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ARTICLE

Confirmation of the Structure of (±)-Preisomide by Total Synthesis

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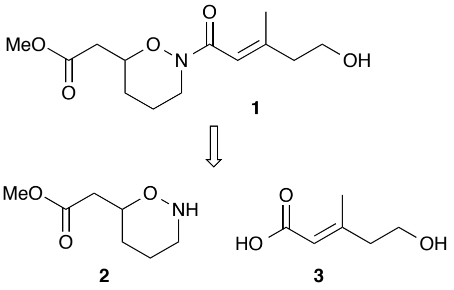
The structure of preisomide has been confirmed by total synthesis involving chemoselective oxazine formation and vinyl iodide carbonylation in six steps (longest linear sequence) and 23% overall yield.

Introduction

A large number of natural products containing the hydroxylamine moiety has been reported.[1] In the absence of crystallographic information, deducing the presence of the hydroxylamine is difficult as its presence is not apparent from ^{1}H NMR, ^{13}C NMR and infrared spectroscopy, while natural abundance ^{15}N NMR is very challenging. Unequivocal total synthesis is one method to validate structural proposals.[2]

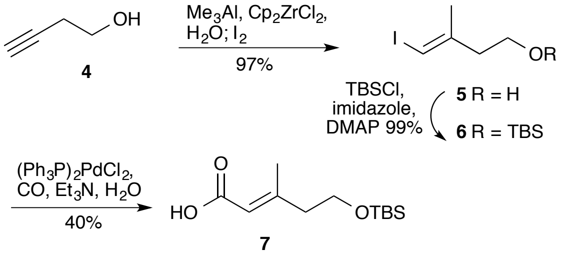
Recently, the isolation of (±)-preisomide **1** from the fungus *Preussia isomera* was reported.[3] This compound was suggested to be an *N*-acyltetrahydro-1,2-oxazine based, largely, on mass spectroscopic data. Such *N*-acyl tetrahydro-1,2-oxazine are unusual as natural products.[4] We, therefore, embarked on the total synthesis in order to determine whether the proposed structure is correct.



Scheme 1. (±)-Preisomide **1** retrosynthesis

Results and discussion

A simple disconnection yields tetrahydro-1,2-oxazine **2** and *E*-anhydromevalonic acid **3** (Scheme 1). The reported syntheses of acid **3** and its derivatives are long[5] or proceed with poor control of alkene stereochemistry.[6] We, therefore, developed a shorter and completely stereocontrolled method (Scheme 2). Carbozirconation of 3-butyn-1-ol **4** with trimethylaluminium and zirconocene dichloride followed by quenching with iodine according to the method of Negishi[7] yielded vinyl iodide **5** as a single isomer. We note that the carbozirconation is greatly accelerated by the presence of a trace of water.[8] After protection as its TBS ether **6**, palladium catalysed carbonylation in wet THF then yielded carboxylic acid **7**. The modest yield of 40% is due to purification issues.



Scheme 2. Anhydromevalonate **7** synthesis

To synthesise oxazine **2**,[9] 4-penten-1-ol **8** was subjected to cross-metathesis with methyl acrylate (Scheme 3).[10] The resulting alcohol **9** was converted to the corresponding aldehyde **10** by the method of Anelli.[11] Grigg *et al.* have reported that treatment of this aldehyde with hydroxylamine under mildly basic conditions yields nitrone **12**.[12] In contrast, inspired by a report by Yasui *et al.*,[13] use of *O*-acetylhydroxylamine as its trifluoroacetate salt in the presence of excess potassium carbonate gave the desired dihydrooxazine **11** as the major product (33%) in a tandem condensation-intramolecular oxa-Michael addition, accompanied by some of nitrone **12** (17%). These compounds were easily separable by chromatography. During further optimisation of this reaction, it was found that a combination of *N*,*O*-diacetylhydroxylamine[14] and excess potassium carbonate gave dihydrooxazine **11** in reasonable yield (60%), accompanied by just a trace of nitrone **12**. In contrast to this,

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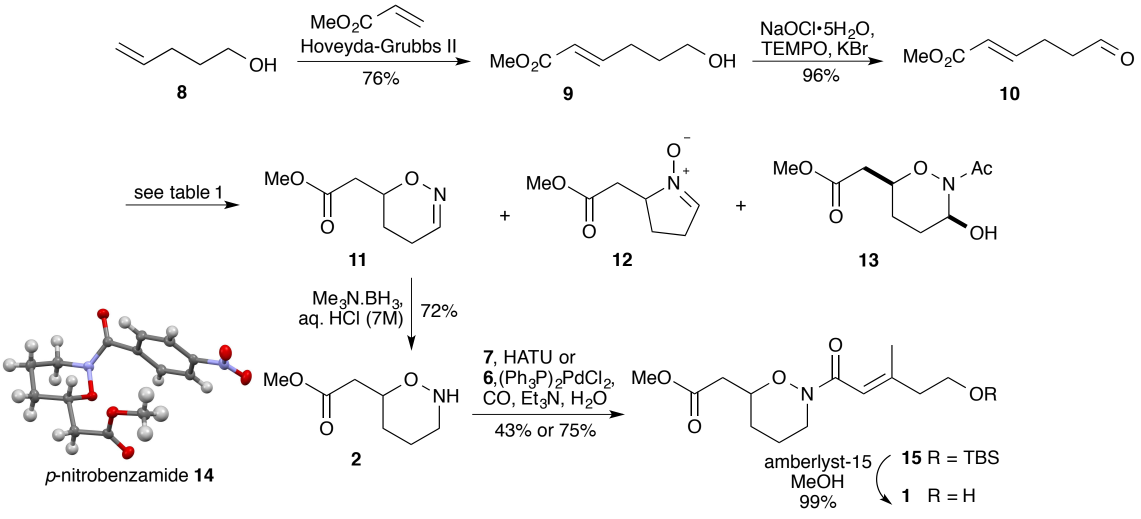
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x use of *N*-acetylhydroxylamine[15] gave aminal **13** as the only product.[16]



Scheme 3. Synthesis of preisomide

Table 1. Dihydrooxazine formation

entry	hydroxylamine reagent	conditions	oxazine **11**	nitrone **12**	aminal **13**
1	$HONH_2•HCl$	Na_2CO_3	-	51[a]	0
2	$AcONH_2•HO_2CCF_3$	K_2CO_3 (5 eq.)	33	17	0
3	AcONHAc	K_2CO_3 (5 eq.)	60	trace	0
4	HONHAc	K_2CO_3 (5 eq.)	0	0	47

a. see Grigg *et al.*[12]

Dihydrooxazine **11** was then reduced to tetrahydrooxazine **2** by the method of Ottenheijm using the trimethylborane-trimethylamine complex in the presence of 7M hydrochloric acid.[17] The structure of tetrahydrooxazine **2** was secured by X-ray crystallographic analysis of its *p*-nitrobenzamide derivative **14**.[18] Although the coupling of tetrahydrooxazine **2** with protected anhydromevalonic acid **7** to give the desired amide **15** could be achieved using HATU, it was found to be better to conduct a palladium catalyzed carbonylative coupling reaction[19] between tetrahydrooxazine **2** and iodide **6**. This latter procedure saves one step. Deprotection of *N*-acyloxazine **15** using amberlyst-15 in methanol then gave (±)-preisomide **1**. The ^1H and ^{13}C NMR data for the synthetic compound were in good agreement with those reported for the natural material (Tables 2 and 3).

Conclusions

We have reported an efficient and convergent synthesis of (±)-preisomide **1** in six steps (longest linear sequence) and 23% overall yield. This work also reveals an intriguing reagent-based selectivity in oxazine vs. nitrone formation and a short and stereoselective approach to anhydromevalonic acid derivatives. This work confirms the proposed but unusual *N*-acyl tetrahydro-1,2-oxazine structure of this natural product.

Table 2. ^1H NMR data for natural and synthetic material

reported[3] (d_5-pyridine)	observed (d_5-pyridine)
6.72, s	6.73, s, 1H
6.2, s	6.14, brs, 1H
4.59, d, *J* = 11.7 Hz	4.61, brd, *J* = 13.3 Hz, 1H
4.26, m	4.32 – 4.24, m, 1H
4.06, t, *J* = 6.5 Hz	4.07, t, *J* = 7.0 Hz, 2H
3.66, s	3.68, s, 3H
2.97, m	3.01 – 2.96, m, 1H
2.64, m	2.73 – 2.61, m, 3H
2.54, dd, *J* = 16.1, 3.5 Hz	2.55, dd, *J* = 16.1, 3.7 Hz, 1H
2.42, s	2.44, s, 3H
1.59, m	1.69 – 1.33, m, 4H
1.52, m	
1.42, m	

Table 3. ^{13}C NMR data for natural and synthetic material

reported[3] (d_5-pyridine)	observed[a] (d_5-pyridine)
170.9	171.4
166.5	167.0
154.2	154.7
116.3	116.8
79.3	79.7
60.4	60.9
51.7	52.2
45.3	45.8
41.7	42.3
39.2	39.7
29.5	30.0
22.8	23.2
19.1	19.6

a. the consistent difference of 0.5 or 0.4 ppm may be due to different referencing

Experimental

General experimental

All reagents were obtained from commercial suppliers and used without further purification unless where indicated otherwise. Reactions requiring anhydrous or air free conditions were performed under an atmosphere of nitrogen. Glassware was oven dried at 120 °C and cooled under vacuum. Anhydrous THF and ether were distilled from sodium metal and benzophenone under nitrogen. Anhydrous toluene was distilled from sodium and anhydrous dichloromethane was distilled from calcium hydride. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance III 400 spectrometer, a 500MHz ECZ Luminous (JNM-ECZL series) a JEOL ECA400 UltraShield in $CDCl_3$. Chemical shifts are given in parts per million (ppm) with residual protic solvent as the internal standard. Coupling constants are given in Hertz. Low resolution mass spectra were recorded on a (LRMS) Thermo Scientific LTQ XL with a quadrupole ion trap equipped with Thermo Ultimate LC. High resolution mass spectra were recorded on a Waters Xevo G2-X2 MS in either positive or negative mode equipped with Waters Acquity UPLC. Analytical thin layer chromatography was performed on Merck DC pre coated TLC plates with 0.25 mm Kieselgel 60 F_{254}. The plates were visualised with a 254 nm UV lamp, or by staining with ammonium molybdate or potassium permanganate. Flash chromatography was performed on silica gel 230-400 mesh.

(*E*)-4-Iodo-3-methylbut-3-en-1-ol (5)

Trimethylaluminium solution (64 mL, 2 M in toluene, 128.4 mmol, 3 equiv.) was added dropwise to a solution of zirconocene dichloride (2.50 g, 8.56 mmol, 0.2 equiv.) in anhydrous dichloromethane (50 mL) at -25 °C. Separately, trimethylaluminium solution (6 mL, 2M in toluene, 12.0 mmol, 0.28 equiv.) was added dropwise to a solution of 3-butyn-1-ol (3.01 g, 42.8 mmol) in dichloromethane (50 mL). The alcohol solution was then added to the zirconocene dichloride solution. Water (1.16 mL, 64.2 mmol, 1.5 equiv.) was added slowly. The reaction mixture was stirred overnight at -25 °C. A solution of iodine (16.3 g, 64.2 mmol, 1.5 equiv.) in anhydrous ether (50 mL) was added to the reaction mixture. The mixture was stirred for four hours at room temperature, then poured onto an ice-cold solution of saturated potassium-sodium tartrate (20 mL). The aluminium salts were allowed to settle, and the mixture was filtered and washed with dichloromethane. The solvent was removed in vacuo and the residue purified by flash column chromatography on silica gel using 50% ethyl acetate-hexane as the eluent to give iodide **5** as a clear oil (8.84 g, 41.7 mmol, 97%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 6.01 (s, 1H), 3.71 (t, *J* = 6.2 Hz, 2H), 2.47 (t, *J* = 6.2 Hz, 2H), 1.87 (s, 3H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 144.6, 76.7, 60.1, 42.4, 23.8.

IR (neat, cm^{-1}): 3348, 2939, 2912, 2881, 1431, 1377, 1273, 1141, 1045, 767, 667.

HRMS (ESI-Quadrupole): m/z: $[M+H]^+$ Calcd for $[C_5H_{10}IO]^+$: 212.9776; found: 212.9771.

(*E*)-*t*-Butyl((4-iodo-3-methylbut-3-en-1-yl)oxy)dimethylsilane (6)[20]

t-Butyldimethylsilyl chloride (5.25 g, 34.8 mmol, 1.2 equiv.) was added in one portion to a solution of iodide **5** (6.15 g, 29.0 mmol), imidazole (4.34 g, 63.8 mmol, 2.2 equiv.) and DMAP (354 mg, 2.9 mmol, 0.1 equiv.) in anhydrous THF (20 mL). The mixture was stirred at room temperature for 1 hour. The mixture was filtered and the solvent was removed *in vacuo*. The residue was purified by flash column chromatography on silica gel using 5% ethyl acetate-hexane as the eluent to give ether **6** as a clear oil (9.35 g, 28.6 mmol, 99%).

^{1}H NMR ($CDCl_3$, 400 MHz): δ 5.93 (s, 1H), 3.69 (t, *J* = 6.6 Hz, 2H), 2.42 (t, *J* = 6.6 Hz, 2H), 0.88 (s, 9H), 0.03 (s, 6H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 145.2, 76.3, 61.3, 42.6, 25.9, 24.2, 18.2, −5.3.

IR (neat, cm^{-1}): 2951, 2927, 2897, 2858, 1469, 1435, 1381, 1253, 1103, 833, 810, 775.

HRMS (ESI-Quadrupole): m/z: $[M+H]^+$ Calcd for $[C_{11}H_{24}IOSi]^+$: 327.0641; found: 327.0651.

(*E*)-5-((*t*-Butyldimethylsilyl)oxy)-3-methylpent-2-enoic acid (7)

Triethylamine (12.8 mL, 91.8 mmol, 3 equiv.) and water (5.42 mL, 300 mmol, 10 equiv.) were added to a solution of iodide **6** (9.98 g, 30.6 mmol) and bistriphenylphosphinepalladium(II) dichloride (2.15 g, 3.06 mmol, 10 mol%) in tetrahydrofuran (50 mL). CO gas was bubbled through the mixture for 10 minutes. The mixture was heated at 40 °C with vigorous stirring under a CO atmosphere (balloon) overnight. The solvent was removed *in vacuo* and the residue was purified by vacuum distillation (0.5 Torr, 180 °C) to give carboxylic acid **7** as a viscous yellow oil (2.95 g, 12.1 mmol, 40%).

^{1}H NMR ($CDCl_3$, 400 MHz): 5.72 (s, 1H), 3.76 (t, *J* = 6.5 Hz, 2H), 2.38 (t, *J* = 6.5 Hz, 2H), 2.20 (s, 3H), 0.88 (s, 9H), 0.05 (s, 6H).

^{13}C NMR ($CDCl_3$, 100 MHz): 171.9, 160.2, 116.7, 61.2, 44.2, 25.8, 19.5, 18.2, −5.4.

HRMS (ESI-Quadrupole): m/z: $[M+H]^+$ Calcd for $[C_{12}H_{25}O_3Si]^+$: 245.1573; found: 245.1581.

IR (neat, cm^{-1}): 2953, 2738, 1693, 1643, 1462, 1435, 1381, 1253, 1170, 1103, 1004, 937, 920, 835, 777, 704.

Methyl (*E*)-6-hydroxyhex-2-enoate (9)[10]

A solution of Hoveyda-Grubbs' second generation catalyst (248 mg, 0.35 mmol, 1 mol%), pent-4-en-1-ol (3.59 mL, 34.8 mmol) and methyl acrylate (31.5 mL, 348 mmol, 10 equiv.) in dichloromethane (50 mL) was heated at reflux overnight. The solvent was removed *in vacuo* and the residue purified by flash column chromatography on silica gel using 40% ethyl acetate-hexane as the eluent to give ester **9** as a pale brown oil (3.79 g, 26.4 mmol, 76%).

^{1}H NMR (CDCl$_3$, 500 MHz): 6.98 (dt, *J* = 15.5, 7.0 Hz, 1H), 5.85 (dt, *J* = 15.5, 1.0 Hz, 1H), 3.72 (s, 3H), 3.67 (d, *J* = 6.5 Hz, 2H), 2.31 (q, *J* = 7.3 Hz, 2H), 1.75 – 1.70 (m, 2H).

^{13}C NMR (CDCl$_3$, 100 MHz): 167.1, 148.9, 121.0, 61.5, 51.3, 30.7, 28.4.

Methyl (*E*)-6-oxohex-2-enoate (10)[12]

A solution of potassium bromide (143 mg, 0.96 mmol, 0.1 equiv.) in water (0.5 mL) was added to a solution of ester **9** (1.38 g, 9.57 mmol) and TEMPO (15 mg, 0.0096 mmol, 1 mol%) in dichloromethane (10 mL). The mixture was cooled to 0 °C and an ice-cold solution of sodium hypochlorite pentahydrate (2.36 g, 13.4, 1.5 equiv.) and sodium bicarbonate (238 mg) in water (21 mL) was added. The mixture was stirred for one hour at 0 °C. The layers were separated, and the aqueous layer extracted with dichloromethane (3 x 5 mL). The combined organic layers were dried (MgSO$_4$), filtered and the solvent was removed in vacuo and the residue purified by flash column chromatography on silica gel using 20% ethyl acetate-hexane as the eluent to give aldehyde **10** as a pale yellow oil (1.31 g, 9.23 mmol, 96%).

^{1}H NMR (CDCl$_3$, 400 MHz): δ 9.78 (s, 1H), 6.93 (dt, *J* = 15.7, 6.7 Hz, 1H), 5.84 (dt, *J* = 15.7, 1.4 Hz, 1H), 3.71 (s, 3H), 2.68 – 2.58 (m, 2H), 2.57 – 2.48 (m, 2H).

^{13}C NMR (CDCl$_3$, 100 MHz): δ 200.3, 166.6, 146.6, 121.9, 51.4, 41.7, 24.3.

IR (neat, cm^{-1}): 2951, 2843, 2731, 1720, 1658, 1435, 1319, 1276, 1203, 1165, 1103, 1041, 979.

HRMS (ESI-Quadrupole): m/z: [M+H]$^+$ Calcd for [C$_{11}$H$_{24}$IOSi]$^+$: 327.0641; found: 327.0651.

Methyl 2-(5,6-dihydro-*4H*-1,2-oxazin-6-yl)acetate (11)

A biphasic solution of aldehyde **10** (100 mg, 0.693 mmol), *N*-acetoxyacetamide (244 mg, 2.17 mmol, 3 equiv.) and potassium carbonate (478.5 mg, 3.46 mmol, 5 equiv.) in chloroform (6 mL) and water (2 mL) was stirred overnight. The layers were separated, and the aqueous layer was extracted with dichloromethane (3 x 3 mL). The combined organic layers were dried (MgSO$_4$), and the solvent was removed *in vacuo*. The residue was purified using flash column chromatography on silica gel using 50% ethyl acetate-hexane as the eluent to give oxazine **11** as a colorless oil (65.6 mg, 0.417 mmol, 60%).

^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.24 – 7.23 (m, 1H), 4.25 – 4.13 (m, 1H), 3.71 (s, 3H), 2.74 (dd, *J* = 15.8, 6.7 Hz, 1H), 2.52 (dd, *J* = 15.8, 6.7 Hz, 1H), 2.34 – 2.15 (m, 2H), 2.03 – 1.98 (m, 1H), 1.75 – 1.66 (m, 1H).

^{13}C NMR (CDCl$_3$, 100 MHz): δ 170.5, 148.5, 71.7, 53.2, 38.9, 23.3, 21.2.

IR (neat, cm^{-1}): 2943, 1735, 1647, 1435, 1357, 1288, 1257, 1203, 1172, 999.

HRMS (ESI-Quadrupole): m/z: [M+H]$^+$ Calcd for [C$_7$H$_{12}$NO$_3$]$^+$: 158.0817; found: 158.0821.

Methyl 2-(1,2-oxazinan-6-yl)acetate (2)

A 7 M solution of HCl solution in anhydrous MeOH (4 mL) was added to a solution of dihydrooxazine **11** (200 mg, 1.27 mmol) and borane-trimethylamine complex (185 mg, 2.54 mmol, 2 equiv.) in anhydrous MeOH (5 mL). The mixture was stirred under nitrogen at room temperature for 4 hours. Upon completion of reaction as confirmed by TLC analysis, the reaction was quenched by addition of solid NaHCO$_3$. The mixture was filtered, and the residue was washed with ethyl acetate (3 x 10 mL). The solvent was removed from the combined washings *in vacuo* and the residue was purified by flash column chromatography on silica gel using ethyl acetate as the eluent to give oxazine **2** as a colorless oil (192 mg, 1.20 mmol, 95%).

^{1}H NMR (CDCl$_3$, 500 MHz): δ 4.09 – 4.01 (m, 1H), 3.69 (s, 3H), 3.14 – 3.06 (m, 1H), 2.99 (m, 1H), 2.53 (dd, *J* = 15.4, 7.9 Hz, 1H), 2.38 (dd, *J* = 15.4, 5.2 Hz, 1H), 1.84 – 1.66 (m, 3H), 1.49 – 1.39 (m, 1H).

^{13}C NMR (CDCl$_3$, 100 MHz): δ 171.2, 76.7, 51.7, 48.4, 40.0, 30.0, 24.

IR (neat, cm^{-1}): 2949, 2854, 1732, 1633, 1436, 1359, 1292, 1261, 1205, 1174, 1122, 1080, 1041, 997.

HRMS (ESI-Quadrupole): m/z: [M+Na]$^+$ Calcd for [C$_7$H$_{13}$NO$_3$Na]$^+$: 182.0793; found: 182.0791.

Methyl 2-(2-acetyl-3-hydroxy-1,2-oxazinan-6-yl)acetate (13)

A solution of aldehyde **10** (50 mg, 0.352 mmol) in chloroform (2.5 mL) was added to a solution of *N*-hydroxyacetamide (79 mg, 1.05 mmol, 3 equiv.) and potassium carbonate (242 mg) in water (0.5 mL). The mixture was stirred vigorously overnight. The layers were separated and the aqueous layer was extracted with dichloromethane (3 x 2 mL). The combined organic layers were dried (MgSO$_4$), the solvent was removed *in vacuo* and the residue was purified by flash column chromatography on silica gel to give aminal **13** as a colourless oil (36 mg, 0.166 mmol, 47%).

^{1}H NMR (CDCl$_3$, 500 MHz): δ 5.96 (s, 1H), 4.28 – 4.23 (m, 1H), 3.71 (s, 3H), 2.67 (dd, *J* = 16.4, 9.1 Hz, 1H), 2.51 (dd, *J* = 16.4, 3.9 Hz, 1H), 2.08 (s, 3H), 2.01 – 1.89 (m, 2H), 1.89 – 1.76 (m, 2H).

^{13}C NMR (CDCl$_3$, 100 MHz): δ 170.6 (2C), 78.5, 70.6, 51.8, 38.8, 28.0, 24.3, 20.2.

IR (neat, cm^{-1}): 3439, 2954, 2933, 1732, 1643, 1438, 1415, 1336, 1292, 1263, 1219, 1166, 1114, 1072, 1039, 1002, 933, 852, 783, 704, 651, 615.

HRMS (ESI-Quadrupole): m/z: [M+H]$^+$ Calcd for [C$_9$H$_{16}$NO$_5$]$^+$: 218.1028; found: 218.1026.

Methyl (*E*)-2-(2-(5-((tert-butyldimethylsilyl)oxy)-3-methylpent-2-enoyl)-1,2-oxazinan-6-yl)acetate (15)

By coupling: A solution of tetrahydrooxazine **2** (15.4 mg, 0.097 mmol, 1.2 equiv.) and anhydrous triethylamine (341 µL, 0.24 mmol, 3 equiv.) in anhydrous THF (1 mL) was added to a solution of carboxylic acid **7** (20 mg, 0.081 mmol), DMAP (3 mg, 0.024 mmol, 0.3 equiv.) and HATU (37 mg, 0.097 mmol, 1.2 equiv.) in anhydrous THF (1 mL). The mixture was stirred at room temperature for 4 h. Upon completion as confirmed by TLC analysis, the solvent was removed *in vacuo* and taken up in ethyl acetate (3 mL). The solution was washed with saturated ammonium chloride solution (1 mL) and dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue was purified by flash column chromatography on silica gel using 30% ethyl acetate-hexane as the eluent to give *N*-acyloxazine **15** as a colorless oil (13.4 mg, 0.0347 mmol, 43%).

By carbonylation: CO gas was bubbled through a solution of tetrahydrooxazine **2** (117 mg, 0.74 mmol, 2 equiv.), iodide **6** (120 mg, 0.37 mmol) and bis(triphenylphosphine)palladium (II) dichloride (26 mg, 0.0037 mmol, 10 mol%) and triethylamine (153 µL, 1.10 mmol, 3 equiv.) in anhydrous THF (2 mL) for 5 minutes. The reaction mixture was stirred at 50 °C overnight under a CO atmosphere. The solvent was removed *in vacuo* and the residue taken up in ethyl acetate (5 mL). The solution was washed with water (2 mL) and dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue was purified by flash column chromatography on silica gel using 30% ethyl acetate-hexane as the eluent to give *N*-acyloxazine **15** as a colorless oil (106 mg, 0.275 mmol, 75%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.18 (s, 1H), 4.46 (d, *J* = 13.3 Hz, 1H), 4.23 – 4.14 (m, 1H), 3.83 – 3.73 (t, *J* = 8.8 Hz, 2H), 3.72 (s, 3H), 3.04 (t, *J* = 14.7 Hz, 1H), 2.60 (dd, *J* = 11.0, 3.5 Hz 1H), 2.46 (dd, *J* = 19.5, 5.2 Hz, 1H), 2.40 – 2.34 (m, 2H), 2.15 (s, 3H), 1.90 – 1.65 (m, 4H), 0.88 (s, 9H), 0.05 (s, 6H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.4, 166.1, 153.7, 115.4, 61.7, 51.8, 44.5, 41.3, 39.0, 29.5, 25.8, 22.5, 19.1, 18.2, – 5.4.

IR (neat, cm^{-1}): 2951, 1743, 1654, 1631, 1436, 1257, 1207, 1165, 1101, 835, 777.

HRMS (ESI-Quadrupole): m/z: $[M+H]^+$ Calcd for $[C_{19}H_{36}NO_5Si]^+$: 386.2363; found: 386.2375.

(±)-Preisomide (1)

Amberlyst-15 (10.5 mg) was added to a solution of *N*-acyloxazine **15** (48 mg, 0.125 mmol) in methanol (2 mL). The mixture was stirred at room temperature for 1 hour. Upon completion of reaction, the reaction mixture was filtered, and the solvent was removed *in vacuo*. The crude product was purified by flash column chromatography on silica gel using ethyl acetate as the eluent to give (±)-preisomide **1** as a colourless oil (34 mg, 0.12 mmol, 99%).

^{1}H NMR ($CDCl_3$, 500 MHz): δ 6.25 (s, 1H), 4.49 (brd, *J* = 13.3 Hz, 1H), 4.25 – 4.19 (m, 1H), 3.81 (t, *J* = 5.1 Hz, 2H), 3.74 (s, 3H), 3.10 – 2.94 (m, 1H), 2.59 (dd, *J* = 16.4, 9.3 Hz, 1H), 2.46 (dd, *J* = 16, 4 Hz, 1H), 2.41 (t, *J* = 5.1 Hz, 2H), 2.16 (s, 3H), 1.50 – 1.85 (m, 5H).

^{13}C NMR ($CDCl_3$, 100 MHz): δ 171.0, 166.1, 152.6, 116.0, 78.7, 59.8, 52.0, 44.0, 41.4, 39.0, 29.5, 22.5, 18.5.

^{1}H NMR (pyridine-d$_5$, 500 MHz): δ 6.73 (s, 1H), 6.14 (brs, 1H), 4.61 (brd, *J* = 13.3 Hz, 1H), 4.32 – 4.24 (m, 1H), 4.07 (t, *J* = 7.0 Hz, 2H), 3.68 (s, 3H), 3.01 – 2.96 (m, 1H), 2.73 – 2.61 (m, 3H), 2.55 (dd, *J* = 16.1, 3.7 Hz, 1H), 2.44 (s, 3H), 1.69 – 1.33 (m, 4H).

^{13}C NMR (pyridine-d$_5$, 100 MHz): δ 171.4, 167.0, 154.7, 116.8, 79.7, 60.9, 52.2, 45.8, 42.3, 39.7, 30.0, 23.2, 19.6.

Conflicts of interest

There are no conflicts to declare.

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Notes and references

1 (a) Yan, L.-H.; Li, X.; Wang, B.-G. *Nat. Prod. Rep.* **2023**, in press; (b) R. W. Bates, T. L. Pham, P. Sae-Lao, manuscript in preparation.

2 For a recent contribution from this laboratory, see (a) T. L. Pham, P. Sae-Lao, H. H. M. Toh, D. Csókás, R. W. Bates, *J. Org. Chem.* **2023**, *87*, 16111. For other recent examples, see (b) K. M. Lambert, J. B. Cox, L. Liu, A. C. Jackson, S. Yruegas, K. B. Wiberg, J. L. Wood, *Angew. Chem. Int. Ed.* **2020**, *59*, 9757; (c) C. A. Carson, M. A. Kerr, *Angew. Chem., Int. Ed.* **2006**, *45*, 6560.

3 H.-L. Chen, W.-T. Zhao, Q.-P. Liu, H.-Y. Chen, W. Zhao, D.-F. Yang, X.-L. Yang, *Fitoterapia* **2020**, *141*, 104475.

4 For a related natural product which has the same carboxylic acid moiety, see Y.-L. Jia, M.-Y. Wei, H.-Y. Chen, F.-F. Guan, C.-Y. Wang, C.-L. Shao, *Org. Lett.* **2015**, *17*, 4216.

5 A. Nakayama, Y. Yasumo, Y. Yamamoto, K. Saito, K. Kitsuwa, H. Okamura, T. Shinada, *J. Nat. Prod.* **2022**, *85*, 1052 and references therein.

6 S. Lahore, S. T. Aiwale, P. Sardi, S. Dallavalle, *Tetrahedron Lett.* **2014**, *55*, 4196.

7 (a) C. L. Rand, D. E. Van Horn, M. W. Moore, E. Negishi, *J. Org. Chem.* **1981**, 46, 4093; (b) Cantagrel, G.; Meyer, C.; Cossy, J. *Synlett* **2007**, 2983.

8 P. Wipf, S. Lim, *Angew. Chem. Int. Ed. Engl.* **1993**, 32, 1068.

9 For the synthesis of related oxazines, see (a) I. A. O'Neil, A. J. Potter, *Chem. Commun.* **1998**, 1487; (b) M. Gärtner, M. Jäkel, M. Achatz, C. Sonnenschein, O. Tverskoy, G. Helmchen, *Org. Lett.* **2011**, *13*, 2810.

10 I. R. Hazelden, X. Ma, T. Langer, J. F. Bower, *Angew. Chem. Int. Ed. Engl.* **2016**, 55, 11198.

11 (a) P. L. Anelli, F; Montanari, S. Quici, *Org. Synth.* **1990**, 69, 212; (b) P. L. Anelli, C. Biffi, F; Montanari, S. Quici, *J. Org. Chem.* **1987**, *52*, 2559.

12 R. Grigg, J. Markandu, T. Perrior, S. Surendrakumar, W. J. Warnock, *Tetrahedron* **1992**, *48*, 6929.

13 Y. Yasui, K. Ogata, I. Sato, Y. Hayashi, *Adv. Synth. Catal.* **2014**, 356, 3106.

14 Z. Zhang, Y. Yu, L. S. Liebeskind, *Org. Lett.* **2008**, *10*, 3005.

15 J. Ding, W. Jiang, H.-Y. Bai, T.-M. Ding, D. Gao, X. Bao, S.-Y. Zhang, *Chem. Commun.* **2018**, *54*, 8889.

16 *cis*-Stereochemistry was assigned on the basis that the aminal proton is essentially a singlet, consistent with an axial hydroxy group. For our work on analogous heterocycles, see

R. W. Bates, C. H. Tang, Y. Tan. S. N. bte Buang, *Synlett*, **2012**, 2266.

17 M. W. Tijihuis, J. D. M. Herscheid, H. C. J. Ottenheijm, *Synthesis* **1980**, *11*, 890.

18 Details of the X-ray structure determination have been deposited with the Cambridge Crystallographic Data Centre and may be obtained at http://www.ccdc.cam.ac.uk; CCDC deposition number: 2292753.

19 S. Roy, S. Roy, G. W. Gribble, *Tetrahedron* **2012**, *68*, 9867.

20 K.M. Foote, C. J. Hayes, M. P. John, G. Pattenden, *Org. Biomol. Chem.* **2003**, *1*, 3917.