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Preparation of macrocyclic and 'C-clamp' dicarboxylate compounds

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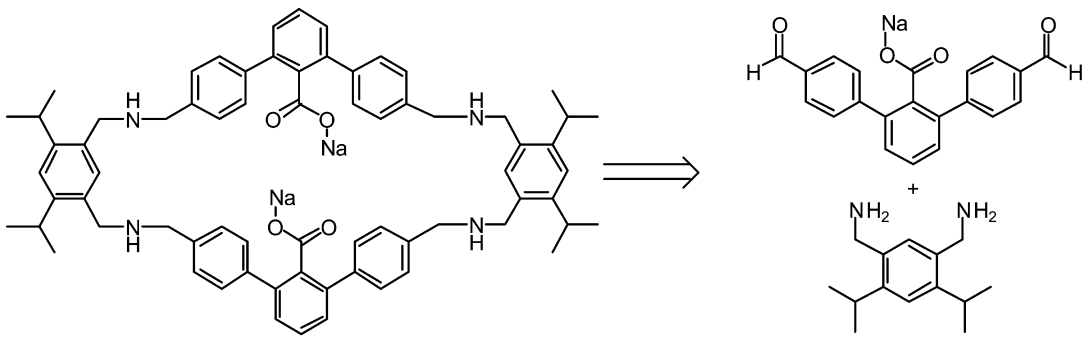
Abstract—Reductive amination of bis-1,3-(aminomethyl)-4,6-diisopropylbenzene with the 4,4″-dicarboxaldehyde of 1,1′:3′,1″-terphenyl-2′-carboxylic acid, sodium salt, afforded a novel macrocyclic dicarboxylate compound in 71% isolated yield. Purification was effected by filtration in a single step. The synthesis and characterization of two new 'C-clamp' compounds, which also contain two *m*-terphenyl carboxylates but exhibit much greater degree of flexibility, are also described. These compounds are of interest as potential ligands or for host–guest chemistry.

1. Introduction

Supramolecular chemists have prepared a large array of macrocyclic host compounds, beginning with crown ethers[1] and cryptands[2,3] in the late sixties and extending into compounds with almost all known functional groups.[4] There are relatively few examples in the literature of macrocyclic compounds with at least two carboxylic acid groups oriented *endo* within their cavity.[5–8] The paucity of macrocycles with *endo*-oriented carboxylates has been ascribed to the difficulty of balancing the building of a macrocycle of sufficient size to allow the desired orientation of the carboxylates while simultaneously keeping the macrocycle rigid enough to enforce an *endo*-orientation over transannular, intermolecular interactions. Such would result in the formation of hydrogen bonded polymers instead of discrete complexes.[6] The ability to prepare macrocyclic multicarboxylate compounds is desirable because the carboxylic acid is a versatile functional group that can be used to form hydrogen bonds to guest molecules or to ligate transition metals towards such ends as modeling the active sites of metalloenzymes and proteins.

Historically there have been two synthetic strategies for preparing *endo* oriented multicarboxylate macrocycles: four component Williamson ether syntheses[6–8] and two component *N*-alkylation reactions.[5] All of these strategies suffer from low cyclization yields, 10 to 50% under the best circumstances, and the need for column chromatography to purify the macrocycle. We wish to report here a new type of macrocyclic dicarboxylate compound (**1**, Scheme 1) prepared by reductive amination in isolated yields of 70%, the purification of which requires nothing more complicated than filtration.



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Scheme 1.

Keywords: macrocycle; host–guest chemistry; dicarboxylate.

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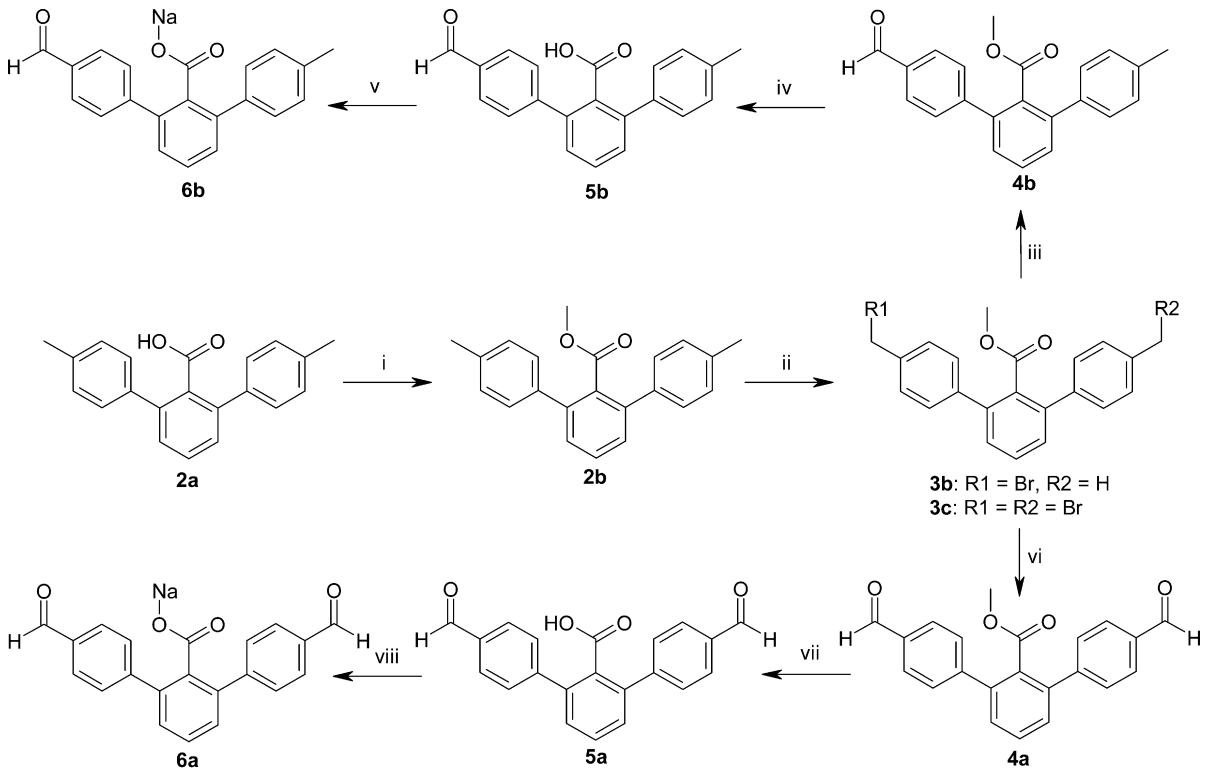


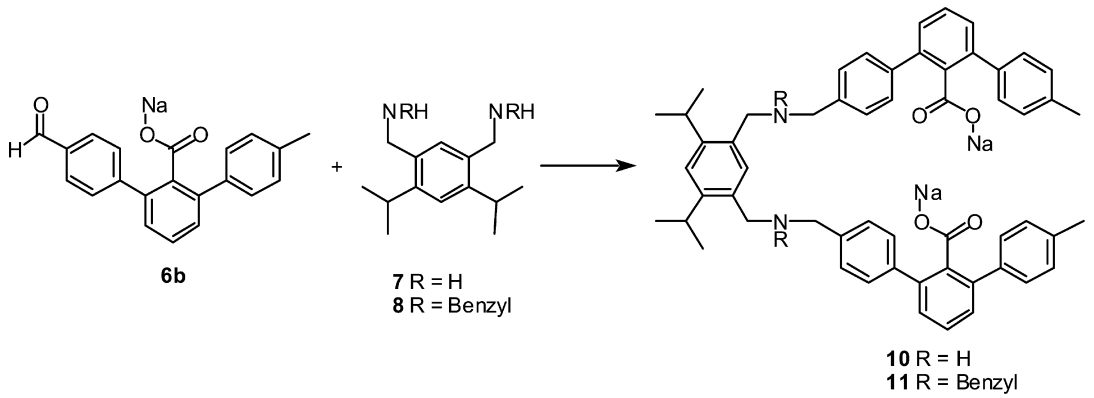
Scheme 2. (i) (1) $(MeO)_2SO_2$, K_2CO_3, Acetone, 94%; (2) H_2O. (ii) NBS, benzoyl peroxide, CCl_4. (iii) (1) DMSO, $NaHCO_3$; (2) H_3O^+, 18% (2 steps). (iv) (1) LiI, Pyridine; (2) H_3O^+, 80%. (v) NaOH, MeOH, 96%. (vi) (1) DMSO, $NaHCO_3$; (2) H_3O^+, 39% (2 steps). (vii) (1) LiI, Pyridine; (2) H_3O^+, 96%. (vii) NaOH, MeOH, 99%.

2. Results and discussion

A retrosynthetic analysis (Scheme 1) of macrocycle **1** shows that this compound can be assembled from two starting materials, a diamine and a dialdehyde, which, when coupled via reductive amination would result in the desired product. Several other groups have used imine formation to prepare macrocycles[9–11] and conversion of imines to amines is a straightforward process.[12] Our laboratory has published a series of papers in which *m*-terphenyl carboxylates such as **2a** (Scheme 2) were used as ligands for transition metals including iron, nickel, cobalt, and zinc.[13,14] The *m*-terphenyl carboxylate iron complexes have provided insights into the chemistry of non-heme diiron metalloenzymes such as the hydroxylase component of soluble methane monooxygenase (sMMO) and the R2 subunit of ribonucleotide reductase (RNR-R2). Transition metal complexes of ligands like **1** could be of further use in studies of this kind.

The compound 2,6-di(*p*-tolyl)benzoic acid,[15] **2a**, has previously been used as a starting material to prepare 4,4″-bis(bromomethyl)-[1,1′:3′,1″-terphenyl]-2′-carboxylic acid, **3a**, which was a component of a Williamson ether synthesis to prepare thioether linked dicarboxylic macrocycles.[7] Benzylic bromides can be oxidized to aldehydes using the Kornblum oxidation,[16] but test reactions showed the free acid of **3a** to be incompatible with this reaction. Therefore, we elected first to protect the carboxylic acid as its methyl ester using dimethyl sulfate and potassium carbonate in acetone to form **2b** in high yield, Scheme 2. The ester **2b** was then brominated using two equivalents of NBS and a catalytic amount of benzoyl peroxide in CCl_4. The bromination reaction resulted in a mixture of six products, where each of the two benzylic positions of **2b** were either unreacted, brominated, or dibrominated, and this mixture of products proved difficult to separate. The crude reaction mixture was carried on to the next step, where a Kornblum oxidation of **3c** with DMSO and sodium bicarbonate resulted in the selective oxidation of the monobrominated benzylic positions to the aldehyde following an acidic workup.[16] After column chromatography the ester dialdehyde **4a** was isolated along with small amounts of the ester monoaldehyde **4b**, Scheme 2. The yield of **4b** could be greatly increased by using a single equivalent of NBS in the bromination step (See Section 4). Saponification of **4a** and **4b** to obtain the free acids **5a** and **5b**, respectively, was accomplished by using LiI in pyridine followed by an acidic workup.[17] Finally, the sodium salts **6a** and **6b** were prepared by reacting **5a** or **5b** with NaOH in MeOH.

The diamine bis-1,3-(aminomethyl)-4,6-diisopropylbenzene, **7**,[18,19] was chosen because its isopropyl groups offered the dual advantage of ^1H NMR spectroscopic handles and increased solubility of these highly aromatic complexes in organic solvents.[20] Diamine **7** was further modified by reductive amination using benzaldehyde and sodium triacetoxyborohydride to give the benzylated compound **8**.[12] Using a benzylated diamine allows one to prepare compounds linked by tertiary instead of secondary amines, Scheme 3. The use of sterically hindered tertiary amines in macrocyclic compounds could prove valuable if they are employed as models for protein and enzyme active sites, because they would provide better steric protection to the metal centers bound inside their pockets. In addition, the



Scheme 3.

presence of the third alkyl group provides a means of introducing additional functionalities for metal coordination or substrate activation.

To test whether amine and aldehyde condensation reactions are a viable method for bringing four components together to form macrocyclic dicarboxylates, we first combined **7** and **4a** under high dilution conditions in MeOH using a syringe pump. The resulting tetraimine diester macrocycle **9**, the dimethyl ester of **1**, was insoluble in MeOH and was isolated by filtration in 57% yield. Compound **9** has been characterized by ^{1}H NMR, FTIR, ESIMS and a single crystal X-ray diffraction study and all data are consistent with its postulated structure. The X-ray diffraction study in conjunction with the preparation of physical CPK models shows that macrocycle **9** is a relatively rigid compound due

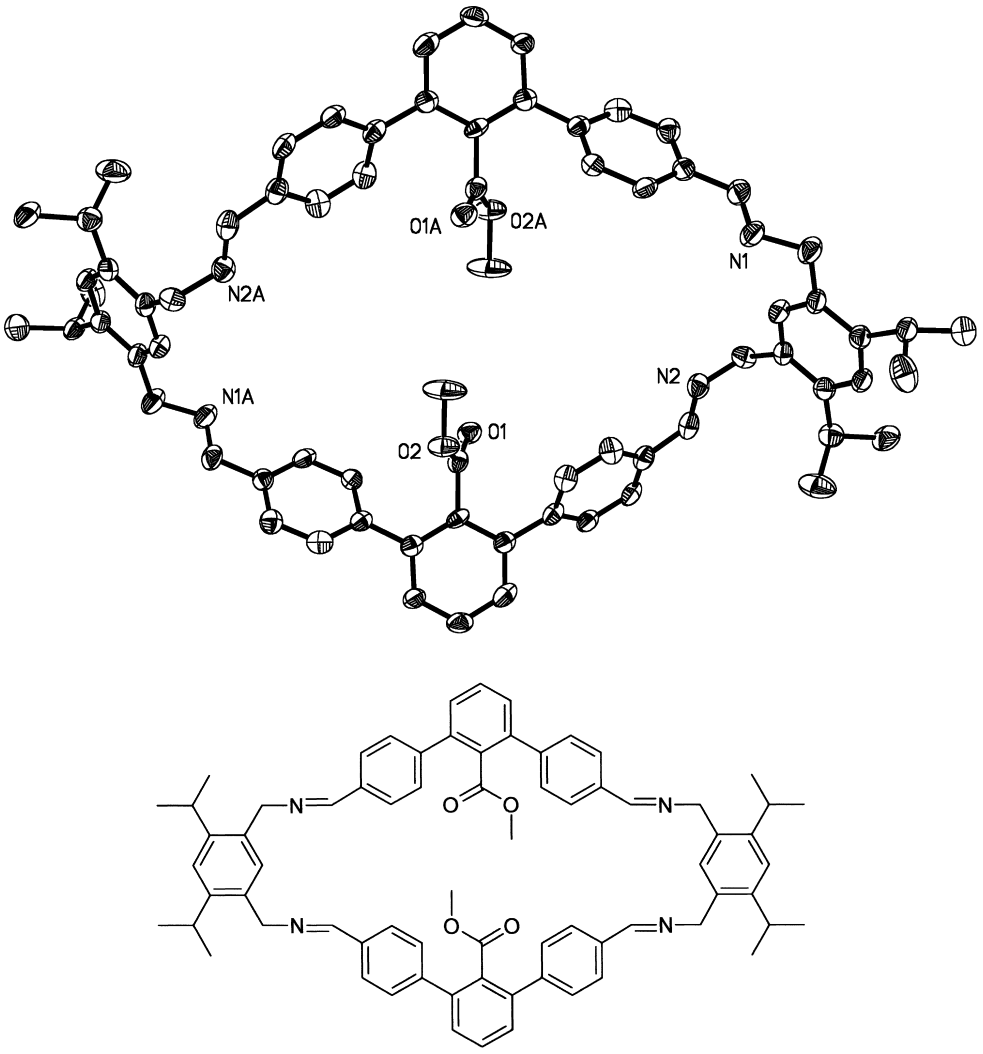


Figure 1. Structure of **9**. Top: solid state structure of **9**·2MeOH showing thermal ellipsoids drawn at 50% probability. Solvent molecules and hydrogen atoms are omitted for clarity. Bottom: CHEMDRAW version of the molecule.

to the four imines that link the components and hold the two *m*-terphenyl carboxylate groups in a parallel planar fashion 3.1 Å apart from one another, Figure 1. It is likely that the rigidity of this structure is one of the factors that leads to its relatively high yielding formation instead of oligomeric and polymeric products, which are commonly encountered in the preparation of organic macrocycles.

Macrocycle **1** is prepared in a similar fashion to **9** by combining **7** and **6a** in a 1:1 fashion under high dilution conditions using a syringe pump. Evaporation of the solvent from the crude reaction mixture and reaction of the resulting oil with $NaBH(OAc)_3$ in 1,2-dichloroethane results in reduction of the imines and formation of the desired macrocycle **1**. The final product is isolated under basic conditions; compound **1** is insoluble in both the CH_2Cl_2 and H_2O used to extract both water soluble and organic impurities from the reaction mixture, allowing isolation by filtration in 70% yield over the two steps. The relatively high yield and ease of purification make this synthetic methodology a superior approach for preparing this class of compounds. Macrocycle **1** has been characterized by ^1H and ^{13}C NMR, FTIR, and ESIMS spectroscopy, and the data are all consistent with its postulated structure. For example, in the ^1H NMR of **1**, the isopropyl groups are represented by a clean doublet at δ 1.21, J=6.8 Hz integrating as 24 protons. Unlike diester **9**, which is soluble in a variety of solvents such as THF, CH_2Cl_2, $CHCl_3$ and MeOH, dicarboxylate **1** is only soluble in more polar solvents such as MeOH or EtOH.

Macrocycles such as **1** are often prepared for use as host compounds for guests of the appropriate size and charge, but they might also serve as ligands for transition metals. For either application it might be useful to remove one of the diamine linkers from **1** in order to prepare a 'C-clamp' type analog. C-clamp compounds would still have two carboxylates capable of forming hydrogen bonds and or ligating to transition metals, but would be considerably more flexible. C-clamp molecules would allow one to investigate the relative contributions of the macrocyclic and chelating effects for any binding event, and their increased flexibility might also allow one to form host–guest complexes with larger molecules. Toward this goal, we combined monoaldehyde **6b**, which was prepared from **4b** isolated in small amounts while purifying **4a** and the synthesis of which was subsequently optimized by reacting one equivalent of NBS with **2b**, with **7**. Reductive amination[12] conditions afforded the C-clamp compound **10**, which contains two *m*-terphenyl carboxylates linked by one aromatic diamine linker, Scheme 3. By substituting the benzylated diamine **8** for **7**, the C-clamp ligand **11** was prepared. Compound **11** contains tertiary amines instead of the secondary amines of **10**, which might provide a better hydrophobic pocket around transition metals bound to the two carboxylates.

3. Conclusion

In conclusion, we have synthesized a new macrocyclic dicarboxylate compound using reductive amination, a procedure that results in higher yields and easier purification than previous synthetic examples for this class of compounds. In addition we have prepared and characterized two new 'C-clamp' compounds, which also contain two *m*-terphenyl carboxylates but generate a compound with a much greater degree of flexibility than **1**. Although these new compounds have not been characterized by combustion analysis, all of them have been examined by multiple analytical techniques and all data are consistent with their postulated structures. Both the macrocyclic and C-clamp molecules are of interest as possible hosts or as ligands for transition metal ions.

4. Experimental

4.1. General considerations

Compounds 4,4″-dimethyl[1,1′:3′,1″]terphenyl-2′-carboxylic acid **2a**,[15] methyl-4,4″-dimethyl[1,1′:3′,1″]terphenyl-2′-carboxylate **2b**,[7] methyl-4,4″-bis(bromomethyl)-[1,1′:3′,1″]-terphenyl-2′-carboxylate **3b**,[7] and bis-1,3-(aminomethyl)-4,6-diisopropylbenzene **7**[18,19] were prepared using methods reported in the literature. All other chemicals were purchased from commercial sources and used as received. Any air sensitive compounds were either handled using standard Schlenk techniques under argon or in a MBraun or Vacuum-Atmospheres glovebox under nitrogen. Reactions requiring a syringe pump made use of a kdScientific model 200 double barrel instrument. For manipulations sensitive to moisture or air, solvents were dried and purified either by standard methods[21] or, in the case of pentane, THF and Et_2O, by passage through alumina columns under nitrogen.

4.2. Physical methods

NMR spectroscopic data were collected on either a Unity 300 MHz, Varian 300 MHz, or Bruker 400 MHz spectrometer and referenced to residual peaks in the deuterated solvents. MS data were obtained on a Bruker Daltonics APEX II 3T FT-ICR-MS instrument with ESI and EI/CI sources. FTIR spectra were recorded on a Bio Rad FTS-135 instrument with WIN-IR software.

4.3. X-Ray structure determination

The structure of **9**·2MeOH was obtained by mounting a crystal covered in paratone-N oil on the tip of a quartz capillary and transferring it to a Bruker (formally Siemens) SMART/APEX X-ray diffractometer.[22] The crystal was cooled to −100°C under a stream of nitrogen. Intensity data were collected during exposure to Mo Kα radiation (λ 0.71073 Å). All data collection and reduction protocols are described elsewhere.[23] The structure was solved by direct methods and difference Fourier methods and refined by full-matrix least-squares methods (SHELXTL).[24] The two solvent molecules were disordered and refined isotropically without hydrogen atoms. All other non-hydrogen atoms in this structure were refined anisotropically. The structure was checked for higher symmetry using the program PLATON.[25] Hydrogen atoms were placed in calculated positions with isotropic thermal parameters set to either 1.5 or 1.2 times the thermal parameter of the carbon to which they are attached (methyl vs all other hydrogen atoms, respectively). Crystallographic data (excluding structure

factors) for **9**·2MeOH have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 200141. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44-1223-336033 or email: deposit@ccdc.cam.ac.uk].

Crystal Data for **9**·2MeOH: $C_{74}H_{72}N_4O_6$, FW=1113.36 g/mol, triclinic, space group $P\bar{1}$, a=7.865 (3) Å, b=11.261 (4) Å, c=18.310 (6) Å, α=78.759 (7)°, β=83.886 (6)°, γ=76.571 (7)°, V=1544.0 (9) Å^3, Z=1, T=173 (2) K, absorption coefficient=0.076 mm^{-1}, θ range for data collection=1.89 to 28.28°, reflections collected=13755, independent reflections=6997 [R(int)=0.0909], data/restraints/parameters=6997/0/379, R1=0.0591, $wR2$=0.1366, largest differntial peak and hole=0.681 and −0.200 e Å^{-3}, respectively.

4.4. Synthetic work

4.4.1. Synthesis of 4-methyl-4″-bromomethyl[1,1′;3′,1″]-terphenyl-2′-carboxylate (3b). The dibrominated *m*-terphenylcarboxylate **3c** is prepared by radical bromination of **2b** using two equivalents of NBS in CCl_4.[7] Preparation of **3b** was optimized by a modification of the literature procedure. Specifically, a portion of **2b** (2.00 g, 6.32 mmol) was dissolved in 50 mL of CCl_4 and brought to reflux. NBS (1.18 g, 6.61 mmol) was added in four equal portions along with a catalytic amount of benzoyl peroxide (~1–2 mg) over a four hour period and then the reaction was refluxed for one additional hour. After the reaction mixture cooled, it was filtered and the solvent removed in vacuo. Radical bromination of the benzylic positions of **2b** resulted in a mixture of products. Examining by ^{1}H NMR a representative reaction where one equivalent of NBS was used indicated that 2.6% of the benzylic positions were dibrominated, 47.7% were monobrominated, and 49.7% were unreacted. If one ignores the dibrominated benzylic positions and assumes a statistical mixture of the three products possible from the monobrominated and unreacted benzylic positions of the *m*-terphenyl carboxylates (**2b**, **3b**, and **3c**), the distribution of products would be ~25% **2b**, ~25% **3c**, and ~50% **3b**. Separation of these products proved difficult, so the crude reaction mixtures were carried on to the next step and purified after oxidation of the monobrominated benzylic positions to the aldehyde. Examining by ^{1}H NMR a representative reaction where two equivalents of NBS were used indicated that 7% of the benzylic positions were dibrominated, 83% were monobrominated, and 10% were unreacted.

4.4.2. Synthesis of methyl-4,4″-diformyl[1,1′;3′,1″]terphenyl-2′-carboxylate (4a). A portion of crude **3c** (1.024 g, 2.159 mmol) was combined with $NaHCO_3$ (3.628 g, 43.18 mmol) in approximately 75 mL of DMSO under argon in a 200 mL Schlenk flask. The reaction mixture was heated to 90°C for 3 h and then allowed to cool to room temperature. Addition of 150 mL of 4N HCl resulted in the precipitation of an orange oily solid, which was separated by decanting off the solvent. The oily solid was then redissolved in CH_2Cl_2, washed with H_2O, dried with $MgSO_4$, and the CH_2Cl_2 was then removed by in vacuo. Chromatography through a 3.5×15 cm column of silica gel using EtOAc/hexanes (1:3) as the eluent resulted in the collection of four fractions. The major fraction was the third band, which contained 279 mg of the desired product. Compound **4a** was isolated as a white powder in 39% yield calculated from **2b**. The other fractions were mixtures of over- and under-brominated products carried through from the previous reactions, which were not oxidized to the desired dialdehyde. ^{1}H NMR ($CDCl_3$): δ 10.08 (s, 2H, C(O)*H*), 7.95 (d, J=8.7 Hz, 4H, C*H*), 7.55–7.65 (m, 5H, C*H*), 7.46 (d, J=7.5 Hz, 2H, C*H*), 3.39 (s, 3H, CO_2CH_3); ^{13}C NMR ($CDCl_3$): δ 192.3, 169.3, 146.6, 139.7, 135.7, 132.7, 130.1, 130.0, 129.7, 129.3, 52.5; ESIMS (*m*/*z*): $[M]^+$ Calcd for $C_{22}H_{16}O_4$, 344.1043; Found, 344.1033; mp 156–157.5°C.

4.4.3. Synthesis of methyl-4-formyl-4″-methyl[1,1′;3′,1″]-terphenyl-2′-carboxylate (4b). Compound **4b** was prepared from **3b** using the same conditions as for preparation of **4a**. Compound **4b** was isolated as a white powder in 18% yield. ^{1}H NMR ($CDCl_3$): δ 10.07 (s, 1H, C(O)*H*), 7.94 (d, J=8.2 Hz, 2H, C*H*), 7.58 (d, J=8.2 Hz, 2H, C*H*), 7.54 (d, J=7.7 Hz, 1H, C*H*), 7.44 (dd, J=7.7, 1.1 Hz, 1H, C*H*), 7.38 (dd, J=7.6, 1.1 Hz, 1H, C*H*), 7.30 (d, J=8.1 Hz, 2H, C*H*), 7.23 (d, J=8.0 Hz, 2H, C*H*), 3.41 (s, 3H, OCH_3), 2.41 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$): δ 192.2, 169.9, 147.1, 140.9, 139.2, 137.7, 137.4, 135.6, 132.8, 130.0, 129.9, 129.8, 129.4, 129.3, 128.6, 128.4, 52.2, 21.4; ESIMS (*m*/*z*): M^+ Calcd for $C_{22}H_{18}O_3$, 330.1256; Found, 330.1242; mp 115.5–117°C.

4.4.4. General method for the synthesis of 4,4″-diformyl-[1,1′;3′,1″]terphenyl-2′-carboxylic acid (5a) and 4-formyl-4″-methyl[1,1′;3′,1″]terphenyl-2′-carboxylic acid (5b). A portion of the methyl ester **4a** (0.972 g, 2.82 mmol) was combined with 7.5 equiv. of LiI (2.83 g, 21.2 mmol) in 40 mL of anhydrous pyridine and refluxed in the dark under Ar for five days. The reaction mixture was then allowed to cool and poured into 300 mL of ice cold 6N HCl. The organic products were extracted with 100 mL of $CHCl_3$, washed three times with 100 mL of H_2O, dried over $MgSO_4$, and then the solvents were removed in vacuo. Drying under vacuum overnight resulted in the isolation of **5a** as a brown solid in 80% yield. A similar reaction starting with **4b** resulted in the isolation of **5b** in 94% yield. **5a**: ^{1}H NMR ($CDCl_3$): δ 10.06 (s, 2H, C(O)*H*), 7.92–7.89 (m, 4H, C*H*), 7.64–7.58 (m, 5H, C*H*), 7.40–7.43 (m, 2H, C*H*); ^{13}C NMR (CD_3OD): δ 192.2, 171.6, 146.4, 139.5, 135.6, 131.5, 130.2, 13.0, 129.7, 129.3. **5b**: ^{1}H NMR ($CDCl_3$): δ 10.07 (s, 1H, C(O)*H*), 8.00 (d, 2H, C*H*), 7.53–7.59 (m, 3H, C*H*), 7.44 (d, 1H, C*H*), 7.29–7.39 (m, 3H, C*H*), 7.23 (d, 2H, C*H*), 2.41 (s, 3H, CH_3); ^{13}C NMR (CD_3OD): δ 193.8, 173.2, 148.5, 141.5, 139.9, 138.9, 138.7, 137.1, 135.1, 131.0, 130.7, 130.7, 130.5, 130.1, 129.7, 129.6.

4.4.5. General synthesis of sodium 4,4″-diformyl-[1,1′;3′,1″]terphenyl-2′-carboxylate (6a) and sodium 4-formyl-4″-methyl[1,1′;3′,1″]terphenyl-2′-carboxylate (6b). A portion of **5a** (277 mg, 0.839 mmol) was combined with 1 equiv. of NaOH (33.5 mg, 0.839 mmol) in 25 mL of MeOH and stirred for 0.5 h at 40°C. Removal of the solvent in vacuo resulted in the isolation of 284 mg of **6a** (96%) as a beige solid. A similar reaction starting with **5b** afforded **6b** in 99% yield. **6a**: ^{1}H NMR ($CDCl_3$): δ 10.01 (s, 2H, C(O)*H*),

7.93–7.78 (m, 8H, C*H*), 7.45–7.38 (m, 3H, C*H*); ^{13}C NMR (CD_3OD): δ 194.3, 176.8, 149.8, 142.4, 138.6, 136.8, 130.9, 130.7, 130.6, 128.4; FTIR (KBr, cm^{-1}): 3427 (br), 3286 (br), 3174 (br), 3051 (w), 2919 (w), 2842 (w), 2736 (C(O)H, w), 1701 (C(O)H, s), 1605 (s), 1567 (s), 1515 (m), 1448 (m), 1410 (s), 1386 (s), 1307 (w), 1212 (m), 1169 (m), 1018 (w), 844 (m), 828 (m), 805 (s), 771 (m); ESIMS (*m/z*): $[M-Na]^-$ Calcd for $C_{21}H_{13}O_4$, 329.0808; Found, 329.0802. **6b**: ^{1}H NMR (CD_3OD): δ 10.00 (s, 1H, C(O)*H*), 7.93 (d, 2H, C*H*), 7.63 (d, 2H, C*H*), 7.52 (d, 2H, C*H*), 7.35–7.41 (m, 3H, C*H*), 7.20 (d, 2H, C*H*), 2.36 (s, 3H, CH_3); FTIR (KBr, cm^{-1}): 3655 (m), 3380 (br), 3206 (w), 3033 (w), 2963 (w), 2844 (w), 2727 (C(O)H, w), 1687 (C(O)H, s), 1604 (s), 1572 (s), 1452 (m), 1417 (m), 1377 (m), 1306 (m), 1213 (m), 1168 (m), 1107 (w), 1014 (w), 850 (m), 802 (m), 754 (m), 542 (m); ESIMS (*m/z*): $[M+Na]^+$ Calcd for $C_{21}H_{15}O_3Na_2$, 361.0811; Found, 361.0808.

4.4.6. Synthesis of benzyl[5-(benzylaminomethyl-2,4-diisopropylbenzyl)]amine (8). A portion of **7** (3.803 g, 17.2 mmol) was combined with 2 equiv. of benzaldehyde (3.650 g, 34.4 mmol) and 2.6 equiv. of $NaHB(OAc)_3$ (9.475 g, 44.7 mmol) in 100 mL of 1,2-dichloroethane and stirred overnight under Ar. The reaction mixture was then quenched with 100 mL of NaOH, followed by extraction of the organic components with CH_2Cl_2 (3×20 mL), washing of the organic layer with H_2O (20 mL), and drying over $MgSO_4$. The resulting oil was dried on a vacuum line for 1 h. Column chromatography through silica gel using EtOAc/hexanes/triethylamine (16:8:1) resulted in the isolation of 0.903 g (13%) of the desired product as a clear oil. ^{1}H NMR ($CDCl_3$): δ 7.28–7.44 (m, 12H, C*H*), 3.93 (s, 4H, CH_2), 3.85 (s, 4H CH_2), 3.25 (sept, J=5.2 Hz, 2H, C*H*(CH_3)$_2$), 1.58 (s, 2H, N*H*), 1.30 (d, J=6.8 Hz, 12H, CH(CH_3)$_2$); ^{13}C NMR (CD_3Cl): δ 146.2, 140.6, 134.1, 130.1, 128.4, 128.2, 126.9, 122.4, 54.1, 50.7, 28.8, 24.5; ESIMS (*m/z*): $[M+H]^+$ Calcd for $C_{28}H_{37}N_2$, 401.2951; Found, 401.2947.

4.4.7. Synthesis of 9. A portion of **4a** (0.100 g, 0.305 mmol) was dissolved in a mixture of 40 mL of MeOH and 10 mL of CH_2Cl_2 and loaded into a 50 mL syringe. A portion of **7** (0.067 g, 0.305 mmol) was dissolved in 50 mL of MeOH and loaded into a second 50 mL syringe. With the use of a syringe pump the two reactants were added simultaneously to a 1000 mL round bottom flask containing 250 mL of MeOH at a rate of 2 mL/h. Upon the completion of the addition (25 h), the mixture was allowed to stir for an additional 6 h. The resulting reaction mixture contained a white precipitate that was collected by filtration and dried on filter paper to yield 0.0603 g of **9** as a white powder. Removing half of the remaining reaction mixture in vacuo and allowing the mixture to stand overnight yielded a second crop of 0.0285 g of **9** (total yield, 57%). Recrystallization by vapor diffusion of pyridine into a solution of **9** in MeOH resulted in the isolation of colorless blocks, which were analyzed by X-ray crystallography. ^{1}H NMR ($CDCl_3$): δ 8.35 (s, 4H, N=C*H*), 7.74 (d, J=6.8 Hz, 8H, C*H*), 7.4 (m, 4H, C*H*), 7.29–7.31 (m, 12H, C*H*), 7.18 (s, 2H, C*H*), 4.90 (s, 8H, NCH_2), 3.31 (quint, J=6.6 Hz, 4H, C*H*(CH_3)$_2$), 3.27 (s, 6H, CO_2CH_3), 1.31 (d, J=6.6 Hz, 24H, CH(CH_3)$_2$); FTIR (KBr, cm^{-1}): 3471 (br), 3353 (br), 2961 (s), 2868 (m), 1724 (s), 1643 (m), 1609 (m), 1586 (w), 1563 (w), 1458 (m), 1402 (w), 1308 (w), 1265 (s), 1120 (m), 1067 (m), 894 (w), 805 (m), 775 (w), 545 (w); ESIMS (*m/z*): $[M+H]^+$ Calcd for $C_{72}H_{73}O_4N_4$, 1057.5626; Found, 1057.5621.

4.4.8. Synthesis of 1. A portion of **6a** (0.257 g, 0.729 mmol) was dissolved in a mixture of 40 mL of MeOH and 10 mL of CH_2Cl_2 and loaded into a 50 mL syringe. A portion of **7** (0.161 g, 0.729 mmol) was dissolved in 50 mL of MeOH and loaded into a second 50 mL syringe. Using a syringe pump the two reactants were added simultaneously to a 500 mL round bottom flask containing 250 mL of MeOH at a rate of 10 mL/h. After the addition was complete the solvent was removed in vacuo. The reaction mixture was then dissolved in dichloromethane (50 mL) and combined with 5.6 equiv. of $NaBH(OAc)_3$ (0.432 g, 2.04 mmol) and stirred overnight under Ar. The reaction was then quenched with 50 mL of 1 M NaOH and placed in a separatory funnel. Addition of 50 mL of H_2O and 50 mL of CH_2Cl_2 followed by vigorous shaking resulted in the formation of two layers with a white powder suspended at their interface. Filtration of this suspension resulted in the isolation of 0.277 g (70%) of **1** as a white powder. ^{1}H NMR (CD_3OD): δ 7.49 (d, J=8.1 Hz, 8H, C*H*), 7.28 (d, J=8.2 Hz, 8H, C*H*), 7.14–7.24 (m, 10H, C*H*), 3.77 (s, 16H, CH_2), 3.22–3.26 (m, 4H, C*H*(CH_3)$_2$), 1.21 (d, J=6.8 Hz, 24H, CH_3); ^{13}C NMR (CD_3OD): δ 178.0, 147.6, 142.4, 142.3, 139.4, 139.3, 134.7, 131.5, 130.2, 129.8, 129.2, 127.9, 123.3, 54.5, 51.0, 30.0, 24.7; FTIR (KBr, cm^{-1}): 3411 (br), 2960 (s), 2868 (m), 1641 (m), 1562 (s), 1515 (m), 1454 (m), 1409 (m), 1379 (s), 1207 (w), 1083 (w), 892 (w), 848 (m); ESIMS (*m/z*): $[M+H]^+$ Calcd for $C_{70}H_{77}N_4O_4$, 1037.5939; Found, 1037.5990; $[M+Na]^+$ Calcd for $C_{70}H_{76}N_4O_4Na$, 1059.5764; Found, 1059.5790; $[M+2Na-H]^+$ Calcd for $C_{70}H_{75}N_4O_4Na_2$, 1081.5584; Found, 1081.5557.

4.4.9. Synthesis of 10. A portion of **6b** (0.50 g, 1.5 mmol) was combined with one half of an equivalent of **7** (0.163 g, 0.74 mmol) and 125 mL of MeOH and stirred overnight. The MeOH was then removed in vacuo and the resulting oil was redissolved in 1,2-dichloroethane (25 mL), combined with 2.8 equiv. of $NaBH(OAc)_3$ (0.437 g, 2.06 mmol) and stirred overnight under Ar. The reaction was then quenched with 50 mL of 1 M NaOH, extracted with CH_2Cl_2 (3×50 mL), washed with brine (50 mL), and dried over $MgSO_4$. After drying on a vacuum line, 0.448 g (71%) of **10** was isolated as a white powder. ^{1}H NMR (CD_3OD): δ 7.57 (d, 4H, C*H*), 7.45 (d, 4H, C*H*), 7.23–7.36 (m, 13H, C*H*), 7.09–7.23 (m, 3H, C*H*), 3.95 (s, 4H, CH_2), 3.89 (s, 4H, CH_2), 3.10 (sp, 2H, C*H*(CH_3)$_2$), 2.27 (s, 6H, CH_3), 1.18 (d, 12H, CH(CH_3)$_2$; ESIMS (*m/z*): $[M-H]^-$ Calcd for free acid $C_{56}H_{56}N_2O_4$, 819.42; Found, 819.38.

4.4.10. Synthesis for 11. A portion of **6b** (0.711 g, 2.10 mmol) was combined with one half of an equivalent of **8** (421 mg, 1.05 mmol) and 1.3 equiv. of $NaBH(OAc)_3$ (0.579 g, 2.73 mmol) in 25 mL of 1,2-dichloroethane and stirred overnight under Ar. The reaction was quenched with 1 M NaOH (30 mL), extracted with CH_2Cl_2 (3×20 mL), washed with water (25 mL) and dried over $MgSO_4$. After filtration, the solvent was removed in vacuo. The residue was then taken up in EtOAc (10 mL) and sonicated for 10 min. Filtration of the suspension through a 5 μm fritted funnel followed by washing with 10 mL of EtOAc resulted

in the isolation of 150 mg (14%) of **11** as a white powder. ^{1}H NMR ($CDCl_3$): δ 7.49 (d, J=8 Hz, 4H, C*H*), 7.20–7.41 (m, 24H, C*H*), 7.15 (m, 6H, C*H*), 3.50 (s, 4H, C*H*), 3.48 (s, 4H, C*H*), 3.47 (s, 4H, C*H*), 3.25 (sp, J=6.8 Hz, 2H, C*H*(CH_3)$_3$), 2.33 (s, 6H, CH_3), 1.06 (d, J=6.8 Hz, 12H, CH(CH_3)$_3$); ^{13}C NMR (CD_3OD): δ 180.8, 148.7, 142.1, 140.9, 140.8, 140.4, 139.9, 139.7, 139.6, 137.8, 134.5, 133.7, 131.0, 130.4, 130.1, 130.0, 129.8, 129.7, 129.4, 128.3, 128.2, 123.4, 59.8, 59.1, 57.2, 29.0, 24.5, 24.0, 21.4, 21.0; FTIR (KBr, cm^{-1}): 3629 (m), 3546 (m), 3365 (br), 3084 (m), 3060 (m), 3026 (m), 2960 (s), 2925 (m), 2867 (m), 2796 (m), 1739 (w), 1589 (s), 1454 (s), 1415 (s), 1382 (s), 1241 (m), 1187 (w), 1099 (m), 1072 (m), 1052 (m), 1021 (m), 971 (w), 910 (w), 803 (m); ESIMS (m/z): $[M-2Na+H]^+$ Calcd for $C_{70}H_{67}N_2O_4$, 999.51; Found, 999.50.

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