Improved Protein Kinase C Affinity through Final Step Diversification of A Simplified Salicylate-Derived Bryostatin Analog Scaffold

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Supporting Information

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General Methods

Unless otherwise noted, all reactions were run under a nitrogen atmosphere in flame-dried glassware. Reactions were stirred using Teflon-coated magnetic stirrer bars. Reactions were monitored using thin layer silica gel chromatography (TLC) using 0.25 mm silica gel 60F plates with fluorescent indicator from Merck. Plates were visualized by treatment with UV, acidic p-anisaldehyde stain, or KMnO₄ stain with gentle heating. Products were purified by column chromatography using the solvent systems indicated. Silica gel 60, 230-400 mesh, was purchased from Fisher Scientific.

When necessary, solvents and reagents were purified before use. Tetrahydrofuran (THF), diethyl ether (ether), benzene, toluene (PhMe), and dichloromethane were passed through an alumina drying column (Solv-Tek Inc. or Innovative Technologies) using nitrogen pressure. Anhydrous dimethylformamide (DMF), dimethyl sulfoxide (DMSO), acetone, acetonitrile (MeCN), and methanol (MeOH) were obtained from Sigma-Aldrich. Ethyl acetate (EtOAc), petroleum ether, pentane, hexanes, MeOH, ether, dichloromethane, MeCN, PhMe, and THF were obtained from Acros Chemicals. Powdered 4Å molecular sieves (< 5 micron) were purchased from Aldrich and stored/activated as indicated. Amine bases (NEt₃, pyridine, diisopropylamine, diisopropylethylamine [Hünig’s base]) were distilled over CaH₂ under nitrogen. 3,5-Dimethylisoxazole-4-boronic acid was obtained from Synthonix. 4-(Diethylsulfamoyl)benzeneboronic acid was purchased from Alfa-Aesar. 4-Isopropoxycarbonylphenylboronic acid was obtained from Frontier Scientific. All other reagents were purchased from commercial suppliers (Aldrich, Acros) and were either used as received without additional purification or were purified using standard methods. Preparative HPLC was carried out using an MeCN:H₂O gradient using a Shimadzu Prominence system equipped with a Restek 18 column (5 μm, 21 x 250 mm). NMR spectra were measured on a Varian INOVA 500 (¹H at 500 MHz, ¹³C at 125 MHz), a Varian 400 (¹H at 400 MHz, ¹³C at 100 MHz), or a Varian INOVA 600 MHz (¹H at 500 MHz, ¹³C at 150 MHz) magnetic resonance spectrometer, as noted. ¹H chemical shifts are reported relative to the residual solvent peak (chloroform = 7.26 ppm; benzene = 7.16 ppm)¹ as follows: chemical shift (δ), (multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quint. = quintet, hept. = heptet, br = broad, app = apparent), integration, coupling constant(s) in Hz, proton ID [when available, designated by carbon number]). Deuterated solvents were obtained from Cambridge Isotope Laboratories, Inc. Proton assignments were made via 2D spectroscopy (COSY, HSQC, and/or HMBC) or analogy. ¹³C chemical shifts are reported relative to the residual deuterated solvent ¹³C signals (CDCl₃ = 77.16 ppm, C₆D₆ = 128.06 ppm).¹ Infrared spectra were recorded on a Perkin-Elmer 1600 Series Fourier Transform spectrometer (FTIR) and are reported in wavenumbers (cm⁻¹). Optical rotation data were obtained using a JASCO P-2000 Polarimeter are reported as [α]D° (c = grams/100 mL), where D indicates the sodium D line (589 nm) and T indicates temperature (all optical rotation values were obtained at ambient temperature, ca. 22-25 °C). Unless otherwise indicated, optical rotations are the average (± standard deviation) of 10 individual measurements. Optical rotations were not recorded for isomeric mixtures. High resolution mass spectra were obtained at the Vincent Coates Mass Spectrometry Laboratory, Stanford, CA 94305.

¹ Gottlieb, H.; Kotlyar, V.; Nudelman, A. J. Org. Chem. 1997, 62, 7512-7515.
Addendum: Structural Analysis of PKC C1b Domains

This section provides further detail regarding the PKC C1b domain sequences and potential difficulties associated with achieving isoform specificity.

The library of C7'-substituted salicylate-based analogs disclosed in the full manuscript demonstrated a range of modest selectivity profiles between PKCβI and PKCδ (from <1.5-fold for analog 19 to just over 8-fold for analog 23), all of which favored PKCδ. As mentioned in the text, these selectivities can be difficult to explain given the lack of structural data available for the bryostatin-PKC interaction, though potential interactions with the 9th residue of either C1b domain could provide a rationale for these observations. Figure S1 displays the C1b domain sequences of all eight PKC isoforms (βI and βII have entirely homologous C1 domains) sensitive to bryostatin, highlighting the Zn-binding residues in purple and displaying the residues within proximity of the binding pocket in darker black font.

![Figure S1](image)

**Figure S1.** Human PKC C1b Domains. Purple highlight denotes Zn-binding residue. Black font represents residues within the binding loops. The far right column (Overall Pos.) lists the position of these 50mers in the full human PKC sequence. Sequences were all obtained from Steinberg’s review on the structural basis for PKC function, although four residues are incorrect according to uniprot.org (alpha - K40N, V46D; delta - H6Y, S19T).

The high homology quickly becomes obvious when observing it in this format, especially within regions capable of interacting with bryostatin or other allosteric PKC agonists. Residue 9 has the most significant variation amongst isoforms in terms of different side chain functionality (α = G; βI, βII, γ = S; δ = M; ε, η, θ = K). Two different proposals for binding orientations exist in the literature, one of which places the A- and B-ring portion of bryostatin oriented just above residue 9, presumably close enough to interaction if appropriate functionality were incorporated into the small molecule. Given that the salicylate ring occupies similar space to the A- and B-ring system of bryostatin, it was suspected that properly chosen substitutions at C7’ might interact with this residue to elicit isoform selectivity previously inaccessible via through allosteric modulation. One caveat of achieving high selectivity is that slightly enhancing affinity for the target of interest is not enough; one must also abrogate affinity for the undesired targets. While it is inappropriate to make generalized conclusions about the isoform-selective allosteric regulation of PKC based only on the small amount of data provided in the main text, the following speculations represent a perspective that may be validated upon further experimentation.

If the hydrogen bonding interaction between the 2-substituted MeO- and iPrO-Phe substituents (of analogs 16 and 17 respectively) and S9 in PKCβI does indeed explain the slightly enhanced affinity for that isoform relative to the their 4-substituted variants 14 and 15 (as posited in the manuscript), then there

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2 Steinberg, S. “Structural Basis of Protein Kinase C Isoform Function.” *Physiol. Rev.* 2008, 88, 1341-1378.

3 a) Wender, P.; Baryza, J.; Brenner, S.; Clark, M.; Craske, M.; Horan, J.; Meyer, T. *Curr. Drug. Dis. Tech.* 2004, 1, 1; b) Keck, G.; Poudel, Y.; Rudra, A.; Stephens, J.; Kedei, N.; Lewin, N.; Peach, M.; Blumberg, P. *Angew. Chem. Int Ed.* 2010, 94, 4580.
are two possible explanations for the retention of affinity for PKCδ when making the switch from the para- to the ortho-substituted arenes. For one, the M9 side chain of PKCδ could have enough rotational freedom to avoid deleterious steric interactions. The second possibility is that the 2-substituted arene is adopting a different atropisomeric form, rotating its alkoxy group toward the pocket for PKCβI while rotating it away for PKCδ. Given that analogs 18 and 19 (containing the 2,6-bisalkoxy arenes) are potent for both isoforms, the atropisomer-based explanation is ruled out, suggesting the conformational flexibility of the M9 side chain is allowing for the retained affinities to PKCδ. Solution structure NMR efforts have struggled to get clean resolution on these binding loops. Interestingly, even upon addition of known PKC ligands (which should stabilize the residues involved in binding), the motion of these structural elements was still too fast to resolve on the NMR timescale. This suggests a highly dynamic pocket that may be able to tolerate certain levels of steric bulk that would look to be deleterious in static in silico models. It should be noted, however, that this study did not provide a functional assay, so perhaps it was not properly folded at which point allosteric ligands would not be expected to improve resolution. More evidence of the dynamic nature of the C1b bryostatin-binding loops could be inferred from a recent crystallization effort with the PKC0 C1b domain. The authors provided a fully resolved crystal structure of the PKC0 C1b domain, then compared the binding pocket to that of mouse PKCδ C1b domain. They observed a ~0.5Å contraction of the binding pocket in their crystal structure, primarily due to a rotation of W22. In the PKCδ crystal structure, W22 appears to be interacting with a histidine on the hydrophobic side of the C1b domain, whereas in PKC0, W22 was flipped almost 180° due to disruption of the interaction with the histidine (the histidine appeared to prefer a cation-pi interaction with a distal arginine not present in PKC0). Whether or not these interactions are relevant in a dynamic setting is unknown, but it is possible that W22 has several favorable orientations available to it, all of which would alter binding pocket width and thus accessibility. This potentially highly dynamic structure of PKC C1 domains makes it difficult to conclusively determine the reasons for any observed selectivities due to the uncertainty of the true conformation of the bound structure (both ligand and protein). The picture is further complicated by the fact that C1 ligands provide a hydrophobic cap for the domains, allowing for insertion into the phospholipid bilayer which is a necessary event in PKC activation. While there are several structural efforts published targeting PKC, none of these incorporate a membrane surrogate despite its key role in activation of the full-length protein in vivo. The membrane-associative nature of PKC makes this a difficult task, but studies geared at this information are underway in our lab with the collaboration of several others. Ultimately, when pursuing small molecule allosteric PKC modulators, explaining observed isoform selectivities and designing ligands with enhanced selectivities will remain a challenge until we develop a thorough structural understanding of PKC activation, both in its static and dynamic forms.

Of use for anyone investigating C1 domain ligands, the authors of the PKC0 C1b crystal structure provide some useful mutagenesis studies detailing residues critical for binding. These seem to be in good agreement with previous efforts targeting PKCδ.

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4 Ziembka, B.; Booth, J.; Jones, D. “H, 13C and 15N NMR assignments of the C1A and C1B subdomains of PKC-delta.” Biomol. NMR Assign. 2011, 5, 125-129. Of note, the C1a domain was cleanly resolved by NMR.

5 Rahman, G.; Shanker, S.; Lewin, N.; Kedei, N.; Hill, C.; Prasad, V.; Blumberg, P.; Das, J. Biochem. J. 2013, 451, 33-44.

6 Zhang, G.; Kazanietz, M.; Blumberg, P.; Hurley, J. Cell 1995, 81, 917-924.

7 For a recent perspective on PKC as a drug target, see: Mochly-Rosen, D.; Das, K.; Grimes, K. Nature Rev. Drug Disc. 2012, 11, 937-954.

8 Kazanietz, M.; Wang, S.; Milne, G.; Lewin, N.; Liu, H.; Blumberg, P. J. Biol. Chem. 1995, 270, 21852-21859.
Experimental Methods; Characterization and Spectroscopic Data

For ease of comparison, all proton assignments are given by carbon number as it corresponds to the bryostatin 1 scaffold (see Figure S2). For instance, the carbons of the C20 octanoyl chain are both designated as C39-C46, even though analog 3 only contains 33 total carbons.

![Figure S2. Bryostatin 1 carbon numbering](image)

As alluded to in the manuscript, northern fragment 4 was prepared initially by a six step method before transitioning to the five step sequence detailed in the main text. Scheme S1 displays this route which was used to prepare fragment 4 on gram scale, and it was that material that was incorporated into the large-scale preparation of diversifiable analog 3.

Scheme S1: Original Synthesis of the Northern Fragment 4

![Scheme S1](image)

Reagents and Conditions: a) MOMCl, pyridine, CH₂Cl₂, 60 °C, 81%; b) 3-bromo-1-propanol, K₂CO₃, DMF, 60 °C; c) i. TEMPO, Ph(OAc)₂, MeCN, H₂O, rt. ii. NaH₂PO₄, NaClO₂, 2-methyl-2-butene, 0 °C; d) DCC, DMAP, Cl₂CCH₂OH, CH₂Cl₂, rt, 79% over 3 steps; e) CBr₄, iPrOH, 60 °C; f) CrO₃, H₂SO₄, H₂O, acetone, 0 °C to rt, 80% over 2 steps; Tce = 2,2,2-trichloroethyl.

MOM ether S2 was prepared with MOMCl and pyridine in good yield from benzyl alcohol S1. Alkylation with 3-bromo-1-propanol followed by oxidation to the C1 carboxylic acid using a one-flask TEMPO oxidation/Pinnick oxidation sequence then DCC-coupling with 2,2,2-trichloroethanol provided C1 Tce ester S2 in a modest three step yield. Deprotection with CBr₄ in iPrOH and Jones oxidation provided the northern fragment 4 in 51% over six steps.

While this route is nearly identical in overall yield, the extra step necessitates additional solvent, time, and purification costs, thus the shorter route was favored for publication in the main text. Also, benzyl alcohol S1 is suspected to be the reduction product of 5-bromosalicylic acid (5), the starting material for the 5 step route. If this is the case, then the above route would actually require two additional steps if run on process scale, further supporting the choice of the route in Scheme 2.
Procedure for 5-bromo methyl salicylate (6)

2-Hydroxy-5-bromobenzoic acid (5, 125.6 mg, 0.58 mmol) was dissolved in 5.8 mL dry MeOH in a dry vial under N₂. Conc. H₂SO₄ (30 µL, 0.58 mmol) was added, the vial was capped, and the reaction mixture was heated to 85 °C for 24 hrs. The reaction was quenched with 10 mL 4:1 water:sat. NaHCO₃ and diluted with 10 mL ether. The aqueous phase was extracted four times with 10 mL portions of ether. The combined organic phases were then washed with 10 mL brine, dried over anhydrous MgSO₄, filtered to remove solids, and concentrated under vacuum to afford 5-bromo methyl salicylate (6) as a white solid (127.1 mg, 95.0%).

Characterization Data for 5-bromo methyl salicylate (6):

¹H NMR (CDCl₃, 500 MHz): δ = 10.70 (s, 1H, -OH), 7.96 (d, 1H, J = 2.6 Hz, Ar), 7.53 (dd, 1H, J = 8.9, 2.6 Hz, Ar), 6.89 (d, 1H, J = 8.8 Hz, Ar), 3.96 (s, 3H, CO₂Me) ppm

¹³C NMR (CDCl₃, 125 MHz): δ = 169.7, 160.7, 138.6, 132.4, 119.7, 114.0, 111.0, 52.8 ppm

IR (thin film): 1680, 1607, 1470, 1441, 1383, 1332, 1287, 1244, 1206, 1097, 699 cm⁻¹

R_f = 0.50 (5% EtOAc in pentane), one yellow spot. KMnO₄ + UV
Procedure for C1 alcohol 7

Methyl salicylate 6 (125.7 mg, 0.54 mmol) was dissolved in dry DMF (600 µL) in a dry vial under inert atmosphere. K₂CO₃ (113 mg, 0.82 mmol) and 3-bromo-1-propanol (74 µL, 0.82 mmol) were added respectively in one portion each. The vial was capped, and the mixture was heated to 60 °C for 3.5 hrs. The reaction was quenched by pouring into 10 mL sat. NH₄Cl and then diluted with 10 mL ether. The phases were separated, and the aqueous phase was extracted four times with 10 mL portions of ether. The combined organic phases were washed with 10 mL brine, dried over anhydrous magnesium sulfate, filtered to remove solids, and concentrated under vacuum. The crude residue was purified via flash chromatography over silica (20→70% ethyl acetate:pentane, 10% increments). C1 alcohol 7 was obtained as a clear, colorless oil (154 mg, 97.9%).

Characterization Data for C1 alcohol 7:

\(^1\)H NMR (CDCl₃, 600 MHz): δ = 8.01 (d, 1H, J = 2.5 Hz, Ar), 7.57 (dd, 1H, J = 9.0, 2.6 Hz, Ar), 6.87 (d, 1H, J = 8.9 Hz, Ar), 4.20 (t, 2H, J = 5.7 Hz, C3), 3.89 (t, 2H, J = 5.3 Hz, C1), 3.87 (s, 3H, CO₂Me), 2.10 (app quint., 2H, J = 5.0 Hz, C2) ppm

\(^13\)C NMR (CDCl₃, 150 MHz): δ = 165.0, 158.0, 136.8, 134.9, 120.6, 114.4, 112.6, 69.2, 61.8, 52.5, 31.8 ppm

IR (thin film): 3467, 2951, 2881, 1719, 1593, 1488, 1466, 1437, 1395, 1300, 1277, 1247, 1155, 1084, 1050, 963, 813 cm⁻¹

HRMS (ES+, m/z) calculated for C₁₁H₁₃BrNaO₄⁺: 310.9889, Found: 310.9889

Rₐ = 0.25 (50% EtOAc in pentane), one yellow spot, KMnO₄ + UV
Procedure for C1 ester 8

C1 alcohol 7 (118 mg, 0.41 mmol) was dissolved in 9.0 mL MeCN under an inert atmosphere before adding 1.5 mL water. TEMPO (19 mg, 0.12 mmol) and Ph(OAc)$_2$ (394 mg, 1.2 mmol) were added respectively in one portion each. The light red-orange reaction mixture was stirred for 1 hr at room temp at which point starting material had been consumed by TLC analysis. 2-Methyl-2-butene (2.2 mL, 20 mmol), water (750 µL), and NaH$_2$PO$_4$ (490 mg, 4.1 mmol) were added respectively, one portion each. The biphasic mixture was cooled to 0 °C before adding NaClO$_2$ (295 mg, 3.3 mmol) in one portion. The reaction was stirred vigorously for 30 min at 0 °C, starting as a dark red solution and slowly fading to a lighter red with time. The reaction was quenched by pouring into 10 mL sat. Na$_2$S$_2$O$_3$. This mixture was diluted with 10 mL ether, and the phases were separated. The aqueous phase was extracted with four 10 mL portions of ether. The combined organic phases were washed with 10 mL brine, dried over anhydrous magnesium sulfate, filtered to remove solids, and concentrated in vacuo. This mixture was taken up in ~10 mL PhMe and re-concentrated three times in order to remove residual AcOH. The resultant crude yellow oil was moved on without further purification.

Crude C1 carboxylic acid was dissolved in 2.1 mL dry CH$_2$Cl$_2$ in under nitrogen. 2,2,2-Trichloroethanol (59 µL, 0.61 mmol), DCC (126 mg, 0.16 mmol), and DMAP (75 mg, 0.16 mmol) were added respectively in one portion each. The reaction mixture quickly turned cloudy with white precipitate. After 2.5 hrs at room temp, the suspension was concentrated under a stream of nitrogen. The desired product was purified via flash chromatography over silica (3→24% ethyl acetate:pentane, 3% increments, loaded crude residue with PhMe). The desired C1 ester 8 was cleanly afforded as a white solid (124.6 mg, 70.3% over two steps).

Characterization Data for C1 ester 8:

$^1$H MR (CDCl$_3$, 500 MHz): $\delta = 7.89$ (d, 1H, $J = 2.6$ Hz, Ar), 7.54 (dd, 1H, $J = 8.6$, 2.6 Hz, Ar), 6.89 (d, 1H, $J = 8.7$ Hz, Ar), 4.79 (s, 2H, CH$_2$CCl$_3$), 4.35 (t, 2H, $J = 6.1$ Hz, C3), 3.85 (s, 3H, CO$_2$Me), 3.01 (t, 2H, $J = 6.1$ Hz, C2) ppm

$^{13}$C NMR (CDCl$_3$, 125 MHz): $\delta = 169.3, 165.3, 157.1, 136.2, 134.4, 122.6, 115.8, 113.3, 94.8, 74.2, 64.8, 52.4, 34.4$ ppm

IR (thin film): 2953, 1762, 1735, 1488, 1437, 1401, 1280, 1245, 1160, 1098, 1035, 974, 811 cm$^{-1}$

HRMS (ES+, m/z) calculated for C$_{13}$H$_{12}$BrCl$_3$NaO$_5$: 454.8826, Found: 454.8819

$R_f = 0.65$ (30% EtOAc in pentane), one yellow spot, KMnO$_4$ + UV
STANDARD SPECTRUM PARAMETERS

Archive directory: /export/home/alexvess/normal/normal
Sample directory:
File: DSV.117.13-CHAR
Pulse Sequence: 2pse
Solute: C6H6

Dose 11.0 degrees
Acq. time 4.00 sec
Width 800.0 Hz
12 repetitions
measure 1.0, 1.0, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1
DATA PROCESSING
FT size 4096
Total line 10 min

![Spectrum Image]

Archive directory: /export/home/alexvess/normal/normal
Sample directory:
File: DSV.117.13-CHAR
Pulse sequence: 2pse
Solute: C6H6

Dose: 11.0 degrees
Acq. time 4.00 sec
Width 800.0 Hz
12 repetitions
measure 1.0, 1.0, 1, 1, 1, 1, 1, 1, 1, 1, 1, 1
DATA PROCESSING
FT size 4096
Total line 10 min

![Spectrum Image]
Procedure for carboxylic acid 4

Methyl ester 8 (35 mg, 81 µmol) was dissolved in dry 1,2-dichloroethane (DCE; freshly distilled over CaH₂) in a dry vial under N₂. NaI (60 mg, 0.40 mmol) then TMSCl (21 µL, 0.16 mmol) were added in one portion each. Reaction mixture quickly turns light yellow. The vial was capped tightly, and the reaction was heated to 90 °C for 15 hrs. The orange reaction mixture (with some white ppt) revealed nearly complete consumption of starting material by TLC analysis. There also appeared to be a minor amount of 5-bromo methyl salicylate, resulting from C2 deprotonation and elimination of the C3 phenolate. The reaction mixture was concentrated under a stream of nitrogen and purified via flash chromatography over silica (20→50% EtOAc:pentane + 0.1% AcOH, 10% increments, crude residue loaded with PhMe). The product (4) flushed rather quickly with this gradient but was still obtained cleanly as a white solid (28.5 mg, 84.1%).

Characterization Data for carboxylic acid 4:

\[ ^1 \text{H NMR (CDCl}_3, 500 \text{ MHz)}: \delta = 8.29 (d, 1H, J = 2.7 \text{ Hz, Ar}), 7.66 (dd, 1H, J = 8.9, 2.7 \text{ Hz, Ar}), 6.97 (d, 1H, J = 8.8 \text{ Hz, Ar}), 4.83 (s, 2H, } \text{CH}_2\text{CCl}_3, 4.55 (t, 2H, } J = 6.0 \text{ Hz, C3), 3.10 (t, 2H, } J = 6.0 \text{ Hz, C2) ppm} \]

\[ ^{13} \text{C NMR (CDCl}_3, 125 \text{ MHz)}: \delta = 169.0, 165.4, 156.4, 137.6, 136.2, 120.2, 114.9, 114.8, 94.6, 74.3, 65.2, 33.9 \text{ ppm} \]

IR (thin film): 2955, 2604, 1755, 1673, 1595, 1487, 1413, 1318, 1251, 1160, 1101, 1019, 807, 722 cm⁻¹

HRMS (ES+, m/z) calculated for C₁₂H₁₀BrCl₃NaO₅⁺: 440.8669, Found: 440.8659

R_f = 0.40 (40% EtOAc in pentane + one drop AcOH), one yellow spot, KMnO₄ + UV
Procedure for ester 10

Carboxylic acid 4 (1.06 g, 2.5 mmol) was dissolved in 6.0 mL dry CH$_2$Cl$_2$ in dry vial under nitrogenous atmosphere. In a separate vial, C17 alcohol 9 (924 mg, 2.1 mmol) was dissolved in 3 mL dry CH$_2$Cl$_2$ and transferred into the carboxylic acid solution via pipet; the transfer was quantified with three 1 mL portions of dry CH$_2$Cl$_2$. DCC (650 mg, 3.2 mmol) and DMAP (385 mg, 3.2 mmol) were added respectively in one portion each. Reaction mixture was carefully concentrated under vacuum after stirring 3 hrs at room temp. The crude residue was purified via flash chromatography over silica (5→20% ethyl acetate:pentane, 5% increments, residue loaded with PhMe). Ester 10 was afforded as a clear, colorless oil (1.70 g, 96.2%).

Characterization Data for ester 10:

$^1$H NMR (CDCl$_3$, 500 MHz): $\delta$ = 7.86 (d, 1H, $J = 2.6$ Hz, Ar), 7.54 (dd, 1H, $J = 8.9, 2.5$ Hz, Ar), 6.90 (d, 1H, $J = 8.9$ Hz, Ar), 5.95-5.85 (m, 1H, C25), 5.90 (s, 1H, C34), 5.66 (s, 1H, C20), 5.18-5.09 (m, 2H, C26), 4.78 (s, 2H, C$_H$_2Cl$_3$), 4.44 (d, 1H, $J = 11.3$ Hz, C17), 4.35 (t, 2H, $J = 6.5$ Hz, C3), 4.29 (d, 1H, $J = 11.3$ Hz, C17), 4.00-3.94 (m, 1H, C23), 3.69 (s, 3H, CO$_2$Me), 3.43 (d, 1H, $J = 6.4$ Hz, C22), 3.34 (s, 3H, C19-OMe), 3.01 (t, 2H, $J = 6.5$ Hz, C2), 2.50-2.34 (m, 5H, C22, C24, C40), 1.68-1.61 (m, 2H, C41), 1.35-1.20 (m, 8H, C42-C45), 1.12 (s, 3H, C18-Me). IR (thin film): 2930, 2857, 1721, 1666, 1593, 1464, 1435, 1402, 1228, 1154, 1100, 1042, 916, 803, 722 cm$^{-1}$

HRMS (ES+, m/z) calculated for C$_{36}$H$_{48}$BrCl$_3$NaO$_{11}$: 863.1338, Found: 863.1365

$[\alpha]_{D}^{23.5}$° = -10.5 ± 0.1° (c = 2.8, CH$_2$Cl$_2$)

$R_f$ = 0.30 (20% EtOAc in pentane), one reddish-purple spot, p-anisaldehyde + UV
STANDARD SPECTRUM DATA

Archive directory: /export/home/stevens/veraeye/data
Sample directory:

File: exp12s12p.ppt.wav

Scan sequence: alhp
Solvent: CDCl3

Pulse 10.0 degrees
Acq. time 1.000 sec
Width 2000.0 Hz
20 repetitions

GRAPHIC No. 899.799746 mHz

DATA PROCESSING
FT size 8192
Total time 8 hr 5 min

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Procedure for C25 alcohol 11

In a flame-dried flask flushed with nitrogen, K₂OsO₂(OH)₄ (2.0 mg, 5.4 µmol), (DHQD)₂PYR (12.0 mg, 13.6 µmol), K₃Fe(CN)₆ (715 mg, 2.2 mmol), and K₂CO₃ (300 mg, 2.2 mmol) were dissolved in 5.4 mL tBuOH and 5.4 mL H₂O, chilled to 0 ºC, and stirred vigorously for 2 hrs at that temperature to generate an orange, biphasic mixture (overall conc. [Os] = 0.5 mM). In a separate dry vial under an inert atmosphere, C₂⁵-C₂⁶ olefin 10 (73.0 mg, 87 µmol) was dissolved in 360 µL dry THF and cooled to 0 °C. A portion of the dihydroxylation mixture (1.8 mL, 900 pmol [Os]) was taken up via syringe (using a thick gauge needle while still stirring vigorously) and added directly to the starting material solution. This mixture was moved to a 4 ºC cold room and stirred vigorously for 84 hrs at which point the starting material was consumed by TLC analysis. The reaction mixture was diluted with 5 mL H₂O and 5 mL ethyl acetate. The phases were separated, and the aqueous phase was extracted with four 5 mL portions of ethyl acetate. The combined organic phases were washed with 5 mL brine, dried over anhydrous Na₂SO₄, filtered to remove solids, and concentrated under vacuum. The crude residue was purified with flash chromatography over silica (50→75% ethyl acetate:pentane, 5% increments). The C₂⁵-C₂⁶ diol was obtained as a 2:1 mixture of C₂⁵ epimers favoring the desired β-epimer. The slightly yellow oil (57 mg) was moved on without further purification.

The crude product from above was dissolved in 5 mL MeCN and 1.25 mL H₂O under an inert atmosphere. pTsOH·H₂O (123 mg, 0.65 mmol) was added in one portion. The C₁⁹ ketal was fully deprotected after 1.5 hrs stirring at room temp. The reaction mixture was quenched with 10 mL of sat. NaHCO₃, diluted with 10 mL EtOAc, and the phases were separated. The aqueous phase was extracted four times with 10 mL portions of ethyl acetate. The combined organic phases were washed with 10 mL brine, dried over anhydrous Na₂SO₄, filtered to remove solids, and concentrated in vacuo. The crude slightly yellow foam (59 mg) was moved on without further purification.

The crude C₁⁹ hemiketal product was dissolved in 800 µL dry CH₂Cl₂ under a nitrogenous atmosphere. Imidazole (13 mg, 0.20 mmol) was added and stirred 5 min to dissolve before adding TBSCl (16 mg, 0.10 µmol) in one portion. Starting material was consumed after 30 minutes at room temperature. The reaction mixture was concentrated ~3/4 of the way to dryness under a stream of nitrogen before loading directly onto a silica column for purification via flash chromatography (10→40% ethyl acetate:pentane, 5% increments, load was assisted by use of benzene). Fractions still containing a mixture of C₂⁵ epimers were exposed to a 2nd chromatography through a pipet column of silica (16→25% ethyl acetate:pentane). The desired C₂⁵ β-epimer 11 was obtained as a clear, colorless oil (38.4 mg, 45.4% over 3 steps). The C₂⁵ α-epimer was also isolated (19.7 mg) though it was not entirely pure.

Olefin 10 is almost entirely insoluble in 1:1 tBuOH:water, thus it remains as a film on the inside of the vial when attempting this reaction without any THF. This led to the sequestration of Os species and degradation of 10.
**Characterization Data for C25 alcohol II:**

**1H NMR** (CDCl$_3$, 500 MHz): δ = 7.97 (d, 1H, $J = 2.6$ Hz, Ar), 7.57 (dd, 1H, $J = 9.0$, 2.7 Hz, Ar), 6.93 (d, 1H, $J = 8.9$ Hz, Ar), 6.01 (s, 1H, C34), 5.24 (s, 1H, C20), 4.78 (app dd, 2H, $J = 19.2$, 12.0 Hz, CH$_2$CCl$_3$), 4.41 (s, 1H, C19-OH), 4.43-4.33 (m, 2H, C3), 4.36 (d, 1H, $J = 11.2$ Hz, C17), 4.29 (d, 1H, $J = 11.2$ Hz, C17), 4.28-4.21 (m, 1H, C23), 3.88-3.82 (m, 1H, C25), 3.68 (s, 3H, CO$_2$Me), 3.69-3.64 (m, 1H, C22), 3.56 (dd, 1H, $J = 10.2$, 3.6 Hz, C26), 3.41 (dd, 1H, $J = 9.8$, 6.6 Hz, C26), 3.14-3.03 (m, 2H, C2), 2.53 (d, 1H, $J = 4.5$ Hz, C25-OH), 2.36-2.28 (m, 2H, C40), 2.16 (app t, 1H, $J = 12.8$ Hz, C22), 1.65-1.57 (m, 2H, C41), 1.32-1.22 (m, 8H, C42-C45), 1.11 (s, 6H, C18-Me, C18-Me), 0.89 (s, 9H, TBS), 0.87 (t, 3H, $J = 7.1$ Hz, C46), 0.06 (s, 6H, TBS) ppm

**13C NMR** (CDCl$_3$, 125 MHz): δ = 172.2, 169.3, 166.7, 165.1, 156.9, 151.4, 136.8, 135.3, 121.6, 119.8, 115.4, 113.4, 99.7, 94.8, 74.2, 73.9, 71.6, 68.4, 67.6, 67.5, 64.7, 51.4, 42.4, 39.1, 34.7, 33.7, 31.8, 31.3, 29.2, 29.0, 26.1, 24.8, 22.7, 22.4, 20.3, 18.5, 12.2, -5.2, -5.2 ppm

**IR** (thin film): 3491, 2953, 2929, 2857, 1721, 1593, 1464, 1403, 1250, 1155, 1095, 837, 806, 780, 723 cm$^{-1}$

**HRMS** (ES+, m/z) calculated for C$_{41}$H$_{66}$BrCl$_3$NO$_{13}$Si$: 992.2547$, Found: 992.2559

[$\alpha$]$_D^{22\circ c} = -2.8 \pm 0.4^\circ$ (c = 0.55, CH$_2$Cl$_2$)

$\text{R}_f = 0.30$ (30% EtOAc in pentane), one black spot, p-anisaldehyde + UV

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10 Believed to be two unresolved resonances based on analogy to related scaffolds.
**Procedure for C7'-Br analog 3**

Tce ester 11 (338 mg, 0.35 mmol) was dissolved in dry THF (7.0 mL) in a dry vial under nitrogen. Zn dust (90 mg, 1.4 mmol)\(^{11}\) and PPTS (217 mg, 0.87 mmol) were added respectively, one portion each. The reaction was stirred 7 hrs at room temp, but had only reached ~80% conversion. An additional 23 mg of Zn dust (0.35 mmol) was added. After an additional 3 hrs at rt, starting material appeared to be fully consumed (>95% conv.). The reaction was quenched with 5 mL sat. NH\(_4\)Cl and 5 mL H\(_2\)O before diluting with 10 mL ethyl acetate. The phases were separated, and the aqueous phase was extracted with four 10 mL portions of ethyl acetate. The combined organic phases were washed with 10 mL brine, dried over anhydrous Na\(_2\)SO\(_4\), filtered to remove solids, and concentrated under vacuum. The free C1 acid (off-white foam) was moved on without further purification.

The crude seco acid was dissolved in 7.0 mL dry benzene before adding pyridine (140 µL, 1.7 mmol) and 2,4,6-trichlorobenzoyl chloride (65 µL, 0.42 mmol). In a separate dry flask, DMAP (425 mg, 3.5 mmol) was dissolved 75 mL dry benzene and heated to 60 ºC with an attached reflux condensor. After the mixed anhydride mixture had stirred 45 min at room temp (cloudy, slightly yellow mixture), it was transferred via syringe into the hot DMAP solution dropwise over the course of 4 minutes (syringe was inserted from the top of the condenser to avoid warming of the needle during the addition). The transfer was quantified with two 1.5 mL portions of dry benzene. This mixture was stirred at 60 ºC for 1 hr before quenching with 50 mL sat. NH\(_4\)Cl and diluting with 50 mL H\(_2\)O and 100 mL ether. The phases were separated, and the aqueous phase was extracted with 100 mL ether four times. The combined organic phases were washed with 100 mL brine, dried over anhydrous sodium sulfate, filtered to remove solids, and concentrated in vacuo. The crude macrocyclic product was moved on without further purification.

The crude C26 silyl ether was dissolved in 20 mL MeCN and 5 mL H\(_2\)O under an inert atmosphere before adding pTsOH·H\(_2\)O (660 mg, 3.5 mmol) in one portion. The reaction mixture was stirred 1 hr at room temp before quenching with 25 mL sat. bicarb and diluting with 25 mL ethyl acetate. The phases were separated, and the aqueous phase was extracted with four 25 mL portions of ethyl acetate. The combined organic phases were washed with 25 mL brine, dried over anhydrous Na\(_2\)SO\(_4\), filtered to remove solids, and concentrated under vacuum. The crude residue was purified with flash chromatography over silica (40→90% ethyl acetate:pentane, 10% increments). The C7' bromide analog 3 was afforded as a white solid (93.3 mg, 37.8% over 3 steps).

**Characterization Data for C7'-Br analog 3:**

\[^{1}H\text{NMR}\] (CDCl\(_3\), 600 MHz): \(\delta = 7.97\) (d, 1H, \(J = 2.7\) Hz, Ar), 7.57 (dd, 1H, \(J = 8.7, 2.5\) Hz, Ar), 6.97 (d, 1H, \(J = 9.0\) Hz, Ar), 5.98 (s, 1H, C34), 5.39-5.33 (m, 1H, C25), 5.29 (s, 1H, C20), 5.02 (s, 1H, C19-OH), 4.56-4.47 (m, 2H, C3), 4.41 (d, 1H, \(J = 11.1\) Hz, C17), 4.28 (app t, 1H, \(J = 11.4\) Hz, C23), 4.20 (d, 1H, \(J = 11.1\) Hz, C17), 3.81

\(^{11}\)Zn dust, <10 micron (Aldrich) appeared to give the best results during optimization of the reaction.
\(\text{(app td, 1H, } J = 12.2, 3.9 \text{ Hz, C26), 3.73-3.68 (m, 1H, C22), 3.70 (s, 3H, CO}_2\text{Me), 3.65-3.59 (m, 1H, C26),}
2.63-2.48 (m, 2H, C2), 2.36-2.25 (m, 2H, C40), 2.20 (\text{app t, 1H, } J = 12.6 \text{ Hz, C22), 2.01 (app t, 1H, } J = 13.1 \text{ Hz, C24), 1.85 (app t, 1H, } J = 12.6 \text{ Hz, C24), 1.77 (t, 1H, } J = 6.0 \text{ Hz, C26-OH), 1.65-1.57 (m, 2H, C41), 1.31-1.22 (m,}
8H, C42-C45), 1.10 (s, 3H, C18-Me), 1.06 (s, 3H, C18-Me), 0.87 (t, 3H, } J = 7.1 \text{ Hz, C46) ppm}
\text{13C NMR (CDCl}_3, 125 MHz): } \delta = 172.1, 170.4, 166.9, 164.9, 155.0, 151.7, 136.5, 135.4, 125.1, 119.6, 118.6, 115.3, 100.1, 73.5, 72.5, 71.5, 67.5, 65.4, 51.3, 41.5, 35.8, 34.8, 31.8, 31.2, 29.2, 29.0, 24.8, 22.7, 22.0, 20.6, 14.2 \text{ ppm}
\text{IR (thin film): } 3483, 2930, 2857, 1721, 1666, 1595, 1478, 1435, 1408, 1372, 1291, 1264, 1232, 1175, 1153, 1107, 1062, 1004, 968, 820, 736 \text{ cm}^{-1}
\text{HRMS (ES+, } m/z) \text{ calculated for C}_{33}\text{H}_{45}\text{BrNaO}_{12}^+: 735.1987, \text{ Found: 735.1985}
\\text{[\epsilon\]_D^{23.3\circ} = -18.5 \pm 1.5^\circ (c = 0.20, CH}_2\text{Cl}_2)
\text{R}_f = 0.30 (0.70\% EtOAc in pentane), one red spot, p-anisaldehyde + UV}

\text{12 Suspected to be two unresolved peaks based on analogy to similar compounds.}
Procedure for C7’-octyl analog 12

Pd(OAc)$_2$ (2.6 mg, 12 µmol), S-Phos (9.5 mg, 23 µmol), and 1-trans-octenyl boronic acid (7.2 mg, 46 µmol) were dissolved in 300 µL dioxane in a dry vial under inert atmosphere. The vial was flushed with Ar and stirred 15 min at room temp. In a separate dry vial, CsF (9.8 mg, 65 µmol, stored at >200 ºC) was cooled under a stream of nitrogen. Aryl bromide 3 (6.0 mg, 8.4 µmol) was dissolved in 350 µL dioxane under N$_2$; this solution was transferred into the vial containing CsF via syringe, and the transfer was quantified with two 150 µL portions of dioxane. The Pd$_0$ solution (having stirred 15 min) was transferred via syringe into the starting material solution over the course of 15 seconds. Reaction mixture was orange at this point. The vial was flushed with Ar, capped, sealed, and heated 2 hrs at 60 ºC. The dark reaction mixture with black precipitate was filtered through a plug of celite, eluting with ~25 mL ethyl acetate before concentrating under vacuum. The crude residue was purified via flash chromatography over a silica pipet column (60→70% ethyl acetate:pentane). The resultant yellow film was revealed to be a 1.8:1 mixture of octenyl isomers and was further purified with reverse phase HPLC (70→100% MeCN:H$_2$O, 35 min run, residue loaded with MeOH). Product eluted at 34 minutes, but the cis and trans isomers were still inseparable. This mixture (white solid, 5.1 mg, 74.1% combined yield) was moved on without further purification.

The C7’ octenyl-substituted analog mixture was dissolved in 1.5 mL dry THF in a dry vial. Pd/C (10%, ~0.5 mg) was added, and the vial was flushed with a balloon volume of H$_2$. The mixture was stirred 4 hrs at room temp under a balloon of H$_2$. The starting material was consumed by TLC analysis. Reaction mixture was filtered through a plug of celite, eluting with ~25 mL ethyl acetate before concentrating under vacuum. Reverse phase HPLC was used to purify the crude residue (70→100% MeCN:H$_2$O, 35 min run, residue loaded with 9:1 MeOH:DMSO). Product eluted after 34 minutes (product potentially not fully eluted from the column). The C7’ octyl-substituted analog 12 was obtained as a white solid (2.2 mg, 31.9% over 2 steps).

Characterization Data for C7’-octyl analog 12:

$^1$H NMR (CDCl$_3$, 600 MHz): δ = 7.65 (d, 1H, $J$ = 2.2 Hz, Ar), 7.28-7.25 (m, 1H, Ar), 6.97 (d, 1H, $J$ = 8.6 Hz, Ar), 5.99 (s, 1H, C34), 5.40-5.35 (m, 1H, C25), 5.29 (s, 1H, C20), 5.20 (s, 1H, C19-OH), 4.50 (t, 2H, $J$ = 5.2 Hz, C3), 4.40 (d, 1H, $J$ = 10.8 Hz, C17), 4.30 (app t, 1H, $J$ = 11.4 Hz, C23), 4.19 (d, 1H, $J$ = 10.8 Hz, C17), 3.80 (dd, 1H, $J$ = 12.0, 2.8 Hz, C26), 3.73-3.69 (m, 1H, C22), 3.70 (s, 3H, CO$_2$Me), 3.62 (dd, 1H, $J$ = 11.9, 5.7 Hz, C26), 2.59-2.49 (m, 4H, C2, octyl-CH$_2$), 2.35-2.25 (m, 2H, C40), 2.18 (app t, 1H, $J$ = 12.8 Hz, C22), 2.01 (app t, 1H, $J$ = 12.8 Hz, C24), 1.85 (app t, 1H, $J$ = 12.8 Hz, C24), 1.80 (br s, 1H, C26-OH), 1.70-1.55 (m, 5H, C26-OH, C41, octyl-CH$_2$), 1.34-1.22 (m, 16H, C42-C45, 4 octyl-CH$_2$ units), 1.10 (s, 3H, C18-Me), 1.06 (s, 3H, C18-Me), 0.88 (t, 6H, $J$ = 7.4 Hz, C46, octyl-CH$_3$) ppm
$^{13}$C NMR (CDCl$_3$, 150 MHz): $\delta = 172.1, 170.8, 167.0, 166.5, 153.8, 151.9, 137.7, 133.9, 132.4, 123.2, 119.6, 116.9, 100.1, 73.6, 72.2, 71.5, 67.4, 65.6, 65.4, 51.4, 41.5, 35.9, 35.2, 35.0, 34.9, 31.9, 31.5, 31.2, 29.8, 29.6, 29.4, 24.8, 22.7, 22.2, 20.7, 14.3 ppm$\textsuperscript{13}

IR (thin film): 3472, 2927, 2855, 1721, 1667, 1613, 1495, 1463, 1422, 1375, 1291, 1259, 1231, 1214, 1175, 1155, 1088, 1062, 1005, 729 cm$^{-1}$

HRMS (ES+, m/z) calculated for C$_{41}$H$_{62}$NaO$_{12}^+$: 769.4133, Found: 769.4133

$[\alpha]_D^{28^\circ C} = -14.9 \pm 0.5^\circ$ (c = 0.22, CH$_2$Cl$_2$)

$R_f = 0.15$ (60% EtOAc in pentane), one reddish-purple spot, $p$-anisaldehyde + UV

\textsuperscript{13} $^{13}$C NMR data obtained from HMBC and HSQC NMR data. Multiple resonances are suspected to be more than one unresolved peak (31.9, 29.8, 22.7, 14.3) based on analogy to similar compounds. The resolution of the 2D NMR data was not sufficient to fully differentiate resonances in that region of the spectra, mostly due to the similar shifts in the octyl and octanoyl side chains.
STANDARD PROTON PARAMETERS

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Sample directory:

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Pulse delay 0.500 sec
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Acq. Time 1.000 sec

16 repetitions

Data processing

FT size 4000
Total time 5 min
Procedure for C7'-Ph analog 13
Pd(OAc)$_2$ (1.3 mg, 5.8 µmol), PPh$_3$ (4.8 mg, 18 µmol), phenylboronic acid (2.8 mg, 23 µmol), and K$_2$CO$_3$ (2.6 mg, 18 µmol) were added to a dry vial containing aryl bromide 3 (3.3 mg, 4.6 µmol) under argon. The solids were dissolved in in 500 µL dioxane then the vial was flushed with Ar, capped, and heated 2 hrs at 60 ºC. The dark red reaction mixture was filtered through a plug of celite, eluting with ~20 mL ethyl acetate then concentrating under vacuum. The crude residue was purified via flash chromatography over a silica pipet column (40→60% ethyl acetate:pentane). The resultant yellow solid was further purified with reverse phase HPLC (70→100% MeCN:H$_2$O, 30 min run, residue loaded with a 2:1 mixture of MeOH to MeCN). Product eluted at 21 minutes. The C7' phenyl-substituted analog 13 was obtained as a white solid (1.79 mg, 54.5%).

Characterization Data for C7'-Ph analog 13:
$^1$H NMR (CDCl$_3$, 500 MHz): δ = 8.08 (d, 1H, J = 2.5 Hz, Ar), 7.69 (dd, 1H, J = 8.6, 2.5 Hz, Ar), 7.57 (d, 2H, J = 8.7 Hz, Ph), 7.43 (t, 2H, J = 7.5 Hz, Ph), 7.35 (t, 1H, J = 7.5 Hz, Ph), 7.15 (d, 1H, J = 9.0 Hz, Ar), 6.00 (s, 1H, C34), 5.42-5.35 (m, 1H, C25), 5.32 (s, 1H, C20), 5.19 (s, 1H, C19-OH), 4.63-4.54 (m, 2H, C3), 4.44 (d, 1H, J = 10.8 Hz, C17), 4.32 (app t, 1H, J = 11.3 Hz, C23), 4.23 (d, 1H, J = 11.3 Hz, C17), 3.82 (dd, 1H, J = 12.1, 3.3 Hz, C26), 3.75-3.70 (m, 1H, C22), 3.70 (s, 3H, CO$_2$Me), 3.63 (dd, 1H, J = 11.8, 5.6 Hz, C26), 2.63-2.55 (m, 2H, C2), 2.37-2.25 (m, 2H, C40), 2.20 (app t, 1H, J = 13.2 Hz, C22), 2.03 (app t, 1H, J = 13.2 Hz, C24), 1.86 (app t, 1H, J = 12.5 Hz, C24), 1.71 (br s, 1H, C26-OH), 1.66-1.56 (m, 2H, C41), 1.32-1.22 (m, 8H, C42-C45), 1.13 (s, 3H, C18-Me), 1.08 (s, 3H, C18-Me), 0.88 (t, 3H, J = 7.1 Hz, C46) ppm
$^{13}$C NMR (CDCl$_3$, 125 MHz): δ = 172.1, 170.6, 166.9, 166.2, 155.1, 151.8, 139.4, 136.0, 132.3, 131.3, 129.0, 127.7, 127.0, 123.7, 119.6, 117.2, 100.1, 73.5, 72.3, 71.5, 67.3, 65.5, 65.4, 51.3, 41.5, 35.9, 34.9, 34.8, 31.8, 31.2, 29.2, 29.0, 24.8, 22.7, 22.1, 20.7, 14.2 ppm
IR (thin film): 3475, 2929, 2856, 1720, 1666, 1612, 1483, 1373, 1311, 1261, 1232, 1175, 1154, 1090, 1061, 1004, 915, 763, 731, 698 cm$^{-1}$
HRMS (ES+, m/z) calculated for C$_{39}$H$_{50}$NaO$_{12}^+$: 733.3194, Found: 733.3199
[$\alpha$]$_D^{21}$° = -36.2 ± 1.4° (c = 0.21, CH$_2$Cl$_2$)
$R_f$ = 0.35 (70% EtOAc in pentane), one red spot, p-anisaldehyde + UV (fluorescent blue under short wave)

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14 Yield determined by quantitative $^1$H NMR using benzene as an internal standard and dimethyl terephthalate as an external standard.
Procedure for C7′-(4-OMe-Ph) analog 14
Pd(OAc)₂ (3.8 mg, 17 µmol), S-Phos (14.1 mg, 34 µmol), and 4-methoxyphenyl boronic acid (9.9 mg, 65 µmol) were dissolved in 500 µL dioxane in a dry vial under inert atmosphere. The vial was flushed with Ar and stirred 20 min at room temp. In a separate dry vial, CsF (14.3 mg, 94 µmol, stored at >200 ºC) was cooled under a stream of nitrogen. Aryl bromide 3 (9.7 mg, 13.6 µmol) was dissolved in 500 µL dioxane under N₂; this solution was transferred into the vial containing CsF via syringe, and the transfer was quantified with two 200 µL portions of dioxane. The Pd⁰ solution (having stirred 20 min; cloudy orange) was transferred via syringe into the starting material solution over the course of 15 seconds. Reaction mixture was red at this point. The vial was flushed with Ar, capped, sealed, and heated 1 hr at 60 ºC. Starting material not fully consumed; reaction mixture heated additional 15 min at 60 ºC. The dark reaction mixture with black precipitate was filtered through a plug of celite, eluting with ~25 mL ethyl acetate before concentrating under vacuum. The crude residue was purified via flash chromatography over a silica pipet column (50→75% ethyl acetate:pentane). The resultant yellow solid was further purified with reverse phase HPLC (70→100% MeCN:H₂O, 30 min run, residue loaded with a 3.5:1 mixture of MeOH to MeCN). Product eluted at 20.5 minutes. The C7′-(4-OMe-phenyl)-substituted analog 14 was obtained as a white solid (4.5 mg, 44.6%).

Characterization Data for C7′-(4-OMe-Ph) analog 14:

1H NMR (CDCl₃, 500 MHz): δ = 8.03 (d, 1H, J = 2.4 Hz, Ar), 7.65 (dd, 1H, J = 8.6, 2.5 Hz, Ar), 7.50 (d, 2H, J = 8.6 Hz, C₆H₄R), 7.12 (d, 1H, J = 8.7 Hz, Ar), 6.97 (d, 2H, J = 8.7 Hz, C₆H₄R), 6.00 (s, 1H, C₃4), 5.42-5.36 (m, 1H, C₂5), 5.31 (s, 1H, C₂0), 5.20 (s, 1H, C₁9-OH), 4.61-4.53 (m, 2H, C₃), 4.44 (d, 1H, J = 11.0 Hz, C₁7), 4.32 (app t, 1H, J = 11.0 Hz, C₂3), 4.21 (d, 1H, J = 11.0 Hz, C₁7), 3.85 (s, 3H, OMe), 3.82 (dd, 1H, J = 12.7, 3.7 Hz, C₂6), 3.75-3.70 (m, 1H, C₂2), 3.70 (s, 3H, CO₂Me), 3.63 (dd, 1H, J = 12.2, 5.9 Hz, C₂6), 2.61-2.52 (m, 2H, C₂), 2.37-2.25 (m, 2H, C₄₀), 2.20 (app t, 1H, J = 12.7 Hz, C₂2), 2.03 (app t, 1H, J = 12.4 Hz, C₂4), 1.99 (br s, 1H, C₂6-OH), 1.86 (app t, 1H, J = 12.7 Hz, C₂4), 1.66-1.57 (m, 2H, C₄₁), 1.32-1.21 (m, 8H, C₄₂-C₄₅), 1.12 (s, 3H, C₁₈-Me), 1.08 (s, 3H, C₁₈-Me), 0.88 (t, 3H, J = 7.2 Hz, C₄₆) ppm

13C NMR (CDCl₃, 125 MHz): δ = 172.1, 170.7, 166.9, 166.3, 159.4, 154.6, 151.8, 135.7, 131.9, 131.8, 130.7, 128.0, 123.7, 119.6, 117.3, 114.4, 100.0, 73.5, 72.3, 71.5, 67.4, 65.5, 65.4, 55.5, 51.3, 41.5, 35.8, 34.9, 34.8, 31.8, 31.1, 29.2, 29.0, 24.8, 22.7, 22.1, 20.7, 14.2 ppm

IR (thin film): 3473, 2930, 2856, 1720, 1609, 1488, 1430, 1372, 1175, 1154, 1106, 1050, 1004, 823, 732 cm⁻¹

HRMS (ES⁺, m/z) calculated for C₄₀H₅₂NaO₁₃+: 763.3300, Found: 763.3298

[α]D²⁶° = -20.7 ± 0.3° (c = 0.47, CH₂Cl₂)

Rᵣ = 0.20 (60% EtOAc in pentane), one red spot, p-anisaldehyde + UV (fluorescent blue under short wave)
STANDARD SPECTRUM DESCRIPTIONS

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DATA PROCESSING
FT size 512
Total time 3 min

archive

Archive directory:
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FT size 512
Total time 3 min

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ppm

S28
Procedure for C7’-(4-OiPr-Ph) analog 15
Pd(OAc)$_2$ (3.6 mg, 16 µmol), S-Phos (14.8 mg, 36 µmol), and 4-isopropoxyphenyl boronic acid (12.4 mg, 69 µmol) were dissolved in 500 µL dioxane in a dry vial under inert atmosphere. The vial was flushed with Ar and stirred 20 min at room temp. In a separate dry vial, CsF (13.6 mg, 90 µmol, stored at >200 ºC) was cooled under a stream of nitrogen. Aryl bromide 3 (9.5 mg, 13.3 µmol) was dissolved in 300 µL dioxane under N$_2$; this solution was transferred into the vial containing CsF via syringe, and the transfer was quantified with two 200 µL portions of dioxane. The Pd$_0$ solution (having stirred 20 min) was transferred via syringe into the starting material solution over the course of 15 seconds. Reaction mixture was orange at this point. The vial was flushed with Ar, capped, sealed, and heated 1.5 hrs at 60 ºC. The dark reaction mixture with black precipitate was filtered through a plug of celite, eluting with ~25 mL ethyl acetate before concentrating under vacuum. The crude residue was purified via flash chromatography over a silica pipet column (60→70% ethyl acetate:pentane). Product flushed quickly, possibly as a result of residual dioxane, and thus needed a second silica pipet column to remove Pd-based impurities (50→75% ethyl acetate:pentane). The resultant yellow solid was further purified with reverse phase HPLC (70→100% MeCN:H$_2$O, 30 min run, residue loaded with a 3.5:1 mixture of MeOH to MeCN). Product eluted at 24.6 minutes. The C7’-(4-OiPr-phenyl)-substituted analog 15 was obtained as a white solid (8.5 mg, 83.1%).

Characterization Data for C7’-(4-OiPr-Ph) analog 15:
$^1$H NMR (CDCl$_3$, 500 MHz): δ = 8.02 (d, 1H, J = 2.5 Hz, Ar), 7.64 (dd, 1H, J = 8.7, 2.4 Hz, Ar), 7.47 (d, 2H, J = 8.6 Hz, C$_6$H$_4$R), 7.11 (d, 1H, J = 8.8 Hz, Ar), 6.94 (d, 2H, J = 8.8 Hz, C$_6$H$_4$R), 6.00 (s, 1H, C34), 5.41-5.35 (m, 1H, C25), 5.30 (s, 1H, C20), 5.20 (s, 1H, C19-OH), 4.63-4.52 (m, 3H, C3, OiPr), 4.43 (d, 1H, J = 11.1 Hz, C17), 4.32 (app t, 1H, J = 11.8 Hz, C22), 4.21 (d, 1H, J = 10.9 Hz, C17), 3.82 (dd, 1H, J = 12.4, 3.1 Hz, C26), 3.75-3.70 (m, 1H, C22), 3.70 (s, 3H, CO$_2$Me), 3.63 (dd, 1H, J = 12.1, 5.8 Hz, C26), 2.61-2.52 (m, 2H, C2), 2.37-2.25 (m, 2H, C40), 2.19 (app t, 1H, J = 13.0 Hz, C22), 2.02 (app t, 1H, J = 12.2 Hz, C24), 2.01 (br s, 1H, C26-OH), 1.86 (app t, 1H, J = 13.0 Hz, C24), 1.66-1.56 (m, 2H, C41), 1.36 (d, 6H, J = 6.1 Hz, OiPr), 1.32-1.23 (m, 8H, C42-C45), 1.12 (s, 3H, C18-Me), 1.07 (s, 3H, C18-Me), 0.87 (t, 3H, J = 7.3 Hz, C46) ppm
$^{13}$C NMR (CDCl$_3$, 125 MHz): δ = 172.1, 170.7, 166.9, 166.3, 157.7, 154.5, 151.8, 135.8, 131.8, 131.6, 130.7, 128.0, 123.7, 119.6, 117.3, 116.2, 100.0, 73.5, 72.3, 71.5, 70.1, 67.4, 65.5, 65.4, 51.3, 41.5, 35.8, 34.9, 34.8, 31.8, 31.3, 29.2, 29.0, 24.8, 22.7, 22.2, 22.1, 20.7, 14.2 ppm
IR (thin film): 3474, 2930, 2856, 1739, 1720, 1608, 1488, 1430, 1372, 1233, 1175, 1154, 1107, 1047, 1004, 822 cm$^{-1}$
HRMS (ES+, m/z) calculated for C$_{42}$H$_{56}$NaO$_{13}$+: 791.3613, Found: 791.3633
$[\alpha]_D^{26}$° = -28.5 ± 0.3° (c = 1.0, CH$_2$Cl$_2$)
$R_f$ = 0.65 (70% EtOAc in pentane), one red spot, p-anisaldehyde + UV (fluorescent blue under short wave)
Procedure for recognition domain 16

Pd(OAc)$_2$ (2.7 mg, 12 µmol), S-Phos (10.1 mg, 25 µmol), and 2-methoxyphenyl boronic acid (8.2 mg, 54 µmol) were dissolved in 250 µL dioxane in a dry vial under inert atmosphere. The vial was flushed with Ar and stirred 20 min at room temp. In a separate dry vial, CsF (14.2 mg, 93 µmol, stored at >200 ºC) was cooled under a stream of nitrogen. Aryl bromide 3 (6.2 mg, 8.7 µmol) was dissolved in 250 µL dioxane under N$_2$; this solution was transferred into the vial containing CsF via syringe, and the transfer was quantified with two 200 µL portions of dioxane. The Pd$_0$ solution (having stirred 20 min; cloudy orange) was transferred via syringe into the starting material solution over the course of 15 seconds. Reaction mixture was red-orange at this point. The vial was flushed with Ar, capped, and heated 1.5 hr at 60 ºC. The dark reaction mixture with black precipitate was filtered through a plug of celite, eluting with ~25 mL ethyl acetate then concentrating under vacuum. The crude residue was purified via flash chromatography over a silica pipet column (50→75% ethyl acetate:pentane). The resultant yellow solid was further purified with reverse phase HPLC (70→100% MeCN:H$_2$O, 30 min run, residue loaded with a 2:1 mixture of MeOH to MeCN). Product eluted at 20.5 minutes. The C7’-(2-OMe-phenyl)-substituted analog 16 was obtained as a white solid (3.8 mg, 59.5%).

Characterization Data for recognition domain 16:

$^1$H NMR (CDCl$_3$, 500 MHz): δ = 8.01 (d, 1H, J = 2.2 Hz, Ar), 7.66 (dd, 1H, J = 8.7, 2.5 Hz, Ar), 7.35-7.30 (m, 2H, C$_6$H$_4$OMe), 7.10 (d, 1H, J = 8.7 Hz, Ar), 7.02 (t, 1H, J = 7.6 Hz, C$_6$H$_4$OMe), 6.97 (d, 1H, J = 8.0 Hz, C$_6$H$_4$OMe), 6.00 (s, 1H, C34), 5.41-5.35 (m, 1H, C25), 5.31 (s, 1H, C19-OH), 4.63-4.53 (m, 2H, C3), 4.42 (d, 1H, J = 11.4 Hz, C17), 4.33 (app t, 1H, J = 11.4 Hz, C23), 4.21 (d, 1H, J = 11.2 Hz, C17), 3.82 (dd, 1H, J = 11.9, 5.6 Hz, C26), 2.62-2.56 (m, 2H, C2), 2.37-2.25 (m, 2H, C40), 2.20 (app t, 1H, J = 13.1 Hz, C22), 2.03 (app t, 1H, J = 13.1 Hz, C24), 1.86 (app t, 1H, J = 13.1 Hz, C24), 1.78 (br s, 1H, C26-OH), 1.65-1.57 (m, 2H, C41), 1.33-1.22 (m, 8H, C42-C45), 1.12 (s, 3H, C18-Me), 1.07 (s, 3H, C18-Me), 0.88 (t, 3H, J = 7.3 Hz, C46) ppm

$^{13}$C NMR (CDCl$_3$, 125 MHz): δ = 172.1, 170.7, 166.9, 166.3, 156.5, 154.7, 151.8, 135.0, 133.6, 133.3, 130.8, 129.1, 128.8, 123.1, 121.1, 119.6, 116.3, 111.3, 100.1, 73.5, 72.2, 71.5, 67.2, 65.6, 65.3, 55.7, 51.3, 41.5, 35.9, 35.0, 34.8, 31.8, 31.2, 29.2, 29.0, 24.8, 22.7, 22.1, 20.7, 14.2 ppm

IR (thin film): 3472, 2930, 2856, 1738, 1720, 1667, 1599, 1505, 1483, 1463, 1408, 1372, 1259, 1175, 1154, 1106, 1060, 1036, 1004, 914, 754, 731 cm$^{-1}$

HRMS (ES+, m/z) calculated for C$_{40}$H$_{52}$NaO$_{13}$$: 763.3300, Found: 763.3301

$[a]^{22.5}_{D} = -33.4 ± 0.3^{°} (c = 0.5, CH$_2$Cl$_2$)$

$R_f$ = 0.55 (70% EtOAc in pentane), one red spot, p-anisaldehyde + UV (fluorescent blue under short wave)
Procedure for recognition domain 17

Pd(OAc)$_2$ (2.7 mg, 12 µmol), S-Phos (9.5 mg, 23 µmol), and 2-isopropoxyphenyl boronic acid (8.8 mg, 49 µmol) were dissolved in 250 µL dioxane in a dry vial under inert atmosphere. The vial was flushed with Ar and stirred 20 min at room temp. In a separate dry vial, CsF (9.9 mg, 65 µmol, stored at >200 ºC) was cooled under a stream of nitrogen. Aryl bromide 3 (6.3 mg, 8.8 µmol) was dissolved in 250 µL dioxane under N$_2$; this solution was transferred into the vial containing CsF via syringe, and the transfer was quantified with two 200 µL portions of dioxane. The Pd$_0$ solution (having stirred 20 min; cloudy orange) was transferred via syringe into the starting material solution over the course of 15 seconds. Reaction mixture was red-orange at this point. The vial was flushed with Ar, capped, and heated 1.5 hr at 60 ºC. The dark reaction mixture with black precipitate was filtered through a plug of celite, eluting with ~25 mL ethyl acetate then concentrating under vacuum. The crude residue was purified via flash chromatography over a silica pipet column (50→75% ethyl acetate:pentane). The resultant yellow solid was further purified with reverse phase HPLC (70→100% MeCN:H$_2$O, 30 min run, residue loaded with a 3.5:1.5 mixture of MeOH to MeCN). Product eluted at 24.0 minutes. The C7’- (2-OiPr-phenyl)-substituted analog 17 was obtained as a white solid (5.46 mg, 80.4%).

Characterization Data for recognition domain 17:

$^1$H NMR (CDCl$_3$, 500 MHz): δ = 8.04 (d, 1H, $J = 2.3$ Hz, Ar), 7.72 (dd, 1H, $J = 8.6, 2.3$ Hz, Ar), 7.33 (dd, 1H, $J = 7.7, 1.6$ Hz, C$_6$H$_4$OiPr), 7.27 (dt, 1H, $J = 7.8, 1.4$ Hz, C$_6$H$_4$OiPr), 7.08 (d, 1H, $J = 8.7$ Hz, Ar), 7.00 (t, 1H, $J = 7.5$ Hz, C$_6$H$_4$OiPr), 6.97 (d, 1H, $J = 8.6$ Hz, C$_6$H$_4$OiPr), 6.00 (s, 1H, C24), 5.52 (s, 1H, C20), 5.22 (s, 1H, C19-OH), 4.62-4.52 (m, 2H, C3), 4.48 (sept., 1H, $J = 5.8$ Hz, OiPr), 4.41 (d, 1H, $J = 10.7$ Hz, C17), 4.33 (app t, 1H, $J = 11.2$ Hz, C23), 4.25 (d, 1H, $J = 11.2$ Hz, C17), 3.82 (dd, 1H, $J = 12.5, 3.5$ Hz, C26), 3.74-3.70 (m, 1H, C22), 3.70 (s, 3H, CO$_2$Me), 3.64 (dd, 1H, $J = 12.0, 5.8$ Hz, C26), 2.64-2.57 (m, 2H, C2), 2.37-2.25 (m, 2H, C40), 2.20 (app t, 1H, $J = 12.7$ Hz, C22), 2.03 (app t, 1H, $J = 12.7$ Hz, C24), 1.86 (app t, 1H, $J = 12.7$ Hz, C24), 1.85 (br s, 1H, C26-OH), 1.65-1.57 (m, 2H, C41), 1.31-1.23 (m, 8H, C42-C45), 1.27 (app t, 6H, $J = 5.6$ Hz, OiPr), 1.11 (s, 3H, C18-Me), 0.88 (t, 3H, $J = 7.1$ Hz, C46) ppm

$^{13}$C NMR (CDCl$_3$, 125 MHz): δ = 172.1, 170.7, 166.9, 166.3, 154.9, 154.6, 151.8, 154.6, 151.8, 135.1, 133.6, 133.5, 130.9, 129.9, 128.9, 122.8, 121.1, 119.6, 116.0, 114.8, 100.1, 73.6, 72.0, 71.5, 70.9, 67.1, 65.6, 65.4, 51.3, 41.5, 35.9, 35.0, 34.8, 31.8, 31.2, 29.2, 29.0, 24.8, 22.7, 22.2, 22.1, 20.6, 14.2 ppm

IR (thin film): 3472, 2929, 2856, 1739, 1720, 1666, 1598, 1503, 1480, 1407, 1372, 1258, 1230, 1174, 1153, 1106, 1090, 1060, 1004, 915, 753, 731 cm$^{-1}$

HRMS (ES+, m/z) calculated for C$_{42}$H$_{56}$NaO$_{13}$$^+$: 791.3613, Found: 791.3639

$[\alpha]_D^{20\circ}$c = -62.8 ± 0.3° (c = 0.5, CH$_2$Cl$_2$)

$R_f$ = 0.45 (60% EtOAc in pentane), one red spot, p-anisaldehyde + UV (fluorescent blue under short wave)
STANDARD PROTON PARAMETERS

Archive directory: /export/home/stevense/wnarry/data
Sample directory:

File: S34.nmr.18
Pulse Sequence: alpal
Solvent: CHCl3

Pulse 90° degrees
Avg. time 1.008 sec
Width 3920.8 Hz
96 repetitions

S34

Total time 2 min

gilper

Archive directory: /export/home/stevense/wnarry/data
Sample directory:

File: S34.nmr.18
Pulse Sequence: alpal
Solvent: CHCl3

User: 1-15-97
Relax. delay 1.000 sec
Pulse 90° degrees
Avg. time 1.000 sec
Width 3920.8 Hz
1172 repetitions

S34

Total time 12 hr. 32 min
Procedure for C7’-(2,6-bis(OMe)-Ph analog 18

Pd(OAc)$_2$ (2.8 mg, 12 µmol), S-Phos (10.2 mg, 25 µmol), and 2,6-bis(methoxy)phenyl boronic acid (9.0 mg, 49 µmol) were dissolved in 250 µL dioxane in a dry vial under inert atmosphere. The vial was flushed with Ar and stirred 20 min at room temp. In a separate dry vial, CsF (9.8 mg, 65 µmol, stored at >200 ºC) was cooled under a stream of nitrogen. Aryl bromide 3 (6.8 mg, 9.5 µmol) was dissolved in 250 µL dioxane under N$_2$; this solution was transferred into the vial containing CsF via syringe, and the transfer was quantified with two 250 µL portions of dioxane. The Pd$^0$ solution (having stirred 20 min; cloudy orange) was transferred via syringe into the starting material solution over the course of 15 seconds. Reaction mixture was red-orange at this point. The vial was flushed with Ar, capped, and heated 2 hrs at 60 ºC. The dark reaction mixture with black precipitate was filtered through a plug of celite, eluting with ~25 mL ethyl acetate then concentrating under vacuum. The crude residue was purified via flash chromatography over a silica pipet column (50→75% ethyl acetate:pentane). The resultant yellow solid was further purified with reverse phase HPLC (70→100% MeCN:H$_2$O, 30 min run, residue loaded with a 2:1 mixture of MeOH to MeCN). Product eluted at 18.5 minutes. The C7’-(2,6-bis(OMe)-phenyl)-substituted analog 18 was obtained as a white solid (4.8 mg, 65.7%).

Characterization Data for C7’-(2,6-bis(OMe)-Ph analog 18:

$^1$H NMR (CDCl$_3$, 500 MHz): δ = 7.85 (d, 1H, J = 2.3 Hz, Ar), 7.46 (dd, 1H, J = 8.5, 2.2 Hz, Ar), 7.27 (t, 1H, J = 8.3 Hz, C$_6$H$_3$R$_2$), 7.08 (d, 1H, J = 8.7 Hz, Ar), 6.63 (d, 2H, J = 8.4 Hz, C$_6$H$_3$R$_2$), 6.00 (s, 1H, C$_3$), 5.42-5.36 (m, 1H, C$_2$), 5.30 (s, 1H, C$_9$-OH), 5.22 (s, 1H, C$_8$-OH), 4.61-4.51 (m, 2H, C$_3$), 4.39 (d, 1H, J = 11.3 Hz, C$_1$), 4.33 (app t, 1H, J = 11.3 Hz, C$_2$), 4.24 (d, 1H, J = 11.3 Hz, C$_17$), 3.83 (dd, 1H, J = 12.1, 3.2 Hz, C$_2$), 3.74 (s, 6H, Ar(OMe)$_2$), 3.74-3.70 (m, 1H, C$_2$), 3.64 (dd, 1H, J = 11.3 Hz, C$_2$), 2.68-2.56 (m, 1H, C$_2$), 2.37-2.25 (m, 2H, C$_4$), 1.93 (br s, 1H, C$_2$-OH), 1.85 (app t, 1H, J = 12.8 Hz, C$_2$), 1.65-1.57 (m, 2H, C$_4$), 1.32-1.21 (m, 8H, C$_4$-C$_5$), 1.11 (s, 3H, C$_1$8-Me), 1.06 (s, 3H, C$_1$8-Me), 0.87 (t, 3H, J = 7.2 Hz, C$_4$) ppm

$^{13}$C NMR (CDCl$_3$, 125 MHz): δ = 172.1, 170.8, 166.9, 166.3, 157.7, 154.6, 151.8, 136.7, 135.4, 129.1, 128.7, 122.6, 119.6, 117.5, 116.0, 104.2, 100.1, 73.6, 71.9, 71.5, 67.1, 65.6, 65.3, 56.0, 51.3, 41.5, 35.9, 35.0, 34.8, 31.8, 31.2, 29.2, 29.0, 24.8, 22.7, 22.1, 20.7, 14.2 ppm

IR (thin film): 3471, 2932, 2856, 1735, 1719, 1666, 1594, 1502, 1473, 1434, 1409, 1372, 1303, 1247, 1230, 1174, 1154, 1110, 1061, 1039, 1005, 915, 731 cm$^{-1}$

HRMS (ES+, $m/z$) calculated for C$_{41}$H$_{54}$NaO$_{14}$+: 793.3406, Found: 793.3414

$[\alpha]_D^{20}$ = -41.7 ± 0.2° (c = 0.65, CH$_2$Cl$_2$)

$R_f$ = 0.25 (60% EtOAc in pentane), one redjexp spot, p-anisaldehyde + UV
Procedure for C7′-(2,6-bis(OiPr)-phenyl) analog 19

Pd(OAc)$_2$ (1.8 mg, 8.0 µmol), S-Phos (6.9 mg, 17 µmol), and boronic acid S6 (7.9 mg, 33 µmol) were dissolved in 200 µL dioxane in a dry vial under inert atmosphere. The vial was flushed with Ar and stirred 20 min at room temp. In a separate dry vial, CsF (14.3 mg, 94 µmol, stored at >200 ºC) was cooled under a stream of nitrogen. Aryl bromide 3 (4.7 mg, 6.6 µmol) was dissolved in 200 µL dioxane under N$_2$; this solution was transferred into the vial containing CsF via syringe, and the transfer was quantified with two 150 µL portions of dioxane. The Pd$_0$ solution (having stirred 20 min; cloudy orange) was transferred via syringe into the starting material solution over the course of 15 seconds. Reaction mixture was red-orange at this point. The vial was flushed with Ar, capped, and heated 1.5 hr at 60 ºC. The dark reaction mixture with black precipitate was filtered through a plug of celite, eluting with ~25 mL ethyl acetate then concentrating under vacuum. The crude residue was purified via flash chromatography over a silica pipet column (40→60% ethyl acetate:pentane). The resultant yellow solid was further purified with reverse phase HPLC (70→100% MeCN:H$_2$O, 30 min run, residue loaded with a 2:1 mixture of MeOH to MeCN).

Product eluted at 25.5 minutes. The C7′-(2,6-bis(OiPr)-phenyl)-substituted analog 19 was obtained as a white solid (3.5 mg, 64.4%).

Characterization Data for C7′-(2,6-bis(OiPr)-phenyl) analog 19:

$^1$H NMR (CDCl$_3$, 500 MHz): δ = 7.92 (d, 1H, J = 2.3 Hz, Ar), 7.52 (dd, 1H, J = 8.6, 2.2 Hz, Ar), 7.18 (t, 1H, J = 8.3 Hz, C$_6$H$_4$R$_2$), 7.05 (d, 1H, J = 8.8 Hz, Ar), 6.60 (d, 2H, J = 8.4 Hz, C$_6$H$_4$R$_2$), 5.99 (s, 1H, C34), 5.42-5.36 (m, 1H, C$_2$), 5.30 (s, 1H, C20), 5.26 (s, 1H, C19-OH), 4.58-4.50 (m, 2H, C3), 4.38 (sept., 1H, J = 6.2 Hz, O$i$Pr), 4.37 (d, 1H, J = 11.0 Hz, C17), 4.34 (app t, 1H, J = 11.0 Hz, C23), 4.31 (d, 1H, J = 11.0 Hz, C17), 3.83 (dd, 1H, J = 12.3, 3.2 Hz, C26), 3.74-3.70 (m, 1H, C22), 3.70 (s, 3H, CO$_2$Me), 3.64 (dd, 1H, J = 12.1, 5.7 Hz, C26), 2.69-2.57 (m, 2H, C22), 2.37-2.25 (m, 2H, C40), 2.20 (app t, 1H, J = 13.0 Hz, C23), 2.02 (app t, 1H, J = 13.4 Hz, C24), 2.00 (br s, 1H, C26-OH), 1.86 (app t, 1H, J = 13.4 Hz, C24), 1.65-1.58 (m, 2H, C41), 1.32-1.21 (m, 8H, C42-C45), 1.20 (d, 6H, J = 6.2 Hz, O$i$Pr), 1.18 (d, 6H, J = 6.2 Hz, O$i$Pr), 1.10 (s, 3H, C18-Me), 1.07 (s, 3H, C18-Me), 0.87 (t, 3H, J = 7.0 Hz, C46) ppm

$^{13}$C NMR (CDCl$_3$, 125 MHz): δ = 172.1, 170.8, 166.9, 166.4, 156.3, 154.4, 151.9, 136.9, 135.9, 129.1, 128.6, 121.7, 120.5, 119.6, 115.4, 107.8, 100.1, 73.6, 71.6, 71.5, 71.2, 66.9, 65.6, 65.3, 51.3, 41.6, 35.9, 34.9, 34.8, 31.8, 31.2, 29.2, 29.0, 24.8, 22.7, 22.2, 22.0, 20.5, 14.2 ppm

IR (thin film): 3470, 2928, 1720, 1589, 1500, 1462, 1408, 1379, 1231, 1175, 1154, 1112, 1061, 1004, 915, 733 cm$^{-1}$

HRMS (ES+, m/z) calculated for C$_{45}$H$_{62}$NaO$_4$: 849.4032, Found: 849.4023

[α]$_D^{23}$° = -36.6 ± 0.4° (c = 0.5, CH$_2$Cl$_2$)

R$_f$ = 0.60 (60% EtOAc in pentane), one red spot, p-anisaldehyde + UV
Procedure for C7'-(4-CO$_2$iPr-Ph) analog 20

Pd(OAc)$_2$ (2.1 mg, 9.4 µmol), S-Phos (7.5 mg, 25 µmol), and 4-(CO$_2$iPr)-phenyl boronic acid (7.4 mg, 36 µmol) were dissolved in 200 µL dioxane in a dry vial under inert atmosphere. The vial was flushed with Ar and stirred 20 min at room temp. In a separate dry vial, CsF (7.5 mg, 49 µmol, stored at >200 ºC) was cooled under a stream of nitrogen. Aryl bromide 3 (5.2 mg, 7.3 µmol) was dissolved in 250 µL dioxane under N$_2$; this solution was transferred into the vial containing CsF via syringe, and the transfer was quantified with two 150 µL portions of dioxane. The Pd$_0$ solution (having stirred 20 min; cloudy orange) was transferred via syringe into the starting material solution over the course of 15 seconds. Reaction mixture was red-orange at this point. The vial was flushed with Ar, capped, and heated 2 hrs at 60 ºC. The dark reaction mixture with black precipitate was filtered through a plug of celite, eluting with ~25 mL ethyl acetate then concentrating under vacuum. The crude residue was purified via flash chromatography over a silica pipet column (50→70% ethyl acetate:pentane). The resultant yellow solid was further purified with reverse phase HPLC (70→100% MeCN:H$_2$O, 30 min run, residue loaded with a 2:1 mixture of MeOH to MeCN). Product eluted at 24.5 minutes. The C7'-(4-CO$_2$iPr-phenyl)-substituted analog 20 was obtained as a white solid (4.56 mg, 78.5%).

Characterization Data for C7'-(4-CO$_2$iPr-Ph) analog 20:

$^1$H NMR (CDCl$_3$, 600 MHz): δ = 8.13 (d, 1H, J = 2.4 Hz, Ar), 8.09 (d, 2H, J = 8.4 Hz, C$_6$H$_4$R), 7.63 (d, 2H, J = 8.4 Hz, C$_6$H$_4$R), 7.17 (d, 1H, J = 8.8 Hz, Ar), 6.00 (s, 1H, C34), 5.40-5.35 (m, 1H, C25), 5.32 (s, 1H, C20), 5.27 (sept., 1H, J = 6.3 Hz, O$i$Pr), 5.15 (s, 1H, C19-OH), 4.63-4.56 (m, 2H, C3), 4.44 (d, 1H, J = 11.2 Hz, C17), 4.32 (app, 1H, J = 11.2 Hz, C23), 4.24 (d, 1H, J = 11.2 Hz, C17), 3.82 (dd, 1H, J = 12.1, 3.2 Hz, C26), 3.74-3.70 (m, 1H, C22), 3.71 (s, 3H, CO$_2$Me), 3.64 (dd, 1H, J = 12.1, 5.8 Hz, C26), 2.65-2.55 (m, 2H, C2), 2.37-2.25 (m, 2H, C40), 2.21 (app t, 1H, J = 12.4 Hz, C22), 2.03 (app t, 1H, J = 12.4 Hz, C24), 1.87 (app t, 1H, J = 12.4 Hz, C24), 1.73 (br s, 1H, C18-OH), 1.65-1.57 (m, 2H, C41), 1.39 (d, 6H, J = 6.3 Hz, O$i$Pr), 1.31-1.23 (m, 8H, C42-C45), 1.13 (s, 3H, C18-Me), 1.08 (s, 3H, C18-Me), 0.88 (t, 3H, J = 7.1 Hz, C46) ppm

$^{13}$C NMR (CDCl$_3$, 150 MHz): δ = 172.1, 170.6, 166.9, 166.0, 155.8, 151.8, 143.5, 134.8, 132.4, 131.6, 130.3, 130.1, 126.8, 123.8, 119.6, 117.2, 100.1, 73.6, 72.4, 71.6, 68.6, 67.5, 65.5, 65.4, 51.3, 41.6, 35.9, 34.9, 34.8, 31.8, 31.2, 29.2, 29.0, 24.8, 22.7, 22.1, 21.7, 20.7, 14.2 ppm

IR (thin film): 3477, 2929, 1717, 1609, 1487, 1463, 1249, 1377, 1264, 1233, 1179, 1156, 1103, 1043, 1005, 917, 775, 731 cm$^{-1}$

HRMS (ES+, m/z) calculated for C$_{43}$H$_{56}$NaO$_{14}$+: 819.3562, Found: 819.3568

$[^{[a]D}]_{D}^{21} = -54.0 \pm 0.7^\circ$ (c = 0.3, CH$_2$Cl$_2$)

$R_f = 0.30$ (60% EtOAc in pentane), one red spot, p-anisaldehyde + UV

Believed to be two unresolved resonances, tentatively assigned as the carbonyl carbon of the CO$_2$iPr group and C10 (salicylate carbonyl).
Procedure for C7'-(5-indolyl) analog 21

Pd(OAc)₂ (2.2 mg, 10 µmol), S-Phos (8.2 mg, 20 µmol), and 5-indolyl boronic acid (6.4 mg, 40 µmol) were dissolved in 250 µL dioxane in a dry vial under inert atmosphere. The vial was flushed with Ar and stirred 15 min at room temp. In a separate dry vial, CsF (8.5 mg, 56 µmol, stored at >200 ºC) was cooled under a stream of nitrogen. Aryl bromide 3 (6.7 mg, 8.0 µmol) was dissolved in 300 µL dioxane under N₂; this solution was transferred into the vial containing CsF via syringe, and the transfer was quantified with two 150 µL portions of dioxane. The Pd₀ solution (having stirred 15 min) was transferred via syringe into the starting material solution over the course of 15 seconds. Reaction mixture was orange at this point. The vial was flushed with Ar, capped, sealed, and heated 2 hrs at 60 ºC. The dark reaction mixture with black precipitate was filtered through a plug of celite, eluting with ~25 mL ethyl acetate before concentrating under vacuum. The crude residue was purified via flash chromatography over a silica pipet column (60→70% ethyl acetate:pentane). The resultant yellow solid was further purified with reverse phase HPLC (70→100% MeCN:H₂O, 30 min run, residue loaded with a 7:3 mixture of MeOH to MeCN). The C7'-(5-indolyl)-substituted analog 21 was obtained as a white solid (4.1 mg, 68.5%).

Characterization Data for C7'-(5-indolyl) analog 21:

\(^1\)H NMR (CDCl₃, 500 MHz): \(\delta = 8.27\) (s, 1H, NH), 8.12 (d, 1H, \(J = 2.5\) Hz, C₈'), 7.82 (s, 1H, indole-C₄), 7.73 (dd, 1H, \(J = 8.5, 2.4\) Hz, C₆'), 7.45 (d, 1H, \(J = 8.6\) Hz, indole-C₇), 7.40 (dd, 1H, \(J = 8.5, 1.9\) Hz, indole-C₆), 7.25 (app t, 1H, \(J = 2.7\) Hz, indole-C₂), 7.13 (d, 1H, \(J = 8.8\) Hz, C₅'), 6.60-6.59 (m, 1H, indole-C₃), 6.01 (s, 1H, C₁₉-OH), 5.31 (s, 1H, C₂₀), 5.24 (s, 1H, C₁₉-OH), 4.61-4.52 (m, 2H, C₃), 4.44 (d, 1H, \(J = 11.3\) Hz, C₁₇), 4.33 (app t, 1H, \(J = 11.8\) Hz, C₂₃), 4.22 (d, 1H, \(J = 11.3\) Hz, C₁₇), 3.82 (dd, 1H, \(J = 12.1, 3.1\) Hz, C₂₆), 3.73 (dd, 1H, \(J = 14.2, 2.3\) Hz, C₂₂), 3.70 (s, 3H, CO₂Me), 3.63 (dd, 1H, \(J = 11.7, 5.9\) Hz, C₂₆), 2.60-2.55 (m, 2H, C₂), 2.37-2.25 (m, 2H, C40), 2.20 (app t, 1H, \(J = 13.0\) Hz, C₂₂), 2.03 (app t, 1H, \(J = 12.6\) Hz, C₂₄), 1.86 (app t, 1H, \(J = 12.6\) Hz, C₂₄), 1.80 (br s, 1H, C₂₆-OH), 1.65-1.57 (m, 2H, C₄₁), 1.34-1.20 (m, 8H, C₄₂-C₄₅), 0.88 (s, 3H, C₁₈-Me), 0.88 (s, 3H, C₁₈-Me), 0.88 (s, 3H, C₁₈-Me), 0.88 (s, 3H, C₁₈-Me), 0.88 (s, 3H, C₁₈-Me), 0.88 (s, 3H, C₁₈-Me), 0.88 (s, 3H, C₁₈-Me), 0.88 ppm.

\(^{13}\)C NMR (CDCl₃, 125 MHz): \(\delta = 172.1, 170.7, 166.9, 166.4, 154.4, 151.8, 137.4, 135.5, 132.4, 131.5, 131.2, 128.5, 125.1, 123.6, 119.6, 117.3, 111.5, 103.2, 100.0, 73.5, 72.3, 71.4, 67.4, 65.5, 65.4, 51.3, 41.5, 35.8, 34.9, 34.8, 31.8, 31.2, 29.2, 29.0, 24.6, 22.7, 22.1, 20.7, 14.1 ppm.

IR (thin film): 3473, 2929, 1720, 1468, 1408, 1232, 1175, 1155, 1090, 1062, 1038, 1004, 805, 766, 731, 680 cm\(^{-1}\).

HRMS (ES+, m/z) calculated for C₄₁H₅₁NNaO₁₂⁺: 772.3303, Found: 772.3322

[\(\alpha\)\]D\(^{24}\) = -44.0 ± 0.7° (c = 0.41, CH₂Cl₂)

\(R_f = 0.45\) (70% EtOAc in pentane), one red spot, p-anisaldehyde + UV (fluorescent blue under short wave)
S42
Procedure for C7'-\((4-\text{SO}_2\text{N(Et)}_2\text{-Ph})\) analog 22
Pd(OAc)$_2$ (1.9 mg, 8.5 µmol), PPh$_3$ (6.9 mg, 26 µmol), 4-diethylsulfamoylphenylboronic acid (8.5 mg, 33 µmol), and K$_2$CO$_3$ (3.6 mg, 26 µmol) were added to a dry vial containing aryl bromide 3 (4.7 mg, 6.6 µmol) under argon. The solids were dissolved in 700 µL dioxane then the vial was flushed with Ar, capped, and heated 2 hrs at 60 ºC. The dark red reaction mixture was filtered through a plug of celite, eluting with ~20 mL ethyl acetate then concentrating under vacuum. The crude residue was purified via flash chromatography over a silica pipet column (50→75% ethyl acetate:pentane). The resultant yellow solid was further purified with reverse phase HPLC (70→100% MeCN:H$_2$O, 30 min run, residue loaded with a 2:1 mixture of MeOH to MeCN). Product eluted at 19.1 minutes. The C7'-sulfamoylphenyl-substituted analog 22 was obtained as a white solid (1.82 mg, 32.7%).

Characterization Data for C7'-\((4-\text{diethylsulfonamide-Ph})\) analog 22:

$^1$H NMR (CDCl$_3$, 500 MHz): δ = 8.11 (d, 1H, J = 2.5 Hz, Ar), 7.86 (d, 2H, J = 8.4 Hz, C$_6$H$_4$R), 7.19 (dd, 1H, J = 8.8 Hz, Ar), 6.00 (s, 1H, C$_3$), 5.41-5.35 (m, 1H, C$_2$), 5.32 (s, 1H, C$_2$), 5.31 (s, 1H, C$_2$), 5.25 (s, 1H, C$_1$), 4.65-4.56 (m, 2H, C$_3$), 4.44 (d, 1H, J = 11.2 Hz, C$_4$), 4.32 (app t, 1H, J = 11.2 Hz, C$_5$), 4.25 (d, 1H, J = 11.2 Hz, C$_6$), 3.85 (dd, 1H, J = 12.1, 3.0 Hz, C$_7$), 3.74-3.70 (m, 1H, C$_8$), 3.71 (s, 3H, CO$_2$Me), 3.64 (dd, 1H, J = 12.3, 5.9 Hz, C$_9$), 3.27 (q, 4H, J = 7.2 Hz, NEt$_2$), 2.67-2.55 (m, 2H, C$_10$), 2.37-2.25 (m, 2H, C$_11$), 2.21 (app t, 1H, J = 13.1 Hz, C$_12$), 1.75 (br s, 1H, C$_13$), 1.68-1.68 (m, 2H, C$_14$), 1.33-1.22 (m, 8H, C$_15$), 1.15 (t, 6H, J = 7.0 Hz, NEt$_2$), 1.12 (s, 3H, C$_16$-Me), 0.88 (t, 3H, J = 7.1 Hz, C$_17$) ppm

$^{13}$C NMR (CDCl$_3$, 125 MHz): δ = 172.1, 170.5, 166.9, 165.9, 156.0, 151.7, 139.4, 134.1, 132.4, 131.7, 127.6, 127.5, 123.8, 119.6, 117.3, 100.1, 73.9, 72.4, 71.6, 67.2, 66.5, 65.4, 64.8, 64.2, 41.6, 35.8, 34.9, 34.8, 31.8, 31.2, 29.2, 29.0, 24.8, 22.1, 20.7, 14.3, 14.2 ppm

IR (thin film): 3477, 2930, 1738, 1720, 1610, 1483, 1424, 1378, 1334, 1261, 1233, 1155, 1092, 1061, 1044, 1005, 933, 695 cm$^{-1}$

HRMS (ES+, m/z) calculated for C$_{43}$H$_{59}$N$_2$NaO$_7$S$^+$: 868.3548, Found: 868.3542

$[\alpha]_D^{35.5^\circ} = -33.9 \pm 0.2^\circ$ (c = 0.3, CH$_2$Cl$_2$)

$R_f = 0.55$ (80% EtOAc in pentane), one red spot, p-anisaldehyde + UV

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16 Yield determined by quantitative $^1$H NMR using benzene as an internal standard and dimethyl terephthalate as an external standard.
Procedure for C7’-(3,5-dimethylisoxazole) analog 23
Pd(OAc)2 (2.5 mg, 11 µmol), PPh3 (11.4 mg, 43 µmol), 3,5-dimethylisoxazole-4-boronic acid (6.2 mg, 44 µmol), and K2CO3 (6.8 mg, 49 µmol) were added to a dry vial containing aryl bromide 3 (6.8 mg, 9.5 µmol) under argon. The solids were dissolved in 950 µL dioxane then the vial was flushed with Ar, capped, and heated 2 hrs at 60 ºC. The dark red reaction mixture was filtered through a plug of celite, eluting with ~20 mL ethyl acetate then concentrating under vacuum. The crude residue was purified via flash chromatography over a silica pipet column (60→80% ethyl acetate:pentane). The resultant yellow solid was further purified with reverse phase HPLC (70→100% MeCN:H2O, 30 min run, residue loaded with a 2:1 mixture of MeOH to MeCN). Product eluted at 14.5 minutes. The C7’-isoxazole-substituted analog 23 was obtained as a white solid (3.10 mg, 44.6%).

Characterization Data for C7’-(3,5-dimethylisoxazole) analog 23:

**1H NMR** (CDCl3, 500 MHz): δ = 7.74 (d, 1H, J = 2.4 Hz, Ar), 7.36 (dd, 1H, J = 8.6, 2.4 Hz, Ar), 7.15 (d, 1H, J = 8.5 Hz, Ar), 6.00 (s, 1H, C34), 5.41-5.35 (m, 1H, C25), 5.31 (s, 1H, C20), 5.11 (s, 1H, C19-OH), 4.62-4.56 (m, 2H, C3), 4.43 (d, 1H, J = 11.1 Hz, C17), 4.31 (app t, 1H, J = 11.1 Hz, C23), 4.23 (d, 1H, J = 11.1 Hz, C17), 3.82 (dd, 1H, J = 12.0, 3.2 Hz, C26), 3.74-3.70 (m, 1H, C22), 3.70 (s, 3H, CO2Me), 3.64 (dd, 1H, J = 12.1, 5.8 Hz, C26), 2.67-2.55 (m, 2H, C2), 2.40 (s, 3H, isoxazole-Me), 2.37-2.25 (m, 2H, C40), 2.27 (s, 3H, isoxazole-Me), 2.21 (app t, 1H, J = 13.0 Hz, C22), 2.04 (app t, 1H, J = 13.0 Hz, C24), 1.87 (app t, 1H, J = 13.0 Hz, C24), 1.75 (br s, 1H, C26-OH), 1.65-1.57 (m, 2H, C41), 1.31-1.23 (m, 8H, C42-C45), 1.13 (s, 3H, C18-Me), 1.08 (s, 3H, C18-Me), 0.88 (t, 3H, J = 7.1 Hz, C46) ppm

**13C NMR** (CDCl3, 125 MHz): δ = 172.1, 170.6, 166.9, 165.8, 162.7, 155.2, 151.7, 134.3, 133.3, 125.2, 123.8, 119.6, 117.1, 115.2, 100.1, 73.5, 72.4, 71.6, 67.1, 65.5, 65.4, 51.3, 41.5, 35.8, 34.9, 34.8, 31.8, 31.2, 29.2, 29.0, 24.8, 22.7, 22.1, 20.7, 14.2, 11.8, 11.0 ppm

**IR** (thin film): 3478, 2929, 1738, 1720, 1666, 1434, 1376, 1258, 1231, 1175, 1155, 1090, 1062, 1004, 915, 732 cm⁻¹

**HRMS** (ES+, m/z) calculated for C38H51NNaO13⁺: 752.3253, Found: 752.3230

[α]D2.9°C = -16.7 ± 0.2° (c = 0.5, CH3Cl)

RF = 0.15 (70% EtOAc in pentane), one red spot, p-anisaldehyde + UV

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17 Yield determined by quantitative 1H NMR using benzene as an internal standard and dimethyl terephthalate as an external standard.
Procedure for 2,6-bis(isopropoxy) bromobenzene (S5)

Bromobenzene S4 was prepared following precedence from Luning and co-workers. 18 2-Bromoresorcinol (S5, 116 mg, 0.61 mmol) was dissolved in dry PhMe (3.1 mL) in a dry vial under a nitrogenous atmosphere. Triphenylphosphine (480 mg, 1.8 mmol) and iPrOH (240 µL, 3.1 mmol) were added respectively in one portion each. The vial was wrapped in foil and cooled to 0 °C before adding DIAD (360 µL, 1.8 mmol) dropwise over 1 min. The ice bath was removed, and the reaction was stirred at room temp for 15 hrs. The starting material had been consumed as observed by TLC, and the reaction mixture was reduced to half the original volume under a stream of nitrogen. The was directed loaded onto a silica column for purification by flash chromatography (0.5→3.0% ether:pentane, 0.5% increments, additional PhMe was used to complete the transfer of the crude residue). Cleanly obtained the desired bromobenzene S5 as a slightly yellow oil (146.2 mg, 87.2%).

Characterization Data for 2,6-bis(isopropoxy) bromobenzene (S5):

\(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta = 7.14\) (t, 1H, \(J = 8.3\) Hz, Ar), \(6.55\) (d, 2H, \(J = 8.4\) Hz, Ar), \(4.55\) (sept., 2H, \(J = 6.1\) Hz, OiPr), \(1.38\) (d, 12H, \(J = 6.0\) Hz, OiPr) ppm

\(^{13}\)C NMR (CDCl\(_3\), 125 MHz): \(\delta = 156.2, 127.8, 108.3, 105.4, 72.3, 22.3\) ppm

IR (thin film): 2978, 1591, 1461, 1384, 1373, 1252, 1113, 1059, 1035 cm\(^{-1}\)

HRMS (ES+, \(m/z\)) calculated for C\(_{12}\)H\(_{18}\)BrO\(_2\): 273.0485, Found: 273.0487

\(R_f = 0.50\) (4% ether in pentane), one red spot, \(p\)-anisaldehyde + UV

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18 Luning, U.; Abbass, M.; Fahrenkrug, F. “A Facile Route to Aryl-Substituted 1,10-Phanathrolines by Means of Suzuki Coupling Reactions between Areneboronic acids and Halogeno-1,10-phenanthrolines.” Eur. J. Org. Chem. 2002, 3294-3303.
Standard Protein Parameters

Archive directory: /export/home/stevens/vemereo/data
Sample directory:
File: DOM.001.m.p.ppdf.pdf

Pulse Sequence: nucl
Solvent: CDCl3

Pulse 90.8 degrees
Acq. Time 2.000 sec
Width 0.000 Hz
4 repetitions

Spectrum E1: 099.7865737 Hz
Data Processing
FT size 5588
Total time 6 min
Procedure for 2,6-bis(isopropoxy) phenylboronic acid (S6)

Boronic acid S6 was prepared following precedence from Luning and co-workers.\textsuperscript{19} Bromobenzene S5 (69.2 mg, 0.25 mmol) was dissolved in dry THF (1.3 mL) and cooled to -78 °C. nBuLi (2.5 M in hexanes, 111 µL, 0.28 mmol) was added down the side of the vial over 30 seconds. This mixture was stirred for 1 hr at -78 °C. B(OMe)\(_3\) (99 µL, 0.89 mmol) was added dropwise over 30 seconds. After 1 hr at -78 °C, the majority of the dry ice was removed from the cold bath, and the reaction was allowed to stir for an additional hr (bath warmed to ~0 °C in that time). TLC analysis showed consumption of starting material. A small red spot ran just above the starting material and was suspected to be debrominated starting material, potentially from unreacted lithiated starting material that protonated on the TLC plate. The reaction mixture was therefore stirred for an additional 45 min at room temp, but there did not appear to be any change by TLC. The reaction was quenched with 2 mL 1:1 sat. NH\(_4\)Cl:water and diluted with 2 mL ether. The phases were separated, and the aqueous phase was extracted four times with 2 mL portions of ether. The combined organic phases were washed with 2 mL brine, dried over anhydrous Na\(_2\)SO\(_4\), filtered to remove solids, and concentrated under a stream of nitrogen. The crude residue was purified via flash chromatography over silica (4→20% ethyl acetate:pentane, 4% increments, loaded residue with PhMe). Boronic acid S7 was obtained as a clear, colorless oil (53.0 mg, 87.9%). Note: product solidified upon storage at -20 °C and did not return to an oil upon warming to room temp; product appears to be a white solid at room temp.

Characterization Data for 2,6-bis(isopropoxy) phenylboronic acid (S6):

\(^1\)H NMR (CDCl\(_3\), 500 MHz): \(\delta = 7.50\) (br s, 2H, B(OH)\(_2\)), \(7.31\) (t, 1H, \(J = 8.4\) Hz, Ar), \(6.58\) (d, 2H, \(J = 8.5\) Hz, Ar), \(4.69\) (sept., 2H, \(J = 6.1\) Hz, O\textsubscript{i}Pr), \(1.40\) (d, 12H, \(J = 6.1\) Hz, O\textsubscript{i}Pr) ppm

\(^{13}\)C NMR (CDCl\(_3\), 125 MHz): \(\delta = 164.1\), 132.7, 106.5, 71.7, 71.7, 22.2 ppm\textsuperscript{20}

IR (thin film): 3491, 2979, 1594, 1466, 1325, 1229, 1109, 1046, 790, 717 cm\(^{-1}\)

HRMS (ES\(^+\), \(m/z\)) calculated for C\(_{12}\)H\(_{19}\)BNaO\(_4\): 261.1269, Found: 261.1273

\(R_f = 0.35\) (20% EtOAc in pentane), one red spot, \(p\)-anisaldehyde + UV

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\textsuperscript{19} Luning, U.; Abbass, M.; Fahrenkrug, F. “A Facile Route to Aryl-Substituted 1,10-Phananthrolines by Means of Suzuki Coupling Reactions between Areneboronic acids and Halogeno-1,10-phenanthrolines.” \textit{Eur. J. Org. Chem.} 2002, 3294-3303.

\textsuperscript{20} No resonance was detected for the aryl carbon attached to the B(OH)\(_2\) functional group. This is likely the result of \(^{11}\)B-induced splitting and a long relaxation time. The authors listed above also had this issue on analogous 2,6-bis(alkoxy)phenylboronic acids.
Procedure for MOM ether S2

2-Hydroxy-5-bromobenzyl alcohol S1 (2.05 mg, 1.0 mmol) was dissolved in 6.0 mL dry CH₂Cl₂ in a dry vial under an atmosphere of nitrogen. Pyridine (200 µL, 2.5 mmol) and MOMCl (85 µL, 1.1 mmol) were added respectively in one portion each. The reaction was capped, sealed, and refluxed at 60 ºC for 15 hrs. This setup was run in triplicate, side by side. All three replicates were pooled after cooling to room temp and concentrated under vacuum. The crude residue was purified via flash chromatography over silica (7→28% ethyl acetate:pentane, 7% increments, residue loaded with PhMe). MOM ether S2 was obtained as an off-white solid (605 mg, 80.9%).

Characterization Data for MOM ether S2:

¹H NMR (CDCl₃, 600 MHz): δ = 7.31 (dd, 1H, J = 8.7, 2.4 Hz, Ar), 7.21 (d, 1H, J = 2.4 Hz, Ar), 7.17 (s, 1H, OH), 6.78 (d, 1H, J = 8.8 Hz, Ar), 4.72 (s, 2H, CH₂Ar), 4.70 (s, 2H, MOM), 3.42 (s, 3H, MOM) ppm

¹³C NMR (CDCl₃, 150 MHz): δ = 155.2, 132.5, 131.6, 124.5, 118.7, 112.1, 95.8, 67.4, 56.1 ppm

IR (thin film): 3339, 2945, 2889, 1493, 1418, 1271, 1234, 1149, 1100, 1034, 921, 814, 627 cm⁻¹

HRMS (ES+, m/z) calculated for C₉H₁₁BrNaO₃⁺: 268.9784, Found: 268.9785

Rf = 0.40 (30% EtOAc in pentane), one yellow spot, KMnO₄ + UV
STANDARD PHOSPH PARAMETERS

Archive directory:
/export/home/stevens/venusys/data
Sample directory:

File: env2.run

Pulse sequence: alvem
Solvent: CDCl3
Temp. 30.0°C / 296.1 K
Delay: 1.1-5.5

Relax: delay 0.200 sec
Pulse 80.0 degrees
Acq. time 6.666 sec
Width 2000.0 Hz
8 repetitions
ORDERED 1H 90/40.0MHz

DATA PROCESSING

FT size 65536
Total line 8 min

STANDARD CARBON PARAMETERS

Archive directory:
/export/home/stevens/venusys/data
Sample directory:

File: BSTP030100A.1300.chem

Pulse sequence: alvem
Solvent: cdc1

Temp. 25.0°C / 298.1 K
Delay: 1-49

Relax: delay 1.000 sec
Pulse 90.0 degrees
Acq. time 1.200 sec
Width 300.0 Hz
128 repetitions
NORMAL 1K 100.6 MHz
POWDER XI 5.0003001 MHz
Power 20 dB
continuously on
MULTI-18 modulated
data processing
Line broadening 5.0 Hz

Total time 7 hr. 63 min

S52
Procedure for TCE ester S3

MOM ether S2 (1.27 g, 5.1 mmol) was dissolved in 5.1 mL dry DMF in a dry vial under nitrogen. K₂CO₃ (1.07 g, 7.7 mmol) was added in 2 equal portions, one min apart, followed by the addition of 3-bromo-1-propanol (700 µmol, 7.7 mmol) in one portion. The reaction was quenched with 50 mL sat. NH₄Cl and diluted with 50 mL ether. The phases were separated, and the aqueous phase was further extracted with four 50 mL portions of ether. The combined organic phases were washed with 50 mL brine, dried over anhydrous sodium sulfate, filtered to remove solids, and concentrated in vacuo. The crude residue was purified via flash chromatography over silica (8→32% ethyl acetate:pentane, 8% increments). The resultant white solid (1.52 g) was moved on without further purification.

The crude C1 alcohol was dissolved in 105 mL MeCN and 20 mL H₂O in a dry flask under N₂. TEMPO (230 mg, 1.5 mmol) and PhI(OAc)₂ (4.81 g, 15 mmol) were added respectively in one portion each. Starting material was consumed after 1 hr at room temp as visualized by TLC. While still at room temp, 2-methyl-2-butenet (25 mL, 236 mmol), H₂O (6 mL), and Na₂HPO₄ (5.98 g, 50 mmol) were added. The reaction mixture was then cooled to 0 ºC (~10 min) before adding NaClO₂ (4.50 g, 40 mmol) in two equal portions, 3 min apart. Reaction mixture turns a dark red color. After 45 min at 0 ºC, the reaction was quenched with 100 mL sat. Na₂S₂O₃ and diluted with 100 mL ether. The phases were separated, and the aqueous phase was extracted with 100 mL of ether six times. The combined organic phases were washed with 100 mL brine, dried over anhydrous magnesium sulfate, filtered to remove solids, and concentrated in vacuo. The residue was taken up in 50 mL PhMe and re-concentrated to remove any AcOH. The crude yellow oil was immediately moved on without further purification.

The crude C1 carboxylic acid was dissolved in 25 mL dry CH₂Cl₂ in a dry vial under nitrogen. 2,2,2-Trichloroethanol (960 µL, 10.0 mmol), DCC (1.25 g, 6.0 mmol), and DMAP (730 mg, 6.0 mmol) were added respectively, one portion each. After 16 hrs at room temp, the reaction mixture was concentrated under a stream of nitrogen ~3/4 of the way to dryness before loading directly onto a silica column for purification by flash chromatography (2→12% ethyl acetate, 2% increments, excess residue loaded with PhMe). TCE ester S3 was afforded as slightly yellow oil (1.82 g, 78.6% over 3 steps).

Characterization Data for TCE ester S3:

\[ ^1H\text{ NMR (CDCl}_3, 500 MHz): \delta = 7.52 (d, 1H, J = 2.6 Hz, Ar), 7.35 (dd, 1H, J = 8.7, 2.6 Hz, Ar), 6.76 (d, 1H, J = 8.7 Hz, Ar), 4.79 (s, 2H, CH₂Cl), 4.71 (s, 2H, CH₂Ar), 4.54 (s, 2H, MOM), 4.30 (t, 2H, J = 6.2 Hz, C3), 3.40 (s, 3H, MOM), 2.97 (t, 2H, J = 6.2 Hz, C2) \text{ppm} \]

\[ ^13C\text{ NMR (CDCl}_3, 100 MHz): \delta = 169.4, 154.8, 131.5, 131.2, 113.6, 113.0, 96.3, 94.8, 74.2, 63.7, 63.6, 55.5, 34.4 \text{ppm} \]

\[ \text{IR (thin film): 2949, 2887, 1759, 1490, 1464, 1400, 1379, 1245, 1152, 1105, 1049, 918, 800, 721 cm}^{-1} \]

\[ \text{HRMS (ES+,) calculated for C}_{14}H_{16}BrCl_2NaO_5^+: 470.9139, \text{ Found: 470.9129} \]

\[ \text{Rf} = 0.15 (10\% \text{ EtOAc in pentane), one yellow spot, KMnO}_4 + \text{UV} \]
100 ODINE

Archive directory:
/export/home/stieves/chemsys/data
Sample directory:
/file/BSTW.218-c.pH.130

Pulse Sequence: zpul
Solvent: CDCl3
Temp. 20.0 C / 293.1 K
Relax. Delay 1.400 sec
Pulse 35.0 degrees
Avg. Time 1.100 sec
Width 2500.0 Hz
176 repetitions
CHEMPL C12: 200.664512 MHz
CHEMPL H1: 400.131583 MHz
Power 148 W
continuously on
WALTZ-16 modulated
Data Acquisition
Line broadening 0.5 Hz
FF size 1024
Total time 9 hr. 11 min
Alternative procedure for carboxylic acid 4

MOM ether 4 (1.73 g, 3.8 mmol) was dissolved in 19 mL iPrOH in a dry flask under an inert atmosphere. CBr₄ (320 mg, 0.96 mmol) was added in one portion. The flask was capped, sealed, and heated to 60 ºC for 4 hrs before concentrating under vacuum. The crude residue was purified via flash chromatography over silica (6→30% ethyl acetate:petroleum ether, 6% increments, residue was loaded with PhMe). Obtained free alcohol as a slightly yellow oil (1.36 g).

The free alcohol was dissolved in 35 mL dry acetone under an inert atmosphere and cooled to 0 ºC. To a separate dry flask containing CrO₃ (840 mg, 8.4 mmol) was added H₂SO₄ (850 µL) and H₂O (3.3 mL) respectively with the water being added slowly over 1 min. The mixture was stirred 2 min at room temp to fully dissolve CrO₃, generating a bright red solution. The Jones reagent was then added dropwise to the starting material solution via pipet over the course of 3 min. The ice bath was removed after 10 min, and the mixture was stirred for 90 min at room temp at which point the starting material was consumed. A brown precipitate was observed. Reaction was quenched with 7 mL iPrOH, resulting in a blue-green precipitate in a clear, colorless solution. This mixture was filtered through a pad of celite, eluting with ~150 mL ethyl acetate and concentrating under vacuum. The crude mixture was purified by flash chromatography over silica (10→40% ethyl acetate:pentane + 0.1% AcOH, 10% increments, loaded residue with PhMe). After concentration under vacuum, the combined clean fractions were resuspended in 10 mL PhMe and re-concentrated three times to ensure full removal of AcOH. Carboxylic acid 4 was obtained as a white solid (1.29 g, 80.1% over 2 steps). See above for characterization data.