl (20 mL), and the two layers were separated. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic solutions were washed with brine (20 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification by chromatography on silica gel (hexane/EtOAc 4:1) provided isoxazoline **40** (0.52 g, 86% yield) as a clear, colorless oil. No other diastereomer could be detected, as determined by examination of the diastereotopic signals of the proton at C11 (4.0−4.2 ppm) of **40** in the ^{1}H NMR spectrum of the crude material. R_f = 0.31 (3:1 hexane/EtOAc). $[\alpha]_D^{28.0}$ (c 1.080, $CHCl_3$) = −13°. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.60−7.50 (m, 2H), 7.39−7.32 (m, 3H), 5.50 (s, 1H), 4.19 (dd, 1H, J = 9.7, 5.0 Hz), 3.97−3.89 (m, 1H), 3.6 (d, 1H, J = 1.9 Hz), 3.56−3.46 (m, 3H), 3.33−3.23 (m, 1H), 2.82−2.77 (m, 1H), 2.20 (dd, 1H, J = 14.0, 5.3 Hz), 1.98 (d, 1H, J = 6.5 Hz), 1.95−1.88 (m, 2H), 1.77 (dd, 1H, J = 13.7, 5.3 Hz), 1.30 (s, 3H), 1.27 (d, 3H, J = 6.5 Hz), 1.23 (d, 3H, J = 6.2 Hz), 1.18 (d, 3H, J = 7.5 Hz), 1.08 (d, 3H, J = 6.9 Hz), 1.05 (d, 3H, J = 6.5 Hz), 0.90 (s, 9H), 0.88 (t, 9H, J = 7.5 Hz), 0.55 (q, 6H, J = 7.8 Hz), 0.05 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 168.2, 139.0, 128.4, 127.9, 126.2, 102.2, 87.0, 86.0, 85.1, 77.6, 66.2, 64.1, 44.2, 42.3, 36.5, 31.4, 27.8, 26.0, 25.3, 21.8, 20.4, 18.4, 14.6, 10.9, 8.5, 7.3, 6.8, −5.3. IR (thin film) 3458, 2955, 2933, 2876, 1616, 1458, 1406, 1377, 1348, 1253, 1212, 1134, 1110, 1031, 1007, 975, 901, 837, 776, 743, 698, 671 (cm^{-1}). HRMS-MALDI (m/z) calcd for $[C_{37}H_{67}NO_6Si_2Na]^+$, 700.4339; found, 700.4408.

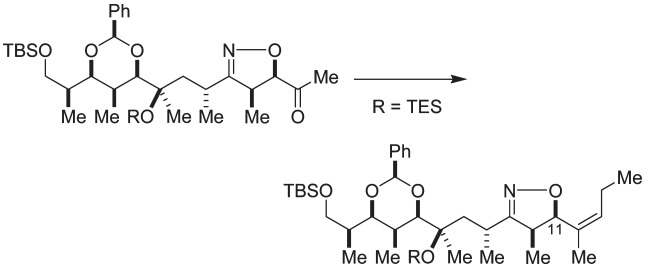
2-*C*-{(2*R*)-2-[(4*S*,5*R*)-5-Acetyl-4-methyl-4,5-dihydroisoxazol-3-yl]propyl}-3,5-*O*-benzylidene-7-*O*-[*tert*-butyl(dimethyl)silyl]-1,4,6-trideoxy-4,6-dimethyl-2-*O*-(triethylsilyl)-L-*glycero*-D-*gulo*-heptitol (41).



To a biphasic solution of isoxazoline **40** (0.52 g, 0.77 mmol, 1.0 equiv), TEMPO (0.018 g, 0.12 mmol, 0.15 equiv), and KBr

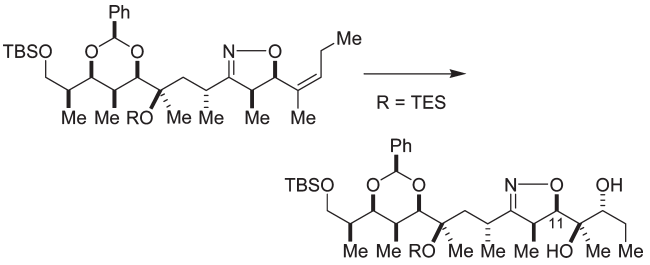
(0.0089 g, 0.077 mmol, 0.10 equiv) in CH_2Cl_2 (8.0 mL) and pH 8.6 buffer (8.0 mL) was slowly added NaOCl (0.5 M in H_2O, 6.1 mL, 3.1 mmol, 4.0 equiv) at 0 °C. After stirring for 1 h at 0 °C, the two layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The organic solution was washed with brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by chromatography on silica gel (hexane/EtOAc 6:1) to afford ketone **41** (0.48 g, 93% yield) as colorless oil. R_f = 0.50 (3:1 hexane/EtOAc). $[\alpha]_D^{23.2}$ (*c* 1.205, $CHCl_3$) = +13°. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.52−7.49 (m, 2H), 7.40−7.33 (m, 3H), 5.50 (s, 1H), 4.75 (d, 1H, *J* = 10.9 Hz), 3.60 (m, 4H), 3.52 (d, 1H, *J* = 4.1 Hz), 2.90−2.85 (m, 1H), 2.25 (s, 3H), 2.21 (dd, 1H, *J* = 14.0, 5.3 Hz), 1.93−1.88 (m, 2H), 1.76 (dd, 1H, *J* = 14.0, 5.3 Hz), 1.33 (s, 3H), 1.23 (d, 3H, *J* = 7.2 Hz), 1.08 (d, 3H, *J* = 6.2 Hz), 1.06 (d, 3H, *J* = 7.2 Hz), 1.05 (d, 3H, *J* = 6.5 Hz), 0.90 (s, 9H), 0.86 (t, 9H, *J* = 7.8 Hz), 0.55 (q, 6H, *J* = 7.8 Hz), 0.06 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 208.4, 166.7, 138.9, 128.5, 128.0, 126.2, 102.3, 87.5, 87.2, 85.1, 77.5, 64.1, 46.7, 42.3, 36.5, 31.4, 28.4, 27.6, 26.0, 25.2, 21.7, 18.4, 14.6, 12.1, 8.5, 7.3, 6.8, −5.3. IR (thin film) 2955, 2876, 1716, 1458, 1407, 1377, 1356, 1252, 1135, 1111, 1031, 1007, 973, 914, 837, 811, 776, 742, 698, 674 (cm^{-1}). HRMS-MALDI (*m*/*z*) calcd for $[C_{37}H_{65}NO_6Si_2Na]^+$, 698.4243; found, 698.4234.

3,5-*O*-Benzylidene-7-*O*-[*tert*-butyl(dimethyl)silyl]-1,4,6-trideoxy-4,6-dimethyl-2-*C*-((2*R*)-2-{(4*S*,5*R*)-4-methyl-5-[(1*Z*)-1-methylbut-1-en-1-yl]-4,5-dihydroisoxazol-3-yl}propyl-2-*O*-(triethylsilyl)-L-*glycero*-D-*gulo*-heptitol (42).



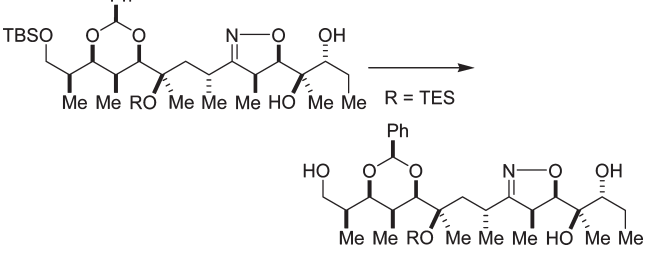
At −78 °C, *t*-BuLi (1.70 M in pentane, 1.88 mL, 3.20 mmol, 5.00 equiv) was added to a suspension of propyltriphenylphosphonium bromide (1.48 g, 3.84 mmol, 6.00 equiv) in THF (60 mL). The reaction mixture slowly turned red, was allowed to warm to rt, and stirred for 2 h. The dark red suspension was cooled to −78 °C before a solution of ketone **41** (0.433 g, 0.640 mmol, 1.00 equiv) in THF (6.0 mL) was added dropwise via cannula. The red mixture was slowly warmed to rt and stirred for 15 h. To the orange suspension were added H_2O (50 mL) and Et_2O (50 mL,) and the two layers were separated. The aqueous phase was extracted with Et_2O (3 × 20 mL). The combined organics were washed with H_2O_2 (3% in H_2O, 50 mL) and brine (20 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification by chromatography on silica gel (hexane/EtOAc 15:1) provided olefin **42** (0.353 g, 78% yield) as a clear, colorless oil and as 33:1 mixture of *Z*/*E* diastereomers, accompanied with 0.020 g of recovered ketone **41** (5%). The diastereomeric ratio was determined by examination of the proton at C11 (5.2−5.3 ppm) of **42** in the ^{1}H NMR spectrum of the crude material. R_f = 0.65 (3:1 hexane/EtOAc). $[\alpha]_D^{25.4}$ (*c* 1.190, $CHCl_3$) = +13°. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.53−7.49 (m, 2H), 7.39−7.30 (m, 3H), 5.51 (s, 1H), 5.35 (t, 1H, *J* = 7.3 Hz), 5.30 (d, 1H, *J* = 10.6 Hz), 3.61 (d, 1H, *J* = 1.9 Hz), 3.57−3.46 (m, 3H), 3.40−3.29 (m, 1H), 2.86−2.78 (m, 1H), 2.20 (dd, 1H, *J* = 14.0, 5.0 Hz), 2.10−1.96 (m, 1H), 1.93−1.84 (m, 3H), 1.77 (dd, 1H, *J* = 14.0, 5.6 Hz), 1.68 (d, 3H, *J* = 1.6 Hz), 1.32 (s, 3H), 1.23 (d, 3H, *J* = 7.2 Hz), 1.08 (d, 3H, *J* = 7.8 Hz), 1.05 (d, 3H, *J* = 6.5 Hz), 1.00 (t, 3H, *J* = 7.5 Hz), 0.96 (d, 3H, *J* = 7.5 Hz), 0.90 (s, 9H), 0.87 (t, 9H, *J* = 7.8 Hz), 0.55 (q, 6H, *J* = 7.8 Hz), 0.52 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 166.5, 139.0, 131.1, 130.8, 128.4, 127.9, 126.2, 102.2, 87.1, 85.1, 82.1, 77.6, 64.0, 45.5, 42.5, 36.5, 31.4, 28.0, 26.0, 25.2, 21.7, 21.2, 20.4, 18.4, 14.6, 14.4, 11.9, 8.4, 7.3, 6.8, −5.3. IR (thin film) 2956, 2932, 2875, 1616, 1457, 1406, 1378, 1348, 1252, 1211, 1111, 1092, 1031, 1007, 973, 924, 837, 776, 742, 698, 671 (cm^{-1}). HRMS-MALDI (*m*/*z*) calcd for $[C_{40}H_{71}NO_5Si_2Na]^+$, 724.4763; found, 724.4755.

3,5-*O*-Benzylidene-7-*O*-[*tert*-butyl(dimethyl)silyl]-1,4,6-trideoxy-2-*C*-((2*R*)-2-{(4*S*,5*R*)-5-[(2*R*)-2-hydroxy-1,1-dimethylbutyl]-4-methyl-4,5-dihydroisoxazol-3-yl}propyl)-4,6-dimethyl-2-*O*-(triethylsilyl)-L-*glycero*-D-*gulo*-heptitol (43).



To a solution of olefin **42** (380 mg, 0.54 mmol, 1.0 equiv) in *t*-BuOH (5.0 mL) and H_2O (5.0 mL) were added $(DHQD)_2$-PHAL (84 mg, 0.11 mmol, 0.20 equiv), $K_3Fe(CN)_6$ (530 mg, 1.6 mmol, 3.0 equiv), K_2CO_3 (220 mg, 1.6 mmol, 3.0 equiv), and methanesulfonylamide (160 mg, 1.6 mmol, 3.0 equiv). The biphasic mixture was cooled to 0 °C before $K_2OsO_4 \cdot H_2O$ (8.0 mg, 0.020 mmol, 0.040 equiv) was added. The suspension slowly turned brown and was stirred for 3.5 h at 0 °C. Then it was quenched with satd aq $Na_2S_2O_3$ (10 mL) and extracted with EtOAc (4 × 10 mL). The organic solution was washed with brine (10 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification by chromatography on silica gel (hexane/EtOAc 6:1 to 3:1) provided diol **43** (320 mg, 81% yield) as a clear, colorless oil. No other diastereomer could be detected, as determined by examination of the proton at C11 (4.0−4.2 ppm) of **43** in the ^{1}H NMR spectrum of the crude material. R_f = 0.30 (3:1 hexane/EtOAc). $[\alpha]_D^{24.0}$ (*c* 0.590, $CHCl_3$) = +9.9°. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.53−7.49 (m, 2H), 7.39−7.32 (m, 3H), 5.50 (s, 1H), 4.25 (d, 1H, *J* = 8.4 Hz), 3.61 (d, 1H, *J* = 1.6 Hz), 3.55−3.46 (m, 3H), 3.28 (s, 1H), 3.24−3.12 (m, 2H), 2.82−2.76 (m, 1H), 2.26−2.19 (m, 2H), 1.92−1.88 (m, 2H), 1.78 (dd, 1H, *J* = 14.0, 5.6 Hz), 1.71−1.65 (m, 1H), 1.46−1.33 (m, 1H), 1.31 (s, 3H), 1.29 (d, 3H, *J* = 8.4 Hz), 1.23 (d, 3H, *J* = 7.2 Hz), 1.23 (s, 3H), 1.09 (t, 3H, *J* = 7.2 Hz), 1.08 (d, 3H, *J* = 6.9 Hz), 1.05 (d, 3H, *J* = 6.5 Hz), 0.90 (s, 9H), 0.88 (t, 9H, *J* = 7.8 Hz), 0.55 (q, 6H, *J* = 7.8 Hz), 0.05 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.5, 139.3, 128.7, 128.2, 126.5, 102.5, 87.2, 86.0, 85.3, 82.4, 77.8, 73.7, 64.2, 45.7, 42.6, 36.6, 31.6, 28.0, 26.1, 25.5, 25.5, 22.4, 21.1, 18.4, 14.7, 13.3, 11.8, 8.5, 7.4, 6.9, −5.2. IR (thin film) 3531, 2956, 1610, 1457, 1406, 1379, 1347, 1252, 1110, 1035, 1008, 975, 910, 837, 776, 735, 698, 672 (cm^{-1}). HRMS-MALDI (*m*/*z*) calcd for $[C_{40}H_{73}NO_7Si_2Na]^+$, 758.4818; found, 758.4810.

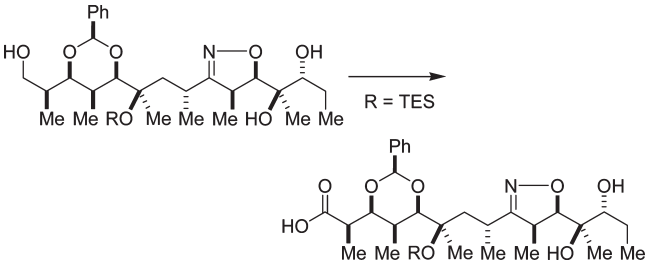
3,5-*O*-Benzylidene-1,4,6-trideoxy-2-*C*-((2*R*)-2-{(4*S*,5*R*)-5-[(1*R*,2*R*)-1,2-dihydroxy-1-methylbutyl]-4-methyl-4,5-dihydroisoxazol-3-yl}propyl)-4,6-dimethyl-2-*O*-(triethylsilyl)-L-*glycero*-D-*gulo*-heptitol (44).



At 0 °C, HF·pyridine (1.0 mL) was added to a solution of diol **43** (325 mg, 0.441 mmol, 1.00 equiv) in pyridine (3.0 mL). The

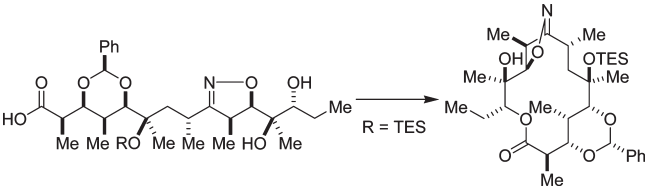
solution was stirred for 3 h at 0 °C and then quenched with H_2O (2 mL) and solid $NaHCO_3$ (2.5 g) with care. The biphasic mixture was extracted with EtOAc (5 × 5 mL). The combined organic solutions were washed with 1 N HCl (50 mL) and brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purification by chromatography on silica gel (hexane/EtOAc 1:1 to 1:3) afforded triol **44** (220 mg, 80% yield) as a colorless foam. R_f = 0.18 (1:1 hexane/EtOAc). $[\alpha]_D^{24.5}$ (*c* 2.650, $CHCl_3$) = −14°. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.53−7.49 (m, 2H), 7.39−7.32 (m, 3H), 5.50 (s, 1H), 4.34 (d, 1H, *J* = 8.7 Hz), 3.70 (d, 1H, *J* = 1.0 Hz), 3.68−3.53 (m, 4H), 3.32−3.18 (m, 2H), 2.92−2.86 (m, 1H), 2.43−2.22 (m, 3H), 2.06−2.00 (m, 1H), 1.90−1.83 (m, 1H), 1.74−1.67 (m, 1H), 1.62 (dd, 1H, *J* = 14.5, 4.9 Hz), 1.45−1.40 (m, 1H), 1.36 (d, 3H, *J* = 7.6 Hz), 1.34 (s, 3H), 1.24 (d, 3H, *J* = 8.9 Hz), 1.23 (s, 3H), 1.08 (t, 3H, *J* = 7.1 Hz), 1.09 (d, 3H, *J* = 6.5 Hz), 1.02 (d, 3H, *J* = 6.7 Hz), 0.85 (t, 9H, *J* = 7.8 Hz), 0.51 (q, 6H, *J* = 7.8 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 170.1, 138.8, 128.5, 127.9, 126.3, 102.5, 86.8, 85.7, 84.3, 81.4, 78.0, 73.9, 63.3, 45.3, 42.6, 36.0, 31.2, 27.0, 26.0, 25.1, 22.5, 20.5, 14.1, 13.1, 11.7, 8.1, 7.3, 6.7. IR (thin film) 3414, 2957, 2875, 1457, 1406, 1376, 1350, 1311, 1238, 1215, 1132, 1105, 1050, 1029, 1013, 974, 743, 698 (cm^{-1}). HRMS-MALDI (*m*/*z*) calcd for $[C_{34}H_{59}NO_7SiNa]^+$, 644.3953; found, 644.3945.

3,5-*O*-Benzylidene-2,4,7-trideoxy-6-*C*-((2*R*)-2-{(4*S*,5*R*)-5-[(2*R*)-2-hydroxy-1,1-dimethylbutyl]-4-methyl-4,5-dihydroisoxazol-3-yl}-propyl)-2,4-dimethyl-3,5-*O*-(1-methylethylidene)-6-*O*-(triethylsilyl)-L-*glycero*-L-*ido*-heptonic Acid (45).



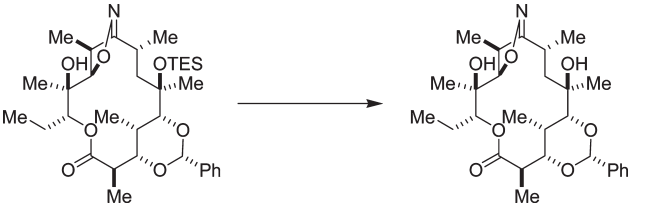
To a biphasic solution of triol **44** (220 mg, 0.35 mmol, 1.0 equiv), TEMPO (8.3 mg, 0.053 mmol, 0.15 equiv), and KBr (4.1 mg, 0.035 mmol, 0.10 equiv) in CH_2Cl_2 (4.0 mL) and pH 8.6 buffer (4.0 mL) was slowly added NaOCl (0.5 M in H_2O, 2.8 mL, 1.4 mmol, 4.0 equiv) at 0 °C. After stirring for 30 min at 0 °C, the two layers were separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The organic solution was washed with brine (10 mL), dried over Na_2SO_4, and concentrated in vacuo. The crude aldehyde was used without further purification. At 0 °C, a premixed solution of 2-methyl-2-butene (0.188 mL, 1.77 mmol, 5.00 equiv) and $NaClO_2$ (96.3 mg, 1.06 mmol, 3.00 equiv) in *t*-BuOH (9.0 mL) and pH 3.8 buffer (1.8 mL) was added to the crude aldehyde (220 mg, 0.355 mmol, 1.00 equiv). After 30 min of stirring at 0 °C, more pH 3.8 buffer (3.0 mL) was added, and the solution was extracted with EtOAc (6 × 5 mL). The organic solution was washed with brine (5 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. Purifiaction by chromatography on silica gel (hexane/EtOAc 2:1 to 2:1 + 1% HOAc) provided *seco*-acid **45** (187 mg, 83% yield over two steps) as a clear, colorless oil. R_f = 0.38 (1:1 hexane/EtOAc + 1% HOAc). $[\alpha]_D^{25.4}$ (*c* 2.650, $CHCl_3$) = −32°. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.51−7.46 (m, 2H), 7.40−7.32 (m, 3H), 5.51 (s, 1H), 4.40 (d, 1H, *J* = 9.1 Hz), 3.75 (s, 1H), 3.73 (dd, 1H, *J* = 10.0, 0.8 Hz), 3.39 (d, 1H, *J* = 9.5 Hz), 3.29−3.24 (m, 1H), 2.81−2.74 (m, 2H), 2.45 (dd, 1H, *J* = 14.7, 3.4 Hz), 1.96−1.91 (m, 1H), 1.74−1.68 (m, 1H), 1.55 (dd, 1H, *J* = 14.6, 5.0 Hz), 1.48−1.42 (m, 1H), 1.37 (d, 3H, *J* = 7.4 Hz), 1.33 (s, 3H), 1.27 (d, 3H, *J* = 6.7 Hz), 1.24 (s, 3H), 1.23 (d, 3H, *J* = 5.5 Hz), 1.09 (t, 3H, *J* = 6.1 Hz), 1.08 (d, 3H, *J* = 6.5 Hz), 0.85 (t, 9H, *J* = 8.0 Hz), 0.50 (q, 6H, *J* = 8.0 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 176.6, 169.3, 138.5, 128.7, 128.0, 126.4, 102.6, 86.7, 85.8, 82.0, 81.8, 78.2, 74.2, 45.2, 42.3, 41.4, 32.1, 26.9, 26.1, 24.9, 22.5, 20.7, 14.8, 12.9, 11.7, 8.1, 7.3, 6.7. IR (thin film) 3450, 2957, 2876, 1722, 1457, 1407, 1379, 1348, 1312, 1274, 1239, 1215, 1129, 1105, 1065, 1028, 1007, 976, 938, 912, 884, 757, 698, 668 (cm^{-1}). HRMS-MALDI (*m*/*z*) calcd for $[C_{34}H_{57}NO_8SiNa]^+$, 658.3746; found, 658.3739.

(1*R*,2*R*,4*R*,8*R*,9*R*,10*R*,13*R*,14*S*,18*S*,19*S*)-10-Ethyl-9-hydroxy-2,4,9,13,18,19-hexamethyl-16-phenyl-2-[(triethylsilyl)oxy]-7,11,15,17-tetraoxa-6-azatricyclo[12.3.1.1^{5,8}]nonadec-5-en-12-one (46).



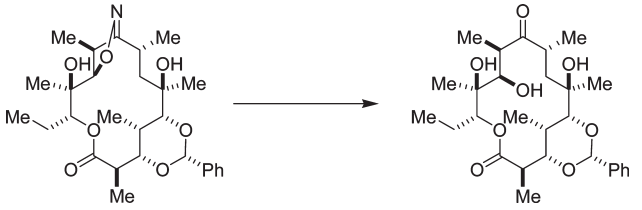
To a solution of acid **45** (136 mg, 0.214 mmol, 1.00 equiv) in THF (4.0 mL) were added NEt_3 (179 μL, 1.28 mmol, 6.00 equiv) and 2,4,6-trichlorobenzoylchloride (167 μL, 1.07 mmol, 5.00 equiv) at 0 °C. The solution turned cloudy and was stirred for 30 min. The colorless suspension was allowed to warm to rt, and toluene (12 mL) was added. This cloudy reaction mixture was added to a 50 °C solution of DMAP (261 mg, 2.14 mmol, 10.0 equiv) in toluene (24.0 mL) via syringe pump over 3 h. After addition, the stirring was maintained for another 45 min at 50 °C before the colorless suspension was filtered over a plug of silica gel (eluent hexane/EtOAc 1:1). The filtrate was concentrated under reduced pressure. Purification by chromatography on silica gel (hexane/EtOAc 10:1 to 6:1 to 3:1) provided macrolactone **46** (103 mg, 78% yield) as a colorless foam and as a mixture of two atropisomers (7:2). R_f = 0.28 and 0.37* (3:1 hexane/EtOAc, *denotes minor isomer). $[\alpha]_D^{22.6}$ (*c* 0.730, $CHCl_3$) = −49°. ^{1}H NMR (300 MHz, $CDCl_3$, *denotes minor isomer) δ: 7.53−7.46 (m, 2H), 7.39−7.30 (m, 3H), 5.58 (s, 1H), 5.43* (s, 1H), 5.03 (dd, 1H, *J* = 10.6, 2.5 Hz), 4.83* (dd, 1H, *J* = 9.0, 1.9 Hz), 4.49* (d, 1H, *J* = 9.5 Hz), 4.15 (d, 1H, *J* = 6.3 Hz), 4.10 (d, 1H, *J* = 1.4 Hz), 3.95 (dd, 1H, *J* = 8.2, 1.1 Hz), 3.90* (dd, 1H, *J* = 6.3, 1.4 Hz), 3.62* (d, 1H, *J* = 1.3 Hz), 3.60−3.50 (m, 1H), 2.91−2.82 (m, 1H), 2.79−2.69 (m, 1H), 2.17−2.05* (m, 1H), 2.04 (s, 1H), 1.93−1.80 (m, 1H), 1.81 (dd, 1H, *J* = 15.1, 7.9 Hz), 1.72−1.64* (ddd, 1H, *J* = 14.4, 7.5, 2.1 Hz), 1.65−1.45 (m, 3H), 1.41* (dd, 1H, *J* = 15.0, 1.6 Hz), 1.28 (s, 3H), 1.27 (d, 3H, *J* = 6.9 Hz), 1.22 (d, 3H, *J* = 7.0 Hz), 1.18 (s, 3H), 1.17 (d, 3H, *J* = 7.0 Hz), 1.01 (d, 3H, *J* = 6.7 Hz), 0.96 (t, 3H, *J* = 7.4 Hz), 0.85 (t, 9H, *J* = 8.0 Hz), 0.59−0.39 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$, *denotes minor isomer) δ: 175.4, 172.3, 165.3*, 138.7, 128.5, 127.8, 126.4, 102.7*, 102.5, 86.9*, 85.4, 84.9*, 84.3, 83.3*, 82.3*, 81.8, 79.1, 78.7*, 78.4, 78.2*, 72.8, 47.4, 45.4*, 43.4*, 42.0, 41.0, 34.4*, 34.2, 27.8, 27.0, 26.4*, 26.1*, 25.6*, 23.0*, 22.6*, 21.4, 21.3, 17.5, 14.0, 12.6*, 11.2*, 11.0, 10.3*, 7.8, 7.3, 6.8. IR (thin film) 3438, 2954, 2876, 1741, 1456, 1379, 1349, 1236, 1159, 1129, 1080, 1007, 972, 908, 741, 699 (cm^{-1}). HRMS-MALDI (*m*/*z*) calcd for $[C_{34}H_{55}NO_7SiNa]^+$, 640.3640; found, 640.3634.

(1*R*,2*R*,4*R*,8*R*,9*R*,10*R*,13*R*,14*S*,16*R*,18*S*,19*S*)-10-Ethyl-2,9-dihydroxy-2,4,9,13,18,19-hexamethyl-16-phenyl-7,11,15,17-tetraoxa-6-azatricyclo[12.3.1.1^{5,8}]nonadec-5-en-12-one.



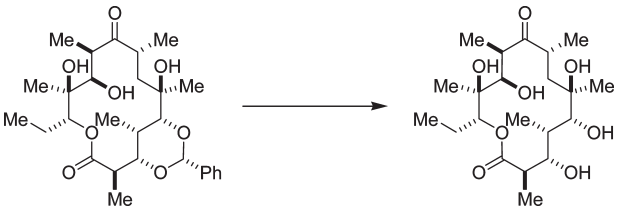
To a solution of macrolactone **46** (39 mg, 0.069 mmol, 1.0 equiv) in CH_3CN (0.50 mL) were added NEt_3 (0.050 mL) and $HF \cdot NEt_3$ (0.50 mL). The clear solution was stirred for 64 h at 30 °C. The reaction was slowly quenched with satd aq $NaHCO_3$ (5 mL) and extracted with EtOAc (5 × 5 mL). The organic solution was washed with brine (2 mL), dried over anhydrous Na_2SO_4, and concentrated in vacuo. Purification by chromatography on silica gel (hexane/EtOAc 1:1) afforded the title diol (32 mg, >99% yield) as a clear, colorless oil and as a 9:1 mixture of atropisomers. R_f = 0.24 (3:1 hexane/EtOAc). $[\alpha]_D^{29.7}$ (*c* 0.190, $CHCl_3$) = −32°. ^{1}H NMR (300 MHz, $CDCl_3$, *denotes minor isomer) δ: 7.50−7.46 (m, 2H), 7.40−7.35 (m, 3H), 5.64 (s, 1H), 5.46* (s, 1H), 4.97 (dd, 1H, *J* = 10.4, 2.7 Hz), 4.84* (dd, 1H, *J* = 11.0, 1.8 Hz), 4.51* (d, 1H, *J* = 10.2 Hz), 4.30 (s, 1H), 4.19 (d, 1H, *J* = 6.3 Hz), 4.15* (d, 1H, *J* = 6.3 Hz), 3.96 (dd, 1H, *J* = 7.3, 1.1 Hz), 3.64* (s, 1H), 3.59−3.49 (m, 1H), 2.95−2.84 (m, 1H), 2.80 (d, 1H, *J* = 1.8 Hz), 2.78−2.69 (m, 1H), 2.15−2.07* (m, 1H), 2.02 (s, 1H), 1.92−1.83 (m, 1H), 1.77 (dd, 1H, *J* = 15.6, 8.6 Hz), 1.66−1.45 (m, 3H), 1.27 (d, 3H, *J* = 6.6 Hz), 1.26 (s, 3H), 1.24 (d, 3H, *J* = 7.2 Hz), 1.2 (s, 3H), 1.19 (d, 3H, *J* = 7.2 Hz), 1.04 (d, 3H, *J* = 6.7 Hz), 0.97 (t, 3H, *J* = 7.4 Hz). ^{13}C NMR (75 MHz, $CDCl_3$, *denotes minor isomer) δ: 175.9, 172.6, 139.0*, 138.8, 129.1, 128.4, 126.5, 102.9, 85.6, 85.0*, 83.7, 83.1*, 82.2*, 81.9, 79.8, 79.4*, 75.0, 74.7*, 73.2, 73.0*, 45.5*, 44.3, 42.3, 41.0, 34.5*, 34.3, 28.0, 27.0, 26.5*, 26.1*, 25.7*, 23.1*, 22.2*, 21.8, 21.2, 17.8, 13.4, 12.8, 11.9*, 11.2, 10.7*, 10.4*, 7.8, 7.7*. IR (thin film) 3437, 2975, 2936, 2878, 1740, 1455, 1378, 1352, 1161, 1124, 1091, 1071, 1049, 1014, 980, 954, 894, 756, 700, 668 (cm^{-1}). HRMS-MALDI (*m*/*z*) calcd for $[C_{28}H_{41}NO_7Na]^+$, 526.2775; found, 526.2769.

3,5-*O*-Benzylidene erythronolide A (47).



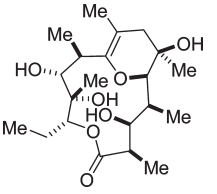
To a solution of diol from the previous experiment (15 mg, 0.030 mmol, 1.0 equiv) in EtOH (0.38 mL) was added acetic acid (8.5 μL, 0.15 mmol, 5.0 equiv) and Raney Ni (W2, spatula tip). The Schlenk flask was purged several times with H_2. The black suspension was stirred rapidly under an atmosphere of H_2 for 20 min. The black reaction mixture was filtered over Celite and eluted with CH_2Cl_2. The filtrate was concentrated in vacuo. Purification by chromatography on silica gel (hexane/EtOAc 2:1) provided **47** (14 mg, 93% yield) as a clear, colorless oil. R_f = 0.35 (1:1 hexane/EtOAc). $[\alpha]_D^{29.7}$ (*c* 0.107, $CHCl_3$) = −36°. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 7.53−7.49 (m, 2H), 7.43−7.38 (m, 3H), 5.68 (s, 1H), 4.87 (dd, 1H, *J* = 10.7, 1.8 Hz), 4.01 (d, 1H, *J* = 1.1 Hz), 3.83 (dd, 1H, *J* = 10.0, 0.8 Hz), 3.77−3.74 (m, 1H), 3.23 (d, 1H, *J* = 5.4 Hz), 3.07−3.02 (m, 1H), 2.97 (dd, 1H, *J* = 10.8, 6.5 Hz), 2.95−2.85 (m, 1H), 2.57 (s, 1H), 2.29 (s, 1H), 2.05−1.93 (m, 1H), 1.79−1.75 (m, 1H), 1.72−1.70 (m, 2H), 1.63−1.52 (m, 1H), 1.35 (d, 3H, *J* = 6.3 Hz), 1.34 (s, 3H), 1.29 (d, 3H, *J* = 6.6 Hz), 1.21 (d, 3H, *J* = 7.1 Hz), 1.18 (d, 3H, *J* = 6.6 Hz), 1.10 (s, 3H), 0.91 (t, 3H, *J* = 7.3 Hz). ^{13}C NMR (75 MHz, $CDCl_3$) δ: 215.3, 176.4, 137.7, 129.1, 128.2, 126.1, 103.3, 86.4, 84.3, 79.0, 75.3, 74.5, 70.3, 46.0, 41.7, 40.9, 38.3, 32.8, 26.8, 21.2, 18.4, 16.2, 13.6, 11.6, 11.0, 7.9. IR (thin film) 3488, 2978, 2938, 2879, 1707, 1456, 1374, 1282, 1175, 1104, 1074, 1047, 1028, 1005, 975, 907, 835, 758, 700, 667 (cm^{-1}). HRMS-MALDI (*m*/*z*) calcd for $[C_{28}H_{42}O_8Na]^+$, 529.2772; found, 529.2765.

Erythronolide A (1c).



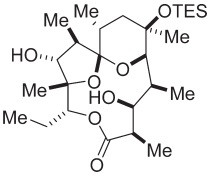
To a solution of **47** (12 mg, 0.024 mmol, 1.0 equiv) in MeOH (0.40 mL) was added $Pd(OAc)_2$ (20 mg, 0.089 mmol, 3.8 equiv) and H_2O (0.030 mL). The brown solution was purged several times with H_2 and a black precipitate appeared. After 2 h and after 4 h of stirring, more $Pd(OAc)_2$ (55 mg, 0.24 mmol, 10 equiv (×2)) were added. Formation of byproduct can be observed by TLC analysis. The black suspension was filtered over Celite with MeOH as eluent. The filtrate was concentrated under reduced pressure. Purification by chromatography on silica gel (hexane/acetone 2:1 to 3:2) provided erythronolide A (**1c**) (4.0 mg, 40% yield) as a clear, colorless solid, accompanied with **47** (3.0 mg, 25%). R_f = 0.20 (1:3 hexane/EtOAc); mp = 171−172 °C; $[\alpha]_D^{23.5}$ (*c* 0.54, CH_3OH) = −36°. ^{1}H NMR (300 MHz, CD_3OD) δ: 5.19 (dd, 1H, *J* = 11.0, 2.3 Hz), 3.86 (d, *J* = 1H, 1.5 Hz), 3.55 (d, 1H, *J* = 10.5 Hz), 3.50 (d, 1H, *J* = 3.2 Hz), 3.18−3.11 (m, 1H), 2.74−2.63 (m, 2H), 2.05−2.00 (m, 1H), 1.94−1.85 (m, 2H), 1.55−1.45 (m, 1H), 1.39 (dd, 1H, *J* = 14.7, 4.2 Hz), 1.29 (s, 3H), 1.18 (d, 3H, *J* = 7.6 Hz), 1.17 (s, 3H), 1.15 (d, 3H, *J* = 6.5 Hz), 1.12 (d, 3H, *J* = 6.6 Hz), 0.98 (d, 3H, *J* = 7.3 Hz), 0.85 (t, 3H, *J* = 7.4 Hz). ^{13}C NMR (75 MHz, CD_3OD) δ: 220.1, 176.1, 81.1, 78.7, 77.0, 75.1, 74.3, 69.5, 44.0, 43.9, 39.8, 38.1, 36.3, 25.1, 21.3, 17.1, 16.2, 14.5, 10.9, 9.5, 6.9. IR (thin film) 3466, 2973, 2937, 2879, 1712, 1456, 1376, 1348, 1267, 1181, 1083, 1035, 980, 957, 912, 737, 704 (cm^{-1}). HRMS-MALDI (*m*/*z*) calcd for $[C_{21}H_{38}O_8Na]^+$, 441.2459; found, 441.2452.

Erythronolide A Enol Ether (48a).



^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.04 (dd, 1H, *J* = 11.0, 2.2 Hz), 3.69−3.63 (m, 3H), 3.02 (s(br), 1H), 2.91−2.66 (m, 2H), 2.78 (d, 1H, *J* = 15.9 Hz), 2.15 (d, 1H, *J* = 15.8 Hz), 1.99−1.65 (m, 5H), 1.59−1.49 (m, 1H), 1.55 (s, 3H), 1.40 (s, 3H), 1.23 (d, 3H, *J* = 6.7 Hz), 1.09 (s, 3H), 1.06 (d, 3H, *J* = 7.3 Hz), 0.96 (d, 3H, *J* = 7.0 Hz), 0.86 (t, 3H, *J* = 7.4 Hz). ^{13}C NMR (75 MHz, CD_3OD) δ: 175.4, 151.0, 102.1, 83.5, 82.3, 82.2, 78.5, 75.4, 70.3, 43.7, 42.2, 34.9, 30.5, 28.4, 21.4, 16.3, 15.2, 14 0.1, 12.0, 10.7, 6.2.

Erythronolide A Ketal (49b).



R_f = 0.23 (1:3 hexane/EtOAc). $[\alpha]_D^{23.1}$ (*c* 0.15, CH_3OH) = +7.4°. ^{1}H NMR (300 MHz, $CDCl_3$) δ: 5.06 (dd, 1H, *J* = 11.8, 3.7 Hz), 3.69 (d, 1H, *J* = 9.6 Hz), 3.49 (dd, 1H, *J* = 11.7, 9.8 Hz), 3.42 (s, 1H), 2.85−2.75 (m, 1H), 2.49−2.39 (m, 1H), 2.31−2.18 (m, 1H), 2.09−2.02 (m, 2H), 1.94−1.81 (m, 1H), 1.78−1.70

(m, 1H), 1.62 (dd, 1H, J = 14.4, 3.7 Hz), 1.40 (d, 3H, J = 6.7 Hz), 1.38 (d, 3H, J = 7.3 Hz), 1.32 (s, 3H), 1.25 (s, 3H), 1.24 (d, 3H, J = 7.5 Hz), 1.19 (s, 3H), 0.94 (t, 9H, J = 7.5 Hz), 0.87 (t, 3H, J = 7.4 Hz), 0.59 (q, 6H, J = 7.7 Hz). ^{13}C NMR (75 MHz, CD_3OD) δ: 173.1, 107.9, 89.2, 83.0, 82.2, 79.3, 77.6, 73.4, 50.5, 45.3, 43.5, 42.8, 34.5, 29.7, 27.3, 25.1, 24.1, 18.4, 16.3, 15.2, 14.6, 10.6, 7.1, 6.7. IR (thin film) 3454, 2925, 2877, 1714, 1461, 1382, 1305, 1239, 1184, 1122, 1056, 1000, 745, 723 (cm^{-1}). HRMS-MALDI (m/z) calcd for $[C_{27}H_{50}O_7SiNa]^+$, 537.3218; found,

Acknowledgment. ETH, SNF, Aventis, Eli Lilly, Merck, and F. Hoffmann-LaRoche are acknowledged for their generous support of our research program. Mr. Jeffrey W. Bode and Ms. Nina Lohse-Fräfel are gratefully acknowledged for their support and numerous fruitful discussions and suggestions. Prof. Bernhard Jaun and Dr. Damien Jeannerat are gratefully acknowledged for analytical support.

Supporting Information Available: Experimental procedures and spectral data for all relevant compounds. This material is available free of charge via the Internet at http://pubs.acs.org.