Amplification of local chirality within a folded dendrimer. An intramolecular ‘sergeants and soldiers’ experiment

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A series of pyridine-2,6-dicarboxamide dendrons having varying proportions of chiral and achiral termini have been prepared. Circular dichroism and X-ray crystallographic studies indicate that these folded dendrons propagate terminal chirality via a ‘sergeants and soldiers’ process. The extent of chiral amplification shows a dependence on dendron generation, but also is affected by the relative positioning of the chiral termini at the periphery of the dendron. Analysis of the crystal structures of the G1 dendrons, 4a-6a, reveals chain–chain and chain–dendron conformational communication, which is likely to be responsible for the chiral amplification observed in solution.

Keywords: sergeants and soldiers; chirality amplification; folded dendrons; unsymmetrical dendrons

1. Introduction

Allosteric proteins exhibit highly nonlinear responses to external stimuli causing small perturbations of a particular parameter to result in very large changes in structure and function (Creighton 1993). The conformational changes associated with allostery in proteins are highly dynamic processes involving multiple, correlated conformational equilibria that occur over relatively long distances within the structure (Jardetzky 1997; Yon et al. 1998; Kern & Zuiderweg 2003). Correlated conformational changes are often linked to chiral amplification phenomenon in synthetic systems (Lockman et al. 2005). Chiral amplification in these systems occurs via a ‘sergeant and soldiers’ mechanism (Green et al. 1989) in which a small fraction of chiral subunits/monomers (‘sergeants’) transmits conformational information to achiral segments (‘soldiers’) of helical polymer chains, (for some reviews, see Green et al. 1999, 2001; Nakano & Okamoto 2001, Maeda & Yashima 2006; Fujiki 2008; Yashima & Maeda 2008) foldamers (Prince et al. 2000; Dolain et al. 2005; Maurizot et al. 2005; Hou et al. 2006; Kolomiets et al. 2007; Cai et al. 2008; Hu et al. 2008; King et al. 2008; Kohmoto et al. 2008; Naidu et al. 2009) or supramolecular assemblies (Engelkamp et al. 1999; Ajayaghosh et al. 2006; Mateos-Timoneda et al. 2006; Nagai et al. 2006;...)
George et al. 2007; Monti et al. 2007; Hembury et al. 2008; Lohr & Wuerthner 2008a, b; Praveen et al. 2008; Kaiser et al. 2009). Although ‘sergeants and soldiers’ chiral amplification has been achieved in dendritic assemblies (Palmand et al. 1997; van Gestel et al. 2005; Wilson et al. 2006; Shao & Parquette 2008; Percec et al. 2009), an intramolecular ‘sergeants and soldiers’ type chiral amplification remains an unrealized objective for dendrimeric systems. However, recent progress towards the incorporation of chiral secondary structure provides an opportunity to explore such chiral amplification in dendrimers (Parquette 2003; Lockman et al. 2005; Gibson & Rendell 2008). In a series of folded dendrimers, preorganized via the conformational preference of a pyridine-2,6-dicarboxamide repeat unit, we observed that coupled motions within the branches were critical for the amplification of chirality throughout the dendrons (Recker et al. 2000; Huang & Parquette 2001; Parquette 2003; Lockman et al. 2005). Recently, the propagation/amplification of local chirality within catalysts derived from these folded dendrons was successfully exploited to achieve high enantioselectivity in a catalytic process (Yu et al. 2008). In most of these systems, each terminal position was functionalized with a chiral fragment. Yet, the chiroptical properties, normalized for the number of chiral termini, increased disproportionately at higher generations. In this manuscript, we constructed dendrons displaying both chiral and achiral terminal groups to explore whether local terminal chirality can be propagated among achiral groups at the periphery of these folded dendrons.

Previously, we reported that water-soluble versions of these dendrons which were terminated with pentaethylene glycol segments exhibited solvent-triggered helical inversions consistent with highly correlated chain–chain and dendron–chain conformational equilibria (Hofacker & Parquette 2005). The first generation dendron adopted an M helical conformation in water and THF, whereas the second and third generation dendrons experienced an M → P helical inversion upon going from THF to water. This solvent-mediated M → P helical transition occurred in conjunction with a shift of two of the four glycol chains, in the G2 dendron, from gauche–gauche<sup>+</sup>–anti to anti–gauche<sup>−</sup>–anti conformations around the respective O–C–C–OMe bonds. Several points of this study are noteworthy. (i) In contrast to poly(ethylene glycol) oligomers, which exhibit an increase in the proportion of the C–C gauche conformations upon transitioning from organic media to water, the dendrons exhibited exclusively C–C gauche conformations in either solvent. This shift towards the lower energy gauche form emerges from the increase in correlated equilibria among the termini at higher generations. (ii) The dendron secondary structure and the terminal chain conformations were strongly correlated. (iii) Conformational changes of a subset of the terminal groups were sufficient to induce a complete helical inversion. These observations suggest the potential of these dendrons to amplify the effect of local chiral structural perturbations via a ‘sergeants and soldiers’ type mechanism.

2. Results and discussion

(a) Synthesis of unsymmetrical dendrons

Our initial approach to prepare dendrons with mixtures of chiral and achiral end groups relied on an ability to separate the statistical distribution of products obtained by reacting equimolar amounts of anthranilates 1 and 2 with
4-chloropyridine-2,6-dicarbonyl chloride (3), see Mitsui & Parquette (2009) in one pot (scheme 1). Fortuitously, the resulting mixture of dendrons could be readily separated by chromatography thereby providing 4a (2R*)G1-Cl, 5a (RR*)G1-Cl and 6a (2R)G1-Cl in 19, 39 and 32% yields, respectively. Symmetrical dendrons 6a and 4a could also be independently prepared in high yields by reaction of 3 with two equivalents of 1 or 2, respectively. In order to progress to the second generation, the focal chloride was converted to the corresponding amine by treatment with sodium azide followed by hydrogenation over Pd/C. Subsequently, symmetrical G2 dendrons displaying four (4R*)G2-Cl (7a), and two (2RR*)G2-Cl (8a) chiral terminal groups were obtained by reaction of 3 with either G1-NH2 dendron 4b or 5b (scheme 2). Similar to G1 dendron 5a, the unsymmetrical dendron with two chiral termini (2R*,2R)G2-Cl (9a) was prepared in 50% yield by reacting an equimolar mixture of 4b and 6b with 3.

However, applying this strategy towards the preparation of (1R*)G2-Cl (12a), having a single chiral group, by reacting 5b and 6b with 3 produced an inseparable mixture of products. Consequently, it was necessary to desymmetrize
the pyridine-2,6-dicarbonyl repeat unit prior to the amide coupling reaction to selectively produce the dendron as a single compound. Accordingly, 3 was converted to 2-allyloxycarbonyl-4-chloro-6-pyridine carbonyl chloride (10) (Yashima & Maeda 2008) and coupled with one equivalent of (2R)G2-NH2 (6b) affording intermediate 11 (scheme 3). Deprotection of the allyl ester using Pd(OAc)$_2$/PPh$_3$/HCO$_2$H/(C$_2$H$_5$)$_3$N followed by conversion to the acid chloride and reaction with (R*R)G2-NH2 (5b) provided the dendron 12a in 57% yield as a pure compound. This strategy similarly provided convenient access to unsymmetrical dendron (2R*,2R)G2-Cl (9a) in 67% yield.

(b) Conformational properties: circular dichroism

The circular dichroism (CD) spectra of first generation dendrons, 4a (2R*)G1-Cl and 5a (RR*)G1-Cl, revealed an intense negative couplet centred at ca 316 nm in CH$_3$CN (figure 1). The bisignet nature of this absorption is due to the excitonic coupling of the $\pi \rightarrow \pi^*$ transitions of the terminal anthranilate chromophores, which are polarized along the axis containing C3 and C6. The presence of the negative couplet indicates that both 4a and 5a adopt an $M$-type helical conformation relating the anthranilate chromophores in CH$_3$CN (Parquette 2003; Lockman et al. 2005; Gibson & Rendell 2008). The spectra were normalized with respect to concentration and the total number of terminal groups to determine the extent of chiral amplification from the chiral (‘sergeants’) to the achiral termini (‘soldiers’). Chiral amplification would be manifested in the CD spectra by the presence of couplets whose intensities were independent
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Scheme 3. (a) Allyl alcohol, H₂O, DMF, (C₂H₅)₃N (23%); (b) (COCl)₂, CH₂Cl₂, DMF (cat.); (c) CH₂Cl₂, pyr.; (d) Pd(OAc)₂, PPh₃, HCO₂H, (C₂H₅)₃N, THF; (e) (COCl)₂, CH₂Cl₂, DMF (cat.); (f) CH₂Cl₂, pyr. 4b and (g) CH₂Cl₂, pyr. 5b.

Figure 1. Molar CD spectra of 4a and 5a in CH₃CN and 4:1 hexane/CH₂Cl₂ at −20°C. Spectra normalized for concentration and number of termini (2). Black line indicates 4a CH₃CN; red line indicates 5a CH₃CN; red dashed line indicates 5a 4:1 hexane/CH₂Cl₂.

of the chiral/achiral proportions. The fact that the relative magnitudes of the couplets for 4a and 5a correlate well with the chiral/achiral ratio indicates that little chiral amplification is occurring at the first generation. It is noteworthy that
whereas 4a and all G2 dendrons (7a–9a, 12a) exhibit an M bias in acetonitrile and hexane/CH$_2$Cl$_2$ (4:1), 5a experiences a M → P helical transition upon going from acetonitrile to hexane/CH$_2$Cl$_2$ (4:1). Although the source of the conformational transition is not known, previous studies in our group have shown that such helical inversions in related PEG terminated dendrons emerge from changes in the conformational preference of the termini that are propagated to the dendron helicity (Hofacker & Parquette 2005).

Comparing the CD spectra of the second generation dendrons containing one (12a), two (8a and 9a) and four (7a) chiral terminal groups revealed a nonlinear relationship between the chiral/achiral ratio and the magnitude of the M helical bias (figure 2). However, the extent of chiral amplification depended critically on the relative positioning of the chiral termini. For example, the amplitude of the excitonic couplet for the dendron having two chiral chains on alternate dendritic branches (2(R*)G2-Cl, 8a) was identical to the corresponding dendron having four chiral termini (7a). In contrast, placing the two chiral groups within a single dendritic branch ((2R*)(2R)G2-Cl, 9a), resulted in a diminished couplet intensity, relative to 7a. The greater efficiency of chiral communication in 8a emerges from the juxtaposition of the chiral groups within a single dendritic branch, as shown in figure 3. A pair of anthranilate terminal groups within a single dendritic branch are forced into a compact, helical conformation as a consequence of the syn–syn conformational preference of the pyridine-2,6-dicarboxamide branch point at the second generational shell. Alternatively, the adjacent packing of two anthranilates on different dendritic branches is mediated by the pyridine-2,6-dicarboxamide branch point.
at the focal shell resulting in less compact packing. Whereas 8a can mediate the relay of chiral information via intra-dendron communication, this relay must occur via an inter-dendron pathway in 9a, which is likely to be less efficient (figure 3).

The effect of dendron generation on the efficiency of stereochemical relay among terminal groups was determined by normalizing the CD intensities for concentration and the number of chiral terminal groups. The normalized CD spectra in figure 4 illustrates that the dendrons can be categorized into three groups with respect to chiral relay efficiency: 5a/4a (G1) < 9a/12a (G2) < 8a (G2). Accordingly, the increased intensity of excitonic couplets at the second generations indicates greater chiral amplification per chiral terminal
group compared with the first generation dendrons. Similarly, G2 dendrons 9a and 12a, which must transfer chirality via an inter-dendritic branch pathway, exhibit nearly identical couplet amplitudes per chiral end group. The increased efficiency at higher generations is consistent with the occurrence of coupled conformational equilibria among the helical subunits that increases with generation.

(c) X-ray crystallographic analysis

A colourless, triclinic crystal of dendron 5a ((R*R)G1-Cl) of space group P1 was obtained by crystallization from CH$_2$Cl$_2$/hexane. Although a helical preference exists in solution, two independent molecules having opposite diastereomeric helical conformations were present in the unit cell (figure 5). The co-crystallization of diastereomeric helical conformations has previously been observed by Huc et al. with oligoamide foldamers (for an example of the co-crystallization of diastereomeric helical oligomers, see Dolain et al. 2005). This behaviour suggests that helical chirality plays a more dominant role in the crystallization process than the stereogenic centres of the termini, causing dendrons 4a–6a to relate as pseudo-enantiomers in the solid state. Inspection of
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Figure 6. The unit cell of the structure of 6a (a). Depiction of terminal group conformational changes with \( P \rightarrow M \) interconversion (b).

these independent structures revealed the presence of correlated conformational equilibria among the terminal ethylene glycol chains, and between the glycol chains and the helicity of the dendron structure. For example, the \( P \rightarrow M \) helical inversion in the solid state is coupled to a shift in the conformation of the chiral terminal chain from \( \text{trans–gauche}^+\text{–trans} \) to \( \text{anticlinal}^–\text{–gauche}^–\text{–anticlinal}^+ \) around the respective \( \text{O}–\text{C(Me)}–\text{C}–\text{OMe} \) bonds. Further, within a particular helical form (\( M \) or \( P \)), the achiral chain adopts a similar conformation as the adjacent chiral glycol unit. Accordingly, both \( \text{OC–CO} \) torsional angles are either \( \text{gauche}^+ \) or \( \text{gauche}^– \) for the \( P \) and \( M \) helical forms, respectively. Dendron 6a ((2R)G1-Cl) also crystallized from \( \text{CH}_2\text{Cl}_2/\text{hexane} \) in space group \( \text{P1} \) with two molecules of opposite helicity in the unit cell. Similar to 5a, the \( P \rightarrow M \) helical inversion was accommodated by a change in the \( \text{O}–\text{C(H)}–\text{C}–\text{OMe} \) chains from \( \text{trans–gauche}^–\text{–trans} \) to \( \text{trans–gauche}^+\text{–trans} \) and from \( \text{trans–gauche}^+\text{–anticlinal}^– \) to \( \text{trans–gauche}^–\text{–anticlinal}^+ \) (figure 6). The changes in the terminal chain conformation that occur with the helical inversion of 5a and 6a represent approximate (for 5a) or actual (for 6a) mirror image reflections. The occurrence of coupled chain–chain and chain–dendron conformational equilibria likely mediates the propagation/amplification of chirality that is observed by CD in the second generation dendrons. In contrast, dendron 4a ((2R*)G1-Cl), which similarly crystallized from \( \text{CH}_2\text{Cl}_2/\text{hexane} \) with two molecules of opposite helicity in the unit cell, exhibited a change in the conformation of one chain from \( \text{trans–trans–gauche}^– \) to \( \text{gauche}^–\text{–trans–trans} \) along the \( \text{O}–\text{C(Me)}–\text{C}–\text{OMe} \) bond (figure 7). The conformation of the adjacent glycol chain remained constant for both helical forms, suggesting an inability to propagate the chirality of the adjacent chiral chain, which may be due to
opposition from the intrinsic stereochemistry of the chain (Green et al. 1995; Cheon & Selinger 2004). Such inefficient propagation of chirality among the terminal groups may be responsible for the greater CD intensity of G2 dendron 8a compared with 9a.

3. Conclusion

A series of folded dendrons with varying proportions of chiral and achiral endgroups have revealed the occurrence of an intramolecular ‘sergeants and soldiers’ type chiral amplification. The extent of chiral amplification is greatest at the second generation, but depends critically on the relative positioning of the chiral termini. The placement of chiral groups in alternate dendritic branches (as in 8a) permits intra-dendron chiral communication between chiral and achiral groups, which is more efficient than the inter-dendron process required in 9a. Analysis of the crystal structures of the G1 dendrons 5a and 6a supports the presence of efficient chain–chain and chain–dendron conformational communication likely to be responsible for the chiral amplification observed in solution.
4. Experimental

Tetrahydrafuran and diethylether were dried by distillation from sodium benzophenone ketyl just prior to use. CH$_2$Cl$_2$ triethylamine were dried by distillation from CaH$_2$. Dimethylformamide was dried by distillation from 4 Å molecular sieves. TLC analysis was performed using Whatman silica gel 60 F$_{254}$ on aluminum-backed plates. Silica gel used for column chromatography was E. Merck silica gel 60 (230–400 mesh). Circular dichroism (CD) measurements were carried out on an Aviv 202 CD spectrometer, using optical grade solvents and 10 mm quartz glass cuvettes. $^1$H NMR and $^{13}$C NMR spectra were recorded on a Bruker DPX-400 or 500 MHz spectrometer. IR spectroscopy was performed on a Perkin Elmer 1320 spectrometer. Electrospray mass spectrometry was performed by The Ohio State University Campus Chemical Instrumentation Center.

(a) (2-Methoxyethyl)anthranilate ($^1$)

A stirred suspension of 2-nitrobenzoic acid (4.7g, 27.9mmol), dry CH$_2$Cl$_2$ (140ml), and dry DMF (100μl) was charged with oxalyl chloride (4.9ml, 7.1g, 55.9mmol) and allowed to react at room temperature (rt) for 1 h. The solvent was removed under reduced pressure followed by drying under vacuum (0.2 mmHg) for 1 h to remove the excess oxalyl chloride. A mixture of 2-methoxyethanol (2ml, 1.93g, 25.4mmol), dry CH$_2$Cl$_2$ (127ml), dry Et$_3$N (7.8ml), and activated sieves (4 Å) was prepared and allowed to stir at rt for 15 min. The 2-nitrobenzoyl chloride was taken up in dry CH$_2$Cl$_2$ (3 × 15 ml portions), added to the solution of the alcohol, and allowed to react at rt for 2 h. The mixture was filtered, washed with CH$_2$Cl$_2$ (100 ml). The organic filtrate was washed with 10% HCl (100 ml) and the aqueous layer was back-extracted with CH$_2$Cl$_2$ (1 × 100 ml). The combined organic extracts were dried with Na$_2$SO$_4$ and concentrated in vacuo (40 mmHg), dissolved in dry EtOAc (500 ml) and Pd/C (10%, 271 mg, 2.5 mmol) was added to the solution. The mixture was then placed under vacuum (40 mmHg) and purged with hydrogen (5×) and hydrogenated at 1 atm for 30 h. The Pd/C was removed by filtration through celite (20 g) with thorough washing with EtOAc (250 ml) and CH$_2$Cl$_2$ (100 ml). The solvent was removed under reduced pressure (40 mmHg) and the residue purified by column chromatography (SiO$_2$) 16% EtOAc : Hex yielded 1 (4.5g, 23.0mmol, 90%) as a yellow oil. $^1$H NMR (400 MHz, CDCl$_3$) δ 3.45 (s, 3H), 3.73 (t, $J = 4.8$ Hz, 2H), 4.46 (t, $J = 4.8$ Hz, 2H), 6.78 (td, $J = 8.0$, 0.8 Hz, 1H), 6.87 (d, $J = 8.4$ Hz, 1H), 7.34 (td, $J = 8.4$, 1.6 Hz, 1H), 7.96 (dd, $J = 8.0$, 1.6 Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 59.07, 63.37, 70.64, 110.82, 116.38, 116.70, 131.43, 134.17, 150.36, 168.00; IR (CDCl$_3$) 3504, 3383, 2892, 2360, 1690, 1614, 1590, 1292, 1247 cm$^{-1}$; HRMS for C$_{10}$H$_{13}$NO$_3$Na (M + Na) (positive ion electrospray) calcd 218.0793, obsd 218.0796.

(b) (1S)-2-Methoxy-1-methylethyl-2-nitrobenzoate

A stirred suspension of 2-nitrobenzoic acid (408mg, 2.4mmol), dry CH$_2$Cl$_2$ (12 ml), and one drop of dry DMF (10 μl) was charged with oxalyl chloride (460 μl, 669 mg, 5.3 mmol) and allowed to react at rt for 1 h. A flow of N$_2$ (g) was placed over the solution for 1 h followed by 16 h under vacuum (0.2 mm Hg) to remove
solvent. A mixture of (2S)-1-methoxy-2-propanol (220μl, 200mg, 2.2mmol), CH₂Cl₂ (5ml), Et₃N (3ml), and activated sieves (4Å) were allowed to stir at rt for 15 min. The 2-nitrobenzoyl chloride was taken up in dry CH₂Cl₂ (3 × 3 ml portions), added to the solution of the alcohol, and allowed to react at rt for 4h. The mixture was filtered, washed with CH₂Cl₂ (5ml), and concentrated in vacuo (40 mm Hg). Purification by flash chromatography (SiO₂) with 16% EtOAc : Hex afforded 2 (378 mg, 1.6 mmol, 72%) as a clear oil. \(^1\)H NMR (400MHz, CDCl₃) δ 1.38 (d, \(J = 6.5, 3\)H), 3.40 (s, 3H), 3.50 (dd, \(J = 10.6, 4.1\)Hz, 1H), 3.55 (dd, \(J = 10.6, 6.0\)Hz, 1H), 5.34 (dqd, \(J = 6.2, 6.5, 4.2\)Hz, 1H), 7.62 (td, \(J = 7.8, 1.6\)Hz, 1H), 7.68 (td, \(J = 7.5, 1.3\)Hz, 1H), 7.75 (dd, \(J = 7.5, 1.5\)Hz, 1H), 7.93 (dd, \(J = 7.9, 1.3\)Hz); \(^1\)C NMR (100MHz, CDCl₃) δ 16.05, 59.16, 71.75, 74.54, 123.86, 127.86, 129.92, 131.51, 132.86, 148.21, 165.36; IR (CDCl₃) 2989, 2937, 2884, 1732, 1537, 1352, 1294, 1257cm⁻¹; HRMS for C₁₁H₁₃NO₅Na (M + Na) (positive ion electrospray) calcd 262.0696, obsd 262.0686.

(c) (1S)-2-Methoxy-1-methylethyl anthranilate 2

(1S)-2-Methoxy-1-methylethyl-2-nitrobenzoate 1 (363mg, 1.5mmol) was dissolved in dry EtOH (8ml), treated with Pd/C (10%, 15mg, 0.14mmol) and hydrogenated under a balloon of H₂ for 14h. The Pd/C was removed by filtration through celite (5g) with EtOAc (100ml). The solvent was evaporated and the residue was purified by column chromatography (SiO₂) 16% EtOAc : Hex affording 2 (281mg, 1.3mmol, 89%) as a white solid. Melting point (mp) = 56–58°C (CH₂Cl₂); \(^1\)H NMR (400MHz, CDCl₃) δ 1.36 (d, \(J = 6.4\)Hz, 3H), 3.41 (s, 3H), 3.52 (dd, \(J = 10.5, 4.2\)Hz, 1H), 3.60 (dd, \(J = 10.5, 6.1\)Hz, 1H), 5.31 (dqd, \(J = 6.4, 6.4, 4.3\)Hz, 2H), 6.69 (td, \(J = 7.0, 1.1\)Hz, 1H), 6.72 (dd, \(J = 8.4, 0.7\)Hz, 1H), 7.29 (td, \(J = 7.0, 1.5\)Hz, 1H), 7.90 (dd, \(J = 8.0, 1.5\)Hz, 1H); \(^1\)C NMR (100MHz, CDCl₃) δ 16.79, 59.23, 69.35, 75.20, 116.91, 117.12, 131.35, 134.03, 167.49; IR (CDCl₃) 3508, 3382, 2930, 2855, 1686, 1616, 1589, 1263, 1248, 1109cm⁻¹; HRMS for C₁₁H₁₅NO₃Na (M + Na) (positive ion electrospray) calcd 232.0944, obsd 232.0949.

(d) (2R*)G1-Cl (4a)

A solution of (1S)-2-methoxy-1-methylethyl anthranilate 2 (236mg, 1.1mmol), CH₂Cl₂ (5ml), and Et₃N (310μl, 2.2mmol) was charged with activated sieves (4Å). 4-Chloropyridine-2,6-dicarbonyl chloride (3) (134mg, 0.56mmol) was added to the mixture in three portions over 15 min. The reaction was allowed to stir at rt for 1h. The sieves were removed by filtration, washed with CH₂Cl₂ (10ml), and the solvent was removed under reduced pressure (40 mm Hg). Purification by flash chromatography (SiO₂) with 20% EtOAc : Hex yielded 4a (300mg, 0.5mmol, 92%) as white solid. Mp = 81–84°C (CH₂Cl₂); \(^1\)H NMR (400MHz, CDCl₃) δ 1.15 (d, \(J = 6.5, 6\)H), 3.22 (s, 6H), 3.33 (dd, \(J = 10.6, 6.4\)Hz, 2H), 3.39 (dd, \(J = 10.6, 5.7\)Hz, 2H), 4.99 (dqd, \(J = 6.4, 6.4, 4.3\)Hz, 2H), 7.21 (td, \(J = 7.1, 1.1\)Hz, 2H), 7.64 (td, \(J = 7.0, 1.6\)Hz, 2H), 8.10 (dd, \(J = 8.0, 1.6\)Hz, 2H), 8.43 (s, 2H), 8.65 (dd, \(J = 8.3, 0.8\)Hz, 2H), 12.72 (s, 2H); \(^1\)C NMR (100MHz, CDCl₃) δ 16.26, 58.88, 70.31, 74.55, 118.44, 121.87, 123.70, 125.31, 131.04, 134.05, 139.80, 148.28, 150.68, 161.03, 166.56; IR (CDCl₃) 3692, 2928, 2855, 1683, 1582, 1532, 1453, 1259, 1084 cm⁻¹; HRMS for C₂₉H₃₀ClN₃O₈Na (M + Na) (positive ion electrospray) calcd 606.1614, obsd 606.1594.
A solution of 2-methoxyethylanthranilate 1 (477 mg, 2.4 mmol) and Et₃N (679 μl, 4.9 mmol) in CH₂Cl₂ (6 ml) was charged with activated sieves (4 Å). 4-Chloropyridine-2,6-dicarbonyl chloride (3) (288 mg, 1.2 mmol) was then added to the mixture in three portions over 15 min and the mixture was stirred at rt for 2 h. The sieves were removed by filtration, washed with CH₂Cl₂ (20 ml), and the solvent was removed under reduced pressure (40 mmHg). Purification by flash chromatography (SiO₂) with 20% EtOAc : Hex yielded 6a (615 mg, 1.1 mmol, 91%) as white solid. Mp = 103–107°C (CH₂Cl₂); 1H NMR (400 MHz, CDCl₃) δ 3.29 (s, 6H), 3.52–3.54 (m, 4H), 4.19–4.21 (m, 4H), 7.22 (td, J = 7.6, 0.8 Hz, 2H), 7.66 (td, J = 7.6, 1.6 Hz, 2H), 8.14 (dd, J = 8.0, 1.6 Hz, 2H), 8.44 (s, 2H), 8.75 (dd, J = 8.0, 0.8 Hz, 2H) 12.65 (s, 2H); 13C NMR (100 MHz, CDCl₃) δ 58.85, 64.21, 70.13, 117.66, 121.63, 123.74, 125.51, 131.29, 134.41, 140.03, 148.19, 150.77, 161.11, 167.11; IR (CDCl₃) 3624, 3482, 2945, 2836, 1686, 1581, 1533, 1337, 1077, 1018 cm⁻¹; HRMS for C₂₇H₂₆ClN₃O₈Na (M+Na) (positive ion electrospray) calcd 578.1301, obsd 578.1308.

A solution of (1S)-2-methoxy-1-methylethylanthranilate 2 (1 g, 4.7 mmol), 2-methoxyethylanthranilate 1 (940 mg, 4.7 mmol), and Et₃N (2.6 ml, 18.8 mmol) in CH₂Cl₂ (25 ml) was charged with activated sieves (4 Å). 4-Chloropyridine-2,6-dicarbonyl chloride (3) (1.1 g, 4.7 mmol) was added to the mixture in one portion. The reaction was allowed to stir at rt for 2 h. The sieves were removed by filtration, washed with CH₂Cl₂ (100 ml), and the solvent was removed under reduced pressure (40 mmHg). Purification by pre-absorbing the mixture of products onto silica and flash chromatography (SiO₂) with 20% EtOAc : Hex yielded (2R*)G1-Cl (4a) (522 mg, 0.9 mmol, 19%), (2R)G1-Cl (6a) (832 mg, 1.5 mmol, 32%), and (RR*)G1-Cl (5a) (1.04 g, 1.8 mmol, 39%) as white solid. Mp = 43–46°C (CH₂Cl₂); 1H NMR (400 MHz, CDCl₃) δ 1.16 (d, J = 6.4, 3H), 3.23 (s, 3H), 3.34 (dd, J = 10.8, 4.0 Hz, 1H), 3.40 (dd, J = 10.8, 6.4 Hz, 1H), 3.50–3.52 (m, 2H), 4.18–4.21 (m, 2H), 4.99 (dqd, J = 6.4, 6.4, 4.0 Hz, 1H), 7.22 (td, J = 8.0, 1.6 Hz, 1H), 7.22 (td, J = 7.0, 2.0 Hz, 1H), 7.65 (td, J = 8.0, 0.8 Hz, 1H), 8.11 (dd, J = 8.0, 1.6 Hz, 1H), 8.13 (dd, J = 8.0, 1.6 Hz, 1H), 8.43 (s, 2H), 8.70 (dd, J = 8.0, 0.8 Hz, 1H), 8.71 (dd, J = 8.0, 0.8 Hz, 1H), 12.70 (s, 1H), 12.73 (s, 1H); 13C NMR (100 MHz, CDCl₃) δ 16.32, 58.84, 58.99, 64.17, 70.13, 70.42, 117.93, 118.16, 121.77, 121.80, 123.73, 123.80, 125.47, 131.16, 131.25, 131.29, 134.41, 140.03, 148.18, 150.73, 150.79, 161.11, 166.67, 167.07; IR (CDCl₃) 3356, 3247, 2989, 2933, 2894, 1684, 1582, 1533, 1453, 1309, 1260, 1084 cm⁻¹; HRMS for C₂₈H₂₈Cl₃N₃O₈Na (M + Na) (positive ion electrospray) calcd 592.1457, obsd 592.1462.

Sodium azide (724 mg, 11.1 mmol) was added to a solution of 4a (650 mg, 1.1 mmol) in DMF (6 ml) and heated to 60°C for 12 h. Excess NaN₃ and inorganic salts were removed by filtration and washed with CH₂Cl₂ (10 ml). The solvent was evaporated and the remaining DMF was removed by Kühlerrohr distillation (40°C, 2 mmHg) to yield a thick yellow liquid. The residue was taken up into EtOAc (100 ml), treated with Pd/C (10%, 12 mg, 0.1 mmol) hydrogenated under...
hydrogen (50 psi) for 20 h. The Pd/C was removed by filtration over celite (5 g) and washed with CH₂Cl₂ (50 ml). The solvent was removed under reduced pressure (40 mmHg). Purification by flash chromatography (SiO₂) with 50% EtOAc : Hex afforded pure 4b (621 mg, 1.09 mmol, 99%) as a white solid. Mp = 154–156°C (CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) δ 1.13 (d, J = 6.0 Hz, 6H), 3.21 (s, 6H), 3.33 (dd, J = 10.8, 4.4 Hz, 2H), 3.39 (dd, J = 10.8, 6.0 Hz, 2H), 5.02 (dqd, J = 6.0, 6.0, 4.4 Hz, 2H), 7.18 (td, J = 7.6, 1.2 Hz, 2H), 7.61 (td, J = 7.6, 1.6 Hz, 2H), 7.64 (s, 2H), 8.08 (dd, J = 8.0, 1.6 Hz, 2H), 8.63 (dd, J = 8.0, 1.2 Hz, 2H), 12.62 (s, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 16.37, 58.94, 70.31, 74.66, 109.98, 118.92, 122.06, 123.46, 131.13, 133.90, 140.02, 150.02, 156.14, 162.88, 166.66; IR (CDCl₃) 3509, 3414, 3350, 3234, 2981, 2928, 2875, 1682, 1582, 1524, 1450, 1111, 1080 cm⁻¹; HRMS for C₂₉H₃₂N₄O₈Na (M + Na) (positive ion electrospray) calcd 587.2112, obsd 587.2097.

A solution of 4b (250 mg, 0.44 mmol), and pyridine (0.5 ml) in CH₂Cl₂ (1.5 ml) was charged with activated sieves (4 Å). 4-Chloropyridine-2,6-dicarbonyl chloride (3) (52 mg, 0.22 mmol) was added to the mixture in two portions over 15 min. The reaction was allowed to stir at rt for 12 h. The sieves were removed by filtration, washed with CH₂Cl₂ (10 ml), and the solvent was removed under reduced pressure (40 mmHg). Purification by flash chromatography (SiO₂) with 2% MeOH : CH₂Cl₂ yielded 7a (230 mg, 0.18 mmol, 81%) as white solid. Mp = 285–288°C (CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃, 60°C) δ 1.07 (d, J = 6.5, 12H), 3.26 (s, 12H), 3.26 (dd, J = 10.5, 4.5 Hz, 4H), 3.32 (dd, J = 10.5, 5.0 Hz, 4H), 4.87 (dqd, J = 6.5, 5.0, 4.5 Hz, 4H), 6.92 (t, J = 7.5 Hz, 4H), 7.11 (t, J = 6.0 Hz, 4H), 7.81 (d, J = 7.5 Hz, 4H), 8.06 (s, 2H), 8.09 (s, 4H), 9.28 (s, 4H), 11.18 (s, 2H), 12.72 (s, 4H); ¹³C NMR (100 MHz, CDCl₃, 60°C) δ 16.22, 58.79, 70.37, 74.55, 115.27, 120.05, 122.50, 123.39, 125.15, 130.68, 132.81, 139.22, 147.09, 148.11, 148.71, 149.76, 160.20, 162.04, 166.08; IR (CDCl₃) 3327, 2990, 1674, 1585, 1531, 1450, 1260 cm⁻¹; HRMS for C₆₅H₆₄ClN₉O₁₈Na (M + Na) (positive ion electrospray) calcd 1316.3950, obsd 1316.3930.

A solution of 5b (100 mg, 0.18 mmol) and pyridine (225 μl) in CH₂Cl₂ (675 μl) was charged with activated sieves (4 Å). 4-Chloropyridine-2,6-dicarbonyl chloride (3) (22 mg, 0.09 mmol) was added to the mixture in three portions over 15 min. The reaction was allowed to stir at rt for 12 h. The sieves were removed by filtration, washed with CH₂Cl₂ (10 ml), and the solvent was removed under reduced pressure (40 mmHg). Purification by flash chromatography (SiO₂) with 50% EtOAc : Hex yielded 8a (98 mg, 0.08 mmol, 86%) as a white solid. Mp = 258–260°C (CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃, 60°C) δ 1.12 (d, J = 6.4 Hz, 6H), 3.20 (s, 6H), 3.21 (s, 6H), 3.30 (dd, J = 10.8, 4.4 Hz, 2H), 3.36 (dd, J = 10.8, 5.6 Hz, 2H), 3.45 (t, J = 10.8 Hz, 4H), 4.13 (t, J = 4.8 Hz, 4H), 4.90 (dqd, J = 6.0, 5.6, 4.4 Hz, 2H), 6.91 (t, J = 8.0 Hz, 2H), 6.93 (t, J = 8.0 Hz, 2H), 7.11 (t, J = 8.4 Hz, 2H), 7.13 (t, J = 8.4 Hz, 2H), 7.80 (d, J = 7.6 Hz, 2H), 7.85 (d, J = 7.6 Hz, 2H), 8.03 (s, 4H), 8.21 (s, 2H), 9.24 (s, 2H), 9.28 (s, 2H), 11.14 (s, 2H), 11.97 (s, 2H), 12.32 (s, 2H); ¹³C NMR (100 MHz, CDCl₃, 55°C) δ
16.24, 58.56, 58.84, 64.13, 70.14, 70.38, 74.63, 115.05, 115.41, 119.26, 120.12, 121.93, 122.84, 123.18, 123.57, 125.14, 130.70, 130.73, 132.79, 132.99, 138.87, 139.47, 147.11, 148.03, 148.59, 149.92, 160.22, 161.94, 162.07, 166.30, 166.34; IR (CDCl$_3$) 3330, 3250, 2987, 2933, 2893, 2822, 1674, 1585, 1533, 1452, 1310, 1260, 1134, 1083cm$^{-1}$; HRMS for C$_{63}$H$_{60}$ClN$_9$O$_{18}$Na (M$^+$Na) (positive ion electrospray) calcd 1288.3637, obsd 1288.3637.

(j) ($2R,2R^*$) $G2$-Cl ($9a$)

A solution of $6b$ (73mg, 0.14mmol), $4b$ (77mg, 0.14mmol), and pyridine (525μl) in CH$_2$Cl$_2$ (175μl) was charged with activated sieves (4Å). 4-Chloropyridine-2,6-dicarbonyl chloride ($3$) (33mg, 0.14mmol) was added to the mixture in one portion. The reaction was allowed to stir at rt for 2h. The sieves were removed by filtration, washed with CH$_2$Cl$_2$ (10ml), and the solvent was removed under reduced pressure (40mmHg). Purification by flash chromatography (SiO$_2$) with 50% EtOAc : Hex yielded $9a$ (88mg, 0.07mmol, 50%) as a white solid. Mp = 248–251°C (CH$_2$Cl$_2$); 1H NMR (400MHz, CDCl$_3$, 60°C) δ 1.09 (d, $J = 6.5$Hz, 6H), 3.18 (s, 6H), 3.23 (s, 6H), 3.28 (dd, $J = 10.5$, 4.8Hz, 2H), 3.34 (dd, $J = 10.5$, 5.5Hz, 2H), 3.47 (t, $J = 4.5$Hz, 4H), 4.15 (t, $J = 4.5$Hz, 4H), 4.89 (dqd, $J = 6.5$, 5.5, 4.8Hz, 2H), 6.92 (t, $J = 7.5$Hz, 4H), 7.12 (t, $J = 7.5$Hz, 4H), 7.81 (d, $J = 8.0$Hz, 2H), 8.03 (s, 1H), 8.04 (s, 1H), 8.09 (s, 2H), 8.13 (s, 2H), 9.26 (s, 2H), 9.27 (s, 2H), 11.13 (s, 1H), 11.14 (s, 1H), 12.11 (s, 2H), 12.17 (s, 2H); 13C NMR (100MHz, CDCl$_3$, 55°C) δ 16.26, 58.61, 58.82, 64.15, 70.17, 70.38, 74.57, 115.23, 120.03, 122.27, 123.38, 125.14, 130.67, 130.77, 132.82, 132.96, 139.17, 147.12, 148.04, 148.62, 149.75, 160.22, 161.98, 166.12; IR (CDCl$_3$) 3689, 3329, 3250, 3085, 2929, 1674, 1583, 1520, 1452, 1354, 1310, 1259cm$^{-1}$; HRMS for C$_{63}$H$_{60}$ClN$_9$O$_{18}$Na (M$^+$Na) (positive ion electrospray) calcd 1288.3637, obsd 1288.3637.

(k) 4-Chloropyridine-2,6-dicarboxylic acid monoallyl ester

4-Chloropyridine-2,6-dicarboxylic acid chloride (2.0g, 8.4mmol) ($3$) was dissolved in dry DMF (20ml). A solution of allyl alcohol (490mg, 574μl, 8.4mmol), water (151mg, 151μl, 8.4mmol), and pyridine (8ml) was added to the reaction all in one portion. The reaction was allowed to stir at rt for 3.5h. Saturated aqueous sodium bicarbonate (10ml) was added to the reaction and allowed to stir for 30min. The resulting residue was dissolved in H$_2$O (10ml) and CHCl$_3$ (20ml). The two phases were separated, the organic layer was dried with MgSO$_4$, and the solvent was removed under reduced pressure (40mmHg) to yield 4-chloropyridine-2,6-dicarboxylic acid diallyl ester (442mg, 1.6mmol, 19%). The aqueous layer was acidified to pH 1 with 10% HCl (50ml) and extracted with CHCl$_3$ (4 × 150ml). The combined extracts were dried with MgSO$_4$, the solvent was removed under reduced pressure (40mmHg) and excess DMF was removed under vacuum (2.0mmHg, 12h). The resulting residue was dissolved in CHCl$_3$ (10ml) and washed with 10% HCl (10ml). The organic layer was dried with MgSO$_4$ and the solvent was removed under reduced pressure (40mmHg) to yield the 4-chloropyridine-2,6-dicarboxylic acid monoallyl ester ($10$) (690mg, 1.91mmol, 23%). Mp = 75–77°C (CHCl$_3$); 1H NMR (500MHz, CDCl$_3$) δ 4.94 (d, $J = 6.0$Hz, 2H), 5.39 (dd, $J = 10.6$, 1.2Hz, 1H), 5.48 (dd, $J = 17.2$, 1.2Hz, 1H),...
A stirred solution of 4-chloropyridine-2,6-dicarboxylic acid monoallyl ester 10 (140 mg, 0.5 mmol), dry CH$_2$Cl$_2$ (2.5 ml), and a drop of dry DMF (5 μl) was charged with oxalyl chloride (82 μl, 120 mg, 0.9 mmol) and allowed to react at rt for 1 h. A flow of N$_2$(g) was placed over the solution for 30 min followed by 15 min under vacuum (0.2 mmHg) to remove solvent and excess oxalyl chloride. A mixture of 6b (140 mg, 0.5 mmol) and dry pyridine (500 μl) in dry CH$_2$Cl$_2$ (1 ml) and activated sieves (4 Å) were then treated dropwise over 15 min with the acid chloride in dry CH$_2$Cl$_2$ (1 ml). After an additional 12 h, the mixture was filtered, washed with CH$_2$Cl$_2$ (25 ml), and concentrated in vacuo (40 mmHg). Purification by flash chromatography (SiO$_2$) with 50% EtOAc : Hex afforded 11 (258 mg, 0.3 mmol, 78%) as a white solid. Mp = 180–183°C (CH$_2$Cl$_2$); 1H NMR (400 MHz, CDCl$_3$) δ 3.29 (s, 6H), 3.54 (t, $J = 4.8$ Hz, 4H), 4.22 (t, $J = 4.8$ Hz, 4H), 5.00 (dd, $J = 6.0$, 0.8 Hz, 2H), 5.43 (d, $J = 10.4$ Hz, 1H), 5.53 (dd, $J = 17.0$, 0.8 Hz, 1H), 6.12 (ddt, $J = 17.0$, 10.4, 6.0 Hz, 1H), 7.21 (t, $J = 7.6$ Hz, 2H), 7.24 (t, $J = 7.6$ Hz, 2H), 8.14 (d, $J = 8.0$ Hz, 2H), 8.33 (d, $J = 2.0$ Hz, 1H), 8.52 (d, $J = 2.0$ Hz, 1H), 8.80 (d, $J = 8.0$ Hz, 2H), 8.85 (s, 2H), 10.39 (s, 1H), 12.69 (s, 2H); 13C NMR (100 MHz, CDCl$_3$) δ 58.84, 64.18, 67.21, 70.16, 114.91, 117.67, 120.00, 121.65, 123.49, 126.32, 128.58, 131.20, 131.31, 134.34, 140.26, 147.60, 147.89, 148.13, 150.15, 150.96, 160.84, 161.95, 162.81, 167.13; IR (CDCl$_3$) 3348, 3254, 2932, 2891, 1686, 1583, 1516, 1454, 1311, 1261, 1131, 1084 cm$^{-1}$; HRMS for C$_{37}$H$_{34}$ClN$_5$O$_{11}$Na (M + Na) (positive ion electrospray) calcd 782.1841, obsd 782.1834.

(m) Allyl deprotection of 11

A solution of formic acid (26 μl, 31 mg, 0.68 mmol) and Et$_3$N (118 μl, 86 mg, 0.85 mmol) was added to a premixed solution of palladium (II) acetate (2.0 mg, 0.009 mmol), triphenylphosphine (4.4 mg, 0.017 mmol) and dry THF (400 μl). After stirring at rt for 5 min the solution was added to a mixture of 11 (258 mg, 0.34 mmol) in dry THF (200 μl). After 1 h at rt, the suspension became homogeneous and then over an additional hour, a white solid was formed. The solid was filtered and washed with THF (10 ml) and 10% HCl (20 ml) to afford 11-CO$_2$H as a white solid (189 mg, 0.26 mmol, 86%). Mp = 126–129°C (MeOH); 1H NMR (400 MHz, DMSO-$d_6$, 90°C) δ 3.18 (s, 6H), 3.49 (t, $J = 4.8$ Hz, 4H), 4.16 (t, $J = 4.8$ Hz, 4H), 7.32 (td, $J = 7.6$, 1.2 Hz, 2H), 7.75 (td, $J = 7.8$, 1.6 Hz, 2H), 8.06 (dd, $J = 7.8$, 1.2 Hz, 2H), 8.36 (d, $J = 2$ Hz, 1H), 8.44 (d, $J = 1.6$ Hz, 1H), 8.61 (d, $J = 8.4$ Hz, 2H), 12.42 (s, 2H), 11.48 (s, 1H), 8.93 (s, 2H); 13C NMR (125 MHz, DMSO-$d_6$, 90°C) δ 58.42, 64.42, 70.02, 115.72, 119.19, 122.15, 124.46, 126.32, 127.70, 131.41, 134.54, 139.73, 146.60, 147.19, 149.23, 149.39, 150.63, 150.71, 162.07, 162.57, 167.03; IR (KBr) 3462, 3342, 3242, 2954, 1733, 1681, 1580, 1516, 1450, 1263, 1221, 1002, 905, 768 cm$^{-1}$; HRMS for C$_{34}$H$_{30}$ClN$_5$O$_{11}$Na (M + Na) (positive ion electrospray) calcd 742.1841, obsd 742.1834.
A stirred solution of $11\text{-CO}_2\text{H}$ (26 mg, 0.03 mmol) and a drop of dry DMF (2 μl) in dry CH$_2$Cl$_2$ (170 μl) was charged with oxalyl chloride 2.0 M/CH$_2$Cl$_2$ (34 μl, 9 mg, 0.07 mmol) and stirred at rt for 2.5 h, then concentrated. CH$_2$Cl$_2$ (200 μl) was added to the resultant acid chloride followed by $5b$ (19 mg, 0.03 mmol) dissolved in dry CH$_2$Cl$_2$ (125 μl) and dry pyridine (25 μl). After 2 h, the solution was washed with 10% HCl (0.5 ml), and the aqueous layer was extracted with CH$_2$Cl$_2$ (1 × 0.5 ml). The organic extracts were combined, dried with MgSO$_4$, and concentrated in vacuo (40 mmHg). Purification by recrystallization from EtOAc afforded $12a$ as a white crystalline solid (24 mg, 0.02 mmol, 57%). Mp = 200–204°C (EtOAc); $^1$H NMR (400 MHz, CDCl$_3$, 60°C) δ 1.13 (d, $J = 6.0$ Hz, 3H), 3.20 (s, 3H), 3.23 (s, 9H), 3.30 (dd, $J = 10.5$, 4.5 Hz, 1H), 3.37 (dd, $J = 10.5$, 5.5 Hz, 1H), 3.45–3.49 (m, 6H), 4.13–4.17 (m, 6H), 4.91 (dqd, $J = 6.0$, 5.5, 4.5 Hz, 1H), 6.90–6.95 (m, 4H), 7.17 (br, s, 4H), 7.80 (d, $J = 8.0$ Hz, 1H), 7.84 (d, $J = 7.5$ Hz, 3H), 8.02 (s, 2H), 8.14 (br, s, 3H), 8.20 (br, s, 1H), 9.24 (s, 1H), 9.25 (s, 2H), 9.28 (s, 1H), 11.12 (s, 2H), 11.97 (s, 1H), 12.11 (br, s, 2H), 12.33 (br, s, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$, 55°C) δ 16.25, 31.85, 58.55, 58.59, 58.84, 64.15, 70.17, 70.38, 74.64, 115.11, 115.20, 115.21, 115.26, 118.31, 119.37, 121.83, 122.16, 122.24, 122.26, 123.21, 123.37, 123.57, 123.64, 125.16, 130.73, 130.78, 131.16, 132.81, 132.98, 134.07, 139.14, 139.46, 139.86, 147.14, 148.03, 148.60, 149.62, 149.77, 149.92, 160.24, 160.27, 161.93, 161.97, 166.31, 166.38, 166.58, 167.02; IR (CDCl$_3$) 3328, 3086, 2932, 2892, 1709, 1676, 1584, 1531, 1452, 1261 cm$^{-1}$; HRMS for C$_6$H$_{58}$ClN$_9$O$_{18}$Na (M + Na) (positive ion electrospray) calcd 1274.3486, obsd 1274.3466.

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References


