A Conformational Study of Cyclohexane-1,3,5-tricarbonitrile Derivatives

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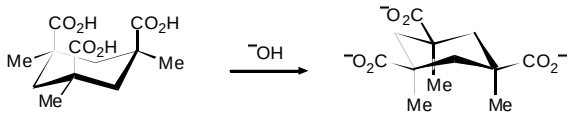
Cyclohexane-1,3,5-tricarbonitrile reached equilibrium having 1,3-*cis*-1,5-*cis* and 1,3-*cis*-1,5-*trans* isomers in a ratio of 3:7. The *cis*,*cis*-isomer preferred the conformation with three equatorial cyano groups, whereas the *cis*,*trans*-isomer displayed two cyano groups on equatorial positions and another cyano group on axial position. Condensation of *cis*,*cis*-cyclohexane-1,3,5-tricarbonitrile with L-(*S*)-valinol by the catalysis of $ZnCl_2$ in refluxing 1,2-dichlorobenzene afforded two isomeric cyclohexane-1,3,5-trioxazolines in favor of the 1,3-*cis*-1,5-*trans* isomer. Metalation of *cis*,*cis*-cyclohexane-1,3,5-tricarbonitrile, followed by alkylations with dimethyl sulfate, benzyl bromide or allyl bromide, gave the corresponding trialkylation products with predominance of 1,3-*cis*-1,5-*trans* isomers. The *cis*,*trans*-isomer showed two cyano groups on axial positions and another cyano group on equatorial position, whereas the *cis*,*cis*-isomer exhibited three axial cyano groups. Treatment of trimethyl *cis*,*cis*-cyclohexane-1,3,5-tricarboxylate with lithium diisopropylamide and dimethyl sulfate afforded mainly the trimethyl ester of Kemp's triacid, which showed three axial carboxylate groups. Two competitive factors, i.e. the steric effect of incoming electrophiles and the dipole-dipole interactions of the cyano or carboxylate groups, might interplay to give different stereoselectivities in these reaction systems.

INTRODUCTION

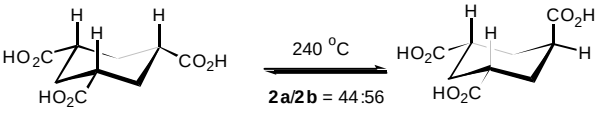
Many efforts have been exerted on the conformational studies of substituted cyclohexanes. Kemp and Petrakis[1] have reported an especially interesting compound *cis*,*cis*-1,3,5-trimethylcyclohexane-1,3,5-tricarboxylic acid **1a** (Kemp's triacid), in which all carboxylic groups are axial. Due to this well-defined conformation, Kemp's acid and its derivatives can be used as the units for molecular recognition.[2-6] For example, the *m*-phenylenediamine bis(Kemp's triacid imide) is utilized as a building block for molecular receptors.[2] It can stabilize carboxylate-bridged dimetallic centers to serve as a functional model of related enzymes.[3] Incorporation of peptide chains on Kemp's triacid can generate collagen-like triple helices.[4] Kemp's triacid disubstituted derivatives are employed as metal ion-separating agents.[5] Kemp's triacid can be linked by crown ethers or porphyrins to function as *C*-cleft agents.[6] Use of Kemp's triacid and its derivatives as a building scaffold for asymmetric synthesis and combinatorial synthesis have been recently explored.[7]

The conformation with three axial carboxylic groups in Kemp's triacid is attributable to the stabilization by intramolecular hydrogen bonding. When Kemp's triacid is treated with NaOH solution,[12] a successive ionization makes a flipping of the cyclohexane ring. This conformational change releases electrostatic repulsion and leads to the thermodynamically more stable conformer with three equatorial carboxylate groups (Eq. 1). *Cis*,*cis*-cyclohexane-1,3,5-tricarboxylic acid **2a** also exists as the conformer having three carboxylic groups on the equatorial positions (Eq. 2). Unlike Kemp's triacid having three axial carboxylic groups, the steric effect by dispositions of three axial carboxylic groups in **2a** might override the effect of intramolecular hydrogen bonding. It is also known[8] that heating of *cis*,*cis*-cyclohexane-1,3,5-tricarboxylic acid **2a** at 240°C causes an isomerization to reach an equilibrium between **2a** and the *cis*,*trans*-isomer **2b** with a ratio of 44:56. The *cis*,*trans*-isomer **2b** exists as the conformer having one axial and two equatorial carboxylic groups, but not the other way around.



1a (Kemp's triacid)
all axial CO_2H

all equatorial CO_2^- (1)



cis-cis
2a

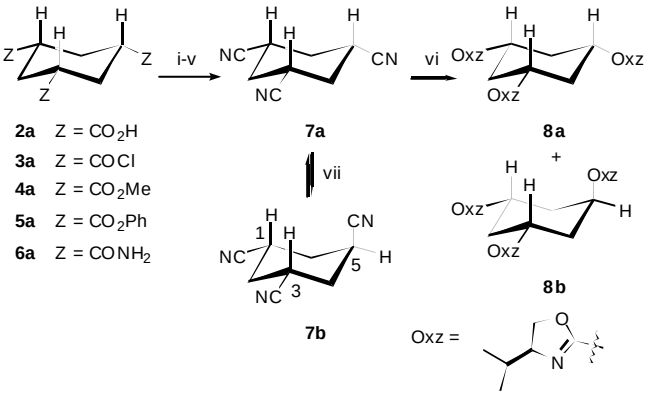
cis-trans
2b (2)

RESULTS AND DISCUSSION

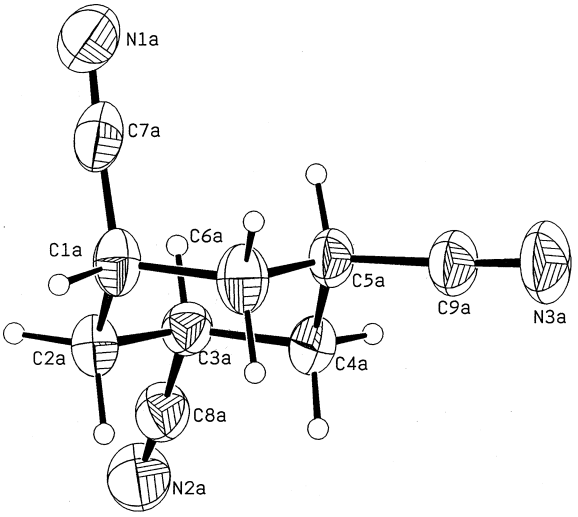
As a continuation of the above-mentioned studies, we

pre pared sev eral de riv a tives of 1,3,5-trisubstituted cyclohexanes and ex am ined their con for ma tions. Triacid **2a** was treated with thionyl chlo ride to give the triacyl chlo ride **3a** (Scheme I).[9] Nucleophilic sub sti tu tion of **3a** with MeOH or PhOH yielded the triesters **4a** and **5a**, respectively.[7,9] Ammonolysis of **5a** in liq uid NH_3 af forded the triamide **6a**.[9] De hy dra tion of the triamide **6a** was car ried out by heat ing with $SOCl_2$ in DMF to give the trinitrile **7a**.[9] All the de riv atives **3a-7a** were shown to have the sym met ric *cis,cis*-structures by NMR anal y ses. No *cis,trans*-iso mers were found. At tempts to con vert triacid **2a** di rectly to the cor re spond ing trioxazolines by treatments with 2-aminoethanol or 2-amino-2-methylpropan-1-ol un der var i ous con di tions failed. The con den sa tion re ac tion of trinitrile **7a** with L-(*S*)-valinol was realized by the catalysis of $ZnCl_2$ in refluxing 1,2-dichlorobenzene.[10,11] How ever, a sig nif i cant isomerization also oc curred un der such re ac tion con di tions, thus two isomeric trioxazolines **8a** and **8b** were ob tained in a ra tio of 3:7. The symmetric *cis,cis*-iso mer **8a** ($C_{24}H_{39}N_3O_3$) showed 8 peaks in the ^{13}C NMR spec trum, whereas the *cis,trans*-iso mer **8b** dis played the 24 car bons as 20 peaks. In the ^1H NMR spectrum of **8a**, the H-1, H-3 and H-5 ap peared at δ_H 2.63 as a triplet of trip lets with large and small cou pling con stants (J = 12.6 and 3.0 Hz), in di cat ing their ax ial dis po si tions. On the other hand, the ^1H NMR spec trum of **8b** showed three sig nals at δ 2.63, 2.78 and 2.84 cor re spond ing to H-1β (ax ial), H-3β (ax ial) and H-5α (equa to rial), re spec tively, due to the unsymmetric ori en ta tion of three oxazoline sub stitu ents.

Scheme I



Reagents and conditions: i, for **3a**: **2a**/$SOCl_2$, reflux, 12 h; >99%. ii, for **4a**: **2a**/$SOCl_2$/MeOH, rt, 4 h; 96%. iii, for **5a**: **3a**/PhOH, pyridine, CH_2Cl_2, 40 °C, 12 h; 90%. iv, for **6a**: **5a**/liquid NH_3, –40 °C to rt, 15 h; 85%. v, for **7a**: **6a**/$SOCl_2$, DMF, 45 °C, 15 h; 65%. vi, L-valinol, cat. $ZnCl_2$, 1,2-dichlorobenzene, reflux, 24 h; **8a**, 20%; **8b**, 45%. vii, *t*-BuOK/*t*-BuOH, rt, 24 h; **7a**/**7b** = 3:7.

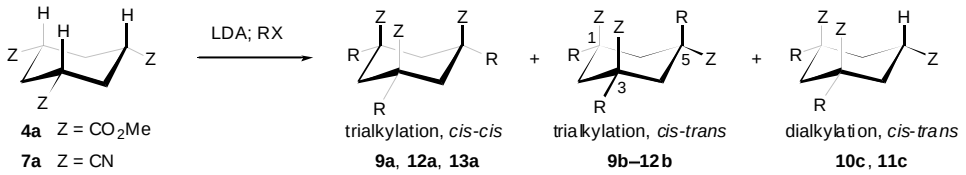


ORTEP Draw ing of Com pound **7b**

When *cis,cis*-trinitrile **7a** was treated with *t*-BuOK in *t*-BuOH so lu tion at room tem per a ture for a pro longed pe riod (24 h), a mix ture of **7a** and the *cis,trans*-iso mer **7b** was obtained in a ra tio of 3:7. Sim i lar treat ment of a 1:1 mix ture of **7a** and **7b** also ended up with the iso meric ra tio of 3:7. The struc ture of **7b** was con firmed by an X-ray dif frac tion anal y sis, which showed two cyano groups on equa to rial po si tions and an other cyano group on ax ial po si tion. The ^{13}C NMR spec trum of **7b** ($C_9H_9N_3$) showed only 6 sig nals due to its sym met ric struc ture. In the ^1H NMR spec trum, H-1 and H-3 on the ax ial po si tions ap peared at δ 2.90, whereas H-5 on the equa to rial po si tion ap peared at a lower field of δ 3.19. Accord ing to an MM3 cal cu la tion, the *cis,trans*-iso mer **7b** is more sta ble than the *cis,cis*-iso mer **7a** bear ing three equa to rial cyano groups by an en ergy dif fer ence of -0.509 kcal mol^{-1}. This cal cu la tion was in agree ment with the ob served iso meric ra tio of **7a**/**7b** (3:7) at equi lib rium. As the CN group has a small size, the steric ef fect should be min i mal. How ever, the ax ial dis po si tion of one CN group in **7b** could re lease the di pole-dipole in ter ac tion with the other two CN groups.[12] Thus, the *cis,trans*-iso mer **7b** is ther mo dy nam i cally more sta ble than the *cis,cis*-iso mer **7a**, which ex erts larger di pole-dipole re pul sions among the three equa to rial cyano groups. The al ter na tive con former of **7b** with two ax ial cyano groups was not observed because these two axial cyano groups would cause se vere di pole-dipole re pul sion. Sim i lar rea sons could be at trib ut able to the pref er a ble conform ers of triacid **2b** and trioxazoline **8b**.

The electrophilic re ac tions of triester **4a** and trinitrile **7a** pro ceeded with dif fer ent stereoselectivities (Ta ble 1).

Table 1. Electrophilic Reactions of Cyclohexane Triester **4a** and Trinitrile **7a**



Reactant	Electrophile	Ratio of Product	Z =	R =
4a	Me_2SO_4	**9a**/**9b** = 85:15	CO_2Me	Me
7a	Me_2SO_4	**10b**/**10c** = 80:20	CN	Me
7a	$PhCH_2Br$	**11b**/**11c** = 41:59	CN	$PhCH_2$
7a	CH_2=$CHCH_2Br$	**12a**/**12b** = 28:72	CN	CH_2=$CHCH_2$
7a	Ph_2PCl	**13a** only	CN	Ph_2P

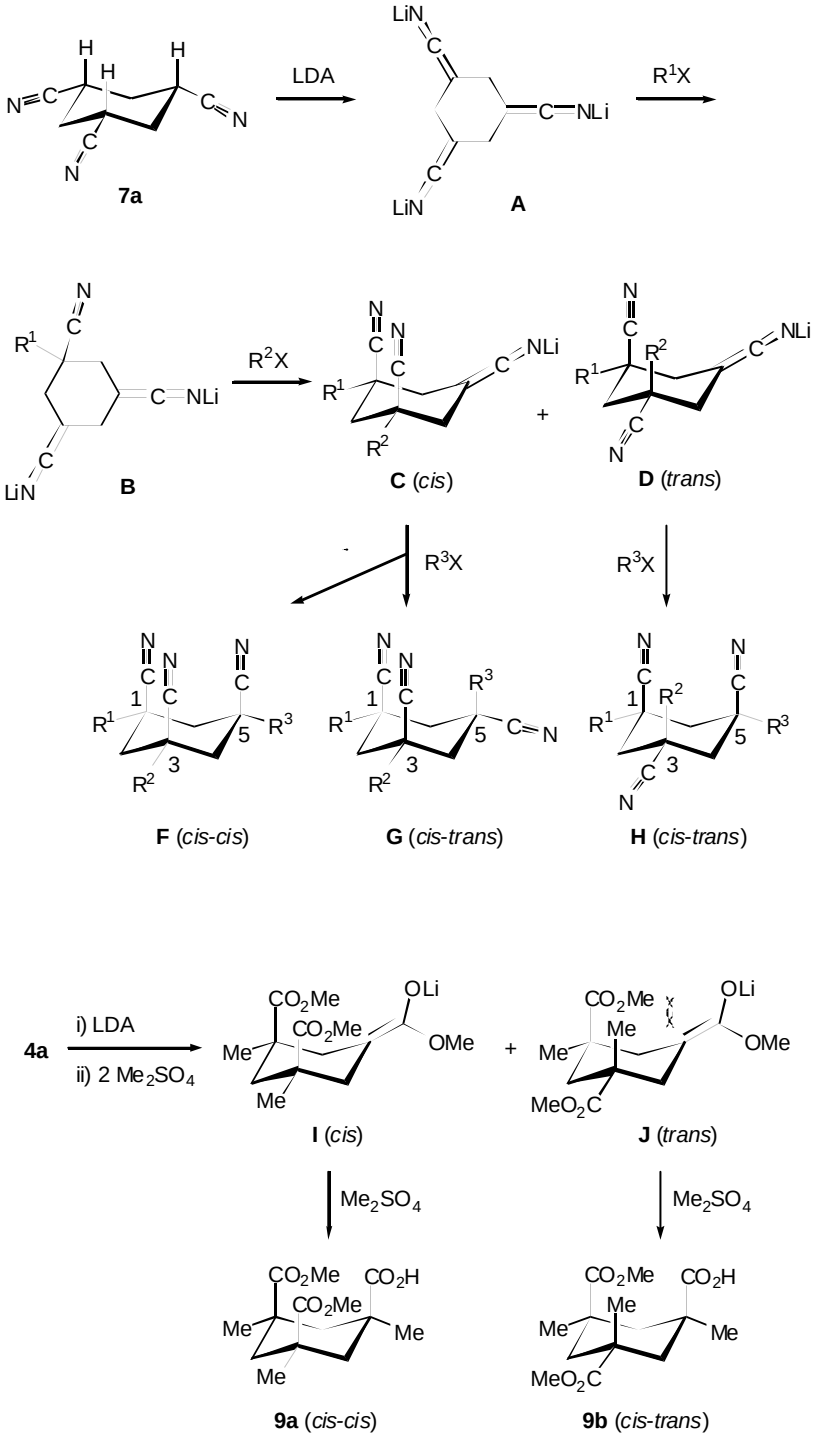
Triester **4a** was treated with LDA (3.3 equiv) in an Et_2O solution at 0 °C, followed by alkylation with excessive amounts of Me_2SO_4, to give Kemp's acid trimethyl ester **9a** and the *cis*,*trans*-isomer **9b** in a ratio of 85:15.[2a] As **9a** was subjected to saponification to give Kemp's triacid **1a**, its structure with three carboxylate groups on the axial positions was established. On the other hand, treatment of the trinitrile **7a** with LDA and Me_2SO_4 in Et_2O/THF solution (v/v, 1:1) at -78 °C gave a trimethylation product **10b** with *cis*,*trans*-configuration (50% yield). No *cis*,*cis*-isomer **10a** was found, though a side product **10c** (11% yield) resulted from an incomplete methylation. A similar alkylation reaction of **7a** with benzyl bromide also gave the tribenzylation product **11b** (24% yield) and the dimethylation product **11c** (35% yield). Using allyl bromide as the electrophile, two triallylation products **12a** and **12b** were obtained in a ratio of 28:72. The structures of these products were determined by spectral methods. For example, NOE experiments were applied to determine the illustrated configuration and conformation of **11b**. Thus, irradiation of the axially oriented H-4α (and H-6α) at δ 1.64 caused enhancements of H-2α (at δ 1.20) and the two methylene signals of C-1 and C-3 allyl groups (at δ 2.36). Irradiation of the methylene signal (at δ 3.04) of C-5 allyl group (on axial position) caused a 16% enhancement of the resonance at δ 2.47 for H-4β and H-6β. The C_2-symmetric nature of the dialkylation products **10c** and **11c** were indicated by their ^{13}C NMR spectra, so that **10c** and **11c** should have the *cis*,*trans*-configurations. Their C-5 protons, appearing at δ 3.20 (tt, J = 12.9, 3.0 Hz) and 3.16 (tt, J = 13.2, 3.3 Hz), displayed the characteristic patterns with large and small coupling constants, being consistent with their axial dispositions in the illustrated conformers.

We speculated that steric effect and dipole-dipole interaction might interplay in these electrophilic reactions to affect the stereoselectivity.[12] The dianionic intermediate **B** might react with a second electrophile to afford the intermediates of *cis*-anion **C** and *trans*-anion **D** (Scheme II). The reaction of **C** with a third electrophile would give either the *cis*,*cis*-product **F** via equatorial attack, or the *cis*,*trans*-product **G** via axial attack. The *cis*,*cis*-product **F** with three axial CN groups would be thermodynamically disfavored because it exhibited severe dipole-dipole repulsions. Except for a bulky electrophile such as Ph_2PCl,[9] alkylations of **C** should occur preferentially from the axial approach to give the *cis*,*trans*-product **G** such as **10b**, **11b**, and **12b** ($R^1 = R^2 = R^3$). The trialkylation products **10b**, **11b**, and **12b** could also be derived from the equatorial alkylations of the *trans*-anion **D**, which had an axial R^2 alkyl group to hinder the axial approach of the third halide molecule. A similar rationale could be applied to the formation of dialkylation products **10c** and **11c**, but not other stereoisomers. In alkylations of the triester **4a**, the *trans*-anion intermediate **J**, having a larger steric effect between the axial Me and CO_2Me groups, was also less favorable than the *cis*-anion intermediate **I**. As Me and CO_2Me groups were more sterically demanding than the CN group (by comparison of **I** and **J** with **C** and **D**), both **I** and **J** would undergo alkylation via the equatorial approach of an Me_2SO_4 molecule to give, respectively, the *cis*,*cis*-product **9a** and the *cis*,*trans*-product **9b**. As a consequence, trimethylation of **4a** led to 85% of **9a** and 15% of **9b**.

EXPERIMENTAL

All reactions requiring anhydrous conditions were conducted in a flame-dried apparatus under an atmosphere of ar-

Scheme II



gon. Sy ringes and nee dles for the trans fer of re agents were dried at 120 °C and al lowed to cool in a des ic ca tor over P_2O_5 be fore use. Ethers were dis tilled from so dium ben zo phe none ketyl; (chlo ri nated) hy dro car bons, and amines from CaH_2. Re ac tions were mon i tored by TLC us ing pre-coated with a 0.25 mm layer of sil ica con tain ing a flu o res cent in di ca tor (Merck Art. 5544). Col umn chro ma tog ra phy was car ried out on Kieselgel 60 (40-63 μm). Op ti cal ro ta tions were mea sured

on a digital polarimeter with a cuvette of 1 cm length. $[\alpha]_D$ Values are given in 10^{-1} deg cm^2 g^{-1}. ^{1}H and ^{13}C NMR spectra were recorded on Bruker AC-200 and AM-300 WB spectrometers. Chemical shifts are reported relative to $CHCl_3$ [δ_H 7.26, δ_C (central line of t) 77.0]. Coupling constants (*J*) are given in Hz. The X-ray diffraction data were collected on a CAD-4 diffractometer. The analyses were carried out on a microVAX III computer using NRC VAX software.

cis,cis-Cyclohexane-1,3,5-tricarboxyl trichloride (3a)[9]

Treatment of *cis,cis*-cyclohexane-1,3,5-tricarboxylic acid **2a** (purchased from Fluka) with thionyl chloride, according to the reported procedure,[9] gave the triacyl chloride **3a** in a quantitative yield. Solid, mp 44-45 °C (lit.[9] mp 44-46 °C); δ_H (200 MHz, $CDCl_3$) 1.67 (3H, dt, *J* 12.6, 12.6), 2.66 (3H, dt, *J* 12.6, 3.6) and 2.84 (3H, tt, *J* 12.6, 3.6); δ_C (50 MHz, $CDCl_3$) 30.3 (3 CH_2), 52.2 (3 CH) and 174.2 (3 C).

Trimethyl _cis,cis_-cyclohexane-1,3,5-tricarboxylate (4a)[7b]

Treatment of the triacid **2a** with thionyl chloride in the presence of MeOH, according to the reported procedure,[7b] gave the triester **4a** (96% yield). δ_H (200 MHz, $CDCl_3$) 1.47 (3H, dt, *J* 12.6, 12.6), 2.23 (3H, br d, *J* 12.6) and 2.39 (3H, dt, *J* 12.6, 3.2); δ_C (50 MHz, $CDCl_3$) 30.4 (3 CH_2), 41.6 (3 CH), 51.8 (3 Me) and 174.4 (3 C).

Triphenyl _cis,cis_-cyclohexane-1,3,5-tricarboxylate (5a)[9]

Treatment of the triacyl chloride **3a** with PhOH in the presence of pyridine, according to the reported procedure,[9] gave the triester **5a** (90% yield). Solid, mp 130-131 °C (lit.[9] mp 130 °C); δ_H (200 MHz, $CDCl_3$) 1.89 (3H, dt, *J* 12.6, 12.6), 2.67 (3H, br d, *J* 12.6), 2.78 (3H, td, *J* 12.6, 3.2), 7.12 (6H, dd, *J* 7.6, 1.0), 7.22 (3H, tt, *J* 7.2, 1.0) and 7.40 (6H, dd, *J* 7.6, 7.2).

cis,cis-Cyclohexane-1,3,5-tricarboxamide (6a)[9]

Treatment of the triester **5a** with liquid ammonia according to the reported procedure[9] gave the triester **4a** (85% yield). Solid, mp 287-289 °C (lit.[9] mp 290 °C); δ_H (300 MHz, CD_3OD) 1.45 (3H, dt, *J* 12.6, 12.6), 2.10 (3H, br d, *J* 12.6) and 2.21 (3H, td, *J* 12.6, 3.3); δ_C (75 MHz, CD_3OD) 34.6 (3 CH_2), 47.2 (3 CH) and 183.9 (3 C).

cis,cis-Cyclohexane-1,3,5-tricarbonitrile (7a) and _cis,trans_-Cyclohexane-1,3,5-tricarbonitrile (7b)

Treatment of the triamide **6a** with thionyl chloride according to the reported procedure[9] gave the trinitrile **7a** (65% yield).

The trinitrile **7a** (30 mg, 0.19 mmol) was treated with *t*-BuOK (10 mg) in a solution of *t*-BuOH (0.3 mL) and THF (2 mL) at room temperature for 24 h. The mixture was concentrated *in vacuo*, dissolved in CH_2Cl_2 (20 mL), washed with water (15 mL) and brine (15 mL), dried (Na_2SO_4), and chromatographed on a silica gel column by elution with EtOAc/hexane (1:1) to give the *cis,cis*-isomer **7a** (8.5 mg, 28%) and the *cis,trans*-isomer **7b** (19.5 mg, 65%).

7a: Solid, mp 174-176 °C (lit.[9] mp 175 °C); δ_H (300 MHz, $CDCl_3$) 1.87 (3H, dt, *J* 12.9, 12.9) and 2.48-2.58 (m, 6H); δ_C (75 MHz, $CDCl_3$) 26.2 (3 CH_2), 30.9 (3 CH) and 118.4 (3 C); *m/z* 160 (M^+ + 1, 5%), 106 (84) and 54 (100).

7b: Solid, mp 152-154 °C; TLC (EtOAc/hexane (3:7)) R_f 0.20; ν_{max} (KBr)/cm^{-1} 2245; δ_H (300 MHz, $CDCl_3$) 1.81-1.94 (3H, m), 2.30 (2H, br d, *J* 13.8), 2.45 (1H, d, *J* 13.8), 2.90 (2H, m), 3.19 (1H, m); δ_C (75 MHz, $CDCl_3$) 23.9 (2 CH_2), 25.2 (CH_2), 30.0 (2 CH), 30.8 (CH), 118.6 (C) and 119.0 (2 C); *m/z* 160 (M^+ + 1, 8%), 159 (1), 106 (98) and 54 (100) (Found: M^+, 159.0818. $C_9H_9N_3$ requires 159.0796). The structure of **7b** was confirmed by an X-ray diffraction analysis.

Crystal data of compound **7b** ($C_9H_9N_3$, *M* = 159.08): monoclinic, space group $P2_1/c$, *Z* = 8, *a* = 14.359(2), *b* = 10.237(8), *c* = 13.124(1) Å, β = 111.769(8)°, *V* = 1791.6(3) Å^3, crystal size 0.4× 0.5×0.6 mm, *T* = 298 K, reflections collected 2575, independent reflections 2287. R_f = 0.037, R_w = 0.033. Refinement method: full-matrix least-squares on F^2. All bond distances and bond angles are as expected. These data are deposited with the Cambridge Crystallographic Data Center.

cis,cis-1,3,5-Tris[(*S*)-4-isopropyl-1,3-oxazolin-2-yl]cyclohexane (8a) and _cis,trans_-1,3,5-Tris[(*S*)-4-isopropyl-1,3-oxazolin-2-yl]cyclohexane (8b)

A mixture of trinitrile **7a** (290 mg, 1.8 mmol), L-(*S*)-valinol (742 mg, 7.2 mmol) and $ZnCl_2$ (30 mg, 0.2 mmol) in 1,2-dichlorobenzene (8 mL) was refluxed at 180 °C for 24 h. The mixture was concentrated, and the residue was dissolved in CH_2Cl_2 (20 mL). The organic phase was washed with water (2 × 15 mL) and brine (2 × 15 mL), dried (Na_2SO_4), and chromatographed on a silica gel column by elution with EtOAc to give the *cis,cis*-isomer **8a** (151 mg, 20%) and the *cis,trans*-isomer **8b** (337 mg, 45%).

8a: Solid, mp 92-94 °C; $[\alpha]^{26}_D$ -65.7 (*c* 1.3, $CHCl_3$); TLC (EtOAc) R_f 0.17; ν_{max} (KBr)/cm^{-1} 1664; δ_H (300 MHz, $CDCl_3$) 0.76 (9H, d, *J* 6.9), 0.84 (9H, d, *J* 6.9), 1.53 (3H, dt, *J* 12.6, 12.6, H-2α, H-4α and H-6α), 1.59-1.70 (3H, m), 2.15 (3H, br d, *J* 12.6, H-2β, H-4β and H-6β), 2.63 (3H, tt, *J* 12.6,

3.0, H-1β, H-3β and H-5β), 3.75-3.86 (6H, m, 3 CH_2O) and 4.08 (3H, dt, *J* 7.2, 7.2, 3 CHN); δ_C (75 MHz, $CDCl_3$) 17.6 (3 Me), 18.5 (3 Me), 32.1 (3 CH_2), 32.2 (3 CH), 36.3 (3 CH), 69.5 (3 CH_2), 71.6 (3 CH) and 168.6 (3 C); *m/z* 417 (M^+, 8%) and 374 (100) (Found: M^+, 417.2988. $C_{24}H_{39}N_3O_3$ requires 417.2991).

8b: Oil; $[\alpha]^{26}_D$ -40.2 (*c* 2.9, $CHCl_3$); TLC (EtOAc) R_f 0.22; ν_{max} (neat)/cm^{-1} 1662; δ_H (300 MHz, $CDCl_3$) 0.77-0.90 (18H, m), 1.44-1.73 (6H, m), 2.17 (1H, br d, *J* 12.9, H-2b), 2.27 (2H, br d, *J* 12.9, H-4β and H-6β), 2.63 (1H, tt, *J* 12.9, 3.3, H-1β), 2.78 (1H, tt, *J* 12.9, 3.3, H-3β), 2.84 (1H, br s, H-5α), 3.77-3.91 (6H, m), 4.05-4.15 (3H, m); δ_C (75 MHz, $CDCl_3$) 17.5 (Me), 17.6 (Me), 17.9 (Me), 18.6 (Me), 18.7 (Me), 18.8 (Me), 30.4 (2 CH_2), 32.2 (CH), 32.3 (CH), 32.4 (CH), 32.5 (CH), 32.6 (CH), 32.7 (CH_2), 32.8 (CH), 69.3 (CH_2), 69.4 (2 CH_2), 71.5 (2 CH), 72.0 (CH), 167.7 (C) and 169.4 (2 C); *m/z* 417 (M^+, 45%) and 374 (100) (Found: M^+, 417.2986. $C_{24}H_{39}N_3O_3$ requires 417.2991).

Trimethyl *cis,cis*-1,3,5-trimethylcyclohexane-1,3,5-tricarboxylate (9a) and Trimethyl *cis,trans*-1,3,5-trimethylcyclohexane-1,3,5-tricarboxylate (9b)

Method A. Treatment of Kemp's acid (purchased from Aldrich) with diazomethane according to the reported procedure[7a] gave the triester **9a** in a quantitative yield.

Method B. Under an atmosphere of argon, a solution of the triester **4a** (8.8 g, 34.3 mmol) in Et_2O (50 mL) was added dropwise to the freshly prepared LDA solution (113 mmol) in Et_2O (100 mL) at 0 °C. The mixture was stirred for 2 h, and Me_2SO_4 (14 mL, 147 mmol) was added. The mixture was warmed, stirred at room temperature for 12 h. The precipitates were filtered off, the filtrate was washed with water (3× 50 mL), HCl (20 mL of 1 M solution) and brine (20 mL), dried (Na_2SO_4), and chromatographed on a silica gel column by elution with EtOAc/hexane (10:1) to give the *cis,cis*-isomer **9a** (6.6 g, 64%) and the *cis,trans*-isomer **9b** (1.2 g, 12%).

9a: Solid, mp 80-81 °C (lit.[7a] mp 79-81 °C); TLC (EtOAc/hexane (10:1)) R_f 0.2; δ_H (200 MHz, $CDCl_3$) 0.86 (3H, d, *J* 14.8), 1.11 (9H, s), 2.63 (3H, d, *J* 14.8) and 3.56 (9H, s); δ_C (50 MHz, $CDCl_3$) 31.0 (Me), 41.2 (3 CH_2), 43.5 (3 C), 51.4 (3 Me) and 176.5 (3 C).

9b: Oil; TLC (EtOAc/hexane (10:1)) R_f 0.2; ν_{max} (neat)/cm^{-1} 1731 and 1715; δ_H (300 MHz, $CDCl_3$) 1.02 (1H, d, *J* 14.7), 1.04 (3H, s), 1.07 (6H, s), 1.65 (2H, d, *J* 14.7), 2.07 (2H, d, *J* 14.7), 2.58 (1H, d, *J* 14.7), 3.52 (6H, s) and 3.54 (3H, s); δ_C (75 MHz, $CDCl_3$) 25.7 (Me), 29.5 (2 Me), 40.1 (2 CH_2), 41.1 (2 C), 41.7 (C), 41.8 (CH_2), 51.5 (2 Me), 51.6 (Me), 177.5 (2 C) and 178.4 (C); *m/z* 300 (M^+, 2%) and 121 (100) (Found: M^+, 300.1583. $C_{15}H_{24}O_6$ requires 300.1573).

***cis,trans*-1,3,5-Trimethylcyclohexane-1,3,5-tricarbonitrile (10b) and *cis,trans*-1,3-Dimethylcyclohexane-1,3,5-tricarbonitrile (10c)**

Under an atmosphere of argon, BuLi (4.2 mL, 6.6 mmol, 1.6 M of hexane solution) was added dropwise to a solution of *i*-Pr_2NH (0.92 mL, 6.6 mmol) in Et_2O (30 mL) at 0 °C. The mixture was stirred for 20 min, cooled to -78 °C, and a solution of the trinitrile **7a** (318 mg, 2 mmol) in THF (30 mL)/Et_2O (15 mL) was added dropwise. After 10 min, Me_2SO_4 (0.63 mL, 6.6 mmol) was added dropwise to the resulting pink solution. The mixture was warmed, stirred at 25 °C for 12 h, and quenched by addition of saturated NH_4Cl. The mixture was concentrated by rotary evaporation, diluted with CH_2Cl_2 (40 mL), washed with water (15 mL) and brine (15 mL), dried (Na_2SO_4), and chromatographed on a silica gel column by elution with EtOAc/hexane (1:1) to give the *cis,trans*-isomer of trialkylation product **10b** (201 mg, 50%) and the dialkylation product **10c** (41 mg, 11%).

10b: Solid, mp 227-229 °C; TLC (EtOAc/hexane (1:1)) R_f 0.28; ν_{max} (KBr)/cm^{-1} 2233; δ_H (300 MHz, $CDCl_3$) 1.22 (1H, d, *J* 14.4), 1.49 (6H, s), 1.70 (2H, d, *J* 14.4), 1.98 (3H, s), 2.38 (2H, d, *J* 14.4) and 2.43 (1H, d, *J* 14.4); δ_C (75 MHz, $CDCl_3$) 22.7 (Me), 29.1 (2 C), 29.7 (2 Me), 32.5 (C), 43.1 (2 CH_2), 43.9 (CH_2), 122.3 (2 C) and 123.5 (C); *m/z* 201 (M^+, 1%) and 134 (100) (Found: M^+, 201.1259. $C_{12}H_{15}N_3$ requires 201.1266) (Anal. Found: C, 71.45; H, 7.49; N, 21.08. $C_{12}H_{15}N_3$ requires C, 71.61; H, 7.51; N, 20.88).

10c: Solid, mp 249-250 °C; TLC (EtOAc/hexane (1:1)) R_f 0.20; ν_{max} (KBr)/cm^{-1} 2236; δ_H (300 MHz, $CDCl_3$) 1.20 (1H, d, *J* 14.4), 1.45 (2H, t, *J* 12.9), 1.48 (6H, s), 2.32 (1H, d, *J* 14.4, H-2β), 2.48 (2H, br d, *J* 12.9, H-4β, 6β) and 3.20 (1H, tt, *J* 12.9, 3.0, H-5); δ_C (75 MHz, $CDCl_3$) 24.2 (C-5), 28.1 (Me-1, 3), 32.0 (C-1, 3), 39.0 (C-4, 6), 43.3 (C-2), 119.1 (CN-5), 120.7 (CN-1, 3); *m/z* 187 (M^+, 1%) and 120 (100) (Found: M^+, 187.1107. $C_{11}H_{13}N_3$ requires 187.1109).

***cis,trans*-1,3,5-Tribenzylcyclohexane-1,3,5-tricarbonitrile (11b) and *cis,trans*-1,3-Dibenzylcyclohexane-1,3,5-tricarbonitrile (11c)**

Alkylation of the trinitrile **7a** (159 mg, 1 mmol) with benzyl bromide (1.2 mL, 10 mmol) in Et_2O solution, by a procedure similar to that for **10b**, gave the trialkylation products **11b** (103 mg, 24%) and the dialkylation product **11c** (119 mg, 35%).

11b: Solid, mp 225-227 °C; TLC (EtOAc/hexane (3:7)) R_f 0.25; ν_{max} (KBr)/cm^{-1} 2235; δ_H (300 MHz, $CDCl_3$) 1.45 (1H, d, *J* 14.4), 1.80 (2H, d, *J* 14.4), 2.30 (1H, d, *J* 14.4), 2.45 (2H, d, *J* 14.4), 2.93 (4H, s), 3.46 (2H, s) and 7.22-7.45 (15H, m); δ_C (75 MHz, $CDCl_3$) 34.4 (2 C), 38.6 (C), 39.5 (CH_2),

39.8 (2 CH_2), 40.8 (CH_2), 48.1 (2 CH_2), 121.7 (2 C), 122.5 (C), 127.7 (CH), 128.2 (2 CH), 128.4 (2 CH), 128.7 (4 CH), 130.5 (4 CH), 130.8 (2 CH), 132.4 (2 C) and 134.4 (C); *m/z* (FAB) 429 (M^+). (Found: M^+, 429.2214. $C_{30}H_{27}N_3$ requires 429.2205).

11c: Solid, mp 262-264 °C; TLC (EtOAc/hexane (3:7)) R_f 0.20; ν_{max} (KBr)/cm^{-1} 2240; δ_H (300 MHz, $CDCl_3$) 1.32 (1H, d, *J* 14.4), 1.54 (2H, t, *J* 13.2), 2.15 (1H, d, *J* 14.4), 2.38 (2H, br d, *J* 13.2), 2.89 (4H, s), 3.16 (1H, tt, *J* 13.2, 3.3) and 7.19-7.37 (10H, m); δ_C (75 MHz, $CDCl_3$) 24.0 (CH), 37.2 (2 C), 37.5 (2 CH_2), 40.1 (CH_2), 46.9 (2 CH_2), 119.3 (C), 119.8 (2 C), 128.2 (2 CH), 128.8 (4 CH), 130.3 (4 CH), 132.4 (2 C); *m/z* (FAB) 339 (M^+) (Found: M^+, 339.1736. $C_{23}H_{21}N_3$ requires 339.1735) (Anal. Found: C, 81.15; H, 6.12; N, 12.48. $C_{23}H_{21}N_3$ requires C, 81.38; H, 6.24; N, 12.38).

***cis*,*cis*-1,3,5-Triallylcyclohexane-1,3,5-tricarbonitrile (12a) and *cis*,*trans*-1,3,5-Triallylcyclohexane-1,3,5-tricarbonitrile (12b)**

Alkylation of the trinitrile **7a** (159 mg, 1 mmol) with allyl bromide (0.52 mL, 6 mmol) in Et_2O solution, by a procedure similar to that for **10b**, gave the trialkylation products **12a** (42 mg, 15%) and **12b** (107 mg, 38%).

12a: Solid, mp > 300 °C (dec.); TLC (EtOAc/hexane (4:6)) R_f 0.05; ν_{max} (KBr)/cm^{-1} 2236; δ_H (200 MHz, $CDCl_3$) 1.07 (3H, d, *J* 14.6), 2.36 (6H, d, *J* 7.4), 2.42 (3H, d, *J* 14.6), 5.16-5.32 (6H, m), 5.79-5.97 (3H, m); δ_C (50 MHz, $CDCl_3$) 34.6 (3 C), 41.1 (3 CH_2), 46.7 (3 CH_2), 119.6 (3 C), 121.8 (3 CH_2), 129.7 (3 CH); *m/z* 279 (M^+, 1%) and 136 (100) (Found: M^+, 279.1730. $C_{18}H_{21}N_3$ requires 279.1735).

12b: Solid, mp 103-105 °C; TLC (EtOAc/hexane (4:6)) R_f 0.20; ν_{max} (KBr)/cm^{-1} 2236; δ_H (300 MHz, $CDCl_3$) 1.20 (1H, d, *J* 14.7, H-2α), 1.64 (2H, d, *J* 14.4, H-4α and H-6α), 2.34 (1H, d, *J* 14.7, H-2β), 2.36 (4H, d, *J* 7.5, 1-CH_2 and 3-CH_2), 2.45 (2H, d, *J* 14.4, H-4β, and H-6β), 3.04 (2H, d, *J* 7.5, 5-CH_2), 5.24 (2H, d, *J* 17.1), 5.32 (2H, d, *J* 10.2), 5.38 (1H, d, *J* 10.2), 5.50 (1H, d, *J* 17.1) and 5.80-5.92 (3H, m); δ_C (75 MHz, $CDCl_3$) 32.9 (2 C), 36.8 (C), 37.7 (CH_2), 39.3 (2 CH_2), 40.6 (CH_2), 46.5 (2 CH_2), 121.3 (2 C), 122.0 (2 CH_2), 122.1 (C), 122.6 (CH_2), 129.3 (2 CH), 130.7 (CH); *m/z* 279 (M^+, 7%) and 136 (100) (Found: M^+, 279.1735. $C_{18}H_{21}N_3$ requires 279.1735).

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Key Words

Cyclohexane-1,3,5-tricarbonitrile; Kemp's triacid; Cyclohexane-1,3,5-trioxazoline; Alkylation.

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