Highly Diastereoselective Synthesis of Pederic Acid Derivatives

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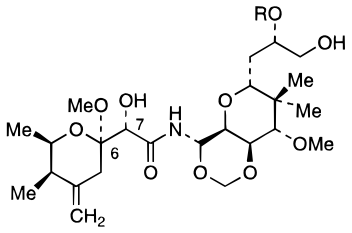
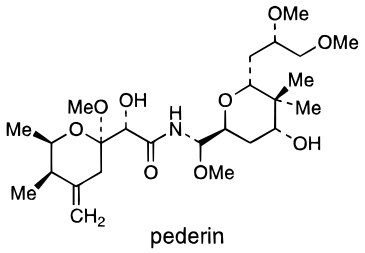
A highly diastereoselective synthesis of methyl pederate (**2**) is described. A critical feature of the successful route is the introduction of the key C(7)-stereocenter at the stage of **4** via an enantioselective, syn-selective aldol reaction of aldehyde **5** and the chiral acyl oxazolidinone **6**. Aldehyde **5**, in turn, was prepared from the readily available aldol derivative **7** via a chelate-controlled reaction with allyltrimethylsilane. Intermediate **4** was elaborated to **2** via the intermediacy of 7-*O*-(3,4-dimethoxybenzyl)pederic acid (**3**), an intermediate in Kishi's syntheses of mycalamides A and B and onnamide A, by way of methyl pyranoside **10** and the fully protected pederic acid derivative **11**.

Mycalamides A and B are a pair of potent antiviral and antitumor agents isolated from a marine sponge of the *Mycale* genus found in Otago Harbor, New Zealand.[1,2] These compounds are sub-nanomolar inhibitors of protein and DNA synthesis and, in addition to their promising antiviral and antitumor activity,[3,4] are reported also to have immunosuppressive activity via inhibition of T-cell activation.[5] As a result, the mycalamides have attracted considerable attention as targets for total synthesis. Kishi reported pioneering total syntheses of mycalamides A and B, as well as of the structurally related marine sponge metabolite onnamide A,[6,7] while Nakata has completed a formal total synthesis of mycalamide A by converging with one of Kishi's advanced mycalamine intermediates.[8−10] In addition, studies on the synthesis of the mycalamides have been reported from the laboratories of Kocienski[11] and Hoffmann[12,13] and our own laboratory.[14,15] Very recently, a total synthesis of 10-*O*-methylmycalamide B was reported by Kocienski.[16]

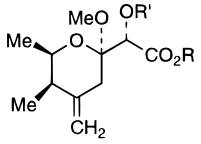
In connection with our ongoing studies on the synthesis of the mycalamides, we required a readily accessible source of a suitably protected derivative of pederic acid, **1**. Owing to the occurrence of pederic acid as a subunit of the powerful insect vesicant pederin,[17] several syntheses of derivatives of **1** have been recorded.[13,18−23] However, none of these prior syntheses was deemed suitable for our purposes: several are quite lengthy, while others require use of expensive (*R*,*R*)-2,3-epoxybutane[24] as starting material for the synthesis of the naturally occurring enantiomer of **1**. We therefore have developed and report herein an enantioselective and highly diastereoselective synthesis of methyl pederate (**2**) that proceeds by way of 7-*O*-(3,4-dimethoxybenzyl)pederic acid (**3**), an intermediate in Kishi's syntheses of mycalamides A, B and onnamide A.[6,7]



mycalamide A (R = H)
mycalamide B (R = Me)



pederin



1, R = R' = H
2, R = Me, R' = H
3, R = H, R' = DMPM

In all but one of the previous syntheses of pederic acid derivatives,[13] the C(6)−C(7) bond was constructed without control of the critical C(7)−(S) hydroxyl stereocenter. This necessitated that several additional manipulations

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(9) Nakata, T.; Fukui, H.; Nakagawa, T.; Matsukura, H. *Heterocycles* **1996**, *42*, 159.
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(11) Davis, J.; Kocienski, P. J.; Boyle, T. *Pol. J. Chem.* **1994**, *68*, 2249.
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(17) Frank, J. H.; Kanamitsu, K. *J. Med. Entomol.* **1987**, *24*, 67 and references cited therein.
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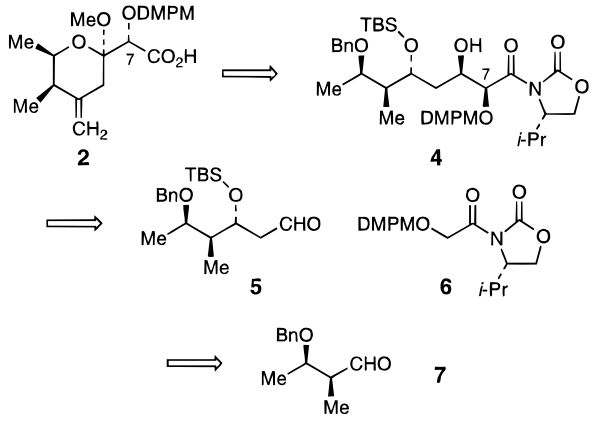
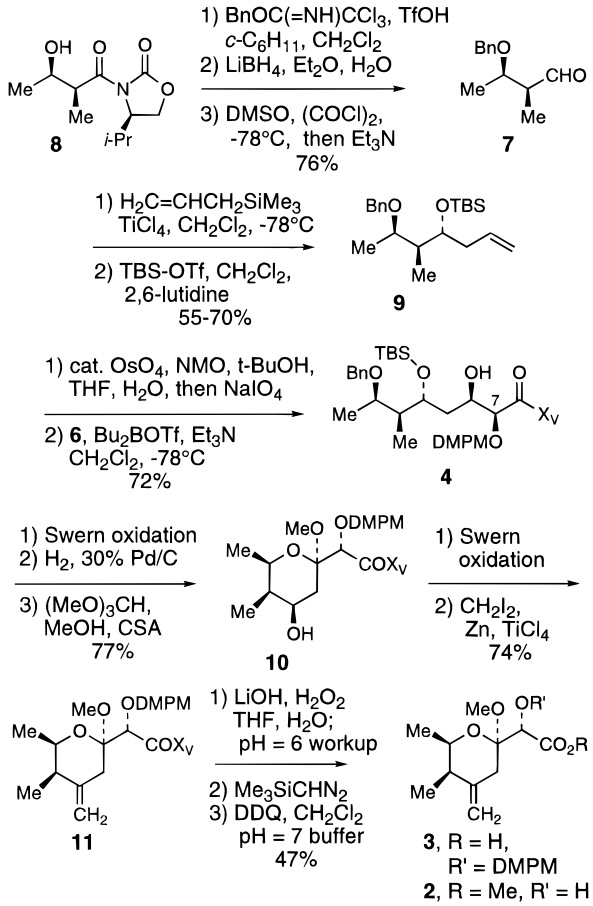
be performed to establish the correct C(7) stereochemistry via reduction of the corresponding ketone.[13,18−23] The plan that we have successfully reduced to practice involves introduction of the C(7)−(S) stereocenter at the stage of **4** via a syn-selective, enantioselective aldol reaction of aldehyde **5** and the chiral acyloxazolidinone **6**.[25,26] Aldehyde **5**, in turn, was prepared from the readily available aldol derivative **7**. Although the C(4)-(*R*)-stereocenter of **4** has no long-term significance to this synthesis, we anticipated that this center could influence the stereoselectivity of the subsequent methyl hemiketalization step (cf., **4** → **10**). Consequently, we elected to use an alkyl ether protecting group in **7** to facilitate control of the 1,3-anti diol relationship in **5** via a chelate-controlled reaction of **7** with allyltrimethylsilane.[27,28]



Aldehyde **7** was synthesized in 76% yield from syn aldol **8**[21,29] by a three-step sequence involving treatment of **8** with benzyl trichloroacetimidate and catalytic triflic acid in cyclohexane−CH_2Cl_2 (87%),[30] reduction of the imide with $LiBH_4$ in wet Et_2O (92%),[31] and oxidation of the resulting primary alcohol via the usual Swern protocol (DMSO, $(COCl)_2$, CH_2Cl_2, −78 °C, then Et_3N; 95% yield).[32] Treatment of **7** with allyltrimethylsilane and $TiCl_4$ in CH_2Cl_2 at −78 °C provided the desired 4(*R*)-homoallylic alcohol with >15:1 selectivity (58−74%),[27,28] which was treated with *tert*-butyldimethylsilyl triflate under standard conditions to give TBS ether **9** in 94% yield. Cleavage of the vinyl group of **9** via a one-pot OsO_4−$NaIO_4$ oxidation[33] (91%) then set the stage for a highly diastereoselective aldol reaction with the enol borane prepared from the chiral glycolate imide **6** and Bu_2BOTf, which provided the syn aldol **4** in 72% yield for the two steps.[25,26,34]

The next stage of the synthesis took advantage of the well-established low kinetic acidity of β-keto imides.[29] Thus, oxidation of **4** by the Swern protocol[32] provided the corresponding β-keto imide (98% based on recovered **4**). The C(2)-benzyl ether was then selectively removed by hydrogenation over 30% Pd/C in MeOH.[35] The resulting hemiacetal was treated with trimethyl orthoformate and 0.05 equiv of camphorsulfonic acid (CSA) in MeOH overnight,[36] which provided **10** in 77% overall yield from **4**. Oxidation of **10** by the Swern protocol[32] (92%) then set the stage for introduction of the exo methylene unit by using the Takai−Nozaki protocol (CH_2I_2, $TiCl_4$, Zn, THF, 86% yield).[37] Finally, hydrolysis of the chiral imide by using LiOH and H_2O_2 in THF−H_2O (pH = 6 work-up)[38,39] provided the very acid-sensitive pederic acid derivative **3** (82% yield), the ^{1}H NMR spectrum of which was in excellent agreement with data kindly provided by Prof. Kishi.[6] For further proof of stereostructure, acid **3** was converted to the corresponding methyl ester by treatment with Me_3SiCHN_2,[40] and then the DMPM ether was removed by treatment with DDQ in an 18:1 mixture of CH_2Cl_2 and pH = 7 phosphate buffer.[6,35] This provided methyl (+)-pederate **2** ($[\alpha]^{23}_D$ +115° (c = 0.3, CH_2Cl_2)), the stereostructure of which was unambiguously assigned by comparison of the ^{1}H NMR data with literature values.[18]



In summary, a highly diastereoselective synthesis of pederic acid derivative **3**, an intermediate in Kishi's

(21) Nakata, T.; Nagao, S.; Oishi, T. *Tetrahedron Lett.* **1985**, *26*, 6465.
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(23) Kocienski, P.; Jarowicki, K.; Marczak, S. *Synthesis* **1991**, 1191.
(24) (*R*,*R*)-2,3-Epoxybutane ($120/g from Acros Organics) can be synthesized in two steps from (*R*,*R*)-2,3-butanediol ($20/g, Aldrich) or in seven steps from dimethyl (*S*,*S*)-tartrate: Byrstrom, S.; Hogberg, H. E.; Norin, T. *Tetrahedron* **1981**, *37*, 2249.
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(27) Heathcock, C. H.; Kiyooka, S.-i.; Blumenkopf, T. A. *J. Org. Chem.* **1984**, 4214.
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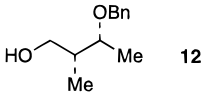
(29) Evans, D. A.; Ennis, M. D.; Le, T.; Mandel, N.; Mandel, G. *J. Am. Chem. Soc.* **1984**, *106*, 1154.
(30) Widmer, U. *Synthesis* **1987**, 568.
(31) Penning, T. D.; Djuric, S. W.; Haack, R. A.; Kalish, V. J.; Miyashiro, J. M.; Rowell, B. W.; Yu, S. S. *Synth. Commun.* **1990**, *20*, 307.
(32) Mancusco, A. J.; Swern, D. *Synthesis* **1981**, 165.
(33) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483 and references cited therein.
(34) Chiral glycolate imide **6** was prepared in 80% yield from (3,4-dimethoxybenzyl)glycolic acid by using the procedure described for the synthesis of the corresponding (*p*-methoxybenzyl)glycolate-derived imide: Evans, D. A.; Kaldor, S. W.; Jones, T. K.; Clardy, J.; Stout, T. J. *J. Am. Chem. Soc.* **1990**, *112*, 7001

mycalamide and onnamide syntheses,[6,7] has been achieved. Further progress on our total synthesis of the mycalamides will be reported in due course.

Experimental Section[41]



12

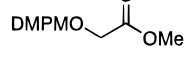
(2*R*,3*R*)-3-(Benzyloxy)-2-methyl-1-butanol (12). To a solution of aldol **8**[21] (7.30 g, 31.9 mmol) in a mixture of cyclohexane (42 mL) and CH_2Cl_2 (21 mL) was added benzyl trichloroacetimidate (10.5 g, 41.4 mmol) followed by triflic acid (0.422 mL). The mixture was stirred for 1 h and then filtered through Celite. The solution was poured into saturated aqueous $NaHCO_3$ (100 mL), and the aqueous layer was extracted with EtOAc (2 × 100 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification of the crude product by flash chromatography (silica gel, 3:1 hexanes−EtOAc) yielded the desired benzyl ether (8.82 g , 87%) as a clear oil: $[\alpha]^{23}_D$ −43° (*c* 0.6, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 (m, 5 H), 4.76 (A of AB, J_{AB} = 11.6 Hz, 1 H), 4.49 (m, 1 H), 4.45 (B of AB, J_{AB} = 12.0 Hz, 1 H), 4.26 (dd, *J* = 9.2, 8.8 Hz, 1 H), 4.18 (dd, *J* = 8.8, 2.8 Hz, 1 H), 4.02 (dq, *J* = 7.2, 7.2 Hz, 1 H), 3.89 (dq, *J* = 5.6, 5.6 Hz, 1 H), 2.29 (m, 1 H), 1.27 (d, *J* = 6.4 Hz, 3 H), 1.23 (d, *J* = 6.4 Hz, 3 H), 0.88 (d, *J* = 7.2 Hz, 3 H), 0.80 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1, 153.8, 138.7, 128.2, 127.3, 76.5, 70.8, 62.9, 58.3, 43.0, 28.3, 17.9, 17.3, 14.5, 12.0; IR ($CDCl_3$) 1776, 1697 cm^{-1}; HRMS for $C_{18}H_{26}O_4N$ (M^+ + H) calcd 320.1855, found 320.1865.

To a 0 °C solution of the above benzyl ether (8.82 g, 27.7 mmol) in Et_2O (553 mL) was added H_2O (0.647 mL) followed by $LiBH_4$ (2 M in THF, 17.9 mL, 35.9 mmol). The solution was stirred at 0 °C for 1 h and then at 23 °C for 1 h. NaOH (1 N, 300 mL) was added dropwise, and the solution was stirred at 23 °C for 1 h. The organic layer was removed, and the aqueous layer was extracted with EtOAc (3 × 200 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification of the crude product by flash chromatography (silica gel, 9:1 to 1:1 hexanes−EtOAc) yielded the desired alcohol **12** (4.95 g, 92%) as a clear, volatile oil: $[\alpha]^{23}_D$ −32° (*c* = 2.4, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.1−7.3 (m, 5 H), 4.55 (A of AB, J_{AB} = 11.6 Hz, 1 H), 4.39 (B of AB, J_{AB} = 12.0 Hz, 1 H), 3.62−3.66 (m, 2 H), 3.49 (dd, *J* = 11.2, 4.4 Hz, 1 H), 2.27 (s(br), 1 H), 1.94 (m, 1 H), 1.14 (d, *J* = 6.0 Hz, 3 H), 0.82 (d, *J* = 7.2 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.4, 128.4, 127.6, 77.8, 70.6, 65.7, 39.2, 14.9, 11.9; IR ($CDCl_3$) 3499 cm^{-1}; HRMS for $C_{12}H_{18}O_2$ (M^+ + H) calcd 195.1380, found 195.1385.

(4*R*,5*S*,6*R*)-6-(Benzyloxy)-4-(*tert*-butyldimethylsiloxy)-5-methyl-1-heptene (9). To a −78 °C solution of $(COCl)_2$ (3.35 g, 2.3 mL, 26.4 mmol) in CH_2Cl_2 (96 mL) was added DMSO (3.74 mL). The solution was warmed to −40 °C for 15 min and then was recooled to −78 °C.[32] To this solution was added dropwise a solution of alcohol **12** (4.66 g, 24.0 mmol) in CH_2Cl_2 (10 mL) followed by Et_3N (16.7 mL, 120 mmol). The reaction mixture was allowed to warm to 0 °C and then poured into saturated aqueous $NaHCO_3$ solution (150 mL). The organic layer was washed with $NaHSO_4$ (75 mL) and $NaHCO_3$ (2 × 75 mL) and then dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification of the crude product by flash chromatography (silica gel, 9:1 to 3:1 hexanes−EtOAc) yielded aldehyde **7** (4.36 g, 95%) as a clear oil. This sensitive intermediate was used directly in the next step without further purification.

To a −78 °C solution of aldehyde **7** (4.36 g, 22.7 mmol) in CH_2Cl_2 (18.4 mL) was added $TiCl_4$ (1.0 M in CH_2Cl_2, 27.2 mL, 27.2 mmol) followed immediately by allyltrimethylsilane (4.69 mL, 29.5 mmol). The reaction mixture was stirred at −78 °C for 16 h and then quenched by addition of saturated NaOMe−MeOH solution (5 mL). The reaction mixture was diluted with CH_2Cl_2 (100 mL) and poured into saturated NH_4Cl solution (200 mL). The aqueous layer was separated and extracted with CH_2Cl_2 (2 × 150 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification of the crude product by flash chromatography (silica gel, 9:1 to 3:1 hexanes−EtOAc) yielded the desired homoallylic alcohol (3.09 g, 13.2 mmol, 58%)[42] as a clear oil: $[\alpha]^{23}_D$ −32° (*c* = 1.4, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (m, 5 H), 5.86−5.98 (m, 1 H), 5.08−5.13 (m, 2 H), 4.61 (A of AB, J_{AB} = 12.0 Hz, 1 H), 4.49 (B of AB, J_{AB} = 11.6 Hz, 1 H), 3.83 (dq, *J* = 7.6, 6.6 Hz, 1 H), 3.71 (dt, *J* = 7.6, 4.0 Hz, 1 H), 3.5 (s(br), 1 H), 2.31−2.38 (m, 1 H), 2.12−2.21 (m, 1 H), 1.82 (ddq, *J* = 7.6, 7.6, 4.0 Hz, 1 H), 1.23 (d, *J* = 6.4 Hz, 3 H), 0.89 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.1, 135.2, 128.3, 127.6, 116.8, 77.4, 72.7, 70.5, 40.9, 39.6, 15.0, 12.3; IR ($CDCl_3$) 3478, 3054, 2984 cm^{-1}; HRMS for $C_{15}H_{23}O_2$ (M^+ + H) calcd 235.1691, found 235.1690. Anal. Calcd for $C_{15}H_{22}O_2$: C, 76.88; H, 9.46. Found: C, 77.57; H, 9.46.

To a solution of the homoallylic alcohol from the preceding experiment (3.09 g, 13.2 mmol) in CH_2Cl_2 (27 mL) at −78 °C was added 2,6-lutidine (3.09 mL, 26.5 mmol) followed by TBSOTf (3.95 mL, 17.2 mmol). The solution was stirred for 30 min at −78 °C, warmed to 0 °C for 30 min, and then diluted with CH_2Cl_2 (100 mL) and poured into saturated $NaHCO_3$ (100 mL). The aqueous layer was separated and extracted with EtOAc (2 × 100 mL). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification of the crude reaction mixture by flash chromatography (silica gel, 95 : 5 hexanes−EtOAc) yielded TBS ether **9** (4.32 g, 94%) as a clear oil: $[\alpha]^{23}_D$ −25° (*c* = 1.6, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 (m, 5 H), 5.82−5.94 (m, 1 H), 5.02−5.08 (m, 2 H), 4.60 (A of AB, J_{AB} = 11.6 Hz, 1 H), 4.38 (B of AB, J_{AB} = 11.6 Hz, 1 H), 3.81 (q, *J* = 6.0 Hz, 1 H), 3.64 (dq, *J* = 5.4, 1.2 Hz, 1 H), 2.16−2.28 (m, 2 H), 1.58−1.68 (m, 1 H), 1.20 (d, *J* = 6.4 Hz, 3 H), 0.94 (d, *J* = 6.4 Hz, 3 H), 0.89 (s, 9 H), 0.044 (s, 3 H), 0.023 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.3, 135.6, 128.2, 127.3, 127.2, 116.5, 75.4, 72.9, 70.4, 45.2, 37.6, 25.9, 17.6, 9.4, −4.2, −4.6; IR ($CDCl_3$) 3054, 2962, 2892, 2856, 1422, 1278, 1249, 1052 cm^{-1}; HRMS for $C_{17}H_{27}O_2Si$ (M^+ − ^{t}Bu) calcd 291.1773, found 291.1772. Anal. Calcd for $C_{21}H_{36}O_2Si$: C, 72.46; H, 10.40. Found: C, 70.46; H, 10.42.



13

Methyl [3,4-Dimethoxybenzyl)oxy]acetate (13). A mixture of (3,4-dimethoxyphenyl)methyl 2,2,2-trichloroacetimidate[43] (8.00 g, 2.57 mmol), methyl glycolate (2.10 g, 23.4 mmol), and pyridinium *p*-toluenesulfonate (0.294 g, 1.17 mmol) in CH_2Cl_2 (46 mL) was stirred for 36 h. The solution was concentrated in vacuo and filtered to give a yellow oil. Purification of the crude product by flash chromatography (silica gel, 50% hexanes−EtOAc) afforded DMPM ether **13** (5.49 g, 98%) as a white solid: m.p. 60−61 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93 (d, *J* = 2.0 Hz, 1 H), 6.88 (dd, *J* = 2.0, 8.0 Hz, 1 H), 6.82 (d, *J* = 8.0 Hz, 1 H), 4.56 (s, 2 H), 4.08 (s, 2 H), 3.88 (s, 3 H), 3.86 (s, 3 H), 3.75 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 149.0, 148.8, 129.4, 120.7, 111.3, 110.8, 73.1,

(35) Horita, K.; Yoshioka, T.; Tanaka, T.; Oikawa, Y.; Yonemitsu, O. *Tetrahedron* **1986**, *42*, 3021.

(36) Formation of the methyl hemiketal is fast under these conditions (<1 h). Cleavage of the TBS ether requires the overnight reaction period.

(37) Hibino, J.; Okazoe, T.; Takai, K.; Nozaki, H. *Tetrahedron Lett.* **1985**, *26*, 5579.

(38) Evans, D. A.; Britton, T. C.; Ellman, J. A. *Tetrahedron Lett.* **1987**, *28*, 6141.

(39) Use of a pH = 6 aqueous phase is critical to the success of this experiment. Substantial decomposition of **3** occurred in experiments in which the pH of the aqueous phase was not carefully controlled.

(40) Aoyama, T.; Shioiri, T. *Chem. Pharm. Bull.* **1981**, *29*, 3249.

(41) For general experimental details, see: Roush, W. R.; Hunt, J. A. *J. Org. Chem.* **1995**, *60*, 798. Unless otherwise noted, all compounds purified by chromatography are sufficiently pure (>95% by ^{1}H NMR analysis) for use in subsequent reactions.

(42) The yield of the homoallylic alcohol was 74% when the allylation was performed on a 1 g (5 mmol) scale.

(43) Wessel, H.-P.; Iversen, T.; Bundle, D. R. *J. Chem. Soc., Perkin Trans. 1* **1985**, 2247.

66.7, 55.8, 55.7, 51.7; IR ($CDCl_3$) 3010, 1755, 1610 cm^{-1}; HRMS calcd for $C_{12}H_{16}O_5$ (M^+) 240.0993, found 240.1002. Anal. Calcd for $C_{12}H_{16}O_5$ C, 59.99; H, 6.71. Found: C, 59.75; H, 6.74.

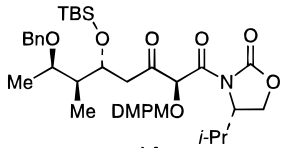
3-[[(3,4-Dimethoxybenzyl)oxy)acetyl]-4(*S*)-isopropyloxazolidin-2-one (6). To a solution of methyl ester **13** (5.49 g, 22.9 mmol) in a solution of THF/H_2O (60 mL, 60 mL) was added NaOH (2.75 g, 69 mmol). The solution was stirred for 30 min, and then a solution of Et_2O:hexanes (5 mL:50 mL) was added and the layers were separated. The aqueous layer was acidified to pH = 4 with 1 N HCl and extracted with EtOAc (2 × 50 mL). The aqueous layer was further acidified to pH = 2 and extracted with EtOAc (2 × 50 mL). The combined organic extracts were washed with H_2O (2 × 75 mL) and brine (50 mL), dried (Na_2SO_4), and concentrated in vacuo. The resulting acid (4.96 g, 96%) was dried by concentration from benzene (2 × 10 mL) to remove residual H_2O and then used directly in the next step. ^1H NMR (400 MHz, $CDCl_3$) data for carboxylic acid: δ 6.83−6.92 (m, 3 H), 4.59 (s, 2 H), 4.12 (s, 2 H), 3.89 (s, 3 H), 3.88 (s, 3 H).

To a −78 °C solution of the above carboxylic acid (6.45 g, 28.5 mmol) in THF (50 mL) was added *n*-BuLi (2.47 M in hexanes, 12.3 mL, 30.4 mmol). The solution was stirred for 10 min, and then oxalyl chloride (2.49 mL, 28.5 mmol) was added dropwise. The solution was warmed to 23 °C and stirred for 1 h. The resulting solution of the acid chloride was used immediately in the following step.

To a −78 °C solution of 4(*S*)-isopropyloxazolidinone[25] (3.49 g, 27.0 mmol) in THF (40 mL) was added *n*-BuLi (10.9 mL, 27.0 mmol) dropwise. The resulting heterogeneous solution was stirred for 20 min, at which time the acid chloride (see preceding paragraph) was added. The solution was stirred for 15 min and then warmed to 0 °C and quenched with saturated aqueous NH_4Cl (50 mL). The solution was extracted with EtOAc (3 × 50 mL), and the combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification of the crude reaction mixture by flash chromatography (silica gel, 1:1 hexanes−EtOAc) afforded imide **6** (5.65 g, 62%) as a clear oil: $[\alpha]^{25}_D$ +58.6°; ^1H NMR (400 MHz, $CDCl_3$) δ 6.97 (d, J = 2.0 Hz, 1 H), 6.91 (dd, J = 2.0, 8.0 Hz, 1 H), 6.83 (d, J = 8.0 Hz, 1 H), 4.67 (s, 2 H), 4.60 (s, 2 H), 4.44 (m, 1 H), 4.33 (dd, J = 9.2, 8.0 Hz, 1 H), 4.25 (dd, J = 3.2, 9.2 Hz, 1 H), 3.89 (s, 3 H), 3.87 (s, 3 H), 2.43 (m, 1 H), 0.93 (d, J = 6.8 Hz, 3 H), 0.87 (d, J = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.1, 153.9, 149.1, 148.9, 129.7, 120.8, 111.4, 110.9, 73.4, 69.3, 64.4, 58.2, 55.9, 55.8, 28.2, 17.8, 14.6; IR ($CDCl_3$) 3015, 1780, 1720, 1610, 1595; HRMS calcd for $C_{17}H_{23}NO_6$ (M^+) 337.1519, found 337.1542. Anal. Calcd for $C_{17}H_{23}NO_6$: C, 60.52; H, 6.87; N, 4.15. Found: C, 60.42; H, 6.94; N, 4.01.

(4*S*)-[(2*S*,3*R*,5*R*,6*S*,7*R*)-7-(Benzyloxy)-5-(*tert*-butyldimethylsiloxy)-3-hydroxy-2-[(3,4-dimethoxybenzyl)oxy]-6-methyloctanoyl]-4-isopropyl-2-oxazolidinone (4). To a solution of TBS ether **9** (1.39 g, 3.97 mmol) in *t*-BuOH (14.3 mL), THF (4.3 mL), and H_2O (1.4 mL) was added 4-methylmorpholine *N*-oxide (0.56 g, 4.77 mmol) followed by OsO_4 (0.1 M in toluene, 2.0 mL, 0.2 mmol). The solution was stirred for 1.5 h, at which time additional H_2O (6.5 mL) was added followed by $NaIO_4$ (2.54 g, 11.9 mmol). After being stirred for an additional 30 min, the reaction mixture was diluted with saturated aqueous Na_2SO_3 (25 mL). The resulting mixture was stirred for 1 h and then extracted with Et_2O (3 × 30 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4), and concentrated in vacuo. Purification of the crude reaction mixture by flash chromatography (silica gel, 9:1 hexanes−EtOAc) afforded the intermediate aldehyde (1.27 g, 91%) as a clear oil, which was stored at −78 °C until it used in the subsequent aldol reaction.

To a −78 °C solution of Bu_2BOTf (1.15 mL, 4.60 mmol) in CH_2Cl_2 (4.6 mL) was added Et_3N (0.66 mL, 4.82 mmol) dropwise with stirring. After 1 min, a solution of chiral imide **6** (1.48 g, 4.38 mmol) in CH_2Cl_2 (7.7 mL) was added dropwise. The resulting yellow solution was stirred at −78 °C for 3 h and then warmed to 0 °C and stirred for an additional 30 min to ensure complete enolization. The resulting light brown solution was recooled to −78 °C, and then a solution of aldehyde from the preceding experiment (0.77 g, 2.19 mmol) in CH_2Cl_2 (3.4 mL) was added. The solution was stirred for 3 h and then warmed to 0 °C and stirred for an additional 30 min. MeOH (15 mL), pH = 7 buffer solution (20 mL), and 30% H_2O_2 (4 mL) were then added sequentially, and the solution was warmed to 23 °C and stirred for 1 h. The aqueous layer was then removed and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuo. Purification of the crude product by flash chromatography (silica gel, 2:1 hexanes−EtOAc) afforded aldol **4** (1.19 g, 79%) as a white foam: $[\alpha]^{23}_D$ +8° (c = 1.3, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.33 (m , 5 H), 6.70−6.90 (m, 3 H), 5.15 (d, J = 3.2 Hz, 1 H), 4.58 (A of AB, J_{AB} = 11.6 Hz, 1 H), 4.58 (A′ of AB, $J_{A'B'}$ = 11.6 Hz, 1 H), 4.46 (B of AB, J_{AB} = 12.0 Hz, 1 H), 4.39 (br q, J = 4.4 Hz, 1 H), 4.35 (B′ of AB, $J_{A'B'}$ = 12.0 Hz, 1 H), 4.21 (d, J = 4.8 Hz, 1 H), 4.02−4.09 (m, 2 H), 3.84−3.87 (m, 1 H), 3.86 (s, 3 H), 3.84 (s, 3 H), 3.40 (dq, J = 6.2, 6.0 Hz, 1 H), 2.42 (s (br), 1 H), 2.37 (m, 1 H), 1.76 (q, J = 5.6 Hz, 1 H), 1.69 (ddd, J = 14.2, 10.8, 2.0 Hz, 1 H), 1.53 (ddd, J = 14.0, 8.8, 2.0 Hz, 1 H), 1.11 (d, J = 6.0 Hz, 3 H), 0.96 (d, J = 7.2 Hz, 3 H), 0.91 (d, J = 6.0 Hz, 3 H), 0.86 (s, 9 H), 0.80 (d, J = 7.2 Hz, 3 H), 0.038 (s, 3 H), 0.025 (s, 3 H); ^{13}C (100 MHz, $CDCl_3$) δ 170.7, 153.7, 148.9, 138.9,129.5, 128.2, 127.5, 127.3, 121.1, 111.7, 110.6, 79.3, 76.4, 73.0, 70.5, 70.1, 69.2, 63.9, 59.0, 55.8, 45.5, 35.5, 28.4, 25.8, 18.0, 14.4, 9.3, −4.6, −4.7; IR ($CDCl_3$) 3569, 2961, 1780, 1709 cm^{-1}; FAB for $C_{37}H_{57}O_9SiNNa$ (M^+ + Na) calcd 710, found 710. Anal. Calcd for $C_{37}H_{57}O_9SiN$: C, 64.59; H, 8.35; N, 2.03. Found: C, 64.44; H, 7.83; N, 1.94.



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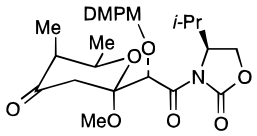
(4*S*)-[(2*S*,5*R*,6*S*,7*R*)-7-(Benzyloxy)-5-(*tert*-butyldimethylsiloxy)-3-oxo-2-[(3,4-dimethoxybenzyl)oxy]-6-methyloctanoyl]-4-isopropyl-2-oxazolidinone (14). To a solution of $(COCl)_2$ (0.188 mL, 2.16 mmol) in CH_2Cl_2 (20 mL) at −78 °C was added DMSO (0.306 mL, 4.32 mmol). The solution was warmed to −40 °C for 15 min and recooled to −78 °C, and then a solution of alcohol **4** (1.35 g, 1.96 mmol) in CH_2Cl_2 (5 mL) was added dropwise followed by Et_3N (1.37 mL, 9.83 mmol). The reaction mixture was allowed to warm to 0 °C and poured into saturated aqueous $NaHCO_3$ solution (100 mL). The organic layer was washed with aqueous $NaHSO_4$ (25 mL) and aqueous $NaHCO_3$ (2 × 25 mL) and then dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification of the crude product by flash chromatography (silica gel, 9:1 to 3:1 hexanes−EtOAc) yielded recovered alcohol **4** (300 mg, 22%) and the desired β-keto imide **14** (1.03 g, 77%; >98% based on recovered **4**) as a clear oil: $[\alpha]^{23}_D$ +22° (c = 2.1, CH_2Cl_2); ^1H NMR (400 MHz, $CDCl_3$) δ 7.32 (m , 5 H), 6.70−6.90 (m, 3 H), 5.46 (s(br), 1 H), 4.64 (A of AB, J_{AB} = 11.6, 1 H), 4.59 (B of AB, J_{AB} = 11.6, 1 H), 4.54 (A′ of AB′, $J_{A'B'}$ = 11.6, 1 H), 4.34 (B′ of A′B′, $J_{A'B'}$ = 11.6 Hz, 1 H), 4.30 (m, 2 H), 4.26 (t, J = 8.4 Hz, 1 H), 4.18 (dd, J = 8.8, 2.4 Hz, 1 H), 3.87 (s, 3 H), 3.84 (s, 3 H), 3.34 (dq, J = 6.0, 6.0 Hz, 1 H), 2.75−2.90 (m, 2 H), 2.31 (m, 1 H), 1.73 (m, 1 H), 1.18 (d, J = 6.4 Hz, 3 H), 0.909 (d, J = 6.8 Hz, 3 H), 0.89 (d, J = 6.8 Hz, 3 H), 0.83 (s, 9 H), 0.81 (d, J = 6.8 Hz, 3 H), 0.031 (s, 3 H), −0.028 (s, 3 H); ^{13}C (100 MHz, $CDCl_3$) δ 203.5, 167.7, 153.7, 149.1, 144.0, 138.9, 128.7, 128.2, 127.8, 127.3, 121.5, 111.8, 110.7, 83.6, 76.5, 74.0, 70.7, 68.8, 64.1, 58.7, 55.8, 45.9, 42.7, 28.6, 25.8, 17.8, 17.7, 14.6, 9.4, −4.8, −4.9; IR ($CDCl_3$) 1782, 1710 cm^{-1}; FAB mass spectrum for $C_{37}H_{57}O_9SiNNa$ (M^+ + Na), calcd 708, found 708. Anal. Calcd for $C_{37}H_{57}O_9SiN$: C, 64.78; H, 8.08; N, 2.04. Found: C, 64.70; H, 7.77; N, 1.87.

(4*S*)-[(α*S*,2*R*,4*R*,5*R*,6*R*)-α-[(3,4-Dimethoxybenzyl)oxy]-2-methoxy-5,6-dimethyl-4-hydroxy-2H-pyranyl]-4-isopropyl-2-oxazolidinone (10). A solution of the β-keto imide **14** (1.03 g, 1.50 mmol) in MeOH (30 mL) was flushed with a stream of H_2 for 1 min, and then 30% Pd/C (72 mg) was added. The solution was stirred for 24 h at ambient temperature under a steady stream of H_2. The solution was then filtered through silica gel and evaporated to give the crude product that was used directly in the subsequent step.

A solution of the crude hemiketal in MeOH (10 mL) was treated with $HC(OMe)_3$ (0.250 mL) and catalytic camphorsulfonic acid (CSA) (17 mg). The mixture was stirred for 8 h, and $NaHCO_3$ (100 mg) was added.[36] The reaction mixture was concentrated in vacuo, and the crude product was purified by flash chromatography (silica gel, 3:1 to 1:3 hexanes−EtOAc) to yield ketal **10** (584 mg, 79%) as a clear oil: $[\alpha]^{23}_D$ +109° (*c* = 1.6, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.78−6.96 (m, 3 H), 5.81 (s, 1 H), 4.55 (A of AB, J_{AB} = 12.4 Hz, 1 H), 4.51 (B of AB, J_{AB} = 11.6 Hz, 1 H), 4.25−4.28 (m, 1 H), 4.07−4.18 (m, 3 H), 3.87 (s, 3 H), 3.85 (s, 3 H), 3.72 (dq, *J* = 6.4, 2.0 Hz, 1 H), 3.12 (s, 3 H), 2.12−2.21 (m, 1 H), 1.96 (dd, *J* = 13.6, 4.8 Hz, 1 H), 1.82 (dd, *J* = 13.2, 11.6 Hz, 1 H), 1.73−1.80 (m, 1 H), 1.03 (d, *J* = 6.4 Hz, 3 H), 0.89 (d, *J* = 7.2 Hz, 3 H), 0.79 (d, *J* = 6.8 Hz, 3 H), 0.68 (d, *J* = 6.8 Hz, 3 H); ^{13}C (100 MHz, $CDCl_3$) δ 171.1, 154.0, 148.8, 148.7, 129.2, 121.4, 111.8, 110.5, 101.5, 73.0, 72.9, 67.8, 67.2, 63.9, 59.4, 55.7, 48.2, 38.3, 30.8, 29.6, 17.8, 17.4, 15.0, 3.5; IR ($CDCl_3$) 2970, 1782, 1702 cm^{-1}; HRMS for $C_{25}H_{38}O_9N$ (M^+ + H) calcd 496.2536, found 496.2537.



15

(4*S*)-[(α*S*,2*R*,5*R*,6*R*)-α-[(3,4-Dimethoxybenzyl)oxy]-2-methoxy-5,6-dimethyl-4-oxo-2*H*-pyranyl]-4-isopropyl-2-oxazolidinone (15). To a solution of $(COCl)_2$ (0.113 mL, 1.29 mmol) in CH_2Cl_2 (12 mL) at −78 °C was added DMSO (0.183 mL, 2.59 mmol). The solution was warmed to −40 °C for 15 min and then recooled to −78 °C. To this solution was added dropwise a solution of alcohol **10** (0.584 g, 1.17 mmol) in CH_2Cl_2 (1 mL) followed by Et_3N (0.822 mL, 5.89 mmol). The reaction mixture was allowed to warm to 0 °C and poured into saturated aqueous $NaHCO_3$ solution (50 mL). The organic layer was separated and washed with aqueous $NaHSO_4$ (25 mL) and aqueous $NaHCO_3$ (2 × 25 mL) and then dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification of the crude product by flash chromatography (silica gel, 9:1 to 1:1 hexanes−EtOAc) yielded ketone **15** (0.533 g, 92%) as a clear oil: $[\alpha]^{23}_D$ +75° (*c* = 1.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.79−6.93 (m, 3 H), 5.95 (s, 1 H), 4.53 (s, 2 H), 4.32−4.37 (m, 1 H), 4.16−4.24 (m, 2 H), 4.05 (dq, *J* = 6.0, 3.2 Hz, 1 H), 3.87 (s, 3 H), 3.86 (s, 3 H), 3.14 (s, 3 H), 3.07 (d, *J* = 16.0 Hz, 1 H), 2.52 (dd, *J* = 16.0, 1.2 Hz, 1 H), 2.14−2.28 (m, 2 H), 1.10 (d, *J* = 6.4 Hz, 3 H), 0.95 (d, *J* = 7.2 Hz, 3 H), 0.91 (d, *J* = 6.8 Hz, 3 H), 0.82 (d, *J* = 6.4 Hz, 3 H); ^{13}C (100 MHz, $CDCl_3$) δ 209.0, 171.2, 154.0, 148.9, 148.8, 144.0, 129.1, 121.3, 111.7, 110.6, 102.8, 72.9, 72.3, 67.3, 64.0, 59.3, 55.8, 48.7, 40.8, 29.5, 17.8, 16.5, 15.0, 9.8; IR ($CDCl_3$) 2960, 2925, 1780, 1700 cm^{-1}; HRMS for $C_{25}H_{36}O_9N$ (M^+ + H) calcd 494.2380, found 494.2377. Anal. Calcd for $C_{25}H_{35}O_9N$: C, 60.84; H, 7.15; N, 2.84. Found: C, 60.95; H, 7.37; N, 2.58.

(4*S*)-[(α*S*,2*R*,5*R*,6*R*)-α-[(3,4-dimethoxybenzyl)oxy]-2-methoxy-5,6-dimethyl-4-methylene-2*H*-pyranyl]-4-isopropyl-2-oxazolidinone (11). A mixture of Zn (122 mg, 1.87 mmol) and CH_2I_2 (0.084 mL, 1.04 mmol) in THF (1.0 mL) was stirred for 30 min at 23 °C. The solution was cooled to 0 °C, and then $TiCl_4$ (0.207 mL, 0.207 mmol) was added, and the solution was allowed to warm to 23 °C and stirred for 30 min. A solution of ketone **15** (96 mg, 0.207 mmol) in THF (1.6 mL) was then added dropwise.[37] The mixture was stirred for 2.5 h and then was poured into saturated aqueous $NaHCO_3$ solution (5 mL). The aqueous layer was extracted with EtOAc (2 × 20 mL), and the combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification of the crude reaction mixture by flash chromatography (silica gel, 9:1 to 1:1 hexanes−EtOAc) yielded **11** (82 mg, 86%) as a clear oil: $[\alpha]^{23}_D$ +260° (*c* = 3.0, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.75−7.00 (m, 3 H), 5.86 (s, 1 H), 4.79 (t, *J* = 2.0 Hz, 1 H), 4.73 (t, *J* = 2.0 Hz, 1 H), 4.57 (A of AB, J_{AB} = 12.0 Hz, 1 H), 4.53 (B of AB, J_{AB} = 12.0 Hz, 1 H), 4.28−4.32 (m, 1 H), 4.12−4.20 (m, 2 H), 3.88 (s, 3 H), 3.85 (s, 3 H), 3.79 (dq, *J* = 6.8, 2.8 Hz, 1 H), 3.16 (s, 3 H), 2.74 (dt, *J* = 2.0, 2.4 Hz, 1 H), 2.72 (t, *J* = 2.0 Hz, 1 H), 2.33 (d, *J* = 15.2 Hz, 1 H), 2.12−2.22 (m, 2 H), 1.01 (d, *J* = 6.4 Hz, 3 H), 0.90 (d, *J* = 7.2 Hz, 3 H), 0.84 (d, *J* = 6.8 Hz, 3 H), 0.81 (d, *J* = 7.2 Hz, 3 H); ^{13}C (100 MHz, $CDCl_3$) δ 171.5, 154.1, 148.9, 148.8, 146.4, 129.4, 121.4, 111.9, 110.6, 109.7, 101.2, 73.2, 68.6, 64.0, 59.5, 55.7, 48.6, 41.2, 32.3, 29.7, 17.9, 17.3, 15.0, 11.6; IR ($CDCl_3$) 2971, 2938, 1782, 1701 cm^{-1}; HRMS for $C_{26}H_{38}O_8N$ (M^+ + H) calcd 492.2587, found 492.2583. Anal. Calcd for $C_{25}H_{35}O_8N$: C, 65.05; H, 7.65; N, 2.89. Found: C, 64.73; H, 8.05; N, 3.89.

7-(3,4-Dimethoxybenzyl)pederic Acid (3). To a 0 °C solution of imide **11** (55 mg, 0.112 mmol) in THF (1.8 mL) and H_2O (0.60 mL) was added 30% H_2O_2 (0.076 mL, 0.672 mmol) followed by LiOH (5.4 mg, 0.224 mmol).[38] The mixture was stirred for 11 h at 23 °C and then diluted with EtOAc (2 mL) and pH 7 buffer (1 mL). The Et_2O layer, containing the oxazolidinone chiral auxiliary, was removed and discarded. The aqueous layer was diluted with pH = 6 buffer (2 mL) and extracted repeatedly with EtOAc (30 × 2 mL).[39] The combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo, giving 34 mg (82%) of acid **3** that was ≥95% pure by ^{1}H NMR analysis. The instability of **3** precluded efforts to obtain analytically pure samples by chromatographic methods. The ^{1}H NMR data for **3** were in complete agreement with data provided by Professor Yoshi Kishi:[6,7] ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.80−7.0 (m, 3 H), 4.87 (s, 1 H), 4.86 (A of AB, J_{AB} = 11.6 Hz, 1 H), 4.77 (s, 1 H), 4.58 (B of AB, J_{AB} = 11.6 Hz, 1 H), 4.07 (s, 1 H), 3.99 (dq, *J* = 6.4, 2.4 Hz, 1 H), 3.89 (s, 3 H), 3.88 (s, 3 H), 3.01 (s, 3 H), 2.54 (s, 2 H), 2.26 (dq, *J* = 7.2, 2.8 Hz, 1 H), 1.78 (d, *J* = 6.8 Hz, 3 H), 0.99 (d, *J* = 7.2 Hz, 3 H); HRMS for $C_{18}H_{25}O_6$ (M^+ − OMe) calcd 349.1644, found 349.1655.

Methyl Pederate (2). To a solution of the sensitive acid **3** (15 mg, 0.039 mmol) in THF (1.0 mL) and MeOH (0.500 mL) was added $TMSCHN_2$ (0.059 mL, 2 M in hexane, 0.118 mmol).[40] The solution was concentrated in vacuo, and the crude reaction mixture was purified by flash chromatography (silica gel, 1:1 hexanes−EtOAc) yielding the DMPM protected methyl ester (11 mg, 71%).

To a solution of the above methyl ester (10 mg, 0.026 mmol) in CH_2Cl_2 (0.246 mL) was added pH = 7 aqueous buffer (0.013 mL) followed by DDQ (6.5 mg, 0.029 mmol).[6,7] The mixture was stirred for 30 min before additional DDQ was added (3 mg). The mixture was stirred for 1 h and then poured into saturated aqueous $NaHCO_3$ solution (10 mL). The aqueous layer was extracted with EtOAc (2 × 10 mL), and the combined organic phases were dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification of the crude product by flash chromatography (silica gel, 2% MeOH:CH_2Cl_2) yielded methyl pederate (**2**) as a clear oil (80%): $[\alpha]^{23}_D$ +115° (*c* = 0.3, CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.84 (t, *J* = 2.0 Hz, 1 H), 4.73 (t, *J* = 1.6 Hz, 1 H), 4.36 (d, *J* = 5.6 Hz, 1 H), 3.92 (dq, *J* = 6.4, 2.4 Hz, 1 H), 3.83 (s, 3 H), 3.30 (s, 3 H), 2.91 (d, *J* = 5.6 Hz, 1 H), 2.37 (A of AB, dt, *J* = 14.0, 2.0 Hz, 1 H), 2.31 (B of AB, J_{AB} = 14.4 Hz, 1 H), 2.22 (dq, *J* = 7.2, 2.8 Hz, 1 H), 1.16 (d, *J* = 6.4 Hz, 3 H), 0.94 (d, *J* = 6.8 Hz, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.8, 146.0, 110.1, 99.5, 72.5, 69.4, 52.6, 48.8, 41.3, 33.5, 29.7, 17.7, 11.6; HRMS for $C_{11}H_{17}O_4$ (M^+ − OMe) calcd 213.1122, found 213.1089.

The ^{1}H NMR data obtained for **2** were in excellent agreement with literature values.[18]

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Supporting Information Available: Copies of ^{1}H NMR spectra of intermediates **2**, **3**, **10**, and **12** (4 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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