Total Synthesis of Bacterial 5-(3-Indolyl)oxazole Alkaloids: Pimprinols A–C

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This paper is dedicated to the memory of Professor József Reiter.

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Abstract
Pimprinols A, B, and C are bacterial 5-(3-indolyl)oxazole alkaloids that have been isolated from Streptomyces sp. Lv3–13. In this paper, we report a new synthesis of pimprinol A and the first total synthesis of pimprinol B and pimprinol C. In addition, antipodes of the naturally occurring pimprinols A and C, as well as the racemates of these two alkaloids were also prepared. In the pivotal step, the 1,3-oxazole ring was constructed by a Nicolaou’s modified Robinson–Gabriel cyclization.

Key words
oxazole, natural products, bacterial alkaloids, pimprinols A–C, total synthesis

Oxazole ring-containing compounds are significant representatives of natural products and synthetic pharmaceuticals.1–5 The bacterial alkaloids pimprinols A–C [(R)-1, 2, (R)-3; Figure 1], which belong to the 5-(3-indolyl)oxazole family, were isolated from the rare actinomycetes, Streptomyces sp. Lv3–13 by Müller and co-workers in 2012.6 All three extracted alkaloids [(R)-1, 2, (R)-3] were described as yellow oils and their structures were elucidated by UV, 1D and 2D NMR spectroscopy, and by HRMS (ESI, +) analysis. The absolute configurations of pimprinol A [(R)-1] and C [(R)-3] were determined by Mosher ester analysis.

The only known synthesis of pimprinol A [(R)-1] was described in 2014 by Wu et al. (Scheme 1).7 In this one-pot method, compound (R)-1 was prepared by treatment of 1-(1H-indol-3-yl)ethane (4) with L-threonine (5, 2 equiv) in the presence of I2 in DMSO at 110 °C. The product was obtained in 70% yield and 96% enantiomeric excess as a pale-brown solid. The alkaloids pimprinol B (2) and C [(R)-3] have not yet been synthesized.

Herein, we would like to report a new total synthesis of pimprinol A [(R)-1] and the first total synthesis of pimprinol B (2) and C [(R)-3]. In addition, antipodes and racemates of pimprinol A and C were also prepared.

Initially, the synthesis of racemic pimprinol A [(rac)-1] was investigated starting from the easily available L-ala- nine [(rac)-6; Scheme 2]. 2-Chloro-1-methyl-2-oxoethyl acetate [(rac)-7] was prepared as previously reported.8–10 Reaction of (rac)-6 with NaN3 in glacial acetic acid, followed by treatment with an excess of SOCl2, afforded compound (rac)-7. Intermediate (rac)-9 was obtained by acylation of tryptamine (8) with (rac)-7 in the presence of Et3N in 88% yield. Oxidation of (rac)-9 with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in a THF–water solvent mixture at 0 °C led to the corresponding acylamino-ketone (rac)-10 in

Figure 1 Chemical structures of pimprinols A–C

Scheme 1 Wu’s synthesis of natural (+)-pimprinol A
excellent yield. The Robinson–Gabriel cyclization of acyl-
amino-ketone (rac)-(10) with propylphosphonic anhydride
(T3P®) under microwave conditions was unsuccessful,
with the starting material being decomposed. Subsequent-
ly, the ring-closure reaction was attempted using Nicolau’s
protocol with POCl3 in pyridine at room temperature.12 In
this reaction, the desired 1,3-oxazole derivative (rac)-(11)
was obtained in 80% yield. Removal of the acetyl group by
alkaline hydrolysis furnished the target molecule, racemic
pimprinol A [(rac)-(1)], in almost quantitative yield.

By following the above synthetic route, natural (+)-pim-
prinol A [(R)-(1)] and its enantiomer (−)-pimprinol A [(S)-(1)]
were prepared starting from (R)-alanine [(R)-(6)] and (S)-ala-
nine [(S)-(6)], respectively. It is important to note that the
substitution of the amino group in alanine occurs by double
inversion,10,11 Natural (+)-pimprinol A [(R)-(1)] was obtained
in four steps from known (1R)-2-chloro-1-methyl-2-
oxoethyl acetate [(R)-(7)] in 60% overall yield and in 98% ee.
(−)-Pimprinol A [(S)-(1)] was synthesized from the corre-
sponding acid chloride (S)-(7) in a similar overall yield (61%).
The enantiomeric purity was 98% also in the final product,
which was determined by chiral chromatographic separa-
tion on a polysaccharide stationary phase (column: 150 × 4.6 mm Lux 5
amylose-1, temperature: 20 °C, mobile phase: acetonitrile with 0.1 %
ethanolamine).

Racemic pimprinol C [(rac)-(3)] was prepared from the
known 1-(chlorocarbonyl)propyl acetate [(rac)-(13)]15,16 by
using an analogous procedure in four steps in 88% overall
yield (Scheme 2). The natural alkaloid pimprinol C [(R)-(3)]
and its enantiomer [(S)-(3)] were synthesized in a similar
manner starting from (1R)- [(R)-(13)]15 and (1S)-1-(chloro-
carbonyl)propyl acetate [(S)-(13)],16 respectively. The latter
compounds were obtained in more than 80% yield and in
98% ee.

Next, the synthesis of pimprinol B (2) was studied from
two readily available oxazole derivatives: methyl [5-(1H-in-
dol-3-yl)-1,3-oxazol-2-yl] acetate (21) and the natural
product labradorin 5 (22; Scheme 3). First, tryptamine (8)
was converted into compounds 21 and 22 through a three-
step procedure involving acylation with the appropriate
acyl chlorides, DDQ mediated oxidation, and T3P®-promot-
ed Robinson–Gabriel cyclodehydration under microwave
conditions in a vent-and-resel vessel. The reaction of ester
21 with MeMgl or MeI was unsuccessful. In both cases the
starting material was recovered. It is hypothesized that the
reaction of oxazole 21 with Grignard or organolithium re-
agent produced an inactive dianion by deprotonation of
both the indole NH and the active methylene group. Water
addition to, or epoxidation of, the isopropylidene double
bond in labradorin 5 (22) was unsuccessful with various re-
agents, such as H5SO4/H2O at room temperature,17 poly-
phosphoric acid (PPA) at 90 °C,18 Hg(OAc)2/THF–H2O then
NaOH/NaBH4,19 HCl/THF–H2O at reflux,20 and meta-chloro-
peroxybenzoic acid (mCPBA) at 0 °C.21 Finally, upon treat-
ment of labradorin 5 (22) with 50% aqueous H2SO4 in boiling
1,4-dioxane22 for 4 days, pimprinol B (2) was produced
with 15% conversion and in 11% isolated yield. The main
component of the residue was the starting material, with
some decomposition detected. It is assumed that the poor
reactivity of the isopropylidene double bond in compound
22 is caused by extensive conjugation.

Finally, a more efficient total synthesis of pimprinol B
(2) was elaborated starting from commercially available 3-
hydroxy-3-methylbutanoic acid (23; Scheme 4). Protection
of the tertiary hydroxyl group of 23 with acetyl chloride
afforded carboxylic acid 24.23 The latter intermediate and
tryptamine (8) were coupled according to Methods A and B.
First carbonyldimidazole (CDI) as coupling agent was used.

![Scheme 2 Synthesis of racemic and optically active pimprinol A and C](image-url)
in the amide formation but this resulted in the required product in only moderate yield. However, applying 1-
[bis(dimethylamino)-methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate (HATU) and
Hünig’s base, furnished the corresponding amide 25 in
good yield. Although Method B resulted in a higher yield,
the final product was contaminated with HATU, which was
difficult to eliminate. Subsequent oxidation of intermediate
25 with DDQ in a THF–water solvent mixture provided β-
keto amide 26. Reaction of compound 26 with POCl₃ in pyr-
idine, followed by alkaline hydrolysis of the ester group
generated pimprinol B in 17% (Method A) and 30% (Method
B) overall yields.

Pimprinols A–C were obtained as colorless crystals with
sharp melting points, unlike the isolated samples. The ana-
lytical data of these synthesized alkaloids are in agreement
with those reported for the natural products. The only sig-
nificant difference was found in the specific rotation val-
ues.

In conclusion, a convergent synthesis of racemic and op-
tically active pimprinols A and C has been developed from
readily available amino acids in six steps using practical and
convenient synthetic methodology. Furthermore, the first
total synthesis of optically inactive pimprinol B was accom-
plished in five steps starting from commercially available
3-hydroxy-3-methylbutanoic acid. In addition, 25 new
Reactions under microwave conditions were carried out with a MicroSYNTH T640 in ‘vent-and-reseal’ vessels with an ATC-FO automatic temperature control and limitation of maximum power to 200–300 W. All melting points were determined with a Büchi B-540 capillary melting point apparatus and are uncorrected. IR spectra were obtained with a Bruker Alpha FT-IR spectrophotometer in KBr pellets or film. 1H and 13C NMR spectra were recorded in DMSO-d6, CDCl3, or CD3OD in 5 mm tubes at r.t., with a Bruker Avance III HD 600 (600 and 150 MHz for 1H and 13C NMR spectra, respectively) or a Bruker Alpha FT-IR spectrophotometer in KBr pellets or film. Mass spectra were recorded with a Bruker O-TOF MAXIS Impact mass spectrometer coupled to a Dionex Ultimate 3000 RS HPLC system with a diode array detector. Reactions were monitored by flash chromatography (CH2Cl2–MeOH). All reagents were purchased from commercial sources and used without further purification. Analytical samples of new compounds were obtained by recrystallization from the solvents or solvent mixtures given below in parentheses. The [α]D values were determined as an average value of three measurements, measured in MeOH.

Compounds (rac)-1, (R)-1, 2, (R)-3, (rac)-9, 17, 18, 20, 22 are described in the literature, while compounds (S)-1, (rac)-3, (S)-3, (R)-9, (S)-9, (rac)-10, (R)-10, (S)-10, (rac)-11, (R)-11, (S)-11, (rac)-14, (R)-14, (S)-14, (rac)-15, (R)-15, (S)-15, (rac)-16, (R)-16, (S)-16, 19, 21, 25, 26, 27 are novel.

**Chromatographic Separation and Conditions**

During chiral separations, a polar organic mode was used on a polysaccharide stationary phase (150 × 4.6 mm Lux 5 μm amyllose-1). The column was purchased from Phenomenex (Torrance, USA). The mobile phase used in this work was acetonitrile (gradient grade) with 0.1% diethylamine. Chemicals were purchased from Merck (Darmstadt, Germany). Chromatographic experiments were performed with a Waters Acquity UPC-H-Class system (Milford, USA) equipped with a quaternary solvent delivery pump, autosampler, photodiode array detector and Empower 3 software. The column temperature was 20 °C. This UHPLC system had a flow-through-needle (FTN) sample injector and 500 nL flow cell. Before analysis, samples were dissolved in pure acetonitrile (0.5 mg/mL); injection volume was 1 μL.

**Preparation of Amides 9, 14, 17, 18; General Procedure**

Tryptamine (8; 14 mmol) and triethylamine (21 mmol, 1.5 equiv) were dissolved in CH2Cl2 (80 mL) and cooled in an ice-water bath. To this solution, the appropriate acyl chloride (15.4 mmol) was added dropwise. After addition of the acyl chloride, the reaction mixture was warmed to rt and stirred for 2 hours. After the reaction was complete, the mixture was washed with water (60 mL), 5% HCl solution (60 mL) and again with water (60 mL). The organic phase was dried over MgSO4, filtered and evaporated to provide the amides (9, 14, 17, 18). The crude products were purified by flash column chromatography (CH2Cl2–MeOH).

2-[(1H-Indol-3-yl)ethyl]amino]-1-methyl-2-oxoethyl acetae [(rac)-9]

Yield: 3.047 g (88%); brown oil.

IR (KBr): 3407, 3311, 1738, 1667, 1537, 1323, 1096, 744 cm⁻¹.

1H NMR (600 MHz, CDCl3): δ = 8.20 (br s, 1 H), 7.61 (d, J = 8.0 Hz, 1 H), 7.39 (d, J = 8.1 Hz, 1 H), 7.26 (br s, 1 H), 7.21 (t, J = 7.3 Hz, 1 H), 7.14 (t, J = 7.7 Hz, 1 H), 6.19 (br s, 1 H), 5.15 (q, J = 6.9 Hz, 1 H), 3.69–3.62 (m, 1 H), 3.61–3.54 (m, 1 H), 3.00 (t, J = 6.7 Hz, 2 H), 1.93 (s, 3 H), 1.43 (d, J = 6.8 Hz, 3 H).

13C NMR (150 MHz, CDCl3): δ = 170.3, 169.4, 136.3, 127.3, 122.23, 122.16, 119.6, 118.6, 112.7, 111.3, 70.6, 39.5, 25.0, 20.9, 17.9 ppm.

**HRMS:** [M + H]+ calcd for C16H21N2O3: 289.1552; found: 289.1546.

**Preparation of Amides 9, 14, 17, 18; General Procedure**

Tryptamine (8; 14 mmol) and triethylamine (21 mmol, 1.5 equiv) were dissolved in CH2Cl2 (80 mL) and cooled in an ice-water bath. To this solution, the appropriate acyl chloride (15.4 mmol) was added dropwise. After addition of the acyl chloride, the reaction mixture was warmed to rt and stirred for 2 hours. After the reaction was complete, the mixture was washed with water (60 mL), 5% HCl solution (60 mL) and again with water (60 mL). The organic phase was dried over MgSO4, filtered and evaporated to provide the amides (9, 14, 17, 18). The crude products were purified by flash column chromatography (CH2Cl2–MeOH).

2-[(1H-Indol-3-yl)ethyl]amino]-1-methyl-2-oxoethyl acetae [(rac)-9]

Yield: 3.047 g (88%); brown oil.

IR (KBr): 3407, 3311, 1738, 1667, 1537, 1323, 1096, 744 cm⁻¹.

1H NMR (600 MHz, CDCl3): δ = 8.20 (br s, 1 H), 7.61 (d, J = 8.0 Hz, 1 H), 7.39 (d, J = 8.1 Hz, 1 H), 7.26 (br s, 1 H), 7.21 (t, J = 7.3 Hz, 1 H), 7.14 (t, J = 7.7 Hz, 1 H), 6.19 (br s, 1 H), 5.15 (q, J = 6.9 Hz, 1 H), 3.69–3.62 (m, 1 H), 3.61–3.54 (m, 1 H), 3.00 (t, J = 6.7 Hz, 2 H), 1.93 (s, 3 H), 1.43 (d, J = 6.8 Hz, 3 H).

13C NMR (150 MHz, CDCl3): δ = 170.3, 169.4, 136.3, 127.3, 122.23, 122.16, 119.6, 118.6, 112.7, 111.3, 70.6, 39.5, 25.0, 20.9, 17.9 ppm.

**HRMS:** [M + H]+ calcd for C16H21N2O3: 289.1552; found: 289.1546.
(1R)-1-[(2-[(1-Indol-3-yl)ethyl]carbamoyl]propyl acetate [(R)-14]
Yield: 3.994 g (99%); brown oil; [α]_D^25 +17.1 (c 1.0, MeOH).
IR (KBr): 3405, 3306, 1738, 1666, 1536, 1324, 745 cm⁻¹.
1H NMR (600 MHz, CDCl_3): δ = 8.17 (br s, 1 H), 7.61 (d, J = 7.9 Hz, 1 H),
7.38 (d, J = 8.2 Hz, 1 H), 7.26 (br s, 1 H), 7.23 (t, J = 7.9 Hz, 1 H), 7.18 (t,
J = 7.9 Hz, 1 H), 7.04 (d, J = 2.3 Hz, 1 H), 6.13 (br s, 1 H), 5.10 (q, J =
4.7 Hz, 1 H), 3.69–3.62 (m, 3 H), 3.61–3.53 (m, 1 H), 3.00 (t, J = 6.7 Hz,
2 H), 1.93 (s, 3 H), 1.91–1.85 (m, 1 H), 1.84–1.77 (m, 1 H), 0.88 (t, J =
7.4 Hz, 3 H).
13C NMR (150 MHz, CDCl_3): δ = 169.59, 169.56, 136.3, 127.3, 122.23,
122.19, 119.6, 118.6, 112.7, 111.3, 74.9, 39.5, 25.1, 25.0, 20.8, 9.0.
HRMS: m/z [M + H]^+ calcd for C_{16}H_{21}N_{2}O_{3}: 289.1552; found: 289.1547.
3-[(2-[(1-Indol-3-yl)ethyl]amino)-1,1-dimethyl-3-oxopropyl acetate (25)
Yield (Method A): 1.149 g (38%); Yield (Method B): 3.387 g (70%);
pale-brown oil.
IR (KBr): 3406, 2935, 1730, 1638, 1253, 833, 743 cm⁻¹.
1H NMR (600 MHz, CDCl_3): δ = 8.33 (br s, 1 H), 7.60 (d, J = 7.9 Hz, 1 H),
7.36 (d, J = 8.1 Hz, 1 H), 7.26 (s, 1 H), 7.20 (t, J = 7.4 Hz, 1 H), 7.12 (t, J =
7.6 Hz, 1 H), 7.02 (d, J = 1.8 Hz, 1 H), 5.80 (br s, 1 H), 3.61 (q, J = 6.5 Hz,
2 H), 2.96 (t, J = 6.8 Hz, 2 H), 2.64 (s, 2 H), 1.73 (s, 3 H), 1.51 (s, 6 H).
13C NMR (150 MHz, CDCl_3): δ = 170.9, 169.4, 136.4, 127.1, 122.2,
122.0, 119.4, 118.6, 112.6, 111.2, 80.6, 47.2, 39.4, 26.5, 25.3, 22.1.
HRMS: m/z [M + H]^+ calcd for C_{17}H_{22}N_{2}O_{3}: 303.1709; found: 303.1703.

Preparation of Ketomides 10, 15, 19, 20, 26; General Procedure
The appropriate amide 9, 14, 17, 18, 25 (4 mmol) was dissolved in THF–H_2O (9:1, 60 mL).
To this solution was added 2.3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ; 8 mmol, 2 equiv) in several
portions at 0 °C. After addition was complete, the mixture was stirred at the same temperature for 2 h (until the consumption of the starting
material as indicated by TLC). The mixture was then poured into EtOAc
(150 mL), extracted with 10% aq. NaHCO_3 (4 × 85 mL), dried over
MgSO_4, filtered and evaporated to give the desired ketoamide. Analytical
samples were obtained by recrystallization from EtOH.
2-[(2-[(1-Indol-3-yl)-2-oxoethyl]amino)-1-methyl-2-oxoethyl acetate [(R)-10]
Yield: 1.096 g (95%); colorless crystals; mp 128–130 °C (EtOH).
IR (KBr): 3278, 3116, 1737, 1666, 1633, 1243, 1048, 756 cm⁻¹.
1H NMR (600 MHz, DMSO-d_6): δ = 12.03 (br s, 1 H), 8.43 (d, J = 3.1 Hz,
1 H), 8.30 (t, J = 5.6 Hz, 1 H), 8.16 (d, J = 7.4 Hz, 1 H), 7.49 (d, J = 7.9 Hz,
1 H), 7.36–7.27 (m, 2 H), 5.07 (q, J = 6.9 Hz, 1 H), 4.48 (d, J = 6.9 Hz,
2 H), 2.10 (s, 3 H), 1.39 (d, J = 7.2 Hz, 3 H).
13C NMR (150 MHz, DMSO-d_6): δ = 190.0, 170.5, 169.9, 136.6, 133.9,
125.6, 123.1, 122.1, 121.3, 114.1, 112.4, 69.8, 45.6, 21.0, 18.1.
HRMS: m/z [M + H]^+ calcd for C_{17}H_{17}N_{2}O_{4}: 289.1188; found: 289.1183.
(1R)-2-[(2-[(1-Indol-3-yl)-2-oxoethyl]amino)-1-methyl-2-oxoethyl acetate [(R)-10]
Yield: 1.049 g (91%); colorless crystals; mp 128–130 °C (EtOH); [α]_D^25 +31.6 (c 1.0, MeOH).
IR (KBr): 3386, 3258, 1743, 1662, 1528, 1230, 745 cm⁻¹.
1H NMR (600 MHz, DMSO-d_6): δ = 12.03 (br s, 1 H), 8.44 (d, J = 3.1 Hz,
1 H), 8.31 (t, J = 5.6 Hz, 1 H), 8.17 (d, J = 7.5 Hz, 1 H), 7.49 (d, J = 7.7 Hz,
1 H), 7.26–7.17 (m, 2 H), 5.07 (q, J = 6.8 Hz, 1 H), 4.48 (d, J = 5.8 Hz,
2 H), 2.10 (s, 3 H), 1.40 (d, J = 6.8 Hz, 3 H).
Yield: 1.247 g (93%); colorless crystals; mp 154–157 °C (EtOH); [\(\delta\) 13C NMR (150 MHz, DMSO-d6): \(\delta = 190.0, 170.6, 169.9, 136.6, 133.9, 125.6, 123.1, 122.1, 121.3, 114.1, 114.2, 69.8, 45.6, 21.0, 18.1.]

HRMS: \(m/z [M + H]^+\) calcd for \(C_9H_{14}N_2O_4\): 289.1188; found: 289.1183.

(15)-2-[(1H-Indol-3-yl)-2-oxoethyl]amino]-1-methyl-2-oxoethylic acid [(S)-15]

Yield: 1.072 g (93%); colorless crystals; mp 134–136 °C (EtOH); [\(\delta\) 13C NMR (150 MHz, DMSO-d6): \(\delta = 190.0, 170.5, 169.9, 136.6, 133.9, 125.6, 123.1, 122.1, 121.3, 114.1, 114.2, 69.8, 45.6, 21.0, 18.1.]

HRMS: \(m/z [M + H]^+\) calcd for \(C_{16}H_{19}N_2O_4\): 303.1345; found: 303.1339.

Methyl 3-[(2-(1H-Indol-3-yl)-2-oxoethyl)amino]-3-oxopropanoate (19)

Yield: 1.086 g (99%); pale-brown crystals; mp 173–176 °C (EtOH).

HR (KBr): 3302, 3219, 1741, 1667, 1625, 1437, 1208, 743 cm\(^{-1}\).

[\(\delta\) 1H NMR (600 MHz, CDCl3): \(\delta = 8.86 (br s, 1 H), 8.35 (t, J = 3.7 Hz, 1 H), 7.96 (d, \(J = 3.1 Hz, 2 H\)), 7.49–7.43 (m, 1 H), 7.37–7.30 (m, 2 H), \(J = 4.3 Hz, 2 H\)].

[\(\delta\) 13C NMR (150 MHz, CDCl3): \(\delta = 184.8, 169.2, 165.1, 136.1, 131.1, 125.2, 124.1, 123.1, 122.2, 115.4, 111.6, 52.6, 46.6, 41.3.]

HRMS: \(m/z [M + H]^+\) calcd for \(C_{16}H_{20}N_2O_4\): 279.0954; found: 275.1024.

N-[(2-(1H-Indol-3-yl)-2-oxoethyl]methylbut-2-ename (20)

Yield: 1.015 g (99%); colorless crystals; mp 243–245 °C (EtOH, decomp.) (lit. \(mp 230–233 °C\)).

HR (KBr): 3335, 3221, 1624, 1536, 1515, 1435, 926, 742 cm\(^{-1}\).

[\(\delta\) 1H NMR (400 MHz, DMSO-d6): \(\delta = 11.99 (br s, 1 H), 8.43 (s, 1 H), 8.22–8.12 (m, 1 H), 8.05 (t, J = 5.6 Hz, 1 H), 7.53–7.45 (m, 1 H), 7.28–7.16 (m, 2 H), 5.81 (s, 1 H), 4.48 (d, \(J = 5.8 Hz, 2 H\)), 2.10 (s, 3 H), 1.81 (s, 3 H).]

[\(\delta\) 13C NMR (100 MHz, DMSO-d6): \(\delta = 190.8, 166.4, 149.0, 136.6, 133.7, 125.6, 123.0, 122.0, 121.3, 119.1, 114.3, 113.2, 45.6, 27.0, 19.5.]

3-[(2-(1H-Indol-3-yl)ethyl]amino]-1,1-dimethyl-3-oxopropyl acetate (26)

Yield: 696 mg (55%); colorless crystals; mp 169–171 °C (EtOH, decomp.).

HR (KBr): 3328, 3243, 1737, 1630, 1431, 1251, 1144, 746 cm\(^{-1}\).

[\(\delta\) 1H NMR (400 MHz, DMSO-d6): \(\delta = 12.01 (br s, 1 H), 8.43 (s, 1 H), 8.20–8.12 (m, 2 H), 7.52–7.47 (m, 1 H), 7.25–7.17 (m, 2 H), 4.47 (d, \(J = 5.6 Hz, 2 H\)), 2.74 (s, 2 H), 1.93 (s, 3 H), 1.51 (s, 6 H).]

[\(\delta\) 13C NMR (100 MHz, DMSO-d6): \(\delta = 190.4, 170.1, 169.1, 136.6, 133.8, 125.6, 123.1, 122.0, 142.1, 114.2, 80.2, 45.9, 45.2, 26.5, 22.5.]

HRMS: \(m/z [M + H]^+\) calcd for \(C_{17}H_{24}N_2O_6\): 317.1501; found: 317.1496.

Formation of Oxazoles 11, 16, 27 in the Presence of POCl3 and Pyridine; General Procedure

Ketoamide (10, 15, 26; 0.6 mmol) was dissolved in pyridine (2 mL), POCl3 (3.24 mmol, 3.4 equiv) was added at r.t. and the reaction mixture was stirred 3 hours. After the reaction was complete (TLC monitoring), EtOAc (40 mL) and 10% aq. NaHCO3 (60 mL) were added to the mixture, the phases were separated, and the aqueous phase was further extracted with EtOAc (3 × 40 mL). The combined organic extracts were washed with water (60 mL) and brine (60 mL), then dried (MgSO4), filtered and evaporated to afford the appropriate products. Analytical samples were obtained by recrystallization from aqueous EtOH.

1-(1H-Indol-3-yl)-1,3-oxazol-2-yl]methy acetate [(rac)-11]

Yield: 130 mg (80%); pale-brown crystals; mp 139–141 °C (EtOH-H2O).

IR (KBr): 3473, 3171, 1750, 1634, 1495, 1221, 1044, 741 cm\(^{-1}\).

[\(\delta\) 1H NMR (600 MHz, CD3OD): \(\delta = 7.80 (dd, \(J = 0.4 Hz, 2 \delta = 7.9 Hz, 1 H\)), 7.65 (s, 1 H), 7.44 (d, \(J = 8.1 Hz, 1 H\)), 7.25 (s, 1 H), 7.20 (t, \(J = 7.1 Hz, 1 H\)), 7.16 (t, \(J = 7.8 Hz, 1 H\)), 6.01 (q, \(J = 6.8 Hz, 1 H\)), 2.12 (s, 3 H), 1.69 (d, \(J = 6.7 Hz, 3 H\)).]
Yield: 157 mg (92%); pale-yellow crystals; mp 116–117 °C (EtOH–H2O).

IR (KBr): 3379, 3183, 1735, 1631, 1460, 1016, 743 cm⁻¹.

1H NMR (600 MHz, CD3OD): δ = 7.46 (d, J = 7.9 Hz, 1 H), 7.26 (s, 1 H), 7.24–7.19 (m, 1 H), 7.17–7.14 (m, 1 H), 6.02 (q, J = 6.8 Hz, 1 H), 2.13 (s, 3 H), 1.69 (d, J = 6.7 Hz, 3 H).

13C NMR (150 MHz, CD3OD): δ = 171.6, 161.3, 150.9, 138.2, 125.3, 124.3, 123.5, 121.5, 119.5, 112.9, 105.0, 57.0, 20.7, 9.7.


Preparation of Oxazoles 21 and 22 with MW Technique in the Presence of Propyolphosphonic Anhydride (T3P®): General Procedure

Ketoamide (19 or 20; 0.5 mmol), T3P® (1 equiv, 2.98 mL, 50% EtOAc solution) and CH3CN (12 mL) were measured into a vent-and-seal vessel and the reaction mixture was stirred at 100 °C for 1 h under microwave irradiation. After cooling to r.t., the mixture was evaporated, the residue was taken up in CH2Cl2 (50 mL) and extracted with sat. aq. NaHCO3 (2 × 25 mL) and water (4 × 25 mL). The organic layer was dried (MgSO4), filtered and evaporated to afford the appropriate product. Analytical samples were obtained by recrystallization from aqueous EtOH.

Methyl [5-(1H-Indol-3-yl)-1,3-oxazol-2-yl]acetate (21)

Yield: 126 mg (98%); brown crystals; mp 158–160 °C (EtOH–H2O).

IR (KBr): 3170, 2899, 1746, 1637, 1251, 1169, 1006, 739 cm⁻¹.

1H NMR (600 MHz, CD3OD): δ = 7.79 (d, J = 7.9 Hz, 1 H), 7.63 (s, 1 H), 7.43 (d, J = 8.0 Hz, 1 H), 7.24 (s, 1 H), 7.20 (t, J = 7.3 Hz, 1 H), 7.15 (t, J = 7.5 Hz, 1 H), 3.99 (s, 3 H), 3.98 (s, 1 H), 3.77 (s, 3 H).

13C NMR (150 MHz, CD3OD): δ = 169.8, 156.9, 151.1, 138.2, 125.3, 124.3, 123.5, 121.4, 120.5, 119.7, 112.8, 105.4, 81.6, 49.1, 38.8, 26.8, 22.4.

Preparation of Pimprinol Alkaloids 1–3; General Procedure

Acetoxy-protected oxazole (11, 16 or 27; 0.7 mmol) was dissolved in MeOH (28 mL) and aq. NaOH (3.08 mmol in 0.5 mL water, 4.4 equiv) was added. The reaction mixture was stirred at r.t. until the reaction was complete, then the solvent was evaporated. The residue was taken up in a mixture of EtOAc (50 mL) and water (50 mL), and the phases were separated. The aqueous mixture was extracted with further EtOAc (3 × 30 mL), and the combined organic phases were dried over MgSO₄, filtered and evaporated. The products were purified by recrySTALLization from MeCN.

1-[(1H-Indol-3-yl)-1,3-oxazol-2-yl]ethanol [(rac)-1]
Yield: 155 mg (97%); pale-yellow crystals; mp 157–160 °C (MeCN) (lit. mp 151–152 °C).
IR (KBr): 3266, 1681, 1440, 1376, 1128, 1098, 972, 732 cm⁻¹. (lit.6 mp 151–152 °C).

Yield: 161 mg (95%); colorless crystals; mp 159–160 °C (MeCN).
IR (KBr): 3221, 1638, 1445, 1338, 1248, 1107, 974, 751 cm⁻¹. (MeCN); [α]D²⁷ +12.8 (c 1.0, MeOH).

13C NMR (150 MHz, CD3OD): δ = 164.5, 150.4, 138.2, 125.3, 124.0, 123.5, 121.4, 120.5, 119.1, 112.8, 105.3, 69.7, 29.6, 10.1.

(1R)-1-[(1H-Indol-3-yl)-1,3-oxazol-2-yl]propan-1-ol [(1R)-3], pimprinol C
Yield: 158 mg (93%); 98% ee; colorless crystals; mp 143–145 °C (MeCN); [α]D²⁷ +12.2 (c 1.0, MeOH).
IR (KBr): 3285, 1634, 1587, 1438, 1258, 1125, 966, 732 cm⁻¹.
1H NMR (600 MHz, CD3OD): δ = 7.82 (d, J = 7.9 Hz, 1 H), 7.65 (s, 1 H), 7.44 (d, J = 8.1 Hz, 1 H), 7.23 (s, 1 H), 7.20 (t, J = 7.2 Hz, 1 H), 7.16 (t, J = 7.8 Hz, 1 H), 7.40 (t, J = 6.9 Hz, 1 H), 2.07–1.93 (m, 2 H), 1.01 (t, J = 7.4 Hz, 3 H) ppm.
13C NMR (150 MHz, CD3OD): δ = 146.5, 150.4, 138.2, 125.3, 124.0, 123.5, 121.4, 120.5, 119.1, 112.8, 105.4, 69.7, 29.6, 10.1.

Supporting Information
Supporting information for this article is available online at https://doi.org/10.1055/s-0039-1690336.

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