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A Stereoselective Route to Aza-*C*-aryl Glycosides from Arynes and Chiral Nitrones

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Arynes are regarded as potential and versatile intermediates in organic synthesis. These highly-reactive, strained and kinetically unstable species have numerous applications in synthetic chemistry. In this article, a highly-diasteroselective and efficient 1,3-dipolar cycloaddition reaction between a range of arynes and sugar-derived cyclic nitrones leading to an interesting class of sugar-based benzo[*d*]isoxazolines is described. These benzo[*d*]isoxazolines upon selective N–O bond cleavage provide various substituted aza-*C*-aryl glycosides in good yield. These substituted pyrrolidine derivatives are chiral aminophenols and could be potential chiral ligands and organocatalysts in asymmetric synthesis.

Introduction

Arynes,[1] once mainly the subject of structural curiosity, now attract the attention of synthetic chemists as reactive intermediates and are now widely employed as reaction partners in organic synthesis. Early syntheses of arynes suffered from several shortcomings such as harsh conditions, multiple reaction steps, limited availability of starting materials and were often low yielding.[2] However, a mild procedure involving fluoride promoted *ortho*-elimination of *o*-(trimethylsilyl)aryl triflates developed by Kobayashi, led to a renaissance of the chemistry of arynes.[3] Among the variety of reactions that arynes[4] undergo, 1,3-dipolar cycloaddition reactions[5] deserve special mention owing to their ability to produce pharmaceutically important nitrogen containing heterocycles. Several dipoles have been systematically studied for their reactivity with arynes, leading to interesting heterocycles. However, only a few nitrones, mostly achiral ones, have been investigated as dipole partners for arynes.[6]

Nitrones have long been used as building blocks in organic synthesis.[7] We and others have explored sugar-derived cyclic nitrones for highly diastereoselective 1,3-dipolar cycloaddition reactions.[8] Thus, based on our recent success on the utility of sugar-derived cyclic nitrones,[9] we envisioned that the reaction of these nitrones with arynes would lead to benzo[*d*]isoxazolines, which upon cleavage of N–O bond would afford *o*-hydroxyaryl-substituted pyrrolidines. Furthermore, this method could be an attractive strategy to make analogues of several naturally occurring aryl-substituted polyhydroxylated pyrrolidines (**1**–**5**, Figure 1).[10] Herein, we report a facile 1,3-dipolar cycloaddition reaction of various arynes with sugar-derived cyclic nitrones to synthesize benzo[*d*]isoxazolines and a range of hydroxyaryl-substituted polyhydroxy-pyrrolidines (Scheme 1). This approach is complimentary to the direct addition of organo-

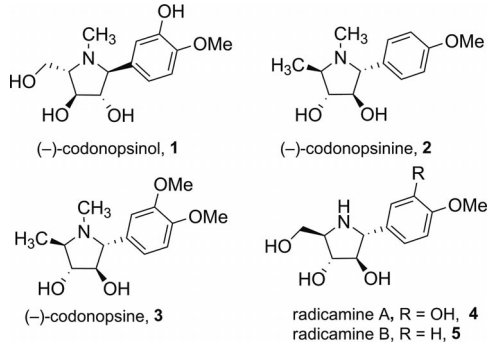
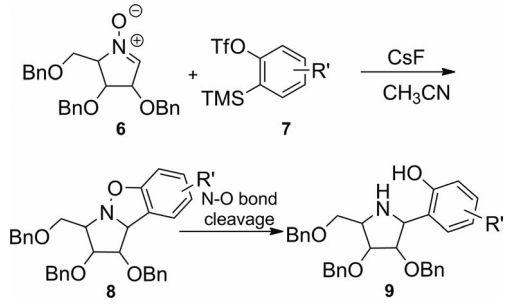


Figure 1. Aryl-substituted polyhydroxy-pyrrolidine natural products.



Scheme 1. 1,3-Dipolar cycloaddition reaction between sugar-derived cyclic nitrones and arynes, and their subsequent N–O bond cleavage.

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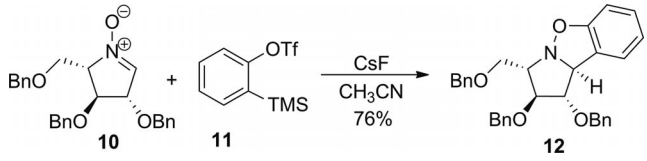
metallic reagents to cyclic nitrones leading to aryl-substituted polyhydroxy-pyrrolidines.[11] However, our strategy provides an additional hydroxy group in the aryl ring and thus the resultant aminophenols with other hydroxy groups, which are already protected, could serve as potential organocatalysts and as chiral ligands in asymmetric synthesis.[11] When we were concluding our investigation, Larock and co-workers reported the synthesis of benzisoxazolines by the coupling of arynes with nitrones.[6a]

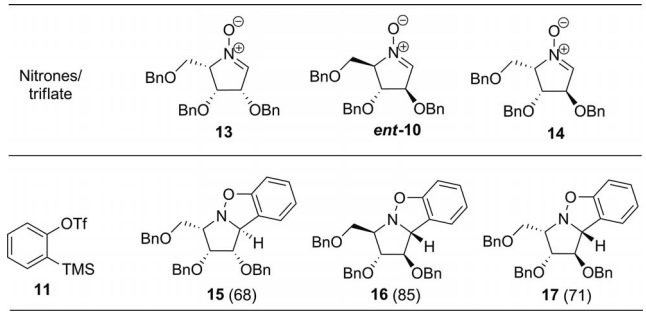
Results and Discussion

The success of this strategy, which depends on the easy availability of the starting materials and in the preparation of sugar-derived cyclic nitrones,[9,10] is well documented. To realize the feasibility of this reaction readily accessible nitrone **10** (from D-xylose) was chosen to identify suitable reaction conditions under which to perform the 1,3-dipolar cycloaddition reaction with simple benzyne. To begin with, KF was chosen as the fluoride source and the reaction was



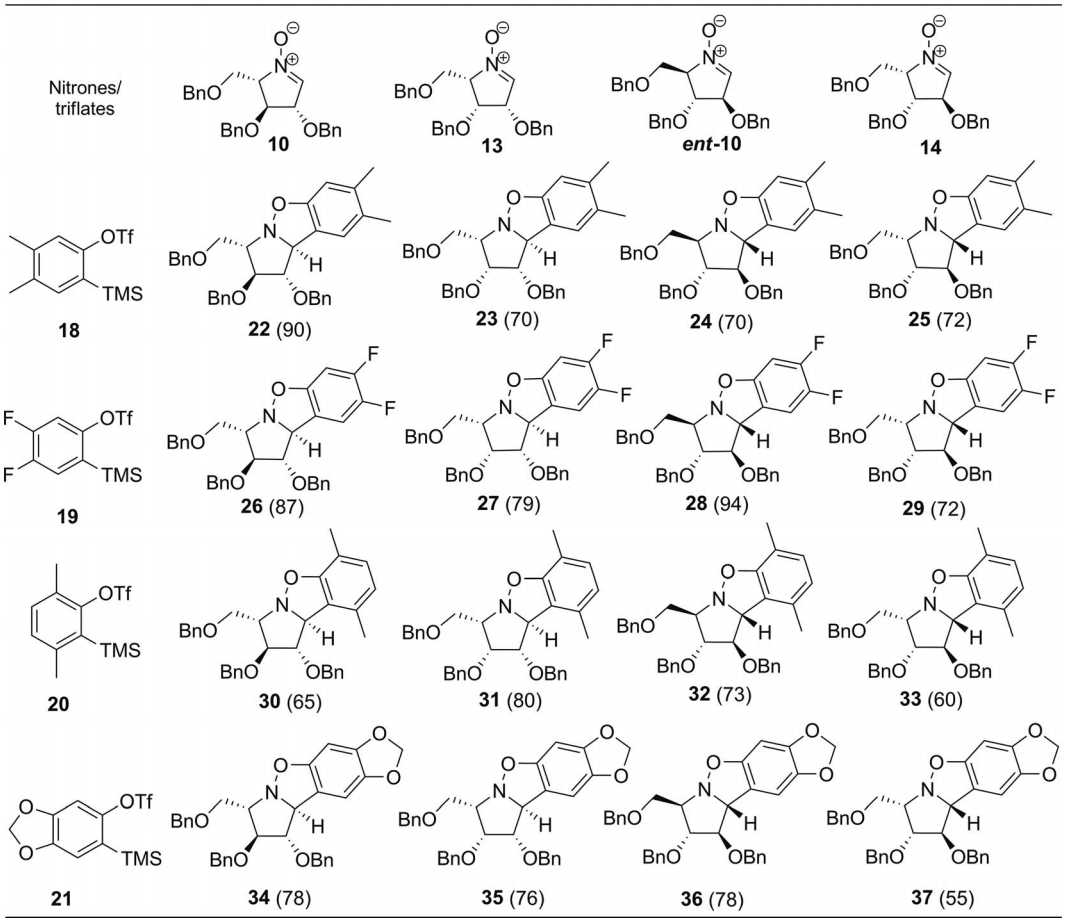
Scheme 2. 1,3-Dipolar cycloaddition reaction between D-xylose-derived cyclic nitrone and benzyne.

Table 1. 1,3-Dipolar cycloaddition reaction between sugar-derived cyclic nitrones and benzyne.[a,b]



[a] 1,3-Dipolar cycloadducts were synthesized from the respective cyclic nitrones and benzyne by using CsF in CH_3CN at room temp. [b] Yields are given in parentheses.

Table 2. 1,3-Dipolar cycloaddition reaction between sugar-derived cyclic nitrones and arynes.[a,b]



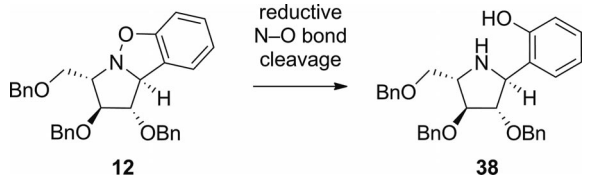
[a] 1,3-Dipolar cycloadducts were synthesized from the respective cyclic nitrones and benzyne by using CsF in CH_3CN at room temp. [b] Yields are given in parentheses.

carried out in the presence of 18-crown-6. Unfortunately, under these conditions only a complex mixture of products was obtained. By using TBAF as the fluoride source lead to some of the required product but the yield was far from satisfactory. Gratifyingly, when nitrone **10** and *o*-(trimethylsilyl)phenyltriflate **11** were mixed in CH_3CN in the presence of CsF at room temperature, desired product **12** was obtained in 76% yield (Scheme 2).

After identifying optimized reaction conditions, we sought to probe the generality of this reaction with other nitrones (**13**, *ent*-**10** and **14**) and *o*-(trimethylsilyl)phenyltriflate **11** (Table 1). Nitrone *ent*-**10** reacted smoothly to provide desired product **16** in excellent yield (85%), whereas nitrones **13** and **14** furnished benzo[*d*]isoxazolines in good yields (68% and 71%, respectively).

Precursor **18** gave good results with nitrones **10**, **13**, *ent*-**10** and **14**, furnishing cycloadduct **22** in excellent yield and **23**, **24** and **25** in good yields, respectively (Table 2). 4,5-Difluorobenzyne precursor **19**, which represents an example of an aryne with a strongly electron-withdrawing group, was then investigated. Reaction of **19** with nitrones **10** and *ent*-**10** afforded desired products **26** and **28** in excellent yield (87% and 94%, respectively) whereas treatment with nitrones **13** and **14** led to cycloadducts **27** and **29** in good yields (79% and 72%, respectively). In a similar way, aryne precursors **20** and **21** were treated with nitrones **10**, **13**, *ent*-**10**

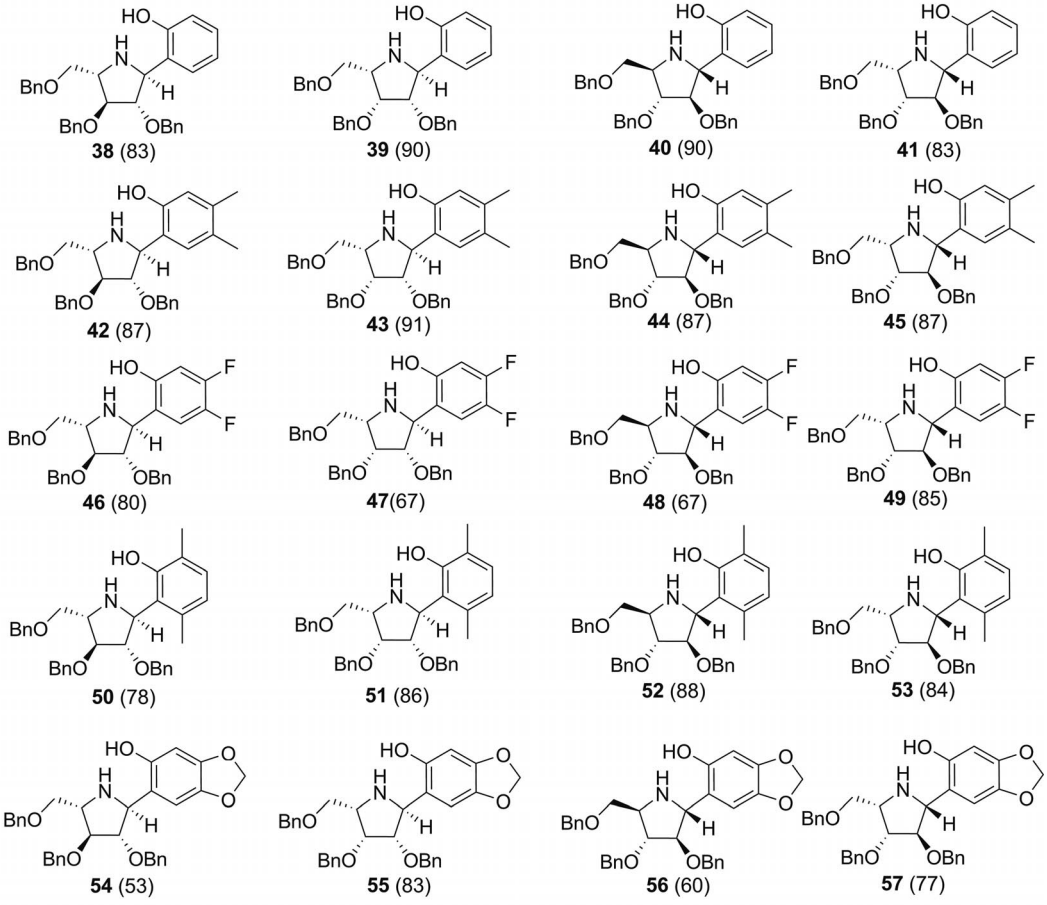
Table 3. Screening of reaction conditions for the N–O bond cleavage of benzo[*d*]isoxazoline.



12 **38**

Entry	Reaction conditions	Yield of **38** [%]
1	$NiCl_2{\cdot}6H_2O$, $NaBH_4$, MeOH, 0.5 h	62[c]
2	$Mo(CO)_6$, CH_3CN, H_2O, reflux, 24 h	40
3	$LiAlH_4$, diethyl ether (or) THF, reflux	0
4	Zn, AcOH, H_2O, room temp., 24 h	33[c]
5	Zn, sonication, 40 °C, 2 h	21[c]
6	Zn, In, aq. NH_4Cl, MeOH, reflux, 24 h	56[c]
7	Zn, AcOH, H_2O, 70 °C, 2 h	83

Table 4. Reductive N–O bond cleavage of benzo[*d*]isoxazolines.[a,b]

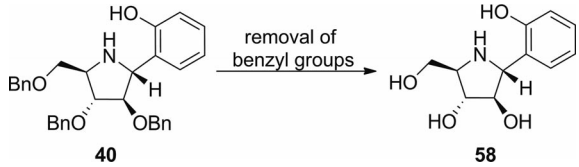


[a] *O*-protected aza-*C*-aryl glycosides were synthesized from the respective cycloadducts by using Zn dust, acetic acid and H_2O at 70 °C. [b] Yields are given in parentheses. [c] Yields are based on recovered starting materials.

and **14** to afford cycloadducts **30**–**37** in good to excellent yields.

Having successfully synthesized a variety of sugar-derived benzo[*d*]isoxazolines, next we turned our attention to transforming these intermediates into the corresponding *O*-protected aza-*C*-aryl glycosides through cleavage of the N–O bond. Although the cleavage of N–O bond and removal of benzyl groups could be performed simultaneously, we were looking for specific reaction conditions to selectively cleave of N–O bond. Initially, cycloadduct **12** was chosen and treated with $NiCl_2{\cdot}6H_2O$ and $NaBH_4$ in MeOH at –40 °C for 30 min.[12] Expected product **38** was obtained in low yield with significant recovery of cycloadduct **12** (Table 3, Entry 1). Attempts to cleave the N–O bond with $Mo(CO)_6$ in CH_3CN and H_2O under reflux conditions[13] did not significantly improve the yield (Table 3, Entry 2). Contrary to our expectations, treatment with LAH in ether and THF[14] under reflux conditions also failed to deliver the required product (Table 3, Entry 3). Attempted reductive cleavage of the N–O bond in the presence of Zn dust under various conditions with different additives was also not helpful either at room temperature,[15] or under sonication at 40 °C[16] (Table 3, Entries 4, 5 and 6).[17] Eventually, treatment of cycloadduct **12** with Zn dust, acetic acid and water at 70 °C for 2 h[18] paved the way for smooth formation of product **38** in 83% yield (Table 3, Entry 7). Thus, a combination of Zn and aqueous acetic acid at 70 °C was identified as the best conditions for the reductive cleavage of the N–O bond. We employed these optimized conditions to other sugar-derived benzo[*d*]isoxazolines, and in all cases we observed fully protected aza-*C*-aryl glycosides in good to excellent yields (Table 4).

After the successful cleavage of the N–O bond, we moved on to study the removal of the benzyl groups to synthesize aryl-substituted polyhydroxy-pyrrolidines (Scheme 3). Our initial attempts under standard conditions, such as Pd-C/H_2 in acidic MeOH and $Pd(OH)_2$-C/H_2 in acidic MeOH, did not provide the desired product which is in agreement with the literature precedence[19] that indicates that the presence of an amine group suppresses the hydrogenolysis of *O*-benzyl groups. Pleasingly, the use of BBr_3 in dichloromethane[20] successfully cleaved all the benzyl groups to furnish the desired product in 88% yield. This condition could be extended to cleave benzyl groups of other sugar-derived benzo[*d*]isoxazolines to a series of aryl-substituted polyhydroxy-pyrrolidines.



40 **58**

Scheme 3. Removal of benzyl groups.

Conclusions

In summary, we have reported the successful 1,3-dipolar cycloaddition reaction between sugar-derived cyclic nitrones and arynes to afford a range of chiral benzo[*d*]isoxazolines that were further converted into a library of *O*-protected aza-*C*-aryl glycosides upon reductive N–O bond cleavage. The cycloaddition reaction was highly diastereoselective and furnished only a single isomer in all the cases. Thus, this two-step protocol is a potential route to various natural and synthetic compounds with an aryl-substituted polyhydroxy-pyrrolidine framework. Furthermore, the aminophenols obtained after N–O bond cleavage might find potential applications in organocatalysis and also as chiral ligands in organic synthesis. Efforts are underway in our laboratory to utilize these new chiral amino alcohols in asymmetric synthesis.

Experimental Section

General Methods: All starting materials and reagents were obtained from commercial suppliers and used without further purification. Tetrahydrofuran was distilled from sodium benzophenone ketyl and toluene from sodium. Dichloromethane, hexane and acetonitrile were freshly distilled from calcium hydride. All solvents for routine isolation of products and chromatography were reagent grade and glass distilled. Air and moisture sensitive reactions were performed under an argon/UHP nitrogen atmosphere. Flash chromatography was performed with silica gel (100–200 mesh, Aceme) with indicated solvents. All reactions were monitored by thin-layer chromatography carried out on 0.25 mm Merck silica plates (60F-254) with the use of UV light as a visualizing agent and 7% ethanolic phosphomolybdic acid and heat as developing agents. Optical rotations were recorded on Rudolph Autopol IV digital polarimeter. HRMS were recorded with a micromass ESI Time of Flight (TOF) mass spectrometer. IR spectra were recorded on a Perkin–Elmer Spectrum One FTIR spectrometer. ^1H and ^{13}C NMR spectra were recorded either Bruker AV 400 MHz instrument in $CDCl_3$. The following abbreviations are used in reporting NMR spectroscopic data: s, singlet; br, broad; d, doublet; t, triplet; q, quartet; dd, doublet of doublets; dt, doublet of triplets; td, triplet of doublets; ABq, AB quartet; m, multiplet.

General Procedure for Cycloaddition: Nitrone (1 mmol) was added to a suspension of CsF (6 mmol) in dry CH_3CN (15 mL). Then, a solution of aryne precursor (1.5 mmol) in CH_3CN (5 mL) was added and the obtained mixture was stirred at room temperature for 1 h. After completion of the reaction (monitored by TLC), the reaction mixture was treated with a saturated aqueous solution of NaCl. The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 × 10 mL). The combined organic extracts were washed with brine, dried with Na_2SO_4, filtered and concentrated under vacuum to obtain the crude product, which was purified by flash column chromatography.

(1*S*,2*S*,3*S*,9b*S*)-1,2-Bis(benzyloxy)-3-(benzyloxymethyl)-1,2,3,9b-tetrahydrobenzo[*d*]pyrrolo[1,2-*b*]isoxazole (12): Following the general procedure, starting from nitrone **10** (50 mg, 0.12 mmol) and aryne precursor **11** (54 mg, 0.18 mmol), cycloadduct **12** was obtained as a white solid (45 mg, 76%) after purification by silica gel column chromatography (6% ethyl acetate/hexanes). R_f = 0.5 (10% ethyl acetate/hexanes); m.p. 81–82 °C. $[\alpha]_D^{20}$ = 61.0 (*c* = 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.09 (m, 17 H), 6.95 (td, *J* = 7.4, 0.8 Hz, 1 H), 6.82 (d, *J* = 8.0 Hz, 1 H), 4.97 (d, *J* = 2.7 Hz, 1 H), 4.74–4.51 (m, 6 H), 4.29 (dd, *J* = 4.8, 3.2 Hz, 1 H), 4.23 (dd, *J* = 7.9, 4.8 Hz, 1 H), 3.80 (dd, *J* = 10.5, 4.4 Hz, 1 H), 3.72 (dd, *J* = 10.5, 4.0 Hz, 1 H), 3.44–3.40 (m, 1 H) ppm. ^{13}C

NMR (100 MHz, $CDCl_3$): δ = 156.1, 138.4, 138.0, 137.6, 129.2, 128.7, 128.5, 128.4, 128.1, 128.0, 127.9, 127.8, 127.7, 127.0, 123.6, 122.1, 108.9, 88.2, 81.6, 73.6, 72.7, 72.6, 72.5, 71.0, 68.0 ppm. IR (neat): $\tilde{\nu}$ = 3019, 2928, 2865, 1654, 1454, 1363, 1286, 1111, 1026, 928, 881, 851, 669 cm^{-1}. HRMS (ESI): calcd. for $C_{32}H_{31}NO_4$ (M + 1)$^+$ 494.2331; found 494.2338.

(1*S*,2*R*,3*S*,9b*S*)-1,2-Bis(benzyloxy)-3-(benzyloxymethyl)-1,2,3,9b-tetrahydrobenzo[*d*]pyrrolo[1,2-*b*]isoxazole (15): Following the general procedure, starting from nitrone **13** (50 mg, 0.12 mmol) and aryne precursor **11** (54 mg, 0.18 mmol), cycloadduct **15** was obtained as a white solid (60 mg, 68%) after purification by silica gel column chromatography (6% ethyl acetate/hexanes). R_f = 0.5 (10% ethyl acetate/hexanes); m.p. 108–109 °C. $[\alpha]_D^{20}$ = 32.4 (*c* = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.26 (m, 15 H), 7.17 (td, *J* = 8.0, 0.7 Hz, 1 H), 7.09 (d, *J* = 7.5 Hz, 1 H), 6.88 (td, *J* = 7.5, 0.8 Hz, 1 H), 6.75 (d, *J* = 8.1 Hz, 1 H), 5.06 (d, *J* = 5.5 Hz, 1 H), 4.78–4.52 (m, 6 H), 4.24 (t, *J* = 4.2 Hz, 1 H), 4.07 (m, 1 H), 4.02 (d, *J* = 9.4 Hz, 1 H), 3.86 (dd, *J* = 9.4, 5.8 Hz, 1 H), 3.61–3.56 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.1, 138.3, 138.2, 137.7, 129.2, 128.7, 128.5, 128.4, 128.1, 128.1, 128.0, 127.9, 127.8, 127.8, 126.7, 123.4, 121.7, 108.2, 100.1, 85.6, 74.0, 73.6, 72.7, 67.8 ppm. IR (neat): $\tilde{\nu}$ = 3071, 2922, 2851, 1652, 1596, 1457, 1361, 1218, 1154, 1098, 1016, 960, 698 cm^{-1}. HRMS (ESI): calcd. for $C_{32}H_{31}NO_4$ (M + 1)$^+$ 494.2331; found 494.2307.

(1*R*,2*R*,3*R*,9b*R*)-1,2-Bis(benzyloxy)-3-(benzyloxymethyl)-1,2,3,9b-tetrahydrobenzo[*d*]pyrrolo[1,2-*b*]isoxazole (16): Following the general procedure, starting from nitrone *ent*-**10** (60 mg, 0.14 mmol) and aryne precursor **11** (65 mg, 0.21 mmol), cycloadduct **16** was obtained as a white solid (60 mg, 85%) after purification by silica gel column chromatography (6% ethyl acetate/hexanes). R_f = 0.5 (10% ethyl acetate/hexanes); m.p. 89–90 °C. $[\alpha]_D^{20}$ = –80.8 (*c* = 0.50, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.17 (m, 14 H), 7.13–7.09 (m, 3 H), 6.95 (td, *J* = 7.4, 0.7 Hz, 1 H), 6.82 (d, *J* = 8.0 Hz, 1 H), 4.97 (d, *J* = 2.7 Hz, 1 H), 4.74–4.51 (m, 6 H), 4.29 (dd, *J* = 4.7, 3.3 Hz, 1 H), 4.23 (dd, *J* = 8.0, 4.8 Hz, 1 H), 3.80 (dd, *J* = 10.4, 4.3 Hz, 1 H), 3.72 (dd, *J* = 10.4, 4.0 Hz, 1 H), 3.44–3.40 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.1, 138.4, 138.0, 137.6, 129.2, 128.7, 128.5, 128.4, 128.1, 128.0, 127.9, 127.8, 127.81, 127.76, 127.01, 123.61, 122.11, 108.9, 88.2, 81.5, 73.6, 72.7, 72.6, 72.5, 71.0, 68.0 ppm. IR (neat): $\tilde{\nu}$ = 3016, 2920, 2853, 1652, 1452, 1366, 1217, 1124, 1034, 879, 695 cm^{-1}. HRMS (ESI): calcd. for $C_{32}H_{31}NO_4$ (M + 1)$^+$ 494.2331; found 494.2331.

(1*R*,2*R*,3*S*,9b*R*)-1,2-Bis(benzyloxy)-3-(benzyloxymethyl)-1,2,3,9b-tetrahydrobenzo[*d*]pyrrolo[1,2-*b*]isoxazole (17): Following the general procedure, starting from nitrone **14** (50 mg, 0.12 mmol) and aryne precursor **11** (54 mg, 0.18 mmol), cycloadduct **17** was obtained as an oil (42 mg, 71%) after purification by silica gel column chromatography (6% ethyl acetate/hexanes). R_f = 0.5 (10% ethyl acetate/hexanes). $[\alpha]_D^{20}$ = –52.2 (*c* = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.25 (m, 13 H), 7.21–7.09 (m, 4 H), 6.91 (td, *J* = 7.4, 0.8 Hz, 1 H), 6.78 (d, *J* = 8.0 Hz, 1 H), 5.25 (d, *J* = 5.6 Hz, 1 H), 4.66–4.54 (m, 4 H), 4.49, 4.38 (ABq, *J* = 12.1 Hz, 2 H), 4.24 (dd, *J* = 5.7, 2.1 Hz, 1 H), 3.96 (t, *J* = 9.2 Hz, 1 H), 3.88 (dd, *J* = 9.2, 5.1 Hz, 1 H), 3.76–3.72 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.2, 138.4, 138.0, 137.8, 128.9, 128.6, 128.5, 128.0, 128.0, 127.9, 127.7, 127.7, 125.4, 123.4, 121.0, 108.0, 81.9, 81.1, 73.7, 72.9, 72.3, 70.8, 69.8, 67.8 ppm. IR (neat): $\tilde{\nu}$ = 3060, 3029, 2923, 2857, 1599, 1479, 1455, 1364, 1242, 1217, 1098, 698 cm^{-1}. HRMS (ESI): calcd. for $C_{32}H_{31}NO_4$ (M + 1)$^+$ 494.2331; found 494.2318.

(1*S*,2*S*,3*S*,9b*S*)-1,2-Bis(benzyloxy)-3-(benzyloxymethyl)-7,8-dimethyl-1,2,3,9b-tetrahydrobenzo[*d*]pyrrolo[1,2-*b*]isoxazole (22): Following the general procedure, starting from nitrone **10** (40 mg, 0.10 mmol) and aryne precursor **18** (50 mg, 0.15 mmol), cycloadduct **22** was obtained as a white solid (45 mg, 90%) after purification by silica gel column chromatography (6% ethyl acetate/hexanes). R_f = 0.5 (10% ethyl acetate/hexanes); m.p. 112–113 °C. $[\alpha]_D^{20}$ = 51.2 (*c* = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.22 (m, 13 H), 7.13–7.11 (m, 2 H), 6.78 (s, 1 H), 6.62 (s, 1 H), 4.91 (d, *J* = 2.9 Hz, 1 H), 4.71, 4.66 (ABq, *J* = 11.5 Hz, 3 H), 4.59, 4.54 (ABq, *J* = 11.5 Hz, 3 H), 4.26–4.20 (m, 2 H), 3.79 (dd, *J* = 10.4, 4.2 Hz, 1 H), 3.71 (dd, *J* = 10.4, 3.9 Hz, 1 H), 3.39–3.35 (m, 1 H), 2.21 (s, 3 H), 2.18 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.5, 138.4, 138.2, 137.8, 137.7, 130.1, 128.7, 128.5, 128.4, 128.1, 128.0, 127.7, 127.7, 127.7, 124.1, 124.2, 109.9, 88.2, 81.6, 73.6, 72.7, 72.6, 72.4, 70.7, 68.1, 20.3, 19.5 ppm. IR (neat): $\tilde{\nu}$ = 3028, 2926, 2857, 1605, 1494, 1453, 1366, 1308, 1216, 1144, 1125, 1094, 1029, 863, 694 cm^{-1}. HRMS (ESI): calcd. for $C_{34}H_{35}NO_4$ (M + 1)$^+$ 522.2644; found 522.2658.

(1*S*,2*R*,3*S*,9b*S*)-1,2-Bis(benzyloxy)-3-(benzyloxymethyl)-7,8-dimethyl-1,2,3,9b-tetrahydrobenzo[*d*]pyrrolo[1,2-*b*]isoxazole (23): Following the general procedure, starting from nitrone **13** (40 mg, 0.10 mmol) and aryne precursor **18** (50 mg, 0.15 mmol), cycloadduct **23** was obtained as a white solid (35 mg, 70%) after purification by silica gel column chromatography (6% ethyl acetate/hexanes). R_f = 0.5 (10% ethyl acetate/hexanes); m.p. 125–126 °C. $[\alpha]_D^{20}$ = 49.6 (*c* = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.26 (m, 15 H), 6.76 (s, 1 H), 6.55 (s, 1 H), 5.00 (d, *J* = 5.3 Hz, 1 H), 4.78–4.51 (m, 6 H), 4.23 (t, *J* = 4.3 Hz, 1 H), 4.06–4.01 (m, 2 H), 3.84 (dd, *J* = 9.4, 5.7 Hz, 1 H), 3.57–3.52 (m, 1 H), 2.19 (s, 3 H), 2.16 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.5, 138.4, 138.3, 137.9, 137.7, 129.7, 128.6, 128.5, 128.4, 128.1, 128.0, 128.0, 127.9, 127.8, 124.0, 123.9, 109.1, 85.6, 74.0, 73.6, 72.6, 71.5, 70.6, 67.9, 20.3, 19.4 ppm. IR (neat): $\tilde{\nu}$ = 3271, 3030, 2926, 2867, 1666, 1489, 1454, 1371, 1217, 1151, 1101, 1013, 695 cm^{-1}. HRMS (ESI): calcd. for $C_{34}H_{35}NO_4$ (M + 1)$^+$ 522.2644; found 522.2656.

(1*R*,2*R*,3*R*,9b*R*)-1,2-Bis(benzyloxy)-3-(benzyloxymethyl)-7,8-dimethyl-1,2,3,9b-tetrahydrobenzo[*d*]pyrrolo[1,2-*b*]isoxazole (24): Following the general procedure, starting from nitrone *ent*-**10** (40 mg, 0.10 mmol) and aryne precursor **18** (50 mg, 0.15 mmol), cycloadduct **24** was obtained as a white solid (40 mg, 70%) after purification by silica gel column chromatography (6% ethyl acetate/hexanes). R_f = 0.5 (10% ethyl acetate/hexanes); m.p. 112–113 °C. $[\alpha]_D^{20}$ = –49.0 (*c* = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.23 (m, 13 H), 7.13–7.11 (m, 2 H), 6.78 (s, 1 H), 6.62 (s, 1 H), 4.91 (s, 1 H), 4.71, 4.67 (ABq, *J* = 11.5 Hz, 3 H), 4.59, 4.54 (ABq, *J* = 11.5 Hz, 3 H), 4.26–4.20 (m, 2 H), 3.79 (dd, *J* = 10.4, 4.2 Hz, 1 H), 3.71 (dd, *J* = 10.5, 3.9 Hz, 1 H), 3.39–3.35 (m, 1 H), 2.21 (s, 3 H), 2.18 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.5, 138.5, 138.2, 137.8, 137.7, 130.1, 128.7, 128.5, 128.4, 128.1, 128.0, 127.7, 127.7, 127.7, 124.3, 124.2, 109.9, 88.2, 81.6, 73.6, 72.7, 72.6, 72.4, 70.7, 68.1, 20.3, 19.5 ppm. IR (neat): $\tilde{\nu}$ = 3028, 2924, 2857, 1654, 1453, 1366, 1216, 1094, 1029, 694 cm^{-1}. HRMS (ESI): calcd. for $C_{34}H_{35}NO_4$ (M + 1)$^+$ 522.2644; found 522.2659.

(1*R*,2*R*,3*S*,9b*R*)-1,2-Bis(benzyloxy)-3-(benzyloxymethyl)-7,8-dimethyl-1,2,3,9b-tetrahydrobenzo[*d*]pyrrolo[1,2-*b*]isoxazole (25): Following the general procedure, starting from nitrone **14** (50 mg, 0.12 mmol) and aryne precursor **18** (60 mg, 0.18 mmol), cycloadduct **25** was obtained as a colorless oil (45 mg, 72%) after purification by silica gel column chromatography (6% ethyl acetate/hexanes). R_f = 0.5 (10% ethyl acetate/hexanes). $[\alpha]_D^{20}$ = –47.6 (*c* = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.32–7.24 (m, 13 H), 7.17–7.14 (m, 2 H), 6.88 (s, 1 H), 6.59 (s, 1 H), 5.18 (d, *J* = 5.8 Hz, 1 H), 4.62–4.51 (m, 5 H), 4.80 (d, *J* = 12.3 Hz, 1 H), 4.21 (dd, *J* =

5.9, 2.2 Hz, 1 H), 4.07 (dd, J = 5.0, 2.2 Hz, 1 H), 3.96 (t, J = 9.1 Hz, 1 H), 3.85 (dd, J = 9.2, 5.0 Hz, 1 H) 2.21 (s, 3 H), 2.18 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.5, 138.4, 138.1, 137.9, 137.4, 128.9, 128.6, 128.5, 128.1, 127.9, 127.9, 127.8, 127.7, 127.1, 126.2, 120.6, 109.0, 81.9, 81.0, 73.6, 72.8, 72.3, 70.6, 69.4, 67.8, 20.4, 19.5 ppm. IR (neat): $\tilde{\nu}$ = 3021, 2924, 2862, 1655, 1493, 1454, 1366, 1263, 1208, 1091, 1028, 694 cm^{-1}. HRMS (ESI): calcd. for $C_{34}H_{35}NO_4$ (M + 1)$^+$ 522.2644; found 522.2620.

(1*S*,2*S*,3*S*,9b*S*)-1,2-Bis(benzyloxy)-3-(benzyloxymethyl)-7,8-difluoro-1,2,3,9b-tetrahydrobenzo[*d*]pyrrolo[1,2-*b*]isoxazole (26): Following the general procedure, starting from nitrone **10** (50 mg, 0.12 mmol) and aryne precursor **19** (60 mg, 0.18 mmol), cycloadduct **26** was obtained as a white solid (55 mg, 87%) after purification by silica gel column chromatography (6% ethyl acetate/hexanes). R_f = 0.5 (10% ethyl acetate/hexanes); m.p. 119–120 °C. $[\alpha]_D^{20}$ = 40.8 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.23 (m, 13 H), 7.13 (d, J = 3.0 Hz, 1 H), 7.11 (d, J = 2.0 Hz, 1 H), 6.75–6.71 (m, 1 H), 6.62 (dd, J = 9.9, 6.1 Hz, 1 H), 4.91 (s, 1 H), 4.67–4.53 (m, 6 H), 4.21–4.16 (m, 2 H), 4.59, 3.75–3.68 (m, 2 H), 3.47–3.43 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.2, 151.9, 149.6, 149.4, 147.6, 147.4, 145.1, 144.9, 138.2, 137.8, 137.3, 128.8, 128.5, 128.4, 128.0, 127.8, 121.9, 111.8, 111.6, 98.6, 98.4, 87.8, 81.7, 73.6, 72.7, 71.6, 68.0 ppm. IR (neat): $\tilde{\nu}$ = 3030, 2923, 2865, 1713, 1494, 1454, 1345, 1244, 1207, 1152, 1125, 1046, 1032, 866, 695 cm^{-1}. HRMS (ESI): calcd. for $C_{32}H_{29}NO_4F_2$ (M + 1)$^+$ 530.2143; found 530.2123.

(1*S*,2*R*,3*S*,9b*S*)-1,2-Bis(benzyloxy)-3-(benzyloxymethyl)-7,8-difluoro-1,2,3,9b-tetrahydrobenzo[*d*]pyrrolo[1,2-*b*]isoxazole (27): Following the general procedure, starting from nitrone **13** (60 mg, 0.14 mmol) and aryne precursor **19** (70 mg, 0.18 mmol), cycloadduct **27** was obtained as a white solid (60 mg, 79%) after purification by silica gel column chromatography (6% ethyl acetate/hexanes). R_f = 0.5 (10% ethyl acetate/hexanes); m.p. 123–124 °C. $[\alpha]_D^{20}$ = 45.6 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.26 (m, 15 H), 6.75–6.71 (m, 1 H), 6.55 (dd, J = 10.0, 6.1 Hz, 1 H), 4.97 (d, J = 5.8 Hz, 1 H), 4.77–4.45 (m, 6 H), 4.24 (t, J = 4.1 Hz, 1 H), 4.01–3.97 (m, 2 H), 3.81 (dd, J = 9.3, 5.7 Hz, 1 H), 3.57–3.53 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.2, 152.1, 151.9, 151.8, 149.7, 149.6, 147.2, 147.1, 144.8, 144.7, 138.1, 138.1, 137.4, 128.8, 128.5, 128.5, 128.4, 128.1, 128.0, 128.0, 127.9, 127.9, 121.6, 121.6, 121.6, 121.5, 111.5, 111.3, 98.0, 97.8, 85.2, 76.7, 74.1, 73.7, 72.8, 71.1, 71.0, 67.6 ppm. IR (neat): $\tilde{\nu}$ = 3032, 2922, 2867, 2351, 1636, 1499, 1349, 1207, 1143, 1102, 924, 864, 696 cm^{-1}. HRMS (ESI): calcd. for $C_{32}H_{29}NO_4F_2$ (M + 1)$^+$ 530.2143; found 530.2130.

(1*R*,2*R*,3*R*,9b*R*)-1,2-Bis(benzyloxy)-3-(benzyloxymethyl)-7,8-difluoro-1,2,3,9b-tetrahydrobenzo[*d*]pyrrolo[1,2-*b*]isoxazole (28): Following the general procedure, starting from nitrone *ent*-**10** (50 mg, 0.12 mmol) and aryne precursor **19** (60 mg, 0.18 mmol), cycloadduct **28** was obtained as a white solid (60 mg, 94%) after purification by silica gel column chromatography (6% ethyl acetate/hexanes). R_f = 0.5 (10% ethyl acetate/hexanes); m.p. 118–119 °C. $[\alpha]_D^{20}$ = –36.2 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.41–7.24 (m, 13 H), 7.13 (d, J = 3.0 Hz, 1 H), 7.11 (d, J = 1.9 Hz, 1 H), 6.75–6.71 (m, 1 H), 6.62 (dd, J = 9.9, 6.1 Hz, 1 H), 4.91 (s, 1 H), 4.67–4.53 (m, 6 H), 4.20–4.18 (m, 2 H), 3.75–3.68 (m, 2 H), 3.48–3.43 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.0, 151.9, 149.7, 149.6, 147.5, 147.3, 145.1, 144.9, 138.2, 137.8, 137.3, 128.8, 128.5, 128.5, 128.4, 128.0, 127.9, 127.8, 127.8, 121.9, 121.9, 121.8, 121.8, 111.8, 111.6, 98.6, 98.4, 87.8, 81.7, 73.6, 72.7, 72.7, 72.6, 71.6, 68.0 ppm. IR (neat): $\tilde{\nu}$ = 3029, 2922, 2856, 1645, 1493, 1454, 1316, 1245, 1208, 1152, 1095, 1046, 866, 695 cm^{-1}. HRMS (ESI): calcd. for $C_{32}H_{29}NO_4F_2$ (M + 1)$^+$ 530.2143; found 530.2124.

(1*R*,2*R*,3*S*,9b*R*)-1,2-Bis(benzyloxy)-3-(benzyloxymethyl)-7,8-difluoro-1,2,3,9b-tetrahydrobenzo[*d*]pyrrolo[1,2-*b*]isoxazole (29): Following the general procedure, starting from nitrone **14** (40 mg, 0.10 mmol) and aryne precursor **19** (48 mg, 0.14 mmol), cycloadduct **29** was obtained as a white solid (36 mg, 72%) after purification by silica gel column chromatography (6% ethyl acetate/hexanes). R_f = 0.5 (10% ethyl acetate/hexanes); m.p. 99–100 °C. $[\alpha]_D^{20}$ = 67.6 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.35–7.25 (m, 13 H), 7.12–7.10 (m, 2 H), 6.86 (td, J = 9.0, 0.6 Hz, 1 H), 6.58 (dd, J = 10.1, 6.2 Hz, 1 H), 5.16 (d, J = 5.6 Hz, 1 H), 4.62–4.47 (m, 5 H), 4.32 (d, J = 12.1 Hz, 1 H), 4.17 (dd, J = 5.7, 2.0 Hz, 1 H), 4.08 (dd, J = 4.9, 2.0 Hz, 1 H), 3.93 (t, J = 9.1 Hz, 1 H), 3.83 (dd, J = 9.2, 5.2 Hz, 1 H), 3.72–3.69 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.8, 152.7, 152.1, 151.9, 149.6, 149.5, 146.9, 146.7, 144.5, 144.4, 138.2, 137.8, 137.4, 128.6, 128.5, 128.2, 128.1, 128.0, 127.9, 127.8, 127.8, 118.5, 118.5, 118.4, 118.4, 113.5, 113.3, 97.7, 97.5, 81.5, 80.8, 73.7, 73.0, 72.4, 70.7, 69.9, 67.6 ppm. IR (neat): $\tilde{\nu}$ = 3032, 2926, 2868, 1645, 1500, 1455, 1359, 1256, 1208, 1154, 1102, 865, 698 cm^{-1}. HRMS (ESI): calcd. for $C_{32}H_{29}NO_4F_2$ (M + 1)$^+$ 530.2143; found 530.2142.

(1*S*,2*S*,3*S*,9b*S*)-1,2-Bis(benzyloxy)-3-(benzyloxymethyl)-6,9-dimethyl-1,2,3,9b-tetrahydrobenzo[*d*]pyrrolo[1,2-*b*]isoxazole (30): Following the general procedure, starting from nitrone **10** (50 mg, 0.12 mmol) and aryne precursor **20** (60 mg, 0.18 mmol), cycloadduct **30** was obtained as a white solid (40 mg, 65%) after purification by silica gel column chromatography (6% ethyl acetate/hexanes). R_f = 0.5 (10% ethyl acetate/hexanes); m.p. 81–82 °C. $[\alpha]_D^{20}$ = 53.4 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = δ = 7.39–7.26 (m, 10 H), 7.25–7.21 (m, 3 H), 7.08–7.06 (m, 2 H), 6.88 (d, J = 7.5 Hz, 1 H), 6.61 (d, J = 7.5 Hz, 1 H), 4.98 (d, J = 3.0 Hz, 1 H), 4.70–4.57 (m, 4 H), 4.54, 4.47 (ABq, J = 11.5 Hz, 2 H), 4.31 (t, J = 3.4 Hz, 1 H), 4.26 (dd, J = 5.7, 3.8 Hz, 1 H), 3.79 (d, J = 5.3 Hz, 2 H), 3.72 (dd, J = 10.7, 5.3 Hz, 1 H), 2.16 (s, 3 H), 2.13 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.0, 138.3, 138.1, 137.7, 131.3, 130.2, 128.6, 128.5, 128.4, 128.0, 128.0, 127.8, 127.7, 127.6, 124.7, 123.0, 115.9, 86.9, 82.8, 73.6, 73.4, 72.5, 72.1, 72.0, 68.7, 18.3, 15.2 ppm. IR (neat): $\tilde{\nu}$ = 3031, 2927, 2233, 1651, 1405, 1260, 1041, 916, 700 cm^{-1}. HRMS (ESI): calcd. for $C_{34}H_{35}NO_4$ (M + 1)$^+$ 522.2644; found 522.2627.

(1*S*,2*R*,3*S*,9b*S*)-1,2-Bis(benzyloxy)-3-(benzyloxymethyl)-6,9-dimethyl-1,2,3,9b-tetrahydrobenzo[*d*]pyrrolo[1,2-*b*]isoxazole (31): Following the general procedure, starting from nitrone **13** (50 mg, 0.12 mmol) and aryne precursor **20** (60 mg, 0.18 mmol), cycloadduct **31** was obtained as a white solid (50 mg, 80%) after purification by silica gel column chromatography (6% ethyl acetate/hexanes). R_f = 0.5 (10% ethyl acetate/hexanes); m.p. 110–111 °C. $[\alpha]_D^{20}$ = 39.8 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.15 (m, 15 H), 6.87 (d, J = 7.5 Hz, 1 H), 6.60 (d, J = 7.5 Hz, 1 H), 5.07 (d, J = 5.5 Hz, 1 H), 4.70–4.44 (m, 6 H), 4.30 (t, J = 4.2 Hz, 1 H), 4.08–02 (m, 2 H), 3.90 (dd, J = 9.5, 6.0 Hz, 1 H), 3.74–3.70 (m, 1 H), 2.21 (s, 3 H), 2.13 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.4, 138.3, 138.3, 137.6, 131.6, 130.3, 128.6, 128.5, 128.5, 128.1, 128.0, 127.9, 127.8, 124.6, 122.7, 115.5, 84.9, 73.8, 73.6, 72.5, 71.7, 71.0, 67.9, 18.6, 15.2 ppm. IR (neat): $\tilde{\nu}$ = 3029, 2916, 2860, 1587, 1497, 1454, 1365, 1308, 1257, 1202, 1138, 1029, 990, 695 cm^{-1}. HRMS (ESI): calcd. for $C_{34}H_{35}NO_4$ (M + 1)$^+$ 522.2644; found 522.2628.

(1*R*,2*R*,3*R*,9b*R*)-1,2-Bis(benzyloxy)-3-(benzyloxymethyl)-6,9-dimethyl-1,2,3,9b-tetrahydrobenzo[*d*]pyrrolo[1,2-*b*]isoxazole (32): Following the general procedure, starting from nitrone *ent*-**10** (50 mg, 0.12 mmol) and aryne precursor **20** (60 mg, 0.18 mmol), cycload-

duct **32** was obtained as a white solid (45 mg, 73%) after purification by silica gel column chromatography (6% ethyl acetate/hexanes). R_f = 0.5 (10% ethyl acetate/hexanes); m.p. 82–83 °C. $[\alpha]_D^{20}$ = –62.7 (c = 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.21 (m, 13 H), 7.08–7.06 (m, 2 H), 6.88 (d, J = 7.5 Hz, 1 H), 6.61 (d, J = 7.5 Hz, 1 H), 4.98 (d, J = 3.0 Hz, 1 H), 4.70–4.45 (m, 6 H), 4.31 (t, J = 3.3 Hz, 1 H), 4.25 (dd, J = 5.7, 3.8 Hz, 1 H), 3.79 (d, J = 5.7 Hz, 2 H), 3.76–3.70 (m, 1 H), 2.16 (s, 3 H), 2.13 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.1, 138.3, 138.1, 137.8, 131.3, 130.2, 128.6, 128.5, 128.4, 128.0, 128.0, 127.8, 127.7, 127.6, 124.7, 123.0, 115.9, 87.0, 82.8, 73.6, 73.4, 72.5, 72.1, 72.0, 68.7, 18.3, 15.1 ppm. IR (neat): $\tilde{\nu}$ = 3030, 2921, 2872, 1587, 1454, 1359, 1216, 1150, 1097, 1028, 967, 695 cm^{-1}. HRMS (ESI): calcd. for $C_{34}H_{35}NO_4$ $(M + 1)^+$ 522.2644; found 522.2629.

(1*R*,2*R*,3*S*,9b*R*)-1,2-Bis(benzyloxy)-3-(benzyloxymethyl)-6,9-dimethyl-1,2,3,9b-tetrahydrobenzo[*d*]pyrrolo[1,2-*b*]isoxazole (33): Following the general procedure, starting from nitrone **14** (60 mg, 0.14 mmol) and aryne precursor **20** (72 mg, 0.22 mmol), cycloadduct **33** was obtained as a colorless oil (45 mg, 60%) after purification by silica gel column chromatography (6% ethyl acetate/hexanes). R_f = 0.5 (10% ethyl acetate/hexanes). $[\alpha]_D^{20}$ = 54.4 (c = 0.50, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.27 (m, 10 H), 7.26–7.21 (m, 3 H), 6.97–6.95 (m, 2 H), 6.88 (d, J = 7.5 Hz, 1 H), 6.59 (d, J = 7.5 Hz, 1 H), 5.24 (d, J = 4.6 Hz, 1 H), 4.65–4.55 (m, 4 H), 4.39, 4.27 (ABq, J = 12.0 Hz, 2 H), 4.17 (dd, J = 4.1, 0.8 Hz, 1 H), 4.11 (dd, J = 4.7, 0.8 Hz, 1 H), 3.98–3.94 (m, 2 H), 3.89–3.85 (m, 1 H), 2.14 (s, 3 H), 2.06 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.3, 138.4, 138.1, 137.7, 131.5, 130.2, 128.6, 128.5, 128.4, 128.0, 128.0, 127.9, 127.8, 127.7, 127.6, 121.6, 121.3, 114.9, 81.3, 81.3, 73.6, 73.0, 72.0, 72.0, 70.6, 67.8, 19.0, 15.3 ppm. IR (neat): $\tilde{\nu}$ = 3031, 2924, 2856, 1455, 1262, 1217, 1093, 1075, 1028, 877, 697 cm^{-1}. HRMS (ESI): calcd. for $C_{34}H_{35}NO_4$ $(M + 1)^+$ 522.2644; found 522.2633.

Compound 34: Following the general procedure, starting from nitrone **10** (40 mg, 0.10 mmol) and aryne precursor **21** (50 mg, 0.14 mmol), cycloadduct **34** was obtained as a white solid (40 mg, 78%) after purification by silica gel column chromatography (8% ethyl acetate/hexanes). R_f = 0.45 (10% ethyl acetate/hexanes); m.p. 116–117 °C. $[\alpha]_D^{20}$ = 16.1 (c = 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.42–7.13 (m, 15 H), 6.46 (d, J = 0.7 Hz, 1 H), 6.37 (s, 1 H), 5.91 (dd, J = 3.3, 1.3 Hz, 2 H), 4.89 (d, J = 2.2 Hz, 1 H), 4.69–4.52 (m, 6 H), 4.21–4.18 (m, 2 H), 3.77 (dd, J = 10.4, 4.3 Hz, 1 H), 3.70 (dd, J = 10.4, 4.1 Hz, 1 H), 3.45–3.41 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.0, 148.6, 143.1, 138.4, 138.1, 137.6, 128.7, 128.5, 128.4, 128.2, 128.0, 127.9, 127.8, 127.7, 117.6, 103.1, 101.8, 92.2, 87.9, 81.6, 73.6, 72.8, 72.7, 72.5, 71.0, 68.1 ppm. IR (neat): $\tilde{\nu}$ = 3035, 2930, 1966, 1648, 1451, 1279, 1120, 1029, 697 cm^{-1}. HRMS (ESI): calcd. for $C_{33}H_{31}NO_6$ $(M + 1)^+$ 538.2230; found 538.2220.

Compound 35: Following the general procedure, starting from nitrone **13** (40 mg, 0.10 mmol) and aryne precursor **21** (50 mg, 0.14 mmol), cycloadduct **35** was obtained as a white solid (40 mg, 78%) after purification by silica gel column chromatography (8% ethyl acetate/hexanes). R_f = 0.45 (10% ethyl acetate/hexanes); m.p. 105–106 °C. $[\alpha]_D^{20}$ = 26.4 (c = 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.24 (m, 15 H), 6.56 (s, 1 H), 6.30 (s, 1 H), 5.90 (s, 2 H), 4.95 (d, J = 5.4 Hz, 1 H), 4.77–4.51 (m, 6 H), 4.23 (t, J = 4.3 Hz, 1 H),4.02–3.98 (m, 2 H), 3.81 (dd, J = 9.0, 5.8 Hz, 1 H), 3.59–3.55 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.9, 148.5, 142.8, 138.3, 138.2, 137.7, 128.7, 128.5, 128.4, 128.2, 128.1, 128.0, 127.9, 127.8, 117.1, 110.1, 102.9, 101.7, 9.5, 85.5, 74.0, 73.6, 72.7, 71.7, 70.7, 67.8 ppm. IR (neat): $\tilde{\nu}$ = 2920, 2852, 2125, 1634, 1452, 1288, 1142, 1099, 1030, 696 cm^{-1}. HRMS (ESI): calcd. for $C_{33}H_{31}NO_6$ $(M + 1)^+$ 538.2230; found 538.2224.

Compound 36: Following the general procedure, starting from nitrone *ent*-**10** (40 mg, 0.10 mmol) and aryne precursor **21** (50 mg, 0.14 mmol), cycloadduct **36** was obtained as a white solid (40 mg, 78%) after purification by silica gel column chromatography (8% ethyl acetate/hexanes). R_f = 0.45 (10% ethyl acetate/hexanes); m.p. 111–112 °C. $[\alpha]_D^{20}$ = –11.9 (c = 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.14 (m, 15 H), 6.46 (s, 1 H), 6.37 (s, 1 H), 5.91 (dd, J = 3.3, 1.3 Hz, 2 H), 4.88 (d, J = 2.2 Hz, 1 H), 4.69–4.52 (m, 6 H), 4.21–4.18 (m, 2 H), 3.76 (dd, J = 10.4, 4.3 Hz, 1 H), 3.70 (dd, J = 10.4, 4.1 Hz, 1 H), 3.45–3.40 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.0, 148.6, 143.1, 138.4, 138.0, 137.6, 128.7, 128.5, 128.4, 128.2, 128.0, 127.9, 127.8, 127.7, 117.6, 103.1, 101.8, 92.2, 87.9, 81.6, 73.6, 72.8, 72.7, 72.5, 71.0, 68.1 ppm. IR (neat): $\tilde{\nu}$ = 3021, 2923, 2852, 2139, 1645, 1450, 1250, 1149, 1118, 1030, 692 cm^{-1}. HRMS (ESI): calcd. for $C_{33}H_{31}NO_6$ $(M + 1)^+$ 538.2230; found 538.2222.

Compound 37: Following the general procedure, starting from nitrone **14** (50 mg, 0.12 mmol) and aryne precursor **21** (60 mg, 0.18 mmol), cycloadduct **37** was obtained as a colorless oil (35 mg, 55%) after purification by silica gel column chromatography (8% ethyl acetate/hexanes). R_f = 0.45 (10% ethyl acetate/hexanes). $[\alpha]_D^{20}$ = 15.2 (c = 0.25, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.27 (m, 15 H), 7.18–7.16 (m, 15 H), 6.57 (s, 1 H), 6.35 (s, 1 H), 5.91 (m, 2 H), 5.13 (d, J = 5.8 Hz, 1 H), 4.62–4.38 (m, 6 H), 4.19 (dd, J = 5.8, 2.2 Hz, 1 H), 4.07 (dd, J = 5.2, 2.2 Hz, 1 H), 3.93 (t, J = 9.2 Hz, 1 H), 3.82 (dd, J = 9.2, 5.2 Hz, 1 H), 3.73–3.68 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.0, 148.6, 143.1, 138.4, 138.0, 137.6, 128.7, 128.5, 128.4, 128.2, 128.0, 127.9, 127.8, 127.7, 117.6, 103.1, 101.8, 92.2, 87.9, 81.6, 73.6, 72.8, 72.7, 72.5, 71.0, 68.1 ppm. IR (neat): $\tilde{\nu}$ = 2950, 2923, 2853, 2137, 2098, 1642, 1585, 1474, 1297, 1216, 1095, 1039, 698 cm^{-1}. HRMS (ESI): calcd. for $C_{33}H_{31}NO_6$ $(M + 1)^+$ 538.2230; found 538.2242.

General Procedure for N–O Bond Cleavage: Zn powder (40 mmol) was added to benzo[*d*]isoxazoline (1 mmol) in AcOH/H_2O (1:1, 30 mL) and the mixture was heated to 70 °C. After 2 h the mixture was cooled to room temperature, filtered and washed with CH_2Cl_2. The solvent was evaporated and ammonia solution (20 mL) and CH_2Cl_2 (20 mL) were added. The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic layers were dried with anhydrous Na_2SO_4, filtered and concentrated under vacuum to obtain the crude product, which was purified by basic alumina flash column chromatography.

2-((2*S*,3*S*,4*S*,5*S*)-3,4-Bis(benzyloxy)-5-(benzyloxymethyl)pyrrolidin-2-yl)phenol (38): Following the general procedure, starting from cycloadduct **12** (30 mg, 0.06 mmol) and Zn dust (157 mg, 2.4 mmol), phenol **38** was obtained as a colorless oil (25 mg, 83%) after purification by basic alumina column chromatography (10% ethyl acetate/hexanes). R_f = 0.4 (10% ethyl acetate/hexanes). $[\alpha]_D^{20}$ = –34.2 (c = 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.24 (m, 14 H), 7.22–7.13 (m, 3 H), 7.05 (dd, J = 7.5, 1.5 Hz, 1 H), 6.84 (dd, J = 8.1, 0.9 Hz, 1 H), 6.79 (td, J = 7.4, 1.0 Hz, 1 H), 4.57–4.47 (m, 4 H), 4.40, 4.36 (ABq, J = 11.4 Hz, 2 H), 4.27–4.20 (m, 2 H), 3.86 (t, J = 4.2 Hz, 1 H), 3.57–3.47 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.1, 138.0, 137.8, 137.7, 129.8, 129.1, 128.9, 128.7, 128.6, 128.5, 128.2, 128.1, 127.9, 127.9, 123.1, 120.7, 119.0, 117.3, 115.4, 88.4, 84.1, 73.3, 73.0, 72.1, 69.2, 64.9, 60.2 ppm. IR (neat): $\tilde{\nu}$ = 3623, 3308, 3062, 3030, 2926, 2856, 1612, 1590, 1494, 1475, 1455, 1363, 1258, 1207, 1026, 909, 698 cm^{-1}. HRMS (ESI): calcd. for $C_{32}H_{33}NO_4$ $(M + 1)^+$ 496.2488; found 496.2493.

2-[(2*S*,3*S*,4*R*,5*S*)-3,4-Bis(benzyloxy)-5-(benzyloxymethyl)pyrrolidin-2-yl]phenol (39): Following the general procedure, starting from cycloadduct **15** (30 mg, 0.06 mmol) and Zn dust (159 mg, 2.4 mmol), phenol **39** was obtained as a white solid (27 mg, 90%) after purification by basic alumina column chromatography (10% ethyl acetate/hexanes). R_f = 0.4 (10% ethyl acetate/hexanes); m.p. 107–108 °C. $[\alpha]_D^{20}$ = –23.9 (*c* = 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.24 (m, 14 H), 7.22–7.13 (m, 3 H), 7.08 (dd, *J* = 8.2, 1.6 Hz, 1 H), 6.79 (s, 1 H), 6.77 (s, 1 H), 4.78 (d, *J* = 11.6 Hz, 1 H), 4.57–4.49 (m, 4 H), 4.48, 4.40 (ABq, *J* = 11.8 Hz, 2 H), 4.10 (t, *J* = 4.1 Hz, 1 H), 3.96 (dd, *J* = 7.8, 4.3 Hz, 1 H), 3.76–3.67 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.2, 138.3, 138.0, 137.9, 128.9, 128.7, 128.6, 128.5, 128.5, 128.0, 128.0, 128.0, 127.9, 127.8, 127.7, 123.4, 119.0, 117.2, 84.9, 73.7, 73.5, 73.1, 68.6, 63.6, 57.9 ppm. IR (neat): $\tilde{\nu}$ = 3623, 3308, 3062, 3030, 2926, 2856, 1612, 1590, 1494, 1475, 1455, 1363, 1258, 1207, 1026, 909, 698 cm^{-1}. HRMS (ESI): calcd. for $C_{32}H_{33}NO_4$ $(M + 1)^+$ 496.2488; found 496.2481.

2-[(2*R*,3*R*,4*R*,5*R*)-3,4-Bis(benzyloxy)-5-(benzyloxymethyl)pyrrolidin-2-yl]phenol (40): Following the general procedure, starting from cycloadduct **16** (50 mg, 0.10 mmol) and Zn dust (265 mg, 4.05 mmol), phenol **40** was obtained as a colorless oil (45 mg, 90%) after purification by basic alumina column chromatography (10% ethyl acetate/hexanes). R_f = 0.4 (10% ethyl acetate/hexanes). $[\alpha]_D^{20}$ = 19.1 (*c* = 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.20 (m, 14 H), 7.20–7.09 (m, 3 H), 7.06 (dd, *J* = 7.5, 1.6 Hz, 1 H), 6.84 (dd, *J* = 8.1, 1.1 Hz, 1 H), 6.79 (td, *J* = 7.5, 1.1 Hz, 1 H), 4.57–4.47 (m, 4 H), 4.40, 4.36 (ABq, *J* = 11.4 Hz, 2 H), 4.27–4.05 (m, 2 H), 3.86 (t, *J* = 4.2 Hz, 1 H), 3.62–3.45 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.1, 138.0, 137.8, 137.7, 129.8, 129.1, 128.9, 128.7, 128.6, 128.5, 128.2, 128.1, 127.9, 127.9, 123.1, 119.1, 117.3, 115.4, 88.4, 84.1, 73.3, 73.0, 72.1, 69.2, 64.9, 60.2 ppm. IR (neat): $\tilde{\nu}$ = 3439, 3329, 3062, 3029, 2927, 2859, 1657, 1589, 1494, 1473, 1454, 1364, 1258, 1217, 1094, 908, 698 cm^{-1}. HRMS (ESI): calcd. for $C_{32}H_{33}NO_4$ $(M + 1)^+$ 496.2488; found 496.2480.

2-[(2*R*,3*R*,4*R*,5*S*)-3,4-Bis(benzyloxy)-5-(benzyloxymethyl)pyrrolidin-2-yl]phenol (41): Following the general procedure, starting from cycloadduct **17** (30 mg, 0.06 mmol) and Zn dust (150 mg, 2.3 mmol), phenol **41** was obtained as a colorless oil (25 mg, 83%) after purification by basic alumina column chromatography (10% ethyl acetate/hexanes). R_f = 0.4 (10% ethyl acetate/hexanes). $[\alpha]_D^{20}$ = 20.7 (*c* = 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.27 (m, 8 H), 7.24–7.19 (m, 3 H), 7.15 (td, *J* = 8.2, 1.6 Hz, 1 H), 6.95–6.93 (m, 2 H), 6.88 (dd, *J* = 7.5, 1.6 Hz, 1 H), 6.84 (dd, *J* = 8.2, 0.8 Hz, 1 H), 6.74 (dd, *J* = 7.4, 1.1 Hz, 1 H), 4.66 (d, *J* = 4.6 Hz, 1 H), 4.60–4.42 (m, 4 H), 4.1 (s, 2 H), 4.03 (dd, *J* = 4.8, 1.4 Hz, 1 H), 3.96–3.92 (m, 2 H), 3.71–3.62 (m, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.1, 138.0, 137.9, 137.9, 128.6, 128.6, 128.3, 128.1, 127.9, 127.9, 127.8, 127.7, 127.6, 120.7, 118.4, 117.1, 84.5, 82.3, 73.4, 72.5, 72.4, 68.1, 64.0, 58.6 ppm. IR (neat): $\tilde{\nu}$ = 3445, 3328, 3060, 3030, 2924, 2857, 1657, 1590, 1494, 1470, 1262, 1094, 698 cm^{-1}. HRMS (ESI): calcd. for $C_{32}H_{33}NO_4$ $(M + 1)^+$ 496.2488; found 496.2490.

2-[(2*S*,3*S*,4*S*,5*S*)-3,4-Bis(benzyloxy)-5-(benzyloxymethyl)pyrrolidin-2-yl]-4,5-dimethylphenol (42): Following the general procedure, starting from cycloadduct **22** (42 mg, 0.08 mmol) and Zn dust (235 mg, 3.6 mmol), phenol **42** was obtained as a colorless oil (37 mg, 87%) after purification by basic alumina column chromatography (10% ethyl acetate/hexanes). R_f = 0.4 (10% ethyl acetate/hexanes). $[\alpha]_D^{20}$ = –10.0 (*c* = 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.25 (m, 14 H), 7.17 (d, *J* = 2.2 Hz, 1 H), 7.15 (d, *J* = 1.6 Hz, 1 H), 6.79 (s, 1 H), 6.65 (s, 1 H), 4.58–4.46 (m, 4 H), 4.44, 4.35 (ABq, *J* = 11.3 Hz, 2 H), 4.22–4.21 (m, 2 H), 3.85 (dd, *J* = 4.8, 3.1 Hz, 1 H), 3.54–3.48 (m, 3 H), 2.19 (s, 3 H), 2.14 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.7, 138.1, 138.0, 137.8, 137.3, 129.9, 128.7, 128.6, 128.5, 128.1, 128.0, 127.9, 127.9, 127.9, 126.7, 120.2, 118.4, 88.7, 84.2, 73.3, 73.0, 72.1, 69.3, 64.6, 60.2, 19.7, 18.8 ppm. IR (neat): $\tilde{\nu}$ = 3430, 3020, 2927, 2857, 1652, 1495, 1454, 1369, 1308, 1217, 1100, 1022, 668 cm^{-1}. HRMS (ESI): calcd. for $C_{34}H_{37}NO_4$ $(M + 1)^+$ 524.2801; found 524.2805.

2-[(2*S*,3*S*,4*R*,5*S*)-3,4-Bis(benzyloxy)-5-(benzyloxymethyl)pyrrolidin-2-yl]-4,5-dimethylphenol (43): Following the general procedure, starting from cycloadduct **23** (36 mg, 0.07 mmol) and Zn dust (180 mg, 2.8 mmol), phenol **43** was obtained as a white solid (33 mg, 91%) after purification by basic alumina column chromatography (10% ethyl acetate/hexanes). R_f = 0.4 (10% ethyl acetate/hexanes); m.p. 137–138 °C. $[\alpha]_D^{20}$ = –14.0 (*c* = 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.21 (m, 14 H), 7.19 (d, *J* = 2.8 Hz, 1 H), 7.17 (d, *J* = 1.8 Hz, 1 H), 6.81 (s, 1 H), 6.59 (s, 1 H), 4.76 (d, *J* = 2.8 Hz, 1 H), 4.57–4.40 (m, 6 H), 4.09 (t, *J* = 4.2 Hz, 1 H), 3.94 (dd, *J* = 7.4, 4.3 Hz, 1 H), 3.76–3.66 (m, 3 H), 2.18 (s, 3 H), 2.13 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.7, 138.4, 138.0, 136.9, 129.7, 128.6, 128.5, 128.4, 127.9, 127.9, 127.9, 127.8, 126.7, 120.5, 118.3, 85.3, 73.6, 73.5, 73.2, 68.6, 63.3, 58.0, 19.7, 18.8 ppm. IR (neat): $\tilde{\nu}$ = 3456, 3326, 3032, 3010, 2922, 2858, 2857, 1661, 1453, 1356, 1308, 1279, 1213, 1158, 1119, 1101, 1063, 1027, 801, 696, 668 cm^{-1}. HRMS (ESI): calcd. for $C_{34}H_{37}NO_4$ $(M + 1)^+$ 524.2801; found 524.2801.

2-[(2*R*,3*R*,4*R*,5*R*)-3,4-Bis(benzyloxy)-5-(benzyloxymethyl)pyrrolidin-2-yl]-4,5-dimethylphenol (44): Following the general procedure, starting from cycloadduct **24** (40 mg, 0.08 mmol) and Zn dust (200 mg, 3.06 mmol), phenol **44** was obtained as a colorless oil (35 mg, 87%) after purification by basic alumina column chromatography (10% ethyl acetate/hexanes). R_f = 0.4 (10% ethyl acetate/hexanes). $[\alpha]_D^{20}$ = 17.1 (*c* = 0.50, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.18 (m, 14 H), 7.17 (d, *J* = 2.0 Hz, 1 H), 7.16 (d, *J* = 1.6 Hz, 1 H), 6.79 (s, 1 H), 6.65 (s, 1 H), 4.57–4.46 (m, 4 H), 4.45, 4.35 (ABq, *J* = 11.4 Hz, 2 H), 4.21–4.20 (m, 2 H), 3.85 (dd, *J* = 4.7, 3.1 Hz, 1 H), 3.55–3.48 (m, 3 H), 2.19 (s, 3 H), 2.14 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.7, 138.1, 138.0, 137.8, 137.3, 129.9, 128.7, 128.5, 128.5, 128.1, 128.0, 127.9, 127.9, 127.9, 126.7, 120.1, 118.4, 88.7, 84.2, 73.3, 73.0, 72.1, 69.3, 64.6, 60.2, 19.7, 18.8 ppm. IR (neat): $\tilde{\nu}$ = 3306, 3030, 2923, 2860, 2857, 1628, 1585, 1497, 1363, 1263, 1207, 1091, 1028, 877, 807, 698, 660 cm^{-1}. HRMS (ESI): calcd. for $C_{34}H_{37}NO_4$ $(M + 1)^+$ 524.2801; found 524.2820.

2-[(2*R*,3*R*,4*R*,5*S*)-3,4-Bis(benzyloxy)-5-(benzyloxymethyl)pyrrolidin-2-yl]-4,5-dimethylphenol (45): Following the general procedure, starting from cycloadduct **25** (40 mg, 0.08 mmol) and Zn dust (210 mg, 3.2 mmol), phenol **45** was obtained as a colorless oil (35 mg, 87%) after purification by basic alumina column chromatography (10% ethyl acetate/hexanes). R_f = 0.4 (10% ethyl acetate/hexanes). $[\alpha]_D^{20}$ = 28.4 (*c* = 0.50, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.19 (m, 14 H), 6.97–6.95 (m, 1 H), 6.65 (s, 1 H), 6.61 (s, 1 H), 4.59–4.41 (m, 5 H), 4.18 (s, 2 H), 4.02 (dd, *J* = 4.8, 1.4 Hz, 1 H), 3.92 (dd, *J* = 4.7, 1.4 Hz, 1 H), 3.70–3.61 (m, 2 H), 2.20 (s, 3 H), 2.12 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.7, 138.1, 138.0, 136.8, 129.3, 128.6, 128.5, 128.3, 128.0, 127.9, 127.7, 127.6, 126.1, 118.2, 117.7, 84.4, 82.4, 73.4, 72.4, 72.4, 68.2, 63.7, 58.6, 19.7, 18.8 ppm. IR (neat): $\tilde{\nu}$ = 3366, 3027, 2927, 2856, 1788, 1748, 1663, 1454, 1217, 1095, 941, 825, 698, 669 cm^{-1}. HRMS (ESI): calcd. for $C_{34}H_{37}NO_4$ $(M + 1)^+$ 524.2801; found 524.2797.

2-[(2*S*,3*S*,4*S*,5*S*)-3,4-Bis(benzyloxy)-5-(benzyloxymethyl)pyrrolidin-2-yl]-4,5-difluorophenol (46): Following the general procedure, starting from cycloadduct **26** (30 mg, 0.06 mmol) and Zn dust (157 mg, 2.4 mmol), phenol **46** was obtained as a colorless oil (24 mg, 80%) after purification by basic alumina column chromatography (10% ethyl acetate/hexanes). R_f = 0.4 (10% ethyl acetate/hexanes). $[\alpha]_D^{20}$ = –27.8 (*c* = 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.24 (m, 14 H), 7.17–7.15 (m, 2 H), 6.79 (dd, *J* = 10.8, 8.8 Hz, 1 H), 6.60 (dd, *J* = 11.8, 7.0 Hz, 1 H), 4.55–4.37 (m, 6 H), 4.16–4.11 (m, 2 H), 3.85 (t, *J* = 3.5 Hz, 1 H), 3.54–3.47 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.6, 154.4, 149.1, 148.9, 147.0, 146.8, 144.7, 144.6, 142.4, 142.3, 137.8, 137.6, 137.5, 129.8, 129.5, 128.7, 128.6, 128.6, 128.5, 128.5, 128.2, 128.1, 128.1, 127.9, 127.9, 127.9, 127.4, 121.9, 118.5, 116.6, 116.5, 106.2, 106.0, 88.4, 83.9, 73.4, 73.1, 72.3, 68.9, 64.1, 60.3 ppm. IR (neat): $\tilde{\nu}$ = 3736, 3324, 3027, 2927, 2855, 1628, 1516, 1364, 1215, 1094, 875, 698 cm^{-1}. HRMS (ESI): calcd. for $C_{32}H_{31}NO_4F_2$ $(M + 1)^+$ 532.2299; found 532.2302.

2-[(2*S*,3*S*,4*R*,5*S*)-3,4-Bis(benzyloxy)-5-(benzyloxymethyl)pyrrolidin-2-yl]-4,5-difluorophenol (47): Following the general procedure, starting from cycloadduct **27** (30 mg, 0.06 mmol) and Zn dust (156 mg, 2.4 mmol), phenol **47** was obtained as a white solid (20 mg, 67%) after purification by basic alumina column chromatography (10% ethyl acetate/hexanes). R_f = 0.4 (10% ethyl acetate/hexanes); m.p. 94–95 °C. $[\alpha]_D^{20}$ = –21.1 (*c* = 0.50, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.25 (m, 14 H), 7.18–7.15 (m, 2 H), 6.84 (dd, *J* = 11.0, 9.0 Hz, 1 H), 6.54 (dd, *J* = 11.9, 7.0 Hz, 1 H), 4.78 (d, *J* = 11.6 Hz, 1 H), 4.57–4.36 (m, 6 H), 4.06 (t, *J* = 4.0 Hz, 1 H), 3.88 (dd, *J* = 8.3, 4.0 Hz, 1 H), 3.69–3.61 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.6, 154.5, 148.8, 148.7, 142.4, 138.1, 137.8, 137.4, 128.7, 128.6, 128.1, 128.1, 128.1, 128.0, 128.0, 127.9, 118.7, 116.6, 116.4, 106.0, 105.8, 85.1, 76.5, 73.8, 73.6, 73.4, 68.5, 68.1, 62.6, 58.0 ppm. IR (neat): $\tilde{\nu}$ = 3336, 3027, 2924, 2853, 1623, 1519, 1495, 1456, 1336, 1215, 1119, 698 cm^{-1}. HRMS (ESI): calcd. for $C_{32}H_{31}NO_4F_2$ $(M + 1)^+$ 532.2299; found 532.2298.

2-[(2*R*,3*R*,4*R*,5*R*)-3,4-Bis(benzyloxy)-5-(benzyloxymethyl)pyrrolidin-2-yl]-4,5-difluorophenol (48): Following the general procedure, starting from cycloadduct **28** (30 mg, 0.06 mmol) and Zn dust (157 mg, 2.4 mmol), phenol **48** was obtained as a colorless oil (20 mg, 67%) after purification by basic alumina column chromatography (10% ethyl acetate/hexanes). R_f = 0.4 (10% ethyl acetate/hexanes). $[\alpha]_D^{20}$ = 10.4 (*c* = 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.26 (m, 14 H), 7.17–7.15 (m, 2 H), 6.79 (dd, *J* = 10.8, 8.8 Hz, 1 H), 6.60 (dd, *J* = 11.8, 7.0 Hz, 1 H), 4.55–4.37 (m, 6 H), 4.16–4.11 (m, 2 H), 3.85 (t, *J* = 3.5 Hz, 1 H), 3.54–3.48 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.6, 154.4, 148.9, 147.0, 137.8, 137.6, 137.5, 128.7, 128.6, 128.6, 128.2, 128.1, 128.1, 128.0, 118.5, 116.7, 116.5, 106.2, 106.0, 88.5, 83.9, 73.4, 73.1, 72.3, 68.9, 64.1, 60.3 ppm. IR (neat): $\tilde{\nu}$ = 3401, 3318, 3027, 2924, 2854, 2853, 2346, 1666, 1517, 1455, 1215, 1095, 698 cm^{-1}. HRMS (ESI): calcd. for $C_{32}H_{31}NO_4F_2$ $(M + 1)^+$ 532.2299; found 532.2294.

2-[(2*R*,3*R*,4*R*,5*S*)-3,4-Bis(benzyloxy)-5-(benzyloxymethyl)pyrrolidin-2-yl]-4,5-difluorophenol (49): Following the general procedure, starting from cycloadduct **29** (20 mg, 0.04 mmol) and Zn dust (99 mg, 1.5 mmol), phenol **49** was obtained as a white solid (17 mg, 85%) after purification by basic alumina column chromatography (10% ethyl acetate/hexanes). R_f = 0.4 (10% ethyl acetate/hexanes); m.p. 91–92 °C. $[\alpha]_D^{20}$ = 28.6 (*c* = 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.27 (m, 8 H), 7.25–7.22 (m, 6 H), 6.98–6.95 (m, 2 H), 6.61 (dd, *J* = 12.3, 7.0 Hz, 1 H), 6.57–6.55 (m, 1 H), 4.59–4.50 (m, 3 H), 4.50, 4.46 (ABq, *J* = 11.9 Hz, 2 H), 4.27, 4.17 (ABq, *J* = 12.3 Hz, 2 H), 4.00 (dd, *J* = 4.6, 1.4 Hz, 1 H), 3.93–3.90 (m, 1 H); 3.88 (dd, *J* = 4.5, 1.4 Hz, 1 H), 3.69 (dd, *J* = 9.7, 5.6 Hz, 1 H), 4.00 (dd, *J* = 9.7, 8.0 Hz, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.7, 156.6, 151.2, 151.0, 148.7, 148.6, 144.4, 144.3, 142.1, 142.0, 137.9, 137.8, 137.6, 128.7, 128.6, 128.4, 128.2, 128.0, 127.9, 127.9, 127.8, 127.77, 116.2, 115.9, 115.7, 105.8, 105.6, 84.1, 81.7, 73.50, 72.6, 72.5, 68.1, 63.5, 58.9 ppm. IR (neat): $\tilde{\nu}$ = 3466, 3328, 3064, 3031, 2924, 2857, 1623, 1520, 1496, 1454, 1396, 1363, 1279, 1151, 1111, 1028, 698 cm^{-1}. HRMS (ESI): calcd. for $C_{32}H_{31}NO_4F_2$ $(M + 1)^+$ 532.2299; found 532.2301.

2-[(2*S*,3*S*,4*S*,5*S*)-3,4-Bis(benzyloxy)-5-(benzyloxymethyl)pyrrolidin-2-yl]-3,6-dimethylphenol (50): Following the general procedure, starting from cycloadduct **30** (23 mg, 0.04 mmol) and Zn dust (115 mg, 1.7 mmol), phenol **50** was obtained as a colorless oil (18 mg, 78%) after purification by basic alumina column chromatography (10% ethyl acetate/hexanes). R_f = 0.4 (10% ethyl acetate/hexanes). $[\alpha]_D^{20}$ = –28.4 (*c* = 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 12.08 (s, 1 H), 7.36–7.25 (m, 10 H), 7.25–7.21 (m, 3 H), 7.09–7.07 (m, 3 H), 6.94 (d, *J* = 7.5 Hz, 1 H), 6.55 (d, *J* = 7.5 Hz, 1 H), 4.62–4.56 (m, 3 H), 4.56, 4.49 (ABq, *J* = 11.9 Hz, 1 H), 4.37–4.30 (m, 3 H), 3.82 (dd, *J* = 5.1, 3.6 Hz, 1 H), 3.62–3.58 (m, 1 H), 3.53 (t, *J* = 9.4 Hz, 1 H), 3.47 (dd, *J* = 9.4, 4.2 Hz, 1 H), 2.26 (s, 3 H), 2.19 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.9, 138.1, 138.0, 137.8, 134.7, 129.8, 128.7, 128.5, 128.4, 128.1, 127.9, 127.9, 127.8, 127.8, 127.7, 123.9, 120.8, 120.8, 88.6, 83.9, 73.3, 73.2, 72.0, 69.6, 59.7, 59.6, 20.1, 15.8 ppm. IR (neat): $\tilde{\nu}$ = 3321, 3063, 3031, 2924, 2859, 1620, 1585, 1454, 1361, 1270, 1206, 1095, 1028, 909, 801 cm^{-1}. HRMS (ESI): calcd. for $C_{34}H_{37}NO_4$ $(M + 1)^+$ 524.2801; found 524.2801.

2-[(2*S*,3*S*,4*R*,5*S*)-3,4-Bis(benzyloxy)-5-(benzyloxymethyl)pyrrolidin-2-yl]-3,6-dimethylphenol (51): Following the general procedure, starting from cycloadduct **31** (30 mg, 0.06 mmol) and Zn dust (156 mg, 2.4 mmol), phenol **51** was obtained as a white solid (26 mg, 86%) after purification by basic alumina column chromatography (10% ethyl acetate/hexanes). R_f = 0.4 (10% ethyl acetate/hexanes); m.p. 119–120 °C. $[\alpha]_D^{20}$ = –41.4 (*c* = 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 12.69 (s, 1 H), 7.36–7.25 (m, 10 H), 7.09–7.05 (m, 3 H), 7.09 (d, *J* = 3.7 Hz, 1 H), 7.08 (d, *J* = 2.1 Hz, 1 H), 6.92 (d, *J* = 7.6 Hz, 1 H), 6.55 (d, *J* = 7.6 Hz, 1 H), 4.86 (d, *J* = 7.9 Hz, 1 H), 4.59–4.47 (m, 4 H), 4.36 (d, *J* = 11.7 Hz, 1 H), 4.15 (t, *J* = 4.4 Hz, 1 H), 4.07 (dd, *J* = 8.0, 4.4 Hz, 1 H), 3.78–3.74 (m, 2 H), 3.71–3.67 (m, 1 H), 2.29 (s, 3 H), 2.16 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = \delta$ = 157.0, 138.5, 138.2, 138.0, 135.0, 129.5, 128.6, 128.5, 128.4, 128.0, 127.9, 127.8, 127.6, 127.5, 123.7, 121.1, 120.7, 84.7, 77.6, 73.7, 73.4, 73.3, 68.6, 59.2, 57.3, 20.0, 15.7 ppm. IR (neat): $\tilde{\nu}$ = 3290, 3030, 2923, 2858, 2697, 2321, 1725, 1581, 1454, 1367, 1311, 1268, 1210, 1115, 1094, 801, 697 cm^{-1}. HRMS (ESI): calcd. for $C_{34}H_{37}NO_4$ $(M + 1)^+$ 524.2821; found 524.2801.

2-[(2*R*,3*R*,4*R*,5*R*)-3,4-Bis(benzyloxy)-5-(benzyloxymethyl)pyrrolidin-2-yl]-3,6-dimethylphenol (52): Following the general procedure, starting from cycloadduct **32** (42 mg, 0.08 mmol) and Zn dust (210 mg, 3.2 mmol), phenol **52** was obtained as a colorless oil (37 mg, 88%) after purification by basic alumina column chromatography (10% ethyl acetate/hexanes). R_f = 0.4 (10% ethyl acetate/hexanes). $[\alpha]_D^{20}$ = 27.3 (*c* = 1.00, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 12.06 (d, *J* = 6.5 Hz, 1 H), 7.37–7.20 (m, 13 H), 7.09 (d, *J* = 2.6 Hz, 1 H), 7.07 (d, *J* = 2.8 Hz, 1 H), 6.95 (d, *J* = 7.6 Hz, 1 H), 6.55 (d, *J* = 7.6 Hz, 1 H), 4.62–4.55 (m, 4 H), 4.48 (d, *J* = 11.9 Hz, 1 H), 4.37–4.29 (m, 3 H), 3.83 (dd, *J* = 5.1, 3.6 Hz, 1 H), 3.63–3.59 (m, 1 H), 3.54 (t, *J* = 9.5 Hz, 1 H), 3.48

(dd, J = 9.5, 4.3 Hz, 1 H), 2.26 (s, 3 H), 2.19 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.9, 138.1, 138.0, 137.8, 134.7, 129.8, 128.7, 128.5, 128.4, 128.1, 127.9, 127.9, 127.8, 127.8, 127.7, 123.9, 120.8, 88.6, 83.9, 73.3, 73.2, 72.0, 69.6, 59.7, 20.1, 15.8 ppm. IR (neat): $\tilde{\nu}$ = 3324, 3030, 2924, 2857, 1615, 1585, 1454, 1361, 1311, 1270, 1207, 1090, 1072, 1028, 801, 698 cm^{-1}. HRMS (ESI): calcd. for $C_{34}H_{37}NO_4$ (M + 1)$^+$ 524.2801; found 524.2791.

2-[(2*R*,3*R*,4*R*,5*S*)-3,4-Bis(benzyloxy)-5-(benzyloxymethyl)pyrrolidin-2-yl]-3,6-dimethylphenol (53): Following the general procedure, starting from cycloadduct **33** (25 mg, 0.05 mmol) and Zn dust (130 mg, 2.0 mmol), phenol **53** was obtained as a colorless oil (21 mg, 84%) after purification by basic alumina column chromatography (10% ethyl acetate/hexanes). R_f = 0.4 (10% ethyl acetate/hexanes). $[\alpha]_D^{20}$ = 15.6 (c = 1.00, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37–7.26 (m, 9 H), 7.24–7.17 (m, 5 H), 6.94–6.89 (m, 3 H), 6.47 (d, J = 7.5 Hz, 1 H), 4.84 (d, J = 4.5 Hz, 1 H), 4.58, 4.52 (ABq, J = 12.0 Hz, 2 H), 4.48 (s, 2 H), 4.11, 4.03 (ABq, J = 12.3 Hz, 2 H), 4.04 (d, J = 1.5 Hz, 1 H), 3.99 (dd, J = 4.5, 1.5 Hz, 1 H), 3.96–3.93 (m, 1 H), 3.71–3.62 (m, 2 H), 2.19 (s, 3 H), 2.04 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 158.9, 138.1, 138.0, 138.0, 133.1, 129.4, 128.7, 128.6, 128.3, 128.1, 127.9, 127.8, 127.8, 127.6, 123.8, 119.9, 117.8, 82.7, 81.6, 73.3, 72.6, 72.3, 67.9, 60.5, 58.1, 19.6, 16.0 ppm. IR (neat): $\tilde{\nu}$ = 3460, 2925, 2857, 1617, 1454, 1270, 1217, 1092, 1028, 699 cm^{-1}. HRMS (ESI): calcd. for $C_{34}H_{37}NO_4$ (M + 1)$^+$ 524.2801; found 524.2794.

6-[(2*S*,3*S*,4*S*,5*S*)-3,4-Bis(benzyloxy)-5-(benzyloxymethyl)pyrrolidin-2-yl]benzo[*d*][1,3]dioxol-5-ol (54): Following the general procedure, starting from cycloadduct **34** (30 mg, 0.06 mmol) and Zn dust (146 mg, 2.24 mmol), phenol **54** was obtained as a colorless oil (16 mg, 53%) after purification by basic alumina column chromatography (15% ethyl acetate/hexanes). R_f = 0.35 (10% ethyl acetate/hexanes). $[\alpha]_D^{20}$ = 5.76 (c = 0.25, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.51–7.26 (m, 14 H), 7.19–7.17 (m, 2 H), 6.51 (s, 1 H), 6.41 (s, 1 H), 5.87 (dd, J = 4.0, 1.2 Hz, 1 H), 4.55–4.42 (m, 6 H), 4.18 (dd, J = 7.6, 4.6 Hz, 1 H), 4.12 (d, J = 7.6 Hz, 1 H), 3.82 (t, J = 4.6 Hz, 1 H), 3.53–3.45 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.1, 147.3, 139.9, 138.1, 137.7, 137.7, 128.4, 128.3, 128.3, 127.8, 127.8, 127.7, 127.7, 127.6, 114.2, 107.9, 100.6, 99.1, 84.7, 73.5, 73.3, 73.0, 68.4, 63.3, 57.6 ppm. IR (neat): $\tilde{\nu}$ = 3730, 3390, 3027, 2961, 2928, 2857, 1732, 1454, 1374, 1283, 1218, 1166, 1113, 953, 697 cm^{-1}. HRMS (ESI): calcd. for $C_{33}H_{33}NO_6$ (M + 1)$^+$ 540.2386; found 540.2385.

6-[(2*S*,3*S*,4*R*,5*S*)-3,4-Bis(benzyloxy)-5-(benzyloxymethyl)pyrrolidin-2-yl]benzo[*d*][1,3]dioxol-5-ol (55): Following the general procedure, starting from cycloadduct **35** (30 mg, 0.05 mmol) and Zn dust (146 mg, 2.24 mmol), phenol **55** was obtained as a white solid (25 mg, 83%) after purification by basic alumina column chromatography (15% ethyl acetate/hexanes). R_f = 0.35 (10% ethyl acetate/hexanes); m.p. 93–94 °C. $[\alpha]_D^{20}$ = –17.9 (c = 0.40, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.40–7.26 (m, 14 H), 7.20–7.18 (m, 2 H), 6.54 (s, 1 H), 6.35 (s, 1 H), 5.86 (dd, J = 6.0, 1.4 Hz, 2 H), 4.76 (d, J = 11.6 Hz, 1 H), 4.56–4.45 (m, 6 H), 4.07 (t, J = 4.1 Hz, 1 H), 3.71–3.64 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.3, 147.5, 140.1, 138.3, 137.9, 137.9, 128.6, 128.5, 128.5, 128.0, 128.0, 127.9, 127.9, 127.8, 114.4, 108.1, 100.8, 99.3, 85.0, 73.7, 73.5, 73.2, 68.6, 63.5, 57.8 ppm. IR (neat): $\tilde{\nu}$ = 3337, 3030, 2925, 2856, 2139, 1632, 1477, 1455, 1365, 1247, 1215, 1182, 1151, 1089, 1039, 865, 698 cm^{-1}. HRMS (ESI): calcd. for $C_{33}H_{33}NO_6$ (M + 1)$^+$ 540.2386; found 540.2386.

6-[(2*R*,3*R*,4*R*,5*R*)-3,4-Bis(benzyloxy)-5-(benzyloxymethyl)pyrrolidin-2-yl]benzo[*d*][1,3]dioxol-5-ol (56): Following the general procedure, starting from cycloadduct **36** (30 mg, 0.05 mmol) and Zn dust (146 mg, 2.24 mmol), phenol **56** was obtained as a colorless oil (18 mg, 60%) after purification by basic alumina column chromatography (15% ethyl acetate/hexanes). R_f = 0.35 (10% ethyl acetate/hexanes). $[\alpha]_D^{20}$ = 18.5 (c = 0.25, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.26 (m, 14 H), 7.24–7.17 (m, 2 H), 6.51 (s, 1 H), 6.41 (s, 1 H), 5.87 (dd, J = 4.1, 1.3 Hz, 1 H), 4.69 (s, 1 H), 4.55–4.41 (m, 5 H), 4.18 (dd, J = 7.6, 4.6 Hz, 1 H), 4.12 (d, J = 7.6 Hz, 1 H), 3.82 (t, J = 4.6 Hz, 1 H), 3.53–3.47 (m, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 153.3, 147.8, 140.1, 138.0, 137.8, 137.7, 128.7, 128.6, 128.6, 128.5, 128.3, 128.1, 127.9, 127.8, 127.8, 127.1, 114.1, 108.2, 100.9, 99.5, 88.5, 84.0, 73.3, 73.1, 72.1, 69.2, 64.8, 60.0 ppm. IR (neat): $\tilde{\nu}$ = 3736, 3365, 2926, 2857, 1749, 1650, 1477, 1363, 1215, 1155, 945, 697 cm^{-1}. HRMS (ESI): calcd. for $C_{33}H_{33}NO_6$ (M + 1)$^+$ 540.2386; found 540.2375.

6-[(2*R*,3*R*,4*R*,5*S*)-3,4-Bis(benzyloxy)-5-(benzyloxymethyl)pyrrolidin-2-yl]benzo[*d*][1,3]dioxol-5-ol (57): Following the general procedure, starting from cycloadduct **37** (30 mg, 0.06 mmol) and Zn dust (157 mg, 2.4 mmol), phenol **57** was obtained as a colorless oil (23 mg, 77%) after purification by basic alumina column chromatography (15% ethyl acetate/hexanes). R_f = 0.35 (10% ethyl acetate/hexanes). $[\alpha]_D^{20}$ = 1.4 (c = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.36–7.20 (m, 17 H), 7.05–7.02 (m, 1 H), 6.55 (s, 1 H), 6.42 (s, 1 H), 5.88 (dd, J = 4.4, 1.4 Hz, 2 H), 4.58–4.37 (m, 5 H), 4.21 (s, 1 H), 4.06–4.00 (m, 2 H), 3.94 (dd, J = 5.5, 1.8 Hz, 1 H), 3.79 (dd, J = 9.4, 4.3 Hz, 1 H), 4.07 (t, J = 9.4 Hz, 1 H), 3.58–3.54 (m, 1 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 152.8, 147.8, 140.2, 138.2, 138.1, 137.7, 128.6, 128.5, 128.0, 127.9, 127.9, 127.8, 127.8, 127.7, 108.1, 100.9, 100.1, 99.5, 89.18, 73.8, 72.6, 71.4, 70.2, 67.7, 60.3 ppm. IR (neat): $\tilde{\nu}$ = 3323, 3029, 2924, 2854, 2137, 1631, 1476, 1455, 1361, 1215, 1185, 1093, 1039, 860, 698 cm^{-1}. HRMS (ESI): calcd. for $C_{33}H_{33}NO_6$ (M + 1)$^+$ 540.2386; found 540.2386.

(2*R*,3*R*,4*R*,5*R*)-2-(Hydroxymethyl)-5-(2-hydroxyphenyl)pyrrolidine-3,4-diol (58): A solution of compound **40** (75 mg, 0.15 mmol) in 3 mL of anhydrous CH_2Cl_2 is cooled to 0 °C and then BBr_3 (113 mg, 0.45 mmol, 1 M solution in CH_2Cl_2) was added dropwise. The mixture was warmed to room temperature for 0.5 h before quenching with distilled water. The mixture was filtered and concentrated under vacuum to get the crude product. The crude compound was purified by basic resin to obtain polyhydroxy-pyrrolidine **58** as a white solid (30 mg, 88%). R_f = 0.2 (10% methanol/ethyl acetate). $[\alpha]_D^{20}$ = 21.8 (c = 2.0, H_2O); m.p. 130–131 °C. ^{1}H NMR (400 MHz, D_2O): δ = 6.89–6.82 (m, 2 H), 6.51–6.46 (m, 2 H), 4.18 (dd, J = 9.6, 8.1 Hz, 1 H), 3.98 (d, J = 9.6 Hz, 1 H), 3.69 (t, J = 8.2 Hz, 1 H), 3.51–3.46 (m, 2 H), 3.42–3.35 (m, 1 H) ppm. ^{13}C NMR (100 MHz, D_2O): δ = 155.0, 131.5, 130.2, 120.5, 118.4, 116.1, 76.3, 73.8, 62.5, 61.3, 57.5 ppm. IR (neat): $\tilde{\nu}$ = 3497, 2870, 2714, 1650, 1465, 1374, 1211, 1045, 921, 828, 770 cm^{-1}. HRMS (ESI): calcd. for $C_{11}H_{15}NO_4$ (M + 1)$^+$ 226.1079; found 226.1079.

Supporting Information (see footnote on the first page of this article): Characterization data including ^{1}H and ^{13}C NMR spectra for all the compounds.

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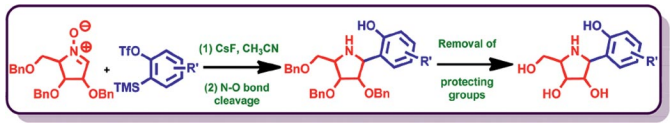
Dipolar Cycloaddition Reactions



An efficient strategy for the synthesis of a variety of aza-*C*-aryl glycosides is described. This strategy involves a stereoselective 1,3-dipolar cycloaddition reaction between arynes and sugar-derived cyclic nitrones followed by reductive N–O bond cleavage and removal of benzyl groups.

Keywords: Glycosides / Cycloaddition / Nitrogen heterocycles / Cyclic nitrones / Arynes

