Diastereofacial-Selective Synthesis of the Trindane-Based Molecular Scaffold *cis*,*cis*,*cis*-2,5,8-Tribenzyltrindane-2,5,8-tricarboxylate and an Arylamine Analogue for the Construction of C_{3v}-Symmetric Architectures

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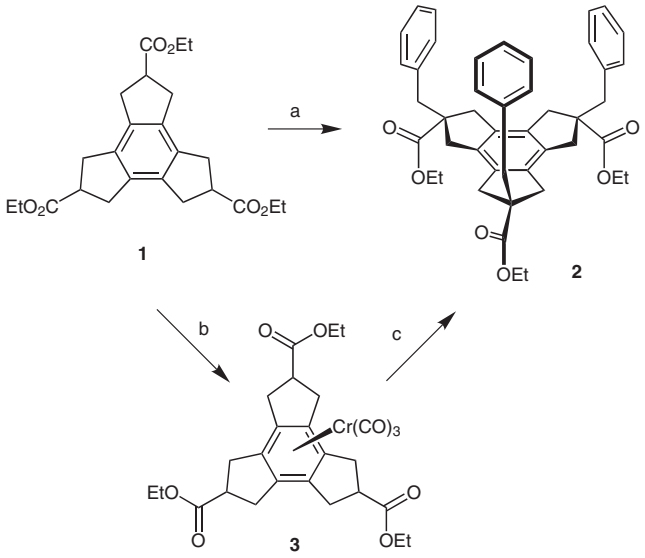
Received 9 July 2007; revised 8 August 2007

Abstract: Efficient syntheses of potentially valuable C_{3v}-symmetric trindane-based triester scaffolds are reported. In the synthesis of 2,5,8-tribenzyltrindane-2,5,8-tricarboxylate by the benzylation of the corresponding triester by treatment with lithium diisopropylamide in tetrahydrofuran, the diastereoselectivity and yield of the *cis*,*cis*,*cis*- and *cis*,*trans*,*trans*-isomers depended primarily on the reaction temperature and the amount of hexamethylphosphoramide used as additive. High diastereofacial selectivity was achieved at –90 °C in tetrahydrofuran, and the *cis*,*cis*,*cis*-isomer was obtained as the major product in 45% yield and in a diastereomeric ratio of 1.12. Under the same reaction conditions the 2,5,8-tris(4-bromobenzyl)trindane-2,5,8-tricarboxylate analogue was synthesized in 46% yield; it was efficiently converted into the 2,5,8-tris(4-aminobenzyl)trindane-2,5,8-tricarboxylate by palladium-catalyzed aromatic C–N bond formation by reaction with hexamethyldisilazide as nitrogen source in the presence of bis(dibenzylideneacetone)palladium with tri-*tert*-butylphosphine as catalyst in toluene.

Key words: trindane, diastereofacial selectivity, benzylation, supramolecular chemistry, receptors

Preorganized molecular structures with groups of appropriate affinity in well-defined orientations are important for high selectivity and association in supramolecular chemistry, and are especially useful in the field of molecular recognition.[1] A number of target molecules for molecular sensors have C_3 symmetry, especially in anions which have diverse geometries compared to most spherical cations.[2] Receptors with C_3 symmetry will efficiently interact with C_3-symmetrical anions such as nitrate, carbonate, chlorate, sulfate, and phosphate in a shape-selective manner.[3] Complementary scaffolds with threefold symmetry are popular as building blocks in supramolecular assemblies.[4]

A novel C_{3v}-symmetric molecular scaffold based on a trindane backbone, providing concave and convergent preorganized functional groups for supramolecular interaction, was recently developed by our group.[5] We have demonstrated its use as an anion receptor with three urea ligands that could strongly interact with the phosphate anion. The synthesis of the key scaffold compound, triethyl *cis*,*cis*,*cis*-2,5,8-tribenzyltrindane-2,5,8-tricarboxylate (**2**) (Scheme 1) required seven steps from hexakis(halomethyl)benzene and was inefficient, especially in the diastereofacial-selective benzylation of triethyl trindane-2,5,8-tricarboxylate (**1**). Previously, the diastereofacial-selective benzylation was achieved by formation of π-complex **3** from a chromium complex and triester **1**, followed by decomplexation of the carbonylchromium complex after alkylation (Scheme 1). Blocking of the central aromatic ring by complexation with hexacarbonylchromium differentiates two diastereofaces, and this results in an enhanced yield of the desired *all-cis*-triester **2** in 68% (Scheme 1). However, direct benzylation of the enolate of triester **1** formed by treatment with lithium diisopropylamide in tetrahydrofuran gave *all-cis* triester **2** in a low yield (21%) of at –30 °C (Scheme 1).



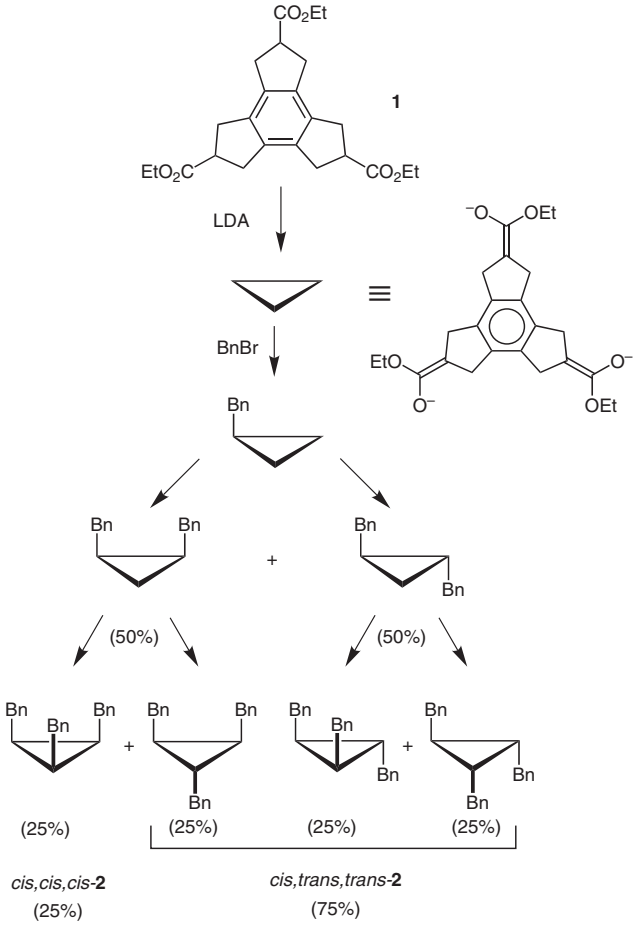
Scheme 1 *Reagents and conditions*: (a) LDA, BnBr, THF, –30 °C, 21%; (b) $Cr(CO)_6$, Bu_2O–THF, reflux, 95%; (c) LDA, BnBr, THF, –30 °C, then I_2, air, 68%.

Here we report the diastereofacial-selective synthesis of *all-cis* triester **2** by the direct benzylation of triester **1**. These reaction conditions could also be applied to the synthesis of a potentially valuable C_{3v}-symmetric trisarylamine scaffold. The efficient syntheses developed for these novel trindane scaffolds can be utilized in a variety of applications, especially in the construction of supramolecular assemblies.

SYNTHESIS 2007, No. 21, pp 3290–3294
Advanced online publication: 16.10.2007
DOI: 10.1055/s-2007-990828; Art ID: F12707SS

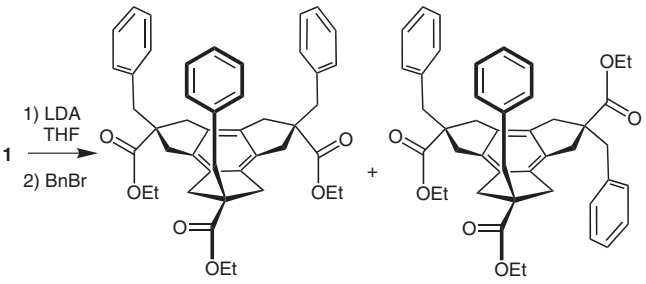
Direct benzylation of **1** will produce the *cis*,*cis*,*cis*-**2** isomer in a maximum yield of 25% if the reaction is considered from a statistical point of view (Scheme 2), because the planar tris(enolate) intermediate of **1** formed by lithium diisopropylamide may react with benzyl bromide at random. However, the characteristics of the reaction intermediates formed during consecutive benzylation (Scheme 2), and formation of the subsequent enolates as well as product **2** may influence the selective formation of *cis*,*cis*,*cis*-**2** over *cis*,*trans*,*trans*-**2** under specific reaction conditions, although these characteristics might not be readily rationalized. Preliminary experiments showed that the yield of *cis*,*cis*,*cis*-**2** formed by direct benzylation of the enolate of **1** formed by treatment with lithium diisopropylamide in tetrahydrofuran varied from 21% at –30 °C to around 30% at –78 °C. We therefore envisaged that an enhanced yield of *cis*,*cis*,*cis*-**2** could be achieved by variation of reaction temperature and amount of additives to the reaction medium, for example hexamethylphosphoramide, which stabilizes the enolates formed by lithium diisopropylamide in tetrahydrofuran.

To investigate the reaction conditions, the reaction temperature was varied from –30 °C to –50 °C, –78 °C, and –90 °C, and the relative amount of hexamethylphosphoramide in tetrahydrofuran was also varied to 5%, 10%, 15%, and 20% (by volume) (Table 1).



Scheme 2 Statistical yields of *cis*,*cis*,*cis*-**2** and *cis*,*trans*,*trans*-**2** isomers resulting from consecutive benzylation of **1**

Table 1 Effects of Solvent Additive and Temperature on the Yields and Diastereoselectivities of **2** Prepared by Benzylation of **1**[a,b]



Temp	Solvent			
	THF	HMPA–THF (5:95)	HMPA–THF (10:90)	HMPA–THF (15:85)
–30 °C	*c*,*c*,*c*: 21% *c*,*t*,*t*: 55% dr: 0.38			
–50 °C	*c*,*c*,*c*: 28% *c*,*t*,*t*: 52% dr: 0.54		*c*,*c*,*c*: 36% *c*,*t*,*t*: 58% dr: 0.62	
–78 °C	*c*,*c*,*c*: 33% *c*,*t*,*t*: 54% dr: 0.61	*c*,*c*,*c*: 34% *c*,*t*,*t*: 54% dr: 0.63	*c*,*c*,*c*: 37% *c*,*t*,*t*: 57% dr: 0.65	*c*,*c*,*c*: 36% *c*,*t*,*t*: 54% dr: 0.67
–90 °C[c]	*c*,*c*,*c*: 45% *c*,*t*,*t*: 40% dr: 1.13		*c*,*c*,*c*: 44% *c*,*t*,*t*: 41% dr: 1.07	

[a] Reagents and conditions: **1** (0.3 mmol), LDA (4.5 equiv), BnBr (3.9 equiv), solvent (10 mL), 6 h.
[b] *c*,*c*,*c* = *cis*,*cis*,*cis*-**2**; *c*,*t*,*t* = *cis*,*trans*,*trans*-**2**; yields (%) are of isolated products, and are the averages of at least two runs; dr = diastereomeric ratio *cis*,*cis*,*cis*-**2**/*cis*,*trans*,*trans*-**2**.
[c] Modified conditions: BnBr (9 equiv), 8 h.

As the reaction temperature was lowered, the yield of the desired product *cis*,*cis*,*cis*-**2** in tetrahydrofuran gradually increased from 21% at –30 °C to 45% at –90 °C, and the total yield of the isomers of **2** also increased from 76% at –30 °C to 87% at –78 °C (Table 1). The total yield at –90 °C was only 85%, compared to 87% at –78 °C (Table 1); this is probably because the reaction temperature was too low for the reaction to proceed efficiently. It is noticeable that as the reaction temperature was lowered from –30 °C to –78 °C, the yield of the desired *cis*,*cis*,*cis*-**2** isomer increased, but the yield of the other diastereomer, *cis*,*trans*,*trans*-**2**, was almost unvaried or slightly decreased, resulting in the diastereomeric ratio *cis*,*cis*,*cis*-**2**/*cis*,*trans*,*trans*-**2** increasing from 0.38 at –30 °C to 0.61 at –78 °C (Table 1). The reaction at –90 °C gave, among the reactions performed, the highest yield of *cis*,*cis*,*cis*-**2**, namely 45%, and the diastereoselectivity reached 1.13 (Table 1), which means that the desired *cis*,*cis*,*cis*-**2** diastereomer become the major product at this low temperature. At temperatures above –78 °C the major product was *cis*,*trans*,*trans*-**2**, which is apparently a thermodynamically more stable product than *cis*,*cis*,*cis*-**2**. However, at very low temperatures, such as –90 °C, the other diastereomer

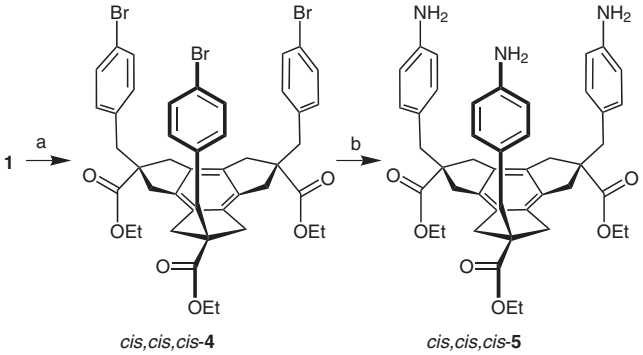
cis,*cis*,*cis*-**2** formed much faster than *cis*,*trans*,*trans*-**2**. It suggests that the *cis*,*cis*,*cis*-**2** isomer is a kinetic product under the given reaction conditions.

Even though it is difficult to estimate the stability of two diastereomers without considering the solvent stabilization, it is reasonable to rationalize that repulsive interactions between the polar ester groups and between the nonpolar benzyl groups might play an important role in the relative stability of the two isomers, as expected from the structure of *cis*,*trans*,*trans*-**2**. Polar solvation stabilization is energetically favored at lower temperature, rather than at higher temperature. At low temperature, attractive solvation interactions between the polar tetrahydrofuran solvent and the ester groups are enhanced, directing the ester groups onto the same diastereoface during formation of *cis*,*cis*,*cis*-**2** from the enol intermediate of 2-benzyltrindane-2,5,8-tricarboxylate at both the second and third benzylation steps.

To increase the yield of the desired *cis*,*cis*,*cis*-**2** diastereomer, hexamethylphosphoramide, which has been used extensively in organolithium chemistry, was chosen as an additive to the reaction medium. It enhances the rates of a wide variety of organolithium reactions, and also has a significant influence on regio- or stereochemistry.[6] In the 5–15% hexamethylphosphoramide in tetrahydrofuran solvent mixture at –78 °C, benzylation reactions of the enolate of **1** generated by lithium diisopropylamide were generally enhanced to give the isomers of **2** in 88–94% total yield, but the diastereoselectivities were almost unaffected at around 0.63–0.67 (Table 1). The 10% hexamethylphosphoramide in tetrahydrofuran mixture was the most effective mixed reaction medium, and lower reaction temperatures led to increased diastereoselectivities, as in pure tetrahydrofuran, from 0.62 at –50 °C to 0.65 at –78 °C and 1.07 at –90 °C (Table 1). Although the hexamethylphosphoramide additive increased the total yield of **2**, the diastereoselectivity was not affected significantly. The highest yield of the desired *cis*,*cis*,*cis*-**2** isomer amongst the reactions performed was 45%, and that was in tetrahydrofuran alone at –90 °C (Table 1).

This highly diastereoselective synthesis allowed us to separate the desired product *cis*,*cis*,*cis*-**2** from the minor diastereomer *cis*,*trans*,*trans*-**2** by means of fractional crystallization. The practical and efficient reaction conditions, easy workup procedure, and simple operation make this method applicable to reaction on large scale, and the product was synthesized in gram quantities, and isolated in 30% yield as crystals from hexane–dichloromethane. These reaction conditions were applied in the preparation of C_{3v}-symmetric tris(arylamine) scaffold **5** via 4-bromobenzyl analogue **4** (Scheme 3). Derivative **5** is a potentially valuable amine for a variety of applications, especially for construction of supramolecular assemblies.

The diastereofacial selectivity of the 4-bromobenzylation of **1** to give *cis*,*cis*,*cis*-**4** (Scheme 3) in tetrahydrofuran was similar to that of the benzylation of **1** to give *cis*,*cis*,*cis*-**2** in tetrahydrofuran. The desired *cis*,*cis*,*cis*-**4** isomer was obtained in 27% yield at –30 °C, 34% yield at –50 °C, 37% yield at –78 °C, and 46% yield at –90 °C, and the diastereoselectivity ratio *cis*,*cis*,*cis*-**4**/*cis*,*trans*,*trans*-**5** was 0.71 at –30 °C, 0.65 at –50 °C, 0.77 at –78 °C, and 1.05 at –90 °C. The additive hexamethylphosphoramide similarly enhanced the total yield of **4** as in the benzylation to prepare **2**, but it also had no noticeable effect on the diastereoselectivity. In 10% hexamethylphosphoramide in tetrahydrofuran at –90 °C, the desired *cis*,*cis*,*cis*-**4** was obtained in up to 46% yield, just comparable with the yield at –90 °C in tetrahydrofuran.



Scheme 3 Reagents and conditions: (a) LDA, PBBBr, THF, –90 °C, 46%; (b) LHMDS, $Pd(dba)_2$, *t*-Bu_3P, THF, 50 °C, 67%.

A number of useful and practical synthetic methods for arylamines have been well developed recently, because of their importance in a variety of fields, especially in pharmaceuticals and electronic materials.[7] To synthesize arylamine scaffold **5** with its three primary aniline moieties from tribromide **4** with its electrophilic ester groups requires a highly efficient synthetic method for triple C–N bond formation. One of the mildest and most convenient synthetic methods to primary anilines from aryl halides is palladium-catalyzed aromatic C–N bond formation, in which hexamethyldisilazide is used in the presence of the bis(dibenzylideneacetone)palladium [$Pd(dba)_2$]/tri-*tert*-butylphosphine catalytic system.[8] Reaction of tribromide **4** with a slight excess of lithium hexamethyldisilazide in the presence of 5 mol% of the catalyst bis(dibenzylideneacetone)palladium and tri-*tert*-butylphosphine (1:1) in toluene gave, after 48 hours at 50 °C, tris(aniline) **5** cleanly in up to 67% yield after hydrolysis of the corresponding silylamine; here the yield of 67% corresponds to 88% yield for each C–N bond formation. The clean conversion of tribromide **4** into tris(aniline) **5** demonstrates that this method is very efficient for aryl bromide reactants with multiple reaction sites, which require very high reaction yields.

In summary, we have developed a synthetic method for the useful C_{3v}-symmetric scaffold **2** by temperature-controlled diastereofacial-selective benzylation of triethyl trindane-2,5,8-tricarboxylate (**1**). These efficient reaction conditions could be extended to the synthesis of the tris(bromobenzyl) analogue **4**, which could be converted into the C_{3v}-symmetric tris(aniline) **5**, potentially valuable for a variety of applications.

All reagents were purchased from Sigma-Aldrich and used as received. THF was freshly distilled from sodium–benzophenone under N_2. Compound **1** was prepared as described previously.[5] TLC analysis was performed on silica gel 60 F_{254} coated glass slides (Merck). Chromatographic purifications were performed by flash chromatography on 70–230 mesh silica gel (Merck). Reaction temperatures at –30, –50 and –90 °C were regulated in an acetone bath cooled by a Flexi-Cool immersion cooler from FTS systems, and –78 °C was achieved in a dry ice–acetone bath. NMR data were obtained at 400 (^{1}H) and 100 MHz (^{13}C) on a Bruker Avance Digital 400 spectrometer. Chemical shifts δ are relative to TMS or residual undeuterated solvent. Infrared spectra were recorded on a Shimadzu IR Prestige-21 spectrometer. HRMS spectra were obtained in ESI positive scan mode on a Q-TOF Premier mass spectrometer from Waters. Elemental analyses were performed by Kyungpook Center for Scientific Instruments.

Determination of Yield and Diastereofacial Selectivity; General Procedure

Reactions were conducted in septum-capped, 25-mL, oven-dried flasks under N_2. All additions were performed with vacuum-dried gas-tight syringes and oven-dried disposable plastic syringes. The yields reported for the final products in Table 1 are isolated yields and are the averages of at least two runs. The *cis*,*cis*,*cis*-**2**/*cis*,*trans*,*trans*-**2** diastereoselectivity ratios of the reaction mixtures were also examined and confirmed from the ^{1}H NMR spectra, beside those of the isolated products. The δ = 2.95–3.10 ^{1}H NMR spectral region showing the methylene groups of the benzyl moieties of the two diastereomers were analyzed by deconvolution of the peaks: *cis*,*cis*,*cis*-**2** shows a singlet at δ = 3.04 and *cis*,*trans*,*trans*-**2** shows five peaks at δ = 2.98, 3.00, 3.01, 3.04, and 3.09.

Synthesis of 2,5,8-Tribenzyltrindane-2,5,8-tricarboxylates 2; Typical Procedure

LDA (2.0 M in heptane–THF–ethylbenzene; 0.68 mL, 1.35 mmol) was added by syringe to a soln of **1** (125 mg, 0.3 mmol) in HMPA–THF (10 mL) cooled at the appropriate temperature. After the mixture had stirred for 60 min, BnBr (140 μL, 1.17 mmol) was added dropwise by syringe. [For the addition of solid PBBBr, PBBBr (292 mg, 1.17 mmol) was dissolved in THF (2 mL) and the soln was added.] After the soln had stirred for 6 h, it was quenched by the addition of sat. aq NH_4Cl (2 mL). The mixture was allowed to warm to r.t., and additional aq NH_4Cl (10 mL) was added. The organic layer was separated and the aqueous layer was extracted with Et_2O (2 × 10 mL). The combined organic fraction was then washed with sat. aq NaCl (15 mL), dried ($MgSO_4$, 10 min), filtered under reduced pressure, and concentrated on a rotary evaporator. The diastereomers were then separated and purified by flash column chromatography (silica gel, CH_2Cl_2–MeOH, 95:5). (CH_2Cl_2 was used as eluent for product **4**.) For the reactions at –90 °C, excess BnBr or PBBBr (2.7 mmol) was added, and longer reaction times were used (up to 8 h).

Triethyl *cis*,*cis*,*cis*-2,5,8-Tribenzyltrindane-2,5,8-tricarboxylate (*cis*,*cis*,*cis*-2)

Mp 120.5–122.0 °C; R_f = 0.20 (silica gel, CH_2Cl_2).

IR (KBr): 3026, 2925, 1720, 1202 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.30–7.10 (m, 15 H), 4.13 (q, *J* = 7.1 Hz, 6 H), 3.22 (d, *J* = 15.9 Hz, 6 H), 3.04 (s, 6 H), 2.88 (d, *J* = 15.9 Hz, 6 H), 1.21 (t, *J* = 7.1 Hz, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.3, 137.9, 135.3, 129.7, 128.2, 126.6, 60.8, 55.7, 43.8, 39.9, 14.2.

HRMS (ESI): *m*/*z* (%) [M + H]$^+$ calcd for $C_{45}H_{48}O_6$: 685.3529 (100), 686.3563 (51.0), 687.3595 (13.9), 688.3625 (2.7); found: 685.3516 (100), 686.3594 (54), 687.3594 (15).

Anal. Calcd for $C_{45}H_{48}O_6$: C, 78.92; H, 7.06. Found: C, 78.88; H, 7.12.

Triethyl *cis*,*trans*,*trans*-2,5,8-Tribenzyltrindane-2,5,8-tricarboxylate (*cis*,*trans*,*trans*-2)

Mp 79.0–80.8 °C; R_f = 0.37 (silica gel, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.17–7.29 (m, 10 H), 7.03–7.10 (m, 5 H), 4.17 (q, *J* = 7.2 Hz, 2 H), 4.15 (q, *J* = 7.2 Hz, 4 H), 3.20–3.30 (m, 6 H), 3.06 (d, *J* = 13.6 Hz, 2 H), 3.00 (s, 2 H), 3.00 (d, *J* = 13.6 Hz, 2 H), 2.93–2.83 (m, 6 H), 1.26 (t, *J* = 7.2 Hz, 3 H), 1.23 (t, *J* = 7.2 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.4, 176.3, 137.88, 137.86, 135.48, 135.43, 135.37, 129.7, 128.2, 126.6, 60.8, 56.0, 55.8, 43.81, 43.76, 40.1, 40.0, 39.7, 14.22, 14.18.

Triethyl *cis*,*cis*,*cis*-2,5,8-Tris(4-bromobenzyl)trindane-2,5,8-tricarboxylate (*cis*,*cis*,*cis*-4)

Mp 141.0–142.8 °C; R_f = 0.43 (silica gel, CH_2Cl_2).

IR (KBr): 3008, 2947, 1750, 1252 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.39 (d, *J* = 8.4 Hz, 6 H), 6.98 (d, *J* = 8.4 Hz, 6 H), 4.12 (q, *J* = 7.2 Hz, 6 H), 3.22 (d, *J* = 15.6 Hz, 6 H), 2.99 (s, 6 H), 2.82 (d, *J* = 15.6 Hz, 6 H), 1.22 (t, *J* = 7.2, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.0, 136.8, 135.2, 131.32, 131.27, 120.7, 60.9, 55.5, 43.2, 39.9, 14.2.

HRMS (ESI): *m*/*z* (%) [M + Na]$^+$ calcd for $C_{45}H_{45}Br_3O_6$: 941.0664 (30.8), 942.0698 (15.7), 943.0648 (94.1), 944.0679 (46.6), 945.0634 (100), 946.0661 (46.9), 947.0630 (40.9), 948.0648 (16.8); found: 941.0609 (35), 942.0858 (18), 943.0662 (99), 944.0695 (51), 945.0735 (100), 946.0553 (57), 947.0603 (46), 948.0546 (41).

Anal. Calcd for $C_{45}H_{45}Br_3O_6$: C, 58.65; H, 4.92. Found: C, 58.41; H, 4.95.

Triethyl *cis*,*trans*,*trans*-2,5,8-Tris(4-bromobenzyl)trindane-2,5,8-tricarboxylate (*cis*,*trans*,*trans*-4)

Mp 45.5–49.8 °C; R_f = 0.67 (silica gel, CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.37 (d, *J* = 8.0 Hz, 4 H), 7.37 (d, *J* = 8.4 Hz, 2 H), 6.95 (d, *J* = 8.0 Hz, 4 H), 6.92 (d, *J* = 8.4 Hz, 4 H), 4.17 (q, *J* = 7.0 Hz, 2 H), 4.14 (q, *J* = 7.2 Hz, 4 H), 3.29–3.19 (m, 6 H), 3.02 (d, *J* = 13.6 Hz, 2 H), 2.96 (s, 2 H), 2.93 (d, *J* = 13.6 Hz, 2 H), 2.87–2.78 (m, 6 H), 1.27 (t, *J* = 7.0 Hz, 3 H), 1.24 (t, *J* = 7.2 Hz, 6 H).

^{13}C NMR (100 MHz, $CDCl_3$,): δ = 176.00, 175.98, 136.79, 136.76, 135.39, 135.32, 135.21, 131.31, 131.30, 131.26, 131.25, 120.64, 60.90, 55.85, 55.66, 43.10, 43.02, 40.34, 39.96, 39.59, 14.25, 14.19.

Large Preparative-Scale Syntheses of *cis*,*cis*,*cis*-2 and *cis*,*cis*,*cis*-4

The reactions were carried out on tenfold scale for **4** and on 20-fold scale for **2**, and were allowed to run for longer time periods.

cis,*cis*,*cis*-2

LDA (2 M in heptane–THF–ethylbenzene; 13.5 mL, 27 mmol) was added dropwise by syringe to a soln of **1** (2.49 g, 6 mmol) in THF (180 mL) cooled at –90 °C under N_2. After the mixture had stirred for 60 min, BnBr (4.4 mL, 36 mmol) was added dropwise by syringe. The soln was allowed to stir for 15 h and was then quenched by the addition of sat. aq NH_4Cl (10 mL). After the mixture had warmed to r.t., additional aq NH_4Cl (90 mL) was added. The organic layer was separated, dried ($MgSO_4$, 10 min), filtered under reduced pressure, and concentrated on a rotary evaporator. Purification of the residue by short-column chromatography (silica gel, hexane–CH_2Cl_2, 6:4) removed most of the *cis*,*trans*,*trans*-**2** diastereomer. The major diastereomer *cis*,*cis*,*cis*-**2** eluted with the

CH_2Cl_2. Concentration and recrystallization (hexane–CH_2Cl_2) of this fraction gave the product as needle-shaped crystals.

Yield: 1.2 g (30%).

***cis*,*cis*,*cis*-4**

LDA (2 M in heptane–THF–ethylbenzene; 6.8 mL, 13.6 mmol) was added dropwise by syringe to a soln of **1** (1.25 g, 3 mmol) in THF (90 mL) cooled at –90 °C under N_2. After the mixture had stirred for 60 min, a soln of PBBBr (4.50 g, 18 mmol) in THF (30 mL) was added dropwise by syringe. The soln was allowed to stir for 15 h and was then quenched by the addition of sat. aq NH_4Cl (10 mL). After the mixture had warmed to r.t., additional aq NH_4Cl (90 mL) was added. The organic layer was separated, dried ($MgSO_4$, 10 min), filtered under reduced pressure, and concentrated on a rotary evaporator. Purification of the residue by column chromatography (silica gel, CH_2Cl_2) gave the product *cis*,*cis*,*cis*-**4** as a slightly yellowish solid.

Yield: 1.27 g (46%).

Triethyl *cis*,*cis*,*cis*-2,5,8-Tris(4-aminobenzyl)trindane-2,5,8-tricarboxylate (*cis*,*cis*,*cis*-5)

A 25-mL round-bottom flask containing **4** (185 mg, 0.2 mmol) was loaded with $Pd(dba)_2$ (17.3 mg, 0.03 mmol), *t*-Bu_3P (9 μL, 0.03 mmol), and LHMDS (0.8 mL, 0.8 mmol), followed by toluene (12 mL) under N_2. The soln was heated at 50 °C for 48 h. The solvent was removed on a rotary evaporator, and the residue was dissolved in CH_2Cl_2 (20 mL). The mixture was washed with 1 M aq HCl (10 mL) followed by sat. aq $NaHCO_3$ (2 × 5 mL). The organic layer was separated, dried ($MgSO_4$, 10 min), filtered under reduced pressure, and concentrated on a rotary evaporator. Purification of the residue by flash column chromatography (silica gel, CH_2Cl_2–MeOH, 96:4) gave the product as a slightly yellowish solid.

Yield: 97 mg (67%); R_f = 0.37 (CH_2Cl_2–MeOH, 95:5).

IR (KBr): 3405, 3372, 2978, 2924, 1716, 1624, 1516, 1184, 733 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 6.89 (d, *J* = 8.4 Hz, 6 H), 6.59 (d, *J* = 8.4 Hz, 6 H), 4.13 (q, *J* = 7.2 Hz, 6 H), 3.65 (br s, 6 H), 3.18 (d, *J* = 15.5 Hz, 6 H), 2.92 (s, 6 H), 2.85 (d, *J* = 15.5 Hz, 6 H), 1.23 (t, *J* = 7.2, 9 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 176.9, 145.3, 135.7, 130.9, 128.2, 115.3, 61.0, 56.2, 43.5, 40.1, 14.6.

HRMS (ESI): *m*/*z* (%) $[M + H]^+$ calcd for $C_{45}H_{51}N_3O_6$: 730.3856 (100), 731.3889 (52.2), 732.3920 (14.5), 733.3949 (2.8); found: 730.3873 (100), 731.3919 (62), 732.3971 (20). 733.3831 (6).

Anal. Calcd for $C_{45}H_{51}N_3O_6$: C, 74.05; H, 7.04; N, 5.76. Found: C, 73.87; H, 7.10; N, 5.85.

Acknowledgment

This work was supported by the Korea Research Foundation Grant funded by the Korean Government (MOEHRD, Basic Research Promotion Fund) (KRF-2006-521-C00101 and KRF-2005-211-C00082).

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