

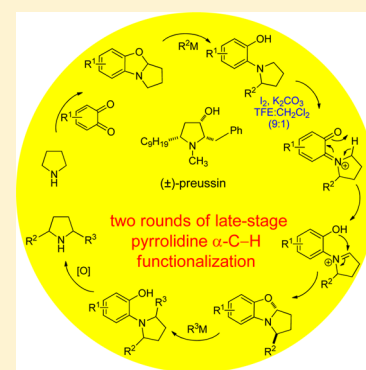
Molecular Iodine-Mediated α -C–H Oxidation of Pyrrolidines to N,O -Acetals: Synthesis of (\pm)-Preussin by Late-Stage 2,5-Difunctionalizations of Pyrrolidine

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Supporting Information

ABSTRACT: We previously reported an iterative synthesis of unsymmetrical 2,5-disubstituted pyrrolidines from pyrrolidine by two rounds of redox-triggered α -C–H functionalization. Although this approach can be used to introduce substituents at the 2- and 5-positions, it is lengthy because the redox auxiliary must be removed and then reinstalled. Therefore, we sought to develop a method to oxidize 2-functionalized pyrrolidine to cyclic N,O -acetal which could then react with a nucleophile for introduction of the 5-substituent. In this work, we found that molecular iodine can mediate the preferential oxidation of secondary over tertiary α -C–H bonds of α -substituted pyrrolidines to form cyclic N,O -acetals, improving the step economy of our previously reported method. With this strategy, (\pm)-preussin and its C(3) epimer were synthesized from (\pm)-pyrrolidin-3-ol.



INTRODUCTION

N,O -Acetals are analogues of acetals in which one oxygen atom in acetal is replaced by a nitrogen atom. N,O -Acetals are present in many bioactive natural products.¹ In addition, N,O -acetals are synthetically useful because they act as masked iminium ions that are stable under aerobic conditions but can be activated toward nucleophilic addition² or oxidation.³ Chiral N,O -acetal synthons have been used in enantioselective syntheses of pyrrolidine and piperidine alkaloids.^{2a,b,4} In analogy to the synthesis of acetals by reactions of aldehydes and diols, N,O -acetals can be synthesized by addition of α -amino alcohols to aldehydes, as well as by other methods.^{4,5} Recently, N,O -acetal construction by direct oxidative C–O bond formation has become a focus of research (Figure 1). The reaction often begins with oxidation of the α -C–H bond of an amine by an intermolecular oxidant to produce an iminium ion, which is attacked by an intra- or intermolecular hydroxy group to generate the N,O -acetal. Previously reported methods have used the following oxidation pathways for iminium ion formation: oxidation by metal-based oxidants combined with an inexpensive terminal oxidant⁶ (e.g., $\text{Cu}(\text{OAc})_2/\text{O}_2$,^{6d} $\text{Ag}_2\text{O}/\text{O}_2$ ^{6f}); oxidation by hypervalent iodine reagents⁷ (e.g., PIDA, PIFA^{7c,e}); redox-neutral type of amine α -oxygenation,^{2c–e,8} anodic oxidation;⁹ photoinduced oxidation.¹⁰ However, most of the previous work involved α -unsubstituted tertiary amines, and more research is necessary to enhance the regioselectivity of the oxidation of α -substituted tertiary amines.

We previously reported an iterative synthesis of unsymmetrical 2,5-disubstituted pyrrolidines from pyrrolidine by two rounds of redox-triggered α -C–H functionalization (Scheme

1).^{2e} In the first round, pyrrolidine reacts with *o*-benzoquinone to generate an N,O -acetal, which then undergoes ring opening by a Grignard or organolithium reagent to introduce the first substituent at the α -position of pyrrolidine. The redox auxiliary is oxidatively removed to give a 2-substituted pyrrolidine. In the second round, the 2-substituted pyrrolidine reacts with *o*-benzoquinone again to reinstall the N,O -acetal in **2**, which also undergoes ring opening by a Grignard or organolithium reagent. Again, the redox auxiliary is removed to give the 2,5-disubstituted pyrrolidine. Although this approach can be used to selectively introduce substituents at the 2- and 5-positions (with the trans product predominating), it is lengthy because the redox auxiliary must be removed and then reinstalled. Therefore, we sought to develop a method to oxidize 2-functionalized pyrrolidine **1**, obtained from the first ring-opening step, to cyclic N,O -acetal **2**, which could then react with a nucleophile for introduction of the 5-substituent (Scheme 1). The challenge was to control the regioselectivity of N,O -acetal formation because oxidation of the tertiary α -C–H, which gives the 2,2-substituted N,O -acetal, proceeds via an iminium ion intermediate that is more thermodynamically stable than the intermediate from oxidation of the secondary α -C–H, which gives the 2,5-substituted N,O -acetal. Herein, we report that with I_2 as the oxidant, the secondary α -C–H of the α -substituted pyrrolidine could be selectively oxidized in the presence of 3 equiv of K_2CO_3 to form a cyclic N,O -acetal. This

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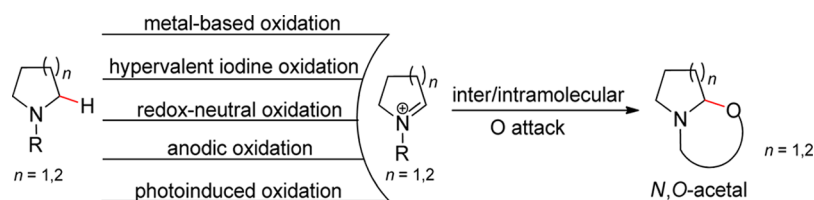


Figure 1. *N,O*-Acetal synthesis by direct oxidative C–O bond formation.

Scheme 1. Synthesis of 2,5-Disubstituted Pyrrolidines by Two-Round Functionalization of Pyrrolidine

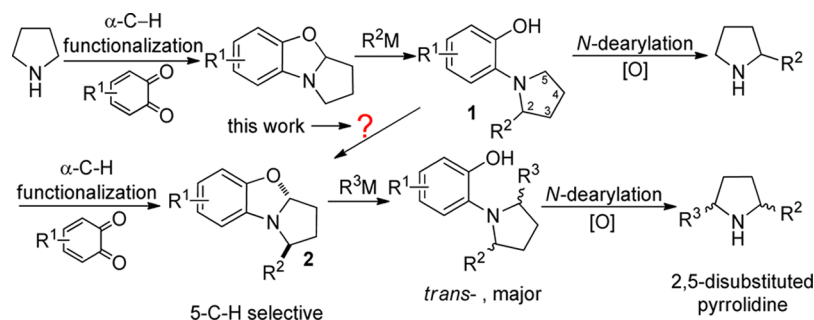
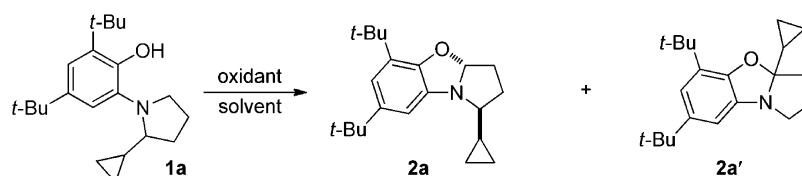


Table 1. Oxidation and Cyclization of *o*-Pyrrolidine-Substituted Phenol **1a**^a



entry	oxidant (equiv)	base (equiv)	solvent	concn of 1a (M)	2a (%) ^b	2a' (%)
1	Cu(OAc) ₂ (0.2)	none	<i>m</i> -xylene	0.03	trace ^c	29 ^c
2	CuCl ₂ (0.2)	none	<i>m</i> -xylene	0.03	49 ^c	0
3	PIDA (1.2)	K ₂ CO ₃ (3.0)	TFE	0.03	38	39
4	PIFA (1.2)	K ₂ CO ₃ (3.0)	TFE	0.03	32	36
5	I ₂ (1.2)	none	TFE	0.03	mess	0
6	I ₂ (1.2)	K ₂ CO ₃ (3.0)	TFE	0.03	75	0
7	I ₂ (1.2)	K ₂ CO ₃ (3.0)	TFE/DCM = (6:1)	0.03	73	0
8	I ₂ (1.2)	K ₂ CO ₃ (3.0)	TFE/DCM = (9:1)	0.03	96 (93 ^d)	0
9	I ₂ (1.2)	K ₂ CO ₃ (3.0)	TFE/DCM = (9:1)	0.05	70	0

^aReaction conditions: **1a** (0.3 mmol) and oxidant in solvent (10 mL) were stirred at rt. ^bDetermined by NMR spectroscopy, with 1,3,5-trimethoxybenzene as the internal standard. ^c**1a** (0.3 mmol) and copper(II) salt (0.06 mmol) in *m*-xylene (10 mL) were heated at 130 °C in air. ^dIsolated yield.

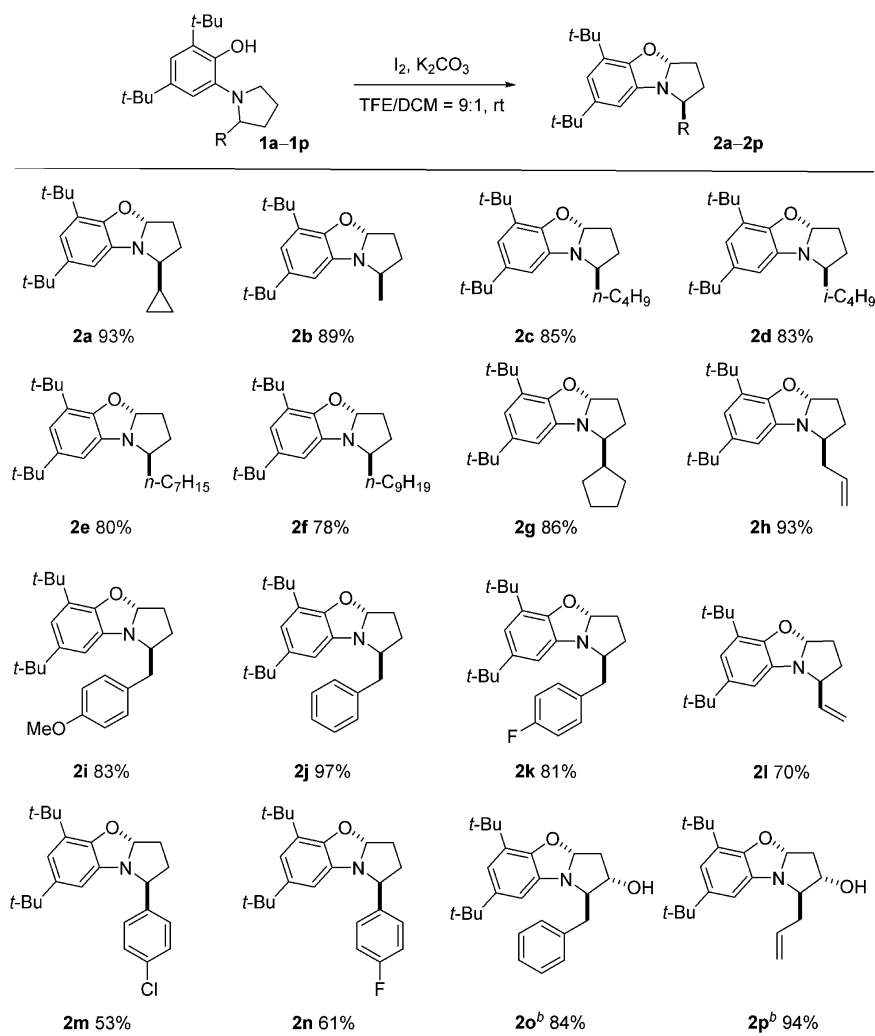
more step-economical method was then used to synthesize the natural product (\pm)-preussin and its C(3) epimer.

RESULTS AND DISCUSSION

First, we oxidized 2,4-di-*tert*-butyl-6-(2-cyclopropylpyrrolidin-1-yl)phenol (**1a**) by various previously reported methods. Specifically, Cu(OAc)₂/O₂^{6d} oxidized the tertiary α -C–H in **1a** to afford 2,2-disubstituted *N,O*-acetal **2a'** in 29% yield (Table 1, entry 1). In contrast, CuCl₂/O₂^{6g} provided desired *trans*-2,5-disubstituted *N,O*-acetal **2a** in 49% yield (entry 2). The use of a hypervalent iodine reagent, PIDA or PIFA, in 2,2,2-trifluoroethanol (TFE)^{7c} resulted in good chemical yields but gave a mixture of two regioisomers in almost equal amounts (entries 3 and 4). Reaction with I₂, a mild, readily available oxidant,¹¹ in TFE gave a complicated reaction mixture (entry 5). However, when K₂CO₃ was added, the reaction cleanly gave *trans*-product **2a** in 75% yield as a single isomer (entry 6). Owing to the poor solubility of **1a** in TFE, we switched to 9:1

TFE/DCM, which improved the yield to 96% (entries 7 and 8). We also evaluated various concentrations and found that the yield dropped at concentrations higher than 0.03 M (entries 8 and 9).

Various alkyl groups are present in 2,5-disubstituted pyrrolidine natural products,¹² so we investigated the reactions of **1** with different alkyl substituents at the α -position of the pyrrolidine ring (Table 2). Within 0.5 h, reactions of **1b–k** exclusively gave desired *N,O*-acetals **2b–k**, respectively. Previously, we found that reinstallation of the *N,O*-acetal by the reaction between *o*-benzoquinone and pyrrolidines with a bulky α -substituent (*n*-heptyl or *n*-nonyl) required at least 48 h.^{2c} With the current method, these reactions could be completed within 0.5 h at room temperature. Note that vinyl- and aryl-substituted substrates **1l–n** were unstable, so they were utilized immediately after purification. By using this procedure, we obtained target products **2l–n** in 53% to 70% yield over two steps. We also tested 2,3-disubstituted

Table 2. Regioselective Oxidative Formation of *N,O*-Acetals **2**^a

^aReaction conditions: **1** (0.3 mmol), I_2 (0.36 mmol), and K_2CO_3 (0.9 mmol) were stirred in 9:1 TFE/DCM (10 mL) at rt. ^bThe reaction was carried out at 0 °C overnight.

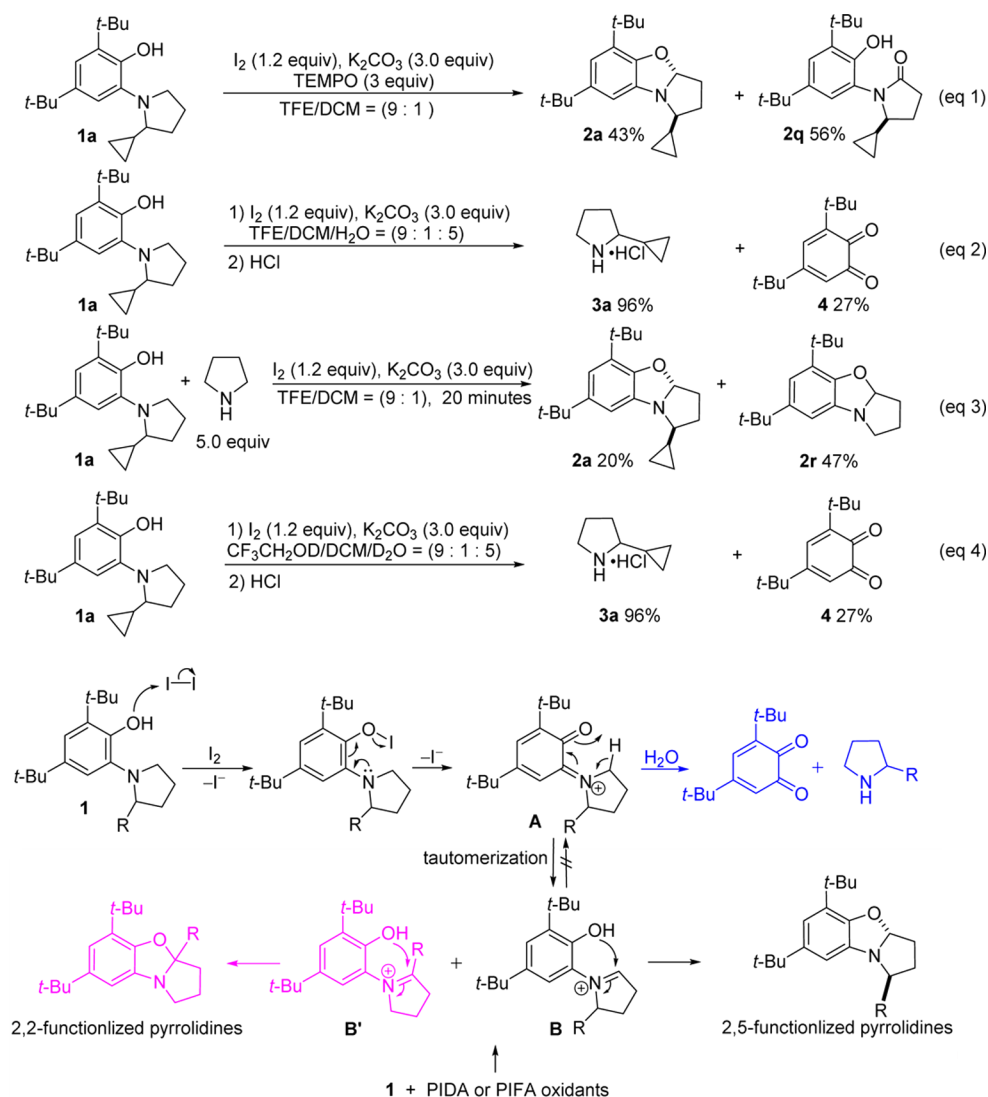
pyrrolidines **1o** and **1p** and were delighted to find that the oxidation-sensitive hydroxyl group was compatible with the reaction conditions, and the desired products **2o** and **2p** were obtained in good yields at 0 °C.

We carried out several experiments to elucidate the reaction mechanism (Scheme 2). Reaction of **1a** in the presence of 3 equiv of TEMPO gave **2a** in 43% yield together with a 56% yield of the amide (**2q**) as the TEMPO oxidation product (Scheme 2, eq 1), showing that the reaction did not go through a free radical mechanism. If the phenoxy group in **1a** was converted to a methyl ether, the resulting substrate did not react and was fully recovered after the reaction (data not shown). This suggested that the reaction began with the oxidation of the phenoxy group. Oxidation of the phenoxy group by I_2 initially gave iminium ion **A**. When H_2O was added to the reaction mixture as a cosolvent, 2-cyclopropylpyrrolidine (**3a**) and 3,5-di-*tert*-butyl-1,2-benzoquinone (**4**), which are the products of hydrolysis of **A**, were obtained (Scheme 2, eq 2). Similarly, the addition of pyrrolidine to the reaction mixture led to the formation of amine exchange product **2r** (Scheme 2, eq 3). Intermediate **A** tautomerized to intermediate **B** through a 1,5-proton shift. Then the cyclization of iminium **B** gave the *trans-N,O*-acetal **2** exclusively. The 2,5-regioselectivity was due

to steric repulsion between the 2-substituent and the carbonyl group during the 1,5-proton shift involved in the transformation of **A** to **B**. When the reaction was carried out in $CF_3CH_2OD/DCM/D_2O$, no deuterium was found in the α -C–H bond of **3a** (Scheme 2, eq 4), showing that **B** could not be converted to **A** (the conversion of **B** to **A** is unfavorable because of the loss of aromaticity). This result suggests that **A** formed first and then tautomerized to **B**, rather than the other way around (it has been reported that **B** can be produced by direct oxidation of tertiary amines^{6d,7c}). However, when PIDA or PIFA was used as the oxidant, the reaction should generate iminium ion **B** and its conformational isomer **B'** in almost equal amount;^{7c,e} the cyclizations of **B** and **B'** afforded equal amounts of 2,5- and 2,2-substituted *N,O*-acetals **2** and **2'**. The reaction also gave 2 equiv of HI, the addition of K_2CO_3 can neutralize the acid generated.

We used the method reported herein to synthesize (\pm)-preussin, which was first isolated in 1988 as a potent antifungal agent¹³ and later revealed to have antitumor and antiviral activities.¹⁴ These bioactivities and its unique all-*cis* structure make it a popular target for total synthesis. More than 30 routes to preussin and (+)-preussin **B**¹⁵ (a heptyl-substituted analogue) have been reported to date, and five of

Scheme 2. Proposed Pathway of the Oxidation Reaction

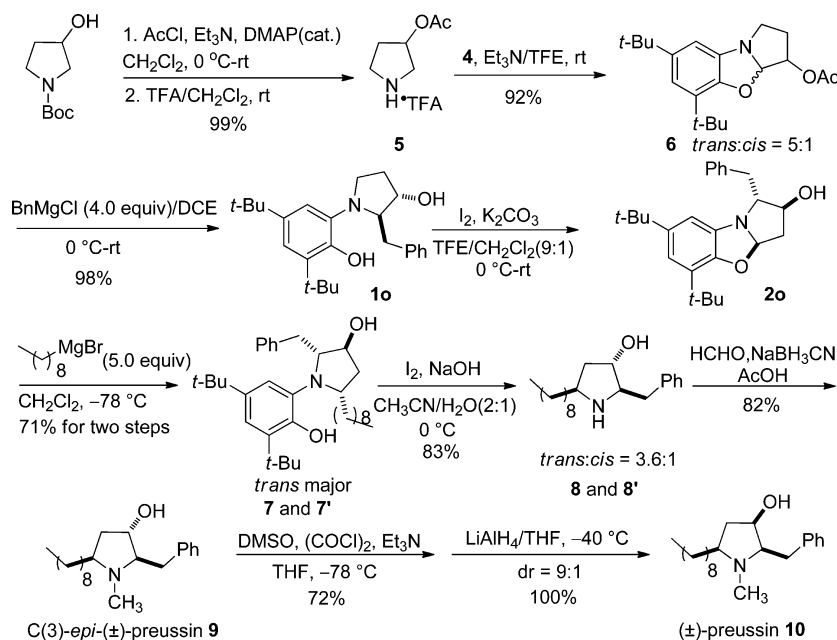


the total syntheses were reported since 2014.^{15a-c,e,f} Syntheses of all eight possible stereoisomers of preussin have also been reported.^{15h,i,l,16} Most of these syntheses start with (L)-phenylalanine derived precursors; after installation of all the substituents in the correct configurations, the linear molecule is then cyclized to form the final pyrrolidine structure.^{15d,f,h,17} We hypothesized that we could use our late-stage two-round α -C-H functionalization protocol for a more-flexible approach to preussin analogues. By employing proper Grignard reagents, other alkyl or aryl substitutions can also be easily introduced at the 2- and 5- positions of pyrrolidine.

We started our synthesis from racemic Boc-protected pyrrolidin-3-ol (Scheme 3, \$9/g, Boc-protected (R)- and (S)-pyrrolidin-3-ol are also commercially available). The acetate of pyrrolidin-3-ol (5) reacted with quinone 4 to give desired *N,O*-acetal 6. The regioselective oxidation of C-2 hydrogen was because of the higher acidity of this hydrogen due to the nearby hydroxy group. Ring opening of 6 with a benzyl Grignard reagent gave *trans*-10 as the only product. The *trans* diastereoselectivity may have resulted from the transient nucleophilic addition to the iminium by the neighboring acetyl carbonyl before the addition of the Grignard reagent (the acetyl group was removed during the treatment of excess amount of

Grignard reagent).¹⁸ The ring opening reaction with the hydroxy group unprotected 6 gave both *trans*- and *cis*-products in almost equal amount. Then 10 was oxidized with $\text{I}_2/\text{K}_2\text{CO}_3$ in 9:1 TFE/DCM to reinstall the *N,O*-acetal moiety, and the resulting compound (20) underwent ring opening by a nonyl Grignard reagent from the opposite side of the C–O bond. *Trans*-diastereoisomer 7 (relative to the hydroxy group) was the major product of the second nucleophilic addition reaction of the *N,O*-acetal. *Trans*-product 7 and *cis*-product 7' were inseparable mixture, also the dr ratio of 7 and 7' cannot be read out from the ^1H NMR spectrum of the crude product because 7' exists as an equilibrium mixture of one major conformer and one minor conformer owing to the restricted rotation of the *trans*-2,5-disubstituted pyrrolidine moiety. The *trans*-major conclusion was deduced from the ratio of products 8 and 8', which were produced from the mixture of 7 and 7'. *N*-Dearylation of 7 followed by reductive amination gave the C(3) epimer of (\pm)-preussin (9). Oxidation and reduction of 9¹⁵ⁱ gave (\pm)-preussin (10), the spectroscopic data of which agreed with the literature.

Scheme 3. Synthesis of (±)-Preussin and Its C(3) Epimer by Late-Stage Functionalizations of Pyrrolidin-3-ol



CONCLUSION

In summary, we found that I₂ mediates regio- and diastereoselective oxidation of the α-C–H bonds of pyrrolidines to form cyclic *N,O*-acetals, thus improving the step economy of our previously reported strategy for synthesizing unsymmetrically 2,5-disubstituted pyrrolidines from pyrrolidine. (±)-Preussin and its C(3) epimer were synthesized by two rounds of functionalization of commercially available (±)-Boc pyrrolidin-3-ol (nine steps, 22% overall yield). Our practical, adaptable strategy for (±)-preussin synthesis is potentially useful for the rapid construction of a library of preussin analogues.

EXPERIMENTAL SECTION

General Information. Unless otherwise noted, all reagents were used without further purification. DCM was distilled from CaH₂ before use. Flash column chromatographies were performed on Qingdao silica gel (200–300 mesh). ¹H, ¹³C spectra were measured on a NMR instrument (400 MHz for ¹H NMR; 100 MHz for ¹³C NMR). Chemical shifts of ¹H NMR spectra were recorded relative to internal standard (TMS δ 0.00). The following abbreviations were used to express the multiplicities: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; br = broad. Chemical shifts of ¹³C NMR spectra were recorded relative to solvent resonance (CDCl₃; δ 77.0). High-resolution mass spectral analyses were performed on a high resolution ESI-FTICR mass spectrometer.

Preparation and Characterization of Substrates. Substrates (1a–k) were synthesized according to our previously reported method.^{2e}

2,4-Di-*tert*-butyl-6-(2-cyclopropylpyrrolidin-1-yl)phenol (1a). A solution of cyclopropylmagnesium bromide (0.5 M in THF, 3 mL, 1.5 mmol) was added dropwise to a solution of 5,7-di-*tert*-butyl-1,2,3,3a-tetrahydrobenzo[*d*]pyrrolo[2,1-*b*]oxazole^{2e} (137 mg, 0.5 mmol) in DCE (10 mL) at 0 °C under Ar. When the reaction completed, the reaction was quenched with saturated aqueous NH₄Cl, extracted with DCM (3×), and dried over MgSO₄. The reaction mixture was concentrated, and the residue was purified by column chromatography (PE/EA = 50:1) to afford the title compound (149 mg, 95% yield) as a colorless oil; *R*_f = 0.30 (PE/EA = 50/1); ¹H NMR (400 MHz, CDCl₃) δ 8.26 (brs, 0.9H), 7.09 (d, *J* = 2.3 Hz, 1H), 7.02 (d, *J* = 2.3 Hz, 1H), 3.23 (ddd, *J* = 9.4, 7.3, 3.8 Hz, 1H), 2.99–2.87 (m,

1H), 2.41–2.30 (m, 1H), 2.17–2.03 (m, 1H), 2.01–1.87 (m, 2H), 1.82–1.60 (m, 1H) 1.41 (s, 9H), 1.27 (s, 9H), 0.66 (ddt, *J* = 13.1, 8.3, 4.1 Hz, 1H), 0.32–0.20 (m, 1H), 0.20–0.05 (m, 1H), 0.05 (dq, *J* = 9.8, 4.9 Hz, 1H), 0.40 (dq, *J* = 10.1, 5.1 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 150.3, 140.7, 135.9, 133.3, 120.3, 116.9, 70.8, 55.3, 34.8, 34.5, 31.7, 30.8, 29.4, 23.4, 14.5, 3.3, 0.5; HRMS (ESI-TOF) *m/z*: [M + H]⁺ Calcd for C₂₁H₃₄NO: 316.2635; found: 316.2640.

2,4-Di-*tert*-butyl-6-(2-methylpyrrolidin-1-yl)phenol (1b). Following the synthetic procedure of 1a, methylmagnesium bromide (3.0 M in Et₂O) was used and the title compound was obtained in 94% yield as a colorless oil; *R*_f = 0.50 (PE/EA = 50/1); ¹H NMR (400 MHz, CDCl₃) δ 8.06 (brs, 0.8H), 7.10 (d, *J* = 2.3 Hz, 1H), 7.06 (d, *J* = 2.3 Hz, 1H), 3.24 (ddd, *J* = 9.5, 7.3, 3.9 Hz, 1H), 3.20–3.08 (m, 1H), 2.83 (q, *J* = 8.7 Hz, 1H), 2.21–2.09 (m, 1H), 2.02–1.83 (m, 2H), 1.63–1.48 (m, 1H), 1.41 (s, 9H), 1.29 (s, 9H), 0.96 (d, *J* = 6.1 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 150.2, 140.9, 135.0, 133.5, 120.5, 116.4, 60.4, 55.5, 34.8, 34.6, 33.0, 31.8, 29.5, 23.0, 19.2; HRMS (ESI-TOF) *m/z*: [M + H]⁺ Calcd for C₁₉H₃₃NO: 290.2478; found: 290.2477.

2,4-Di-*tert*-butyl-6-(2-nonylpyrrolidin-1-yl)phenol (1f). Following the synthetic procedure of 1a, nonyl magnesium bromide (1.0 M in Et₂O) was used and the title compound was obtained in 96% yield as a viscous colorless oil; *R*_f = 0.55 (PE/EA = 50/1); ¹H NMR (400 MHz, CDCl₃) δ 8.06 (brs, 0.9H), 7.10 (s, 0.9H), 7.05 (s, 1H), 3.27–3.16 (m, 1H), 3.04 (d, *J* = 7.9 Hz, 1H), 2.83–2.68 (m, 1H), 2.22–2.05 (m, 1H), 1.97–1.85 (m, 2H), 1.57 (q, *J* = 8.4 Hz, 2H), 1.41 (s, 9H), 1.30 (s, 9H), 1.28–1.09 (m, 15H), 0.86 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 150.1, 140.8, 135.5, 133.5, 120.4, 116.6, 64.9, 55.8, 34.8, 34.5, 34.2, 31.9, 31.7, 30.8, 29.65, 29.56, 29.48, 29.46, 29.3, 26.5, 23.3, 22.7, 14.1; HRMS (ESI-TOF) *m/z*: [M + H]⁺ Calcd for C₂₇H₄₈NO: 402.3730; found: 402.3735.

2,4-Di-*tert*-butyl-6-(2-cyclopentylpyrrolidin-1-yl)phenol (1g). Following the synthetic procedure of 1a, cyclopentylmagnesium bromide (1.0 M in Et₂O) was used and the title compound was obtained in 99% yield as a colorless oil; *R*_f = 0.60 (PE/EA = 50/1); ¹H NMR (400 MHz, CDCl₃) δ 8.18 (brs, 0.8H), 7.10 (d, *J* = 2.3 Hz, 1H), 7.08 (d, *J* = 2.3 Hz, 1H), 3.32–3.11 (m, 2H), 2.87–2.73 (m, 1H), 2.11–1.99 (m, 1H), 1.97–1.77 (m, 3H), 1.74–1.32 (m, 8H), 1.41 (s, 9H), 1.29 (s, 9H), 0.93–0.74 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 150.0, 140.8, 136.2, 133.3, 120.3, 117.1, 68.5, 56.8, 43.6, 34.8, 34.5, 31.7, 30.3, 29.4, 28.3, 28.1, 25.9, 25.4, 23.8; HRMS (ESI-TOF) *m/z*: [M + H]⁺ Calcd for C₂₃H₃₈NO: 344.2948; found: 344.2952.

2,4-Di-*tert*-butyl-6-(2-(4-methoxybenzyl)pyrrolidin-1-yl)phenol (1i). Following the synthetic procedure of 1a, (4-methoxybenzyl)

magnesium chloride (0.05 M in Et₂O)¹⁹ was used and the title compound was obtained in 40% yield as a colorless oil; *R*_f = 0.55 (PE/EA = 50/1); ¹H NMR (400 MHz, CDCl₃) δ 7.90 (brs, 0.8H), 7.16–7.04 (m, 2H), 6.97–6.90 (m, 2H), 6.78–6.70 (m, 2H), 3.75 (s, 3H), 3.36–3.23 (m, 2H), 2.85–2.72 (m, 1H), 2.72–2.61 (m, 1H), 2.47–2.31 (m, 1H), 2.02–1.81 (m, 3H), 1.75–1.59 (m, 1H), 1.42 (s, 9H), 1.30 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 157.8, 149.9, 141.1, 135.0, 133.8, 131.5, 129.9, 120.6, 116.3, 113.6, 66.2, 55.7, 55.2, 39.5, 34.9, 34.6, 31.8, 30.5, 29.5, 22.8; HRMS (ESI-TOF) *m/z*: [M + H]⁺ Calcd for C₂₆H₃₈NO₂: 396.2897; found: 396.2899.

2,4-Di-*tert*-butyl-6-(2-(4-fluorobenzyl)pyrrolidin-1-yl)phenol (1k). Following the synthetic procedure of **1a**, 4-fluorobenzylmagnesium (0.25 M in Et₂O) was used and the title compound was obtained in 85% yield as a colorless oil; *R*_f = 0.50 (PE/EA = 50/1); ¹H NMR (400 MHz, CDCl₃) δ 7.87 (brs, 0.8H), 7.11 (d, *J* = 2.3 Hz, 1H), 7.07 (d, *J* = 2.3 Hz, 1H), 6.99–6.92 (m, 2H), 6.91–6.83 (m, 2H), 3.40–3.23 (m, 2H), 2.84–2.72 (m, 1H), 2.69 (dd, *J* = 13.4, 4.3 Hz, 1H), 2.44 (dd, *J* = 13.4, 8.6 Hz, 1H), 2.05–1.81 (m, 3H), 1.71–1.60 (m, 1H), 1.42 (s, 9H), 1.29 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 161.3 (d, *J* = 244.2 Hz), 149.8, 141.2, 135.0 (d, *J* = 3.1 Hz), 134.8, 133.8, 130.3 (d, *J* = 7.6 Hz), 120.6, 116.3, 114.9 (d, *J* = 21.6 Hz), 65.9, 55.8, 39.6, 34.8, 34.5, 31.7, 30.5, 29.4, 22.8; HRMS (ESI-TOF) *m/z*: [M + H]⁺ Calcd for C₂₅H₃₅FNO: 384.2697; found: 384.2700.

2-Benzyl-1-(3,5-di-*tert*-butyl-2-hydroxyphenyl)pyrrolidin-3-ol (1o). To a solution of *tert*-butyl-3-hydroxypyrrolidine-1-carboxylate (337 mg, 1.8 mmol) in DCM (20 mL) at 0 °C were added NEt₃ (283 mg, 389 μL, 2.8 mmol) and DMAP (24 mg, 0.2 mmol) sequentially under Ar. AcCl (188 mg, 171 μL, 2.4 mmol) was added dropwise, and the reaction was stirred at 0 °C. Upon completion, the reaction was quenched by H₂O and extracted with DCM (50 mL) three times. The combined organic layer was dried with MgSO₄ and concentrated. The residue was purified by chromatography using EA/PE (1:20) to give the double-protected pyrrolidin-3-ol. The protected pyrrolidin-3-ol was stirred in a mixed solvent of DCM (10 mL) and TFA (2 mL). When the reaction was complete, the reaction mixture was concentrated to give **5** (403 mg, 99% yield). ¹H NMR (400 MHz, CDCl₃) δ 8.94 (brs, 1H), 8.78 (brs, 1H), 5.47–5.36 (m, 1H), 3.61–3.44 (m, 4H), 2.34–2.22 (m, 2H), 2.08 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 170.6, 72.2, 51.2, 44.5, 30.6, 20.6; HRMS (ESI-TOF) *m/z*: [M + H]⁺ Calcd for C₆H₁₂NO₂: 130.0863; found: 130.0865.

To a solution of **5** (403 mg, 1.8 mmol) in TFE (60 mL) was added NEt₃ (546 mg, 0.75 mL, 5.4 mmol). Next, 3,5-di-*tert*-butyl-1,2-benzoquinone **4** (436 mg, 1.98 mmol) was added portionwise at 0 °C. Then the reaction was stirred at room temperature. TFE was evaporated when the reaction was completed. The residue was purified by chromatography using EA/PE (1:9) to afford 5,7-di-*tert*-butyl-1,2,3,3a-tetrahydrobenzo[d]pyrrolo[2,1-*b*]oxazole-3-yl acetate **6** as a mixture of trans/cis diastereoisomers (602 mg, 92% yield, trans/cis = 5:1, both trans and cis isomers were used in the next step). Trans isomer: ¹H NMR (400 MHz, CDCl₃) δ 6.83 (d, *J* = 1.9 Hz, 1H), 6.74 (d, *J* = 1.9 Hz, 1H), 5.69 (s, 1H), 5.39–5.25 (m, 1H), 3.64–3.44 (m, 1H), 3.36–3.15 (m, 1H), 2.13 (s, 3H), 2.10–2.00 (m, 1H), 1.92–1.82 (m, 1H), 1.33 (s, 9H), 1.29 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 170.3, 146.8, 144.2, 140.8, 131.0, 117.1, 109.6, 104.4, 78.2, 55.1, 34.7, 34.1, 31.8, 29.4, 29.2, 21.1.

Compound **6** (602 mg) obtained in the previous step was dissolved in DCE (40 mL), and PhCH₂MgCl (7.2 mL, 1.0 M in Et₂O, 7.2 mmol) was added dropwise at 0 °C under Ar. The reaction was diluted with DCM (50 mL) after 2 h, quenched with saturated NH₄Cl (20 mL), and extracted with DCM (50 mL) three times. The organic phase was concentrated and purified by chromatography using EA/PE = 1:9 to give the title compound **1o** (613 mg, 98% yield) as a viscous yellow oil. ¹H NMR (400 MHz, CDCl₃) δ 7.59 (brs, 0.8H), 7.27–7.12 (m, 5H), 7.10–7.05 (m, 2H), 4.26–4.19 (m, 1H), 3.39–3.27 (m, 1H), 3.23–3.15 (m, 1H), 3.11–2.97 (m, 1H), 2.82 (dd, *J* = 13.5, 4.5 Hz, 1H), 2.61–2.47 (m, 1H), 2.31–2.17 (m, 1H), 1.90–1.77 (m, 1H), 1.42 (s, 9H), 1.30 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 149.6, 141.4, 138.1, 134.3, 134.0, 129.1, 128.5, 126.4, 120.9, 116.8, 75.5, 73.5, 53.4, 38.7, 34.8, 34.5, 33.0, 31.7, 29.4; HRMS (ESI-TOF) *m/z*: [M + H]⁺ Calcd for C₂₅H₃₆NO₂: 382.2741; found: 382.2745.

2-Allyl-1-(3,5-di-*tert*-butyl-2-hydroxyphenyl)pyrrolidin-3-ol (1p).

Following the synthetic procedure of **1o**, allylmagnesium bromide (1.0 M in Et₂O) was used and the title compound was obtained in 97% yield as a colorless oil; *R*_f = 0.35 (PE/EA = 20/1); ¹H NMR (400 MHz, CDCl₃) δ 7.73 (brs, 0.9H), 7.17 (s, 1H), 7.13 (s, 1H), 5.81–5.68 (m, 1H), 5.12–5.00 (m, 2H), 4.23 (s, 0.9H), 3.22–3.15 (m, 1H), 3.14–3.04 (m, 2H), 2.29–2.20 (m, 2H), 2.10–2.02 (m, 1H), 1.92–1.86 (m, 1H), 1.74 (brs, 0.9H), 1.40 (s, 9H), 1.29 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 149.8, 141.3, 134.7, 134.4, 133.9, 121.0, 117.7, 117.2, 75.6, 72.2, 53.6, 37.0, 34.8, 34.5, 33.6, 31.7, 29.4; HRMS (ESI-TOF) *m/z*: [M + H]⁺ Calcd for C₂₁H₃₄NO₂: 332.2584; found: 332.2586.

Preparation and Characterization of Products. Typical Procedure for Oxidative N,O-Acetal Formation (2a–k,o,p). 5,7-Di-*tert*-butyl-1-cyclopropyl-1,2,3,3a-tetrahydrobenzo[d]pyrrolo[2,1-*b*]oxazole (**2a**). To a solution of **1a** (95 mg, 0.3 mmol) in 10 mL of 9:1 (V/V) DCM/TFE were added K₂CO₃ (124 mg, 0.9 mmol) and iodine (91 mg, 0.36 mmol) sequentially. Fifteen minutes later, TFE and DCM were evaporated, the residue was dissolved in DCM (30 mL), and the organic phase was washed with aq Na₂S₂O₃, H₂O, and brine. After being dried with MgSO₄, the organic phase was concentrated and the residue was purified by chromatography using EtOAc/PE (1/50) to give the desired compound **2a** (87 mg, 93% yield) as a colorless oil; *R*_f = 0.35 (PE/EA = 50/1); ¹H NMR (400 MHz, CDCl₃) δ 6.85 (d, *J* = 2.0 Hz, 1H), 6.82 (d, *J* = 2.0 Hz, 1H), 5.85 (dd, *J* = 5.3, 3.3 Hz, 1H), 2.69 (q, *J* = 6.7 Hz, 1H), 2.42–2.31 (m, 1H), 2.13–2.00 (m, 2H), 1.88–1.69 (m, 1H), 1.33 (s, 9H), 1.29 (s, 9H), 1.01–0.84 (m, 1H), 0.66–0.57 (m, 1H), 0.55–0.46 (m, 1H), 0.35 (dq, *J* = 9.5, 4.9 Hz, 1H), 0.23 (dq, *J* = 9.5, 4.9 Hz, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 147.8, 142.9, 141.1, 130.5, 116.9, 110.3, 102.6, 72.3, 34.5, 34.1, 31.8, 31.7, 30.2, 29.4, 16.3, 3.7, 1.9; HRMS (ESI-TOF) *m/z*: [M + H]⁺ Calcd for C₂₁H₃₂NO₂: 314.2478; found: 314.2481.

5,7-Di-*tert*-butyl-3a-cyclopropyl-1,2,3,3a-tetrahydrobenzo[d]pyrrolo[2,1-*b*]oxazole (**2a'**). The synthetic procedure followed was the same as for **2a**, except that I₂ was replaced with [bis-(trifluoroacetoxy)iodo]benzene (PIFA). Compound **2a** was obtained in 32% yield, and compound **2a'** was obtained in 36% yield. **2a'**: Colorless oil; *R*_f = 0.40 (PE/EA = 50/1); ¹H NMR (400 MHz, CDCl₃) δ 6.76 (d, *J* = 2.0 Hz, 1H), 6.69 (d, *J* = 2.0 Hz, 1H), 3.37 (dt, *J* = 10.6, 7.1 Hz, 1H), 3.13 (dt, *J* = 11.1, 5.8 Hz, 1H), 2.23–2.10 (m, 2H), 1.85–1.73 (m, 2H), 1.32 (s, 9H), 1.27 (s, 9H), 0.56–0.48 (m, 1H), 0.44–0.33 (m, 3H), 0.07 (s, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 147.8, 142.9, 142.0, 129.7, 116.2, 111.3, 109.6, 57.7, 37.9, 34.6, 34.0, 31.8, 29.3, 24.1, 19.3, 0.71, 0.69. HRMS (ESI-TOF) *m/z*: [M + H]⁺ Calcd for C₂₁H₃₂NO: 314.2478; found: 314.2476.

5,7-Di-*tert*-butyl-1-methyl-1,2,3,3a-tetrahydrobenzo[d]pyrrolo[2,1-*b*]oxazole (**2b**).^{2e} Light yellow solid, mp = 50–51 °C; 89% yield; *R*_f = 0.40 (PE/EA = 50/1); ¹H NMR (400 MHz, CDCl₃) δ 6.84 (d, *J* = 2.1 Hz, 1H), 6.80 (d, *J* = 2.0 Hz, 1H), 5.87 (dd, *J* = 5.5, 3.4 Hz, 1H), 3.36–3.18 (m, 1H), 2.46–2.32 (m, 1H), 2.13–1.98 (m, 2H), 1.65–1.47 (m, 1H), 1.33 (s, 9H), 1.32 (d, *J* = 7.2 Hz, 3H), 1.29 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 147.7, 143.0, 141.2, 130.7, 117.2, 109.8, 102.6, 63.8, 34.6, 34.1, 31.9, 31.8, 31.7, 29.4, 22.3.

5,7-Di-*tert*-butyl-1-butyl-1,2,3,3a-tetrahydrobenzo[d]pyrrolo[2,1-*b*]oxazole (**2c**).^{2e} Colorless oil; 85% yield; *R*_f = 0.40 (PE/EA = 50/1); ¹H NMR (400 MHz, CDCl₃) δ 6.81 (d, *J* = 1.9 Hz, 1H), 6.72 (d, *J* = 1.9 Hz, 1H), 5.84 (dd, *J* = 5.0, 3.0 Hz, 1H), 3.20–3.17 (m, 1H), 2.34–2.25 (m, 1H), 2.10–1.98 (m, 2H), 1.69–1.65 (m, 1H), 1.53–1.39 (m, 6H), 1.33 (s, 9H), 1.29 (s, 9H), 0.95 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 147.6, 143.1, 141.7, 130.5, 116.6, 109.3, 102.3, 68.8, 36.5, 34.6, 34.1, 31.8, 31.7, 29.4, 28.9, 22.7, 14.1.

5,7-Di-*tert*-butyl-1-isobutyl-1,2,3,3a-tetrahydrobenzo[d]pyrrolo[2,1-*b*]oxazole (**2d**).^{2e} Colorless oil; 83% yield; *R*_f = 0.35 (PE/EA = 50/1); ¹H NMR (400 MHz, CDCl₃) δ 6.81 (d, *J* = 2.0 Hz, 1H), 6.72 (d, *J* = 1.9 Hz, 1H), 5.84 (dd, *J* = 5.0, 2.8 Hz, 1H), 3.35–3.23 (m, 1H), 2.36–2.22 (m, 1H), 2.12–2.00 (m, 2H), 1.89–1.74 (m, 1H), 1.65–1.44 (m, 3H), 1.33 (s, 9H), 1.29 (s, 9H), 1.02 (d, *J* = 6.6 Hz, 3H), 0.96 (d, *J* = 6.7 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 147.7, 143.2, 141.8, 130.5, 116.6, 109.4, 102.3, 67.2, 46.5, 34.6, 34.1, 31.81, 31.78,

29.4, 29.2, 25.6, 23.1, 22.7; HRMS (ESI-TOF) m/z : $[M + H]^+$ Calcd for $C_{22}H_{36}NO$: 330.2791; found: 330.2794.

5,7-Di-tert-butyl-1-heptyl-1,2,3,3a-tetrahydrobenzo[d]pyrrolo[2,1-b]oxazole (2e). Colorless oil; 80% yield; R_f = 0.40 (PE/EA = 50/1); 1H NMR (400 MHz, $CDCl_3$) δ 6.81 (d, J = 2.0 Hz, 1H), 6.73 (d, J = 2.0 Hz, 1H), 5.85 (dd, J = 5.1, 3.0 Hz, 1H), 3.24–3.09 (m, 1H), 2.36–2.24 (m, 1H), 2.12–1.98 (m, 2H), 1.73–1.62 (m, 1H), 1.61–1.26 (m, 12H), 1.33 (s, 9H), 1.29 (s, 9H), 0.89 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.7, 143.2, 141.7, 130.6, 116.7, 109.4, 102.3, 68.9, 36.8, 34.6, 34.1, 31.9, 31.83, 31.77, 29.7, 29.4, 29.0, 26.8, 22.8, 14.2; HRMS (ESI-TOF) m/z : $[M + H]^+$ Calcd for $C_{25}H_{42}NO$: 372.3261; found: 372.3258.

5,7-Di-tert-butyl-1-nonyl-1,2,3,3a-tetrahydrobenzo[d]pyrrolo[2,1-b]oxazole (2f). Colorless oil; 78% yield; R_f = 0.45 (PE/EA = 50/1); 1H NMR (400 MHz, $CDCl_3$) δ 6.81 (d, J = 1.9 Hz, 1H), 6.72 (d, J = 2.0 Hz, 1H), 5.84 (dd, J = 5.1, 2.9 Hz, 1H), 3.24–3.13 (m, 1H), 2.36–2.25 (m, 1H), 2.12–1.99 (m, 2H), 1.75–1.62 (m, 1H), 1.56–1.23 (m, 16H), 1.33 (s, 9H), 1.29 (s, 9H), 0.89 (t, J = 6.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.6, 143.1, 141.7, 130.5, 116.6, 109.4, 102.3, 68.8, 36.8, 34.5, 34.1, 31.9, 31.82, 31.78, 31.72, 29.7, 29.6, 29.4, 28.9, 26.8, 22.7, 14.1; HRMS (ESI-TOF) m/z : $[M + H]^+$ Calcd for $C_{27}H_{46}NO$: 400.3574; found: 400.3571.

5,7-Di-tert-butyl-1-cyclopentyl-1,2,3,3a-tetrahydrobenzo[d]pyrrolo[2,1-b]oxazole (2g). White solid, mp = 60–62 °C; 86% yield; R_f = 0.40 (PE/EA = 50/1); 1H NMR (400 MHz, $CDCl_3$) δ 6.77 (d, J = 2.0 Hz, 1H), 6.68 (d, J = 2.0 Hz, 1H), 5.84 (dd, J = 4.9, 2.8 Hz, 1H), 3.12 (td, J = 7.7, 3.7 Hz, 1H), 2.31–2.17 (m, 1H), 2.12–1.84 (m, 4H), 1.80–1.57 (m, 8H), 1.33 (s, 9H), 1.29 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.3, 143.2, 142.0, 130.3, 116.1, 108.8, 102.2, 73.2, 45.9, 34.6, 34.0, 31.8, 31.6, 30.8, 29.6, 29.4, 27.0, 25.15, 25.12; HRMS (ESI-TOF) m/z : $[M + H]^+$ Calcd for $C_{23}H_{36}NO$: 342.2791; found: 342.2789.

1-Allyl-5,7-di-tert-butyl-1,2,3,3a-tetrahydrobenzo[d]pyrrolo[2,1-b]oxazole (2h). Light yellow solid; mp = 45–46 °C; 93% yield; R_f = 0.35 (PE/EA = 50/1); 1H NMR (400 MHz, $CDCl_3$) δ 6.83 (d, J = 2.0 Hz, 1H), 6.77 (d, J = 2.0 Hz, 1H), 5.99–5.88 (m, 1H), 5.86 (dd, J = 5.2, 3.3 Hz, 1H), 5.19–5.08 (m, 2H), 3.36–3.20 (m, 1H), 2.54–2.39 (m, 1H), 2.38–2.22 (m, 2H), 2.13–1.93 (m, 2H), 1.69–1.58 (m, 1H), 1.34 (s, 9H), 1.29 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.6, 143.2, 141.4, 135.9, 130.7, 117.0, 109.5, 102.4, 102.3, 68.4, 41.2, 34.6, 34.1, 31.8, 31.7, 29.4, 28.6.

5,7-Di-tert-butyl-1-(4-methoxybenzyl)-1,2,3,3a-tetrahydrobenzo[d]pyrrolo[2,1-b]oxazole (2i). 83% yield; Colorless oil; R_f = 0.30 (PE/EA = 50/1); 1H NMR (400 MHz, $CDCl_3$) δ 7.24–7.18 (m, 2H), 6.92–6.86 (m, 2H), 6.73 (d, J = 2.0 Hz, 1H), 5.89–5.81 (m, 2H), 3.80 (s, 3H), 3.44–3.32 (m, 1H), 2.85–2.71 (m, 2H), 2.35–2.20 (m, 1H), 2.15–1.98 (m, 2H), 1.69–1.59 (m, 1H), 1.31 (s, 9H), 1.15 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.1, 147.4, 143.1, 141.6, 132.0, 130.6, 130.3, 116.4, 113.8, 109.2, 102.3, 77.2, 71.1, 55.2, 42.9, 34.5, 34.0, 31.6, 29.4, 28.9; HRMS (MALDI-TOF) m/z : $[M + H]^+$ Calcd for $C_{26}H_{36}NO_2$: 394.2741; found: 394.2746.

1-Benzyl-5,7-di-tert-butyl-1,2,3,3a-tetrahydrobenzo[d]pyrrolo[2,1-b]oxazole (2j). White solid; mp = 98–100 °C; 97% yield; R_f = 0.35 (PE/EA = 50/1); 1H NMR (400 MHz, $CDCl_3$) δ 7.37–7.16 (m, 5H), 6.73 (d, J = 2.0 Hz, 1H), 5.89 (d, J = 2.0 Hz, 1H), 5.86 (dd, J = 4.9, 2.9 Hz, 1H), 3.72–3.25 (m, 1H), 2.86 (dd, J = 13.1, 8.4 Hz, 1H), 2.78 (dd, J = 13.0, 5.6 Hz, 1H), 2.35–2.22 (m, 1H), 2.14–2.00 (m, 2H), 1.72–1.60 (m, 1H), 1.30 (s, 9H), 1.14 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.4, 143.2, 141.5, 139.9, 130.4, 129.7, 128.4, 126.3, 116.5, 109.3, 102.3, 71.0, 43.8, 34.5, 34.0, 31.63, 31.56, 29.4, 28.9; HRMS (ESI-TOF) m/z : $[M + H]^+$ Calcd for $C_{25}H_{34}NO$: 364.2635; found: 364.2630.

5,7-Di-tert-butyl-1-(4-fluorobenzyl)-1,2,3,3a-tetrahydrobenzo[d]pyrrolo[2,1-b]oxazole (2k). Colorless oil; 81% yield; R_f = 0.45 (PE/EA = 50/1); 1H NMR (400 MHz, $CDCl_3$) δ 7.29–7.19 (m, 2H), 7.09–6.98 (m, 2H), 6.74 (d, J = 2.0 Hz, 1H), 5.92–5.67 (m, 2H), 3.44–3.23 (m, 1H), 2.87–2.72 (m, 2H), 2.27 (dq, J = 11.4, 5.4 Hz, 1H), 2.14–2.00 (m, 2H), 1.69–1.57 (m, 1H), 1.30 (s, 9H), 1.15 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.6 (d, J = 244.4 Hz), 147.4, 143.2, 141.4, 135.6 (d, J = 3.2 Hz), 131.1 (d, J = 7.6 Hz), 130.5, 116.6,

115.2 (d, J = 20.9 Hz), 109.1, 102.2, 70.9, 42.9, 34.4, 34.1, 31.6, 31.5, 29.4, 28.9; HRMS (ESI-TOF) m/z : $[M + H]^+$ Calcd for $C_{25}H_{33}FNO$: 382.2541; found: 382.2545.

5,7-Di-tert-butyl-1-vinyl-1,2,3,3a-tetrahydrobenzo[d]pyrrolo[2,1-b]oxazole (2l). To a solution of 5,7-di-tert-butyl-1,2,3,3a-tetrahydrobenzo[d]pyrrolo[2,1-b]oxazole **1**^{2e} (82 mg, 0.3 mmol) in DCE (30 mL) was added vinylmagnesium bromide (1.8 mL, 0.5 M in THF, 0.9 mmol) at 0 °C under Ar. When completed, the reaction was diluted with PE (30 mL), quenched with saturated NH_4Cl (10 mL), and extracted with EtOAc (30 mL) three times. The combined organic phase was concentrated and dissolved in a mixed solvent of DCM/TFE (1 mL:9 mL), and then K_2CO_3 (124 mg, 0.9 mmol) and I_2 (91 mg, 0.36 mmol) were added sequentially at room temperature. Fifteen minutes later, TFE and DCM were evaporated, and the residue was dissolved in DCM (30 mL). The DCM layer was washed with aq $Na_2S_2O_3$, H_2O , and brine. After being dried with $MgSO_4$, the organic phase was concentrated and the residue was purified by chromatography using EtOAc/PE (1/50) to give the desired compound **2l** (63 mg, 70% yield) as a colorless oil; 1H NMR (400 MHz, $CDCl_3$) δ 6.84 (d, J = 1.8 Hz, 1H), 6.77 (d, J = 1.8 Hz, 1H), 5.98–5.89 (m, 2H), 5.32 (d, J = 17.0 Hz, 1H), 5.15 (d, J = 10.2 Hz, 1H), 3.70–3.65 (m, 1H), 2.40–2.33 (m, 1H), 2.11–2.01 (m, 2H), 1.75–1.67 (m, 1H), 1.34 (s, 9H), 1.27 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.8, 143.1, 140.9, 140.7, 130.6, 117.0, 115.3, 109.8, 102.3, 70.6, 34.6, 34.1, 31.9, 31.7, 30.6, 29.4.

5,7-Di-tert-butyl-1-(4-chlorophenyl)-1,2,3,3a-tetrahydrobenzo[d]pyrrolo[2,1-b]oxazole (2m). Following the synthetic procedure of **2l**, 4-chlorophenylmagnesium bromide (1.0 M in THF) was used and the title compound was obtained in 53% yield as a colorless oil; R_f = 0.40 (PE/EA = 50/1); 1H NMR (400 MHz, $CDCl_3$) δ 7.43–7.31 (m, 4H), 6.84 (s, 1H), 6.43 (s, 1H), 6.04 (t, J = 4.5 Hz, 1H), 4.34–4.23 (m, 1H), 2.52–2.23 (m, 2H), 2.21–2.07 (m, 1H), 1.90–1.71 (m, 1H), 1.36 (s, 9H), 1.20 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 147.7, 143.4, 142.4, 140.7, 132.7, 130.8, 128.5, 127.9, 117.1, 109.2, 102.2, 70.9, 34.5, 34.2, 33.7, 32.3, 31.7, 29.4; HRMS (ESI-TOF) m/z : $[M + H]^+$ Calcd for $C_{24}H_{31}ClNO$: 384.2089; found: 384.2087.

5,7-Di-tert-butyl-1-(4-fluorophenyl)-1,2,3,3a-tetrahydrobenzo[d]pyrrolo[2,1-b]oxazole (2n). Following the synthetic procedure of **2l**, 4-fluorophenylmagnesium bromide (1.0 M in THF) was used and the title compound was obtained in 61% yield as a colorless oil; R_f = 0.35 (PE/EA = 50/1); 1H NMR (400 MHz, $CDCl_3$) δ 7.47–7.34 (m, 2H), 7.11–6.99 (m, 2H), 6.84 (s, 1H), 6.41 (s, 1H), 6.12–5.96 (m, 1H), 4.28 (t, J = 7.0 Hz, 1H), 2.45–2.26 (m, 2H), 2.20–2.08 (m, 1H), 1.92–1.79 (m, 1H), 1.36 (d, J = 1.8 Hz, 9H), 1.19 (d, J = 1.9 Hz, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.0 (d, J = 244.7 Hz), 147.7, 143.3, 140.8, 139.5 (d, J = 3.1 Hz), 130.9, 128.1 (d, J = 7.6 Hz), 117.2, 115.22 (d, J = 21.5 Hz), 109.3, 102.2, 70.9, 34.5, 34.2, 33.9, 32.4, 31.7, 29.4; HRMS (ESI-TOF) m/z : $[M + H]^+$ Calcd for $C_{24}H_{31}FNO$: 368.2384; found: 368.2381.

1-Benzyl-5,7-di-tert-butyl-1,2,3,3a-tetrahydrobenzo[d]pyrrolo[2,1-b]oxazol-2-ol (2o). The synthetic procedure was the same as for **2a**, except that the reaction was carried out at 0 °C for 14 h; light yellow solid; mp = 111–113 °C; 84% yield; R_f = 0.35 (PE/EA = 20/1); 1H NMR (400 MHz, $CDCl_3$) δ 7.39–7.28 (m, 5H), 6.76 (d, J = 1.7 Hz, 1H), 5.86–5.82 (m, 1H), 5.77 (d, J = 1.6 Hz, 1H), 4.28–4.16 (m, 1H), 3.44 (dd, J = 10.2, 4.7 Hz, 1H), 2.88 (dd, J = 13.0, 4.7 Hz, 1H), 2.62 (dd, J = 12.9, 9.9 Hz, 1H), 2.54–2.41 (m, 2H), 2.01 (d, J = 8.7 Hz, 0.8H), 1.29 (s, 9H), 1.12 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 146.8, 144.0, 142.4, 139.0, 131.2, 129.8, 128.5, 126.5, 117.3, 110.5, 101.8, 80.0, 77.0, 41.7, 39.3, 34.5, 34.1, 31.6, 29.4. HRMS (ESI-TOF) m/z : $[M + H]^+$ Calcd for $C_{25}H_{34}NO_2$: 380.2584; found: 380.2586.

1-Allyl-5,7-di-tert-butyl-1,2,3,3a-tetrahydrobenzo[d]pyrrolo[2,1-b]oxazol-2-ol (2p). The synthetic procedure was the same as for **2o**. Colorless oil; 94% yield; R_f = 0.40 (PE/EA = 20/1); 1H NMR (400 MHz, $CDCl_3$) δ 6.85 (d, J = 2.0 Hz, 1H), 6.80 (d, J = 2.0 Hz, 1H), 5.98 (ddt, J = 16.9, 10.9, 7.1 Hz, 1H), 5.83 (dd, J = 5.0, 1.7 Hz, 1H), 5.22–5.18 (m, 1H), 5.17 (s, 1H), 4.22–4.11 (m, 1H), 3.37–3.25 (m, 1H), 2.63–2.50 (m, 1H), 2.43–2.21 (m, 3H), 1.93 (d, J = 7.9 Hz, 0.9H), 1.33 (s, 9H), 1.29 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ

146.9, 143.9, 142.1, 135.2, 131.4, 117.6, 117.5, 110.4, 101.5, 76.6, 76.4, 39.5, 39.4, 34.6, 34.1, 31.7, 29.4; HRMS (ESI-TOF) m/z : $[M + H]^+$ Calcd for $C_{21}H_{32}NO_2$: 330.2428; found: 330.2432.

5-Cyclopropyl-1-(3,5-ditert-butyl-2-hydroxyphenyl)pyrrolidin-2-one (2g).^{3a} The synthetic procedure followed was the same as for **2a**, except that TEMPO was added before the addition of iodine. Light yellow solid; mp = 153–154 °C; 35% yield; R_f = 0.25 (PE/EA = 9/1); 1H NMR (400 MHz, $CDCl_3$): δ 7.24 (d, J = 2.2 Hz, 1H), 7.11 (s, 0.9H), 6.92 (d, J = 2.3 Hz, 1H), 3.64 (td, J = 8.1, 5.5 Hz, 1H), 2.89–2.56 (m, 2H), 2.46–2.37 (m, 1H), 2.16–1.97 (m, 1H), 1.43 (s, 9H), 1.28 (s, 9H), 0.87–0.85 (m, 1H), 0.41–0.33 (m, 2H), 0.14–0.05 (m, 1H), 0.02–0.00 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 175.2, 148.3, 141.5, 139.2, 126.2, 122.2, 118.9, 66.4, 35.0, 34.4, 34.0, 31.2, 30.6, 29.5, 25.4, 14.8, 4.8.

Total Synthesis of (\pm)-Preussin. 2-Benzyl-1-(3,5-di-tert-butyl-2-hydroxyphenyl)-5-heptylpyrrolidin-3-ol (7 + 7'). To a solution of **1o** (763 mg, 2 mmol) in a mixed solvent of DCM and TFE (60 mL, DCM/TFE = 1:9 (v/v)) were added K_2CO_3 (828 mg, 6 mmol) and iodine (559 mg, 2.2 mmol) at 0 °C sequentially. The reaction was stirred at 0 °C overnight. Upon completion, the solvent was evaporated, the residue was dissolved in DCM (50 mL), and the organic layer was washed with saturated $Na_2S_2O_3$, H_2O , and brine. After being dried with $MgSO_4$, the organic phase was concentrated to give crude **2o**. Crude **2o** was dissolved in the dry DCM (250 mL), and $n-C_7H_{15}MgCl$ (10.0 mL, 1.0 M in Et_2O , 10 mmol) was added dropwise at –78 °C under Ar. The reaction was quenched with saturated NH_4Cl (200 mL) after 24 h and extracted with DCM (100 mL) three times. The combined organic phase was dried and concentrated, and the residue was purified by chromatography using EA/PE = (1:15) to give compound **7**²⁰ and its diastereoisomer **7'** (because of the restricted rotation of the disubstituted pyrrolidine moiety, the 1H NMR spectra of **7'** appears as two conformers) as an inseparable mixture (720 mg, 71% yield, trans isomer major). 1H NMR (400 MHz, $CDCl_3$) δ 7.86 (brs, 0.6H), 7.57–6.70 (m, 7H), 4.24–4.11 (m, 1H), 3.69–3.40 (m, 0.42H, minor isomer), 3.28–3.24 (m, 1.57H, major isomer), 2.79 (dd, J = 13.4, 4.5 Hz, 1H), 2.50 (dd, J = 13.4, 9.7 Hz, 1H), 2.35–2.11 (m, 0.2H, minor isomer), 2.03–1.97 (m, 0.8H, major isomer), 1.91–1.83 (m, 0.9H, major isomer), 1.67–1.05 (m, 34H), 0.86 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.8, 149.8, 149.5, 141.4, 140.3, 140.2, 138.7, 138.4, 138.0, 134.2, 134.0, 133.8, 133.6, 130.9, 130.8, 129.3, 129.0, 128.6, 128.5, 126.4, 126.2, 121.0, 120.0, 119.9, 119.6, 119.2, 117.8, 76.5, 74.9, 74.7, 73.7, 71.6, 67.9, 65.2, 59.6, 58.4, 39.8, 39.5, 38.7, 38.5, 38.1, 34.95, 34.85, 34.8, 34.7, 34.5, 34.33, 34.25, 34.2, 32.0, 31.9, 31.84, 31.81, 31.7, 29.53, 29.47, 29.40, 29.38, 29.3, 26.33, 26.26, 26.0, 22.6, 14.1; HRMS (MALDI-TOF) m/z : $[M + H]^+$ Calcd for $C_{34}H_{54}NO_2$: 508.4149; found: 508.4157.

2-Benzyl-5-heptylpyrrolidin-3-ol (8 + 8'). To a solution of mixed compounds **7** and **7'** (710 mg, 1.4 mmol) in a mixed solvent of aq NaOH (1 M, 20 mL) and MeCN (40 mL) was added I_2 (391 mg, 1.54 mmol) at 0 °C. After 5 min, the reaction was extracted with DCM (40 mL) three times. The combined organic phase was washed with saturated $Na_2S_2O_3$ and brine. After being dried with Na_2SO_4 , the reaction mixture was concentrated and purified by chromatography using MeOH/DCM(1:20) to afford compound **8**²⁰ and **8'** which were inseparable (**8:8'** = 3.6:1 from 1H NMR, 352 mg, 83% yield); 1H NMR (400 MHz, $CDCl_3$) δ 7.48–6.95 (m, 5H), 4.00 (dt, J = 7.7, 3.7 Hz, 1H), 3.33–3.26 (m, 0.23H, minor isomer), 3.24–3.08 (m, 1.73H, major isomer), 2.91–2.75 (m, 1.55H, major isomer), 2.74–2.70 (m, 0.43H, minor isomer), 2.32 (brs, 2H), 1.84–1.77 (m, 1H), 1.69–1.55 (m, 1H), 1.52–1.16 (m, 16H), 0.88 (t, J = 6.7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.1, 138.7, 129.0, 128.72, 128.66, 126.5, 126.4, 76.2, 76.1, 68.5, 66.6, 57.0, 55.6, 41.0, 40.7, 40.4, 39.3, 37.5, 36.6, 31.9, 29.75, 29.65, 29.61, 29.57, 29.3, 27.10, 27.06, 22.7, 14.1; HRMS ((MALDI-TOF) m/z): $[M + H]^+$ Calcd for $C_{20}H_{34}NO$: 304.2635; found: 304.2638.

2-Benzyl-1-methyl-5-nonylpyrrolidin-3-ol (9 + 9'). By using previous reported method,^{17f} the methylation of mixed compound **8** gave C(3)-*epi*-(\pm)-preussin **9** (25 mg, 64% yield) and C(2)-*epi*-(\pm)-preussin **9'** (7 mg, 18% yield). C(3)-*epi*-(\pm)-Preussin **9**:^{17b} 1H

NMR (400 MHz, $CDCl_3$) δ 7.40–7.12 (m, 5H), 4.10–3.91 (m, 1H), 3.05 (dd, J = 13.2, 4.4 Hz, 1H), 2.54 (dd, J = 13.2, 9.6 Hz, 1H), 2.50–2.38 (m, 2H), 2.35 (s, 3H), 1.76 (ddd, J = 13.3, 6.7, 2.7 Hz, 1H), 1.71–1.57 (m, 2H), 1.37–1.05 (m, 16H), 0.88 (t, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.0, 129.3, 128.7, 126.4, 74.7, 64.9, 39.4, 39.2, 39.1, 33.9, 31.9, 30.0, 29.64, 29.60, 29.4, 26.4, 22.7, 14.2.

C(2)-*epi*-(\pm)-Preussin **9'**:²¹ 1H NMR (400 MHz, $CDCl_3$) δ 7.32–7.24 (m, 2H), 7.23–7.11 (m, 3H), 3.90 (d, J = 6.3 Hz, 1H), 3.15 (dd, J = 10.8, 4.2 Hz, 1H), 2.97 (dd, J = 13.4, 4.2 Hz, 1H), 2.72–2.61 (m, 1H), 2.46 (s, 3H), 2.44–2.31 (m, 1H), 2.19 (dd, J = 13.4, 10.7 Hz, 1H), 2.06 (brs, 1H), 1.77–1.61 (m, 1H), 1.51 (dd, J = 14.2, 5.0 Hz, 1H), 1.43–1.14 (m, 15H), 0.88 (t, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.4, 129.0, 128.6, 126.1, 73.9, 73.3, 61.2, 38.9, 35.0, 33.6, 31.9, 31.4, 29.9, 29.7, 29.6, 29.3, 26.2, 22.7, 14.1.

2-Benzyl-1-methyl-5-nonylpyrrolidin-3-ol (10). Following the literature,^{17b} **9** was first oxidized by Swern oxidation and then reduced by $LiAlH_4$ to give (\pm)-preussin **10** (16 mg, 65% yield) whose spectra data matched with those reported.^{15g} 1H NMR (400 MHz, $CDCl_3$) δ 7.35–7.27 (m, 4H), 7.20 (m, 1H), 3.79 (m, 1H), 2.89–2.77 (m, 2H), 2.33 (s, 3H), 2.30–2.22 (m, 1H), 2.22–2.06 (m, 2H), 1.86 (d, J = 8.9 Hz, 1H), 1.72 (m, 1H), 1.41 (dd, J = 13.6, 5.8 Hz, 1H), 1.26 (m, 15H), 0.88 (t, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 139.5, 129.3, 128.4, 126.0, 73.5, 70.5, 65.7, 39.2, 38.6, 35.1, 33.7, 31.9, 29.9, 29.62, 29.58, 29.3, 26.3, 22.7, 14.1.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00361.

Copies of NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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