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Efficient Synthesis and Theoretical Study of Siloxy-Benzocyclooctenes: 7,8-Bis-trimethylsilanyloxy-5,6,9,10-tetrahydro-benzocyclooctene and 6,9-Dimethyl-7,8-bis-trimethylsilanyloxy-5,6,9,10-tetrahydro-benzocyclooctene-6,9-dicarboxylic Acid Diethyl Ester

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Abstract—2-[2-(2,2-Bis-ethoxycarbonyl-ethyl)-benzyl]malonic acid diethyl ester **2**, 3-[2-(2-ethoxycarbonyl-ethyl)-phenyl]-propionic acid ethyl ester **3**, 2-[2-(2,2-bis-ethoxycarbonyl-propyl)-benzyl]-2-methyl-malonic acid diethyl ester **4**, 7,8-bis-trimethylsilanyloxy-5,6,9,10-tetrahydro-benzocyclooctene **5**, and 6,9-dimethyl-7,8-bis-trimethylsilanyloxy-5,6,9,10-tetrahydro-benzocyclooctene-6,9-dicarboxylic acid diethyl ester **6** have been synthesised for study of their spectroscopic and structural features. The synthetic method involved is mono-alkylation of malonic acid diethyl ester and 2-methyl-malonic acid diethyl ester with 1,2-bis-bromomethyl-benzene in DMSO, and yields esters **2** and **4**, respectively. The decarboxylation of **2** by DMSO/LiCl in the presence of a very small amount of water yields diester **3**. Compounds **3** and **4** undergo acyloin condensation to give siloxy-benzocyclooctenes **5** and **6**, respectively. The calculated structures and parameters of bis-siloxy-benzocyclooctene **6** show the reason why cyclization of **4** was independent of the quantity of reagents used.

Introduction

The relative thermodynamic instability of eight-membered rings has made their derivatives relatively difficult to obtain. It is recognized that a complicating factor is the difficulty of getting the ends of the chain to approach each other; since the conformational entropy of a chain compound is greater than that of a ring.[1] However, when esters **3** or **4** are heated with sodium in refluxing inert solvent, acyloin condensation takes place. The yield of this reaction can be improved by running the reaction in the presence of trimethylchlorosilane TMSCl, where the dianionic compound is converted to the bis-silylenol ether.[2] In this process, TMSCl reacts with any basic species formed, thus keeping the reaction mixture neutral and preventing other processes such as Claisen and Diekmann condensations. Additionally, since TMSCl is a poor electron acceptor,[3] acyloin condensation processes are unaffected when this later is present in reaction.

Bis(trimethylsiloxy)alkenes are stable under non-hydrolytic conditions, and can be used for the synthesis of different compounds and study of various reactions. Some uses of these compounds are as follows: solvolysis to acyloins,[4,5] reaction with acetic anhydride to yield α-acetoxy ketones,[6] reaction with 2,4-dinitro phenyl-hydrazine,[7] reaction with bromine or thiocyanates to give diketones, α,α′-dibromo-diketones or isothiocyanosilane,[8,9] reaction with copper(II) salts to yield diketones,[10] synthesis of different heterocyclic derivatives,[11] synthesis of diastereomerically pure vicinal diamines,[12] and so on.

Results and Discussion

Our approach to the synthesis of benzocyclooctene derivatives is based on preparation of 2-[2-(2,2-bis-ethoxycarbonyl-ethyl)-benzyl]malonic acid diethyl ester **2**, 3-[2-(2-ethoxycarbonyl-ethyl)-phenyl]-propionic acid ethyl ester **3**, and 2-[2-(2,2-bis-ethoxycarbonyl-propyl)-benzyl]-2-methyl-malonic acid diethyl ester **4** and acyloin condensation of **3** and **4**. We comment here on the details of this procedure (see Scheme 1).

Solvents have been shown to play an important role in the selectivity control of numerous carbanion reactions.[13] For the alkylation of malonoesters, however, somewhat surprisingly, this intriguing problem has only received sparse attention.[14,15] The available evidence until recently being

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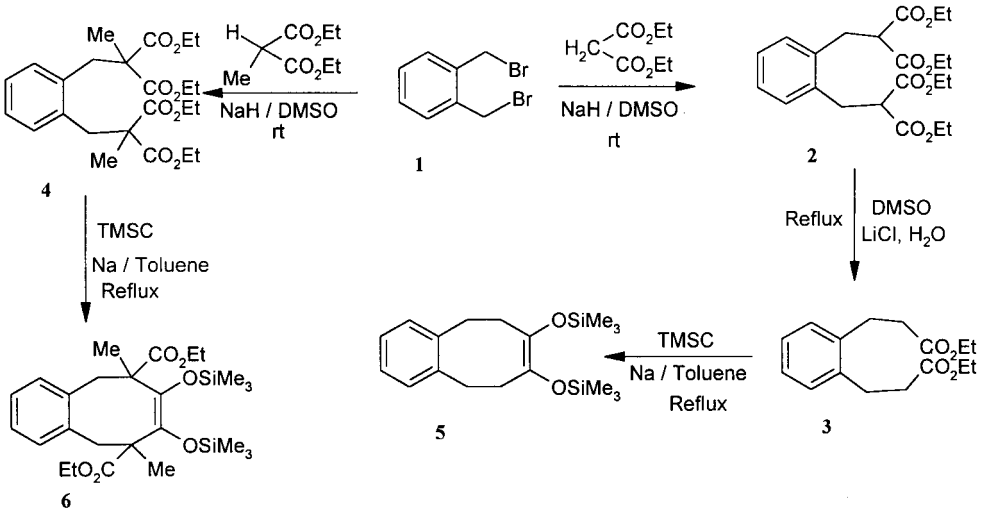
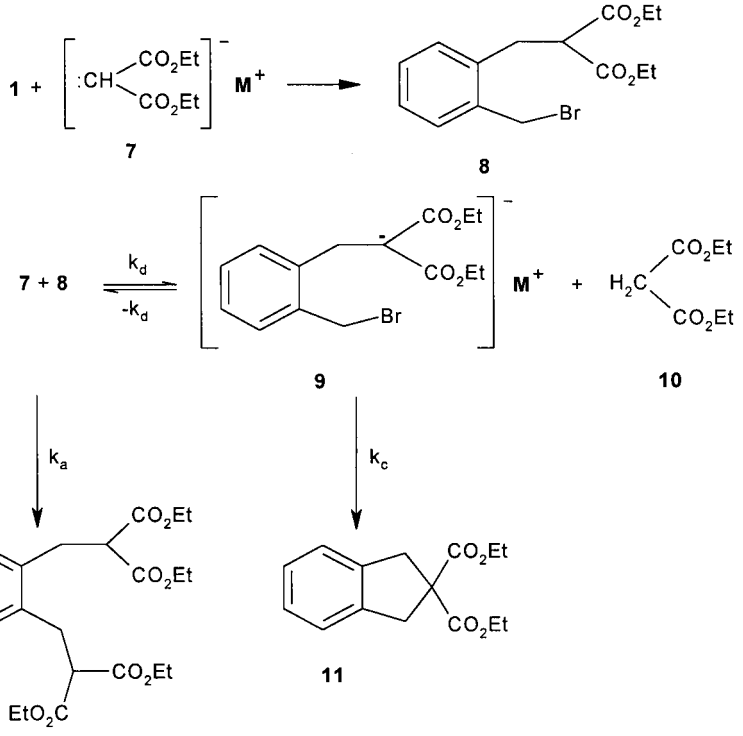


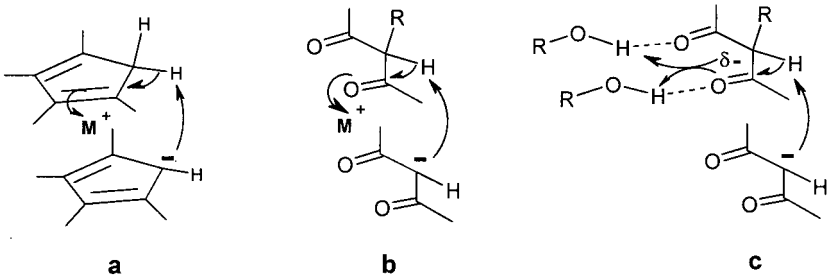
Scheme 1.

based, in most instances, on incomplete and not always reliable data. Zavada et al. however, recently reported, the effects of solvent on the mono- vs dialkylation of alkali salts of diethyl malonate.[16,17] Contrary to the widely held opinion that protic solvents favor monoalkylation whereas aprotic (inert) solvents support dialkylation of the malonate carbanion, exactly the opposite results were obtained in the reaction of the dibromide **1** in ethanol and dimethylsulfoxide, the former solvent strongly preferring dialkylation (cyclization) and the latter monoalkylation. In order to discuss this effect we have shown the alkylation of alkali metal salt of diethyl malonate **7** with the dihalide **1** in the Scheme 2. This scheme summarizes the sequence of reaction steps anticipated[18] in the alkylation.

According to ample literature evidence,[13] a pronounced slowing-down of S_N2 displacement involving a metal salt as nucleophile is usually observed under ion pairing conditions. In contrast, numerous precedents exist in literature,[19] showing that contact ion-paired species may be more reactive than the separated ions in proton-transfer reactions. As a pertinent example, Hogen–Esch and Smid[20] observed that the contact ion-paired species reacted faster than the solvent-separated ion-pair or free carbanion in the proton transfer between fluorene and fluorenyl carbanion. A simple model of the activating effect of the metal counter ion was suggested (Scheme 3a) as an explanation, which can easily be applied to the proton-transfer step in the present reaction (Scheme 3b). Conceivably, hydrogen bonding may exert a



Scheme 2.



Scheme 3.

similar activating effect (Scheme 3c) on the rate of the proton-transfer as the metal ion pairing (Scheme 3b) does in the reaction. This can explain the striking difference in the alkylation selectivity which has been observed between two polar (ion-pairs separation) solvents, the protic ethanol and the aprotic DMSO.

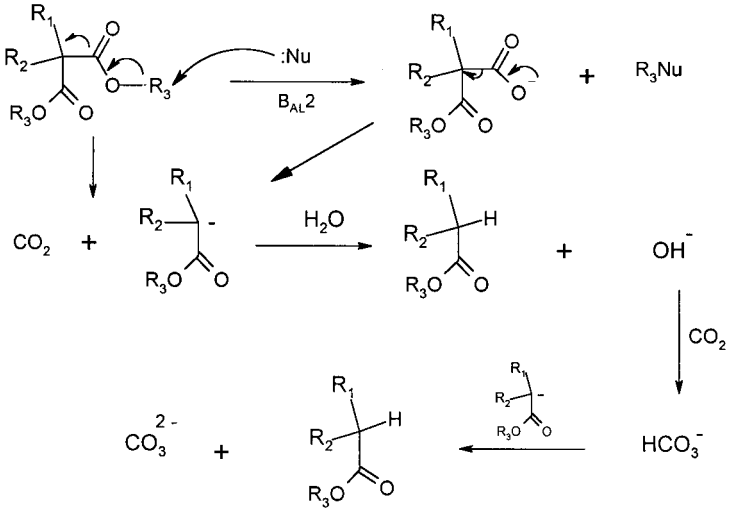
Indeed, hydrogen bonding as well as ion pairing may play an important role in selectivity control, both factors strongly supporting dialkylation. However the selectivity of the alkylation depends most effectively on the solvent polarity, as the bis-monoalkylation prevails in the most polar solvent, DMSO.

Thus monoalkylation of malonic acid diethyl ester and 2-methyl-malonic acid diethyl ester with 1,2-bis-bromomethyl-benzene in DMSO give **2** and **4**, in yields of 83 and 85%, respectively.

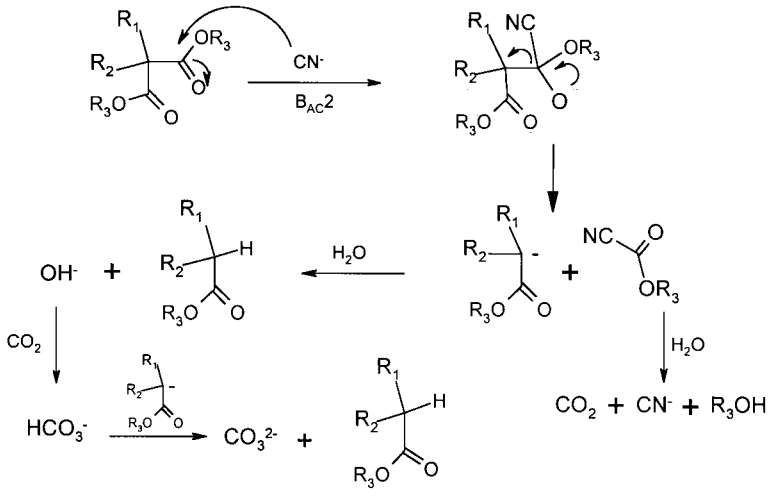
The decarbalkoxylations of geminal diesters by water+DMSO with or without the presence of added salts, is a convenient preparative route leading to esters. This type of reaction has been studied using a variety of substrates and diverse salts.[21] The addition of salts such as KCN, NaCl, or LiCl to the H_2O/DMSO solvent dramatically enhances the decarbalkoxylation rates of these substrates. In the absence of salts it would appear that the mechanism is water catalyzed nucleophilic attack by water at the ester carbonyl similar to the mechanism proposed for neutral hydrolysis of other acyl activated esters. To confirm this idea, the H_2O and D_2O isotope effects were studied in the presence and absence of LiCl, which revealed values of k_{H2O}/k_{D2O} of 2.5 for the compound **2** (no added salt) and 1.08 (1 equiv. LiCl added). The absence of a significant isotope effect in the presence of LiCl is consistent with a nucleophilic catalysis mechanism $B_{AC}2$ or $B_{AL}2$ route involving the nucleophile. In the absence of LiCl it would appear that the mechanism is a water catalysed nucleophilic attack (or a kinetic equivalent) at the ester carbonyl $B_{AC}2$.

Of course, the overall mechanistic route could comprise the simultaneous occurrence of both routes. The pathway outlined below appears to be the dominant mechanistic $B_{AL}2$ route (see Scheme 4).

Since the addition of salts to the solvent system shows an enhancement in the rate of decarbethoxylation, analysis of low boiling materials distilled from the reaction with addition of 2 equiv. KCN was of interest to determine the CH_3CH_2CN/CH_3CH_2OH ratio from a mechanistic point of view. The average experimental result was 0.65. It might also be noted at this point that K_2CO_3 could be isolated in ca. 45% yield and CO_2 was also evolved as evidenced by trapping as $BaCO_3$. The formation of CH_3CH_2CN can only arise from $B_{AL}2$ cleavage as depicted in Scheme 4. A concerted decarbethoxylation to directly yield carbanion must also be considered. However, the isolation of ethanol indicates that



Scheme 4.



Scheme 5.

the $B_{AC}2$ mechanism and/or water catalyzed nucleophilic attack is competitive. Scheme 5 presents the mechanism for this route. Intermediates such as ethyl cyanoformate would be expected to undergo rapid hydrolysis in H_2O/DMSO.[22] The tetraester **2** exhibits dual pathways in which this ester reacts predominantly via the $B_{AC}2$ route.

Conversion of the tetraester **2** to the diester **3**, in a yield of 91%, takes place by refluxing **2** in DMSO/LiCl, in presence of a very small amount of H_2O for 4 h.

The diester **3** was also cyclized via acyloin condensation in high dilution to yield 7,8-bis-trimethylsilanyloxy-5,6,9,10-tetrahydro-benzocyclooctene **5**, 64%. Alkylation of 2-methyl-malonic acid diethyl ester with **1** in DMSO yielded **4**, 85%. Condensation of **4** with 5 and 10 equiv. of sodium/TMSCl yields only one product, 6,9-Dimethyl-7,8-bis-trimethylsilanyloxy-5,6,9,10-tetrahydro-benzocyclooctene-6,9-dicarboxylic acid diethyl ester **6**, in a yield of 71%, regardless of the amount of reagent used. This result provides evidence that the second ester groups are incapable of participating in the acyloin condensation reaction due to their steric situation.

It is notable that compound **6** has two chiral centers, and so it must have two diasteromers: a C_2-symmetric form, *trans*-isomer, and a *meso* form, *cis*-isomer. Based on the chromatographic parameters and their role in separation of nearly related compounds, in one hand, and the possibility of decomposition in the other, we have studied various compositions of TBME, hexane, methanol, CH_3CN and H_2O on different stationary phases to achieve separation of these two isomers using preparative HPLC (70 and 25% of the synthesis product, respectively). The best chromatographic condition found was: a mixture of 98% hexane and 2% TBME as eluent on a normal diol-phase.

Theoretical studies

The problem of finding significantly populated conformations has been one of the major obstacles in studying conformationally flexible molecules. A number of algorithms for locating energy minima on a high-dimensional energy hypersurface have been proposed. They can be classified into two categories, random[23] and systematic.[24] While random generation is the method of choice for macromolecules, the application of a systematic method to a chain molecule (*n* rotatable bonds) is severely limited due to the fact that the number of trial conformations increases at the rate of 3^n.[24a,b]

Eight-membered rings, because of their low barrier of pseudorotation, are highly flexible and the conformation of the ring depends strongly on the number and nature of substituents. Molecular mechanics models are designed to provide good estimates of conformational energy differences, while the semiempirical molecular orbital models are not entirely satisfactory for this purpose.[25] Determination of the conformation of compound **6**, in order to allow examination of possible correlation between molecular structure and the reason why cyclization of **4** was independent of the quantity of reagents used, were carried out by *Metropolis Monte Carlo* (MMC) search using MM+ molecular mechanics by Polak–Ribiere[26] conjugate gradient geometry optimization method.

In Monte Carlo searches that use the random walk, it is often necessary to raise the temperature used in the acceptance test to increase the probability of accepting a high energy conformation to cross a potential barrier. Temperature adjustment is typically done after repeatedly finding the same duplicate conformation or repeatedly rejecting new conformations based on the Metropolis criterion.[27] Rotation is used for acyclic bond dihedral angles and for dihedral angles in the cyclooctene ring, dihedral angles are rotated by the 'torsional flexing' motion of Kolossvary and Guida,[28] which effectively leads to new ring conformations while avoiding large atomic displacements that can decrease the efficiency of optimization. Since molecular flexibility is usually due to rotation of unhindered bond dihedral or torsion angles, with little change in bond lengths or bond angles, a frequent choice (used here) is to only consider the variation of bond torsion angles. This search was done using the program ChemPlus.[29] After the MMC search each conformation of **6** used as starting geometry for subsequent MM+ with Newton–Raphson[26] geometry optimization and

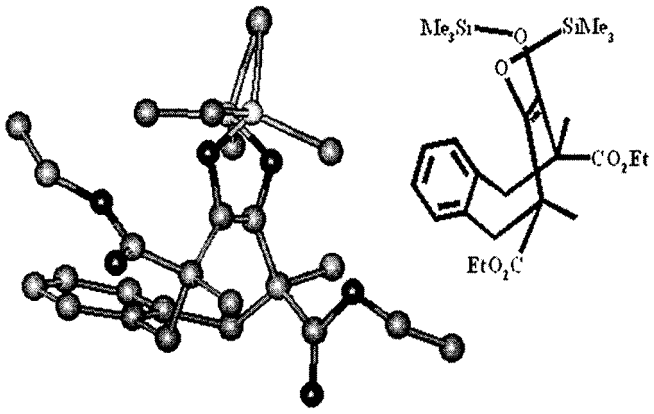


Figure 1. The most favoured conformer of **6** (*trans-TB*).

Table 1. Calculated distances between the carbonyls in conformers of **6** with MM+ and AM1 Å

Method	a. *cis*-skew	b. *cis*-TB	c. *cis*-TB′	d. *trans*-TC	e. *trans*-TB	f. *cis*-TC
MM+	5.02	6.098	3.08	5.10	4.89	2.91
AM1	4.95	6.097	3.01	5.12	4.88	3.03

quantum mechanical semiempirical AM1 (Austin Model 1)[30] calculations using HyperChem.[31]

Our theoretical study also shows that the distance between two carbonyl carbons of ester groups on the first ring created is too long and getting the two ester groups of compound **6** to approach each other is not feasible, whereas the MMC search shows that the most favoured form of this compound is the *trans*-twist boat conformer (see Fig. 1).

The distances between the two carbonyl groups in different conformers of compound **6**, calculated with MM+ and AM1 are shown in Table 1.

Based on NMR data, it can be deduced that the two ester groups in *cis* (*meso*) isomer are more favorably situated in two sides of cyclooctene ring while the latter has its more favoured *twist boat* conformation. This point gives the argument why in *cis* isomer (*meso*) no more the second acyloin condensation does not take place to create a second ring. Since calculated distance between two carbons participating in the condensation is 6.098 Å (*b. cis-TB* conformer). It is worthy to add that small differences between chemical shifts of some apparently equivalent atoms (C, H) must be attributed to decline in symmetry of molecules as they are some what tilted from their higher symmetry.

Conclusion

Based on available knowledge about the mechanism of the synthetic steps, we have deduced appropriate reaction conditions for the synthesis of medium sized (eight-membered) ring compounds fused to benzene, starting from easily made esters for synthesis of other derivatives.[32] Our experimental results, as well as calculations, show the reason why the second ester groups of tetraester **4** are incapable of participating in a condensation reaction to create a second ring, as might have been expected. An attractive extension of the above procedure is its application to the synthesis of relatively thermodynamically unstable benzocyclooctene rings from easily made esters, for the synthesis of their derivatives.

Experimental

All manipulations were performed under an atmosphere of purified argon and using gas/vacuum double manifold and standard Schlenk technique. DMSO, TMSCl and toluene were distilled from CaH_2 immediately prior to use. Elemental analyses: Carlo–Erba Modell 1104; IR: Bruker IFS 25; ^1H and ^{13}C NMR: Bruker AM-400, Bruker AC-200; MS: Varian MAT 311A, Varian MAT 111; melting points: Büchi SMP-20; GC/MS: Top series 8000-Trio 1000 Fison Instruments. The analytic HPLC consisted of a Spectra-Physics SP 8700, solvent delivery system, Knauer refractometer detector model 2025/50 and Zeiss UV-spectrophotometer detector PM2DLC. Stationary phases used were diol-phase, SI-100, RP-18, CN-phase and NH_2-phase columns (250×4.6 mm I.D.; 7 μm). The preparative HPLC consisted of a Gynkotek-high precision pump model 480, Knauer differential-refractometer detector and Knauer UV-photometer. The normal diol-phase column (250×8 mm I.D.; 7 μm) was used. 1,2-Bis-bromomethyl-benzene **1** was prepared following the procedure reported in Ref. 33.

2-[2-(2,2-Bis-ethoxycarbonyl-ethyl)-benzyl]malonic acid diethyl ester 2. Sodium hydride (60% in mineral oil, 2.0 g, 50 mmol) was washed with pentane and suspended in dimethyl sulfoxide (25 mL). A solution of diethyl malonate (8.0 g, 50 mmol) in dimethyl sulfoxide (25 mL) was slowly added to the stirred slurry, followed by 1,2-bis-bromomethyl-benzene (5.28 g, 20 mmol) dissolved in dimethyl sulfoxide (25 mL). After stirring for 30 min at rt, the reaction mixture was poured into water (200 mL), neutralized

with 0.1 M aqueous HCl and extracted with ether (4×40 mL). The combined extracts were washed with water (2×20 mL), dried over $MgSO_4$ and the solvent was evaporated. The unreacted diethyl malonate was distilled off (50°C/0.05 Torr, Kugelrohr) and distillation at 140–150°C/0.05 Torr (Kugelrohr) afforded the product **2**, as a colourless oil (7.05 g, 83%). ^{1}H NMR δ 1.20 (t, 12H, J=7.1 Hz), 3.28 (d, 4H, J=7.6 Hz), 3.70 (t, 2H, J=7.6 Hz), 4.15 (q, 8H, J=7.1 Hz), 7.12 (m, 4H); EI MS m/z (relative intensity) 422 (M^+, 60), 377 (45), 284 (100), 216 (50), 211 (50), 210 (80), 189 (45), 117 (60). Anal. Calcd for $C_{22}H_{30}O_8$ (422.48) C, 62.54; H, 7.16; Found C, 62.28; H, 7.05.

2-[2-(2,2-Bis-ethoxycarbonyl-propyl)-benzyl]-2-methyl-malonic acid diethyl ester 4. The procedure described above was followed using sodium hydride (60% in mineral oil, 2.0 g, 50 mmol), 2-methyl-malonic acid diethyl ester (8.7 g, 50 mmol), and 1,2-bis-bromomethyl-benzene **1** (5.28 g, 20 mmol) to yield **4**, (7.65 g, 85%, 140–150°C/0.05 Torr, Kugelrohr) as white needles, mp 63°C, ^{1}H NMR δ 1.20 (t, 12H, J=7.1 Hz), 3.28 (d, 4H, J=7.6 Hz), 3.70 (t, 2H, J=7.6 Hz), 4.15 (q, 8H, J=7.1 Hz), 7.12 (m, 4H); EI MS m/z (relative intensity) 422 (M^+, 60), 377 (45), 284 (100), 216 (50), 211 (50), 210 (80), 189 (45), 117 (60). Anal. Calcd for $C_{24}H_{34}O_8$ (422.48) C, 63.98; H, 7.61; Found C, 64.13; H, 7.70.

3-[2-(2-Ethoxycarbonyl-ethyl)-phenyl]-propionic acid ethyl ester 3. In a 100 mL rb flask equipped with magnetic stirrer bar and a reflux condenser were placed 2-[2-(2, 2-bis-ethoxycarbonyl-ethyl)-benzyl] malonic acid diethyl ester **2** (6.33 g, 15 mmol), DMSO (50 mL), water (0.5 mL), and LiCl (2.5 g, 60 mmol). The solution was heated to reflux with stirring for 4 h. During this period, the mixture becomes turbid and pale yellow. A quenched aliquot and GC analysis indicated only less than 3% starting tetraester. The reaction mixture was poured into water (200 mL), and extracted with ether (4×40 mL). The combined extracts were washed with water (2×20 mL), dried over $MgSO_4$ and the solvent was evaporated. Distillation at 130–140°C/0.05 Torr (Kugelrohr) afforded the product **3** as a colourless oil (3.78 g, 91%). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.20 (t, 12H, J=7.1 Hz), 3.28 (d, 4H, J=7.6 Hz), 3.70 (t, 2H, J=7.6 Hz), 4.15 (q, 8H, J=7.1 Hz), 7.12 (m, 4H); EI MS m/z (relative intensity) 422 (M^+, 60), 377 (45), 284 (100), 216 (50), 211 (50), 210 (80), 189 (45), 117 (60). Anal. Calcd for $C_{16}H_{22}O_4$ (278.35) C, 69.04; H, 7.97; Found C, 69.23; H, 7.85. GC analysis of low boiling material distilled from the reaction after 4 h heating period (the tetraester **2**, 0.015 mol; KCN, 0.06 mol; and H_2O, 0.03 mol. In 50 mL DMSO) were performed by GC/MS. The average experimental data (CH_3CH_2CN/CH_3CH_2OH ratio) for three times runs was 0.65, no starting material was detected and isolated K_2CO_3 was ca. 46% and CO_2 was evolved as evidenced by trapping as $BaCO_3$. Two runs were performed simultaneously in the same oil bath, and both reactions were quenched with water, extracted with ether and analyzed by GC/MS. In the water run 3 mmol of tetraester **2**, H_2O and 6 mmol LiCl (if present) was dissolved in 15 mL DMSO as the procedure described above. The D_2O run was prepared in an identical fashion, except that D_2O was used. The H_2O and D_2O isotope effects with or without the presence of added LiCl revealed a k_{H2O}/k_{D2O} of 2.5 (not added LiCl) and 1.08 (1 equiv. LiCl added).

7,8-Bis-trimethylsilanyloxy-5,6,9,10-tetrahydro-benzocyclooctene 5. A three neck, round bottom flask was fitted with a Friedrich condenser, a Herschberg stirrer, and a pressurized addition funnel. Septa were placed over the mouths of the condenser and funnel. The system was flame dried under vacuum and purged with argon twice. Toluene (200 mL, distilled from CaH_2, degassed with Ar) was charged into the flask through the addition funnel followed by sodium (10 g, 0.435 mol, 4.8 equiv.) in pieces, cut under pentane. The solution was refluxed (110°C) and stirred for 2 h to produce a sodium dispersion. The addition funnel was charged with toluene (150 mL), 3-[2-(2-ethoxycarbonyl-ethyl)-phenyl]-propionic acid ethyl ester **3** (25 g, 90 mmol, distilled), and trimethylsilyl chloride (54 g, 0.5 mol, 5.5 equiv., distilled from CaH_2). The solution in the addition funnel was mixed via Ar bubbling and then added dropwise over 6 h to the refluxing reaction mixture, with stirring. The reaction mixture turned purple upon addition, becoming brown one-third of the way through the addition. After addition, stirring and refluxes were continued for 12 h. After being cooled to room temperature, the mixture was vacuum filtered through glass wool and then vacuum filtered through 1 cm of Celite on a glass frit to remove residual sodium particles. The resulting light yellow filtrate was distilled to yield **5** (19.37 g, 58 mmol, 64%); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.11 (m, 4H), 2.93 (t, 4H), 2.64 (t, 4H), 0.31 (s, 18H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 139.47, 133.46, 130.31, 126.26, 33.48, 32.33, 0.67; EI MS m/z (relative intensity) 334 (M^+, 26), 219 (10), 147 (38), 129 (9), 117 (21), 104 (11), 75 (28), 73 (100), 45 (16). Anal. Calcd for $C_{18}H_{30}O_2Si_2$ (334.61) C, 64.61; H, 9.04; Found C, 64.81; H, 9.23.

6,9-Dimethyl-7,8-bis-trimethylsilanyloxy-5,6,9,10-tetrahydro-benzocyclooctene-6,9-dicarboxylic acid diethyl ester 6. The procedure described above was followed using sodium (10 g, 0.435 mol, 4.8 equiv.), 2-[2-(2,2-bis-ethoxycarbonyl-propyl)-benzyl]-2-methyl-malonic acid diethyl ester **4** (38 g, 90 mmol, recrystalized from $CHCl_3$), and trimethylsilyl chloride (54 g, 0.5 mol, 5.5 equiv., distilled from CaH_2) to yield **6**, (32.379 g, 64 mmol, 71%) as a pale yellow oil. The resulting **6** was separated into two fractions (diastereomers) by preparative HPLC, using a mixture of 98% hexane and 2% TBME as eluent in a normal diol-phase column. A small amount of corresponding hydrolysis product, α-hydroxyketone derivative was also separated because of instability of bis-trimethylsiloxy-benzocyclooctenes in above mentioned chromatographic condition.

The first fraction (*trans*-diastereomer) was characterized as follows: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.13 (m, 4H), 3.85 (q, 4H), 3.39 (dd, 4H), 1.51 (d, 6H), 1.28 (t, 6H), 0.22 (s, 18H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 149.33, 149.26, 138.97, 138.91, 128.59, 128.42, 125.29, 125.25, 94.33, 94.19, 64.57, 64.26, 33.06, 32.95, 31.43, 14.48, 14.46, 13.91, 13.84, 0.002; EI MS m/z (relative intensity) 466 (1.0), 433 (1.1), 419 (1.5), 409 (1.7), 406 (3.2), 394 (3.5), 379 (4.7), 377 (2.6), 366 (4.7), 360 (2.8), 351 (3.6), 349 (3.1), 321 (15.1), 306 (62.0), 293 (2.4), 278 (53.1), 261

(49.0), 247 (3.6), 232 (40.0), 214 (78.9), 206 (9.0), 199 (5.1), 189 (98.5), 186 (59.0), 159 (46.0), 145 (20.3), 131 (100), 117 (39.4), 105 (28.4),102 (19.0), 91 (41.0), 75 (26.3), 73 (85.8), 59 (7.3), 43 (43.4); CI-CH_4 MS *m/z* (relative intensity) 507 $(M+1)^+$ (3.1), 481 (15.0), 466 (3.0), 451 (4.1), 407 (12.2), 378 (3.0), 363 (5.0), 347 (4.1), 334 (4.0), 334 (100.0), 319 (100.0), 305 (18.0), 275 (7.1), 261 (14.0), 245 (55.0), 229 (51.0), 219 (97.1), 205 (34.0), 191 (12.0), 171 (15.0), 155 (52.0), 147 (100.0), 129 (34.0), 117 (100.0), 104 (38.0), 91 (10.0), 73 (100.0), 45 (38.4), 29 (100.0), 17 (93.1).

The second fraction (*cis*-isomer) was characterized as: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.90 (m, 4H), 3.86 (q, 2H), 3.63 (q, 2H), 3.11 (d, 4H), 1.26 (s, 3H), 1.21 (s, 3H), 1.04 (t, 3H), 0.96 (t, 3H), 0.00 (s, 18H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 149.42, 149.39, 139.19, 138.85, 129.78, 129.35, 126.22, 94.39, 94.16, 64.72, 64.46, 33.81, 33.33, 31.58, 14.93, 14.89, 14.13, 14.08, 0.013; EI MS *m/z* (relative intensity) 466 (1.1), 421 (12.0), 394 (1.0), 378 (5.0), 363 (2.0), 351 (1.0), 349 (1.0), 321 (6.1), 293 (1.0), 278 (18.0), 261 (47.0), 242 (2.3), 232 (42.0), 214 (83.1), 205 (5.1), 199 (5.3), 189 (25.2), 186 (66.0), 171 (3.2), 169 (4.1), 159 (48.2), 158 (46.0), 149 (7.6), 147 (6.7), 145 (10.7), 143 (13.9), 131 (100.0), 129 (4.7), 117 (33.9), 105 (18.8), 102 (18.1), 91 (37.7), 73 (87.3), 61 (7.8), 43 (16.1); CI-CH_4 MS *m/z* (relative intensity) 507 $(M+1)^+$ (3.5), 466 (49.0), 451 (51.2), 435 (43.1), 421 (100.0), 404 (28.2), 391 (13.0), 378 (100.0), 362 (98.1), 347 (40.2), 333 (43.0), 319 (34.0), 305 (41.0), 287 (42.1), 276 (23.1), 232 (100.0), 213 (100.0), 191 (78.0), 187 (100.0), 173 (65.0), 157 (100.0), 147 (100.0), 131 (89.0), 117 (70.0), 103 (32.5), 91 (24.0), 73 (100.0), 41 (56.1), 29 (85.0), 17 (63.0). Anal. Calcd for $C_{26}H_{42}O_6Si_2$ (506.79) C, 61.62; H, 8.35; Found C, 61.51; H, 8.16.

Theoretical calculations of 6,9-dimethyl-7,8-bis-trimethylsilanyloxy-5,6,9,10-tetrahydro-benzocyclooctene-6,9-dicarboxylic acid diethyl ester 6. The structure of **6** was drawn in 2D and was converted to 3D using HyperChem, and pre-minimized by Polak–Ribiere geometry optimization using MM+. The MMC search was carried out using this structure with MM+ and Polak–Ribiere geometry optimization using ChemPlus. This search was executed with range for acyclic or ring torsion variation ±10–120°, Random Walk, and Metropolis Criterion use T=300 K, switch to 400 K. All calculations were performed on a Pentium 166 MHz computer.

The structures **6a–f** were found by MMC, which were re-minimized by Newton–Raphson optimization using MM+. In our semiempirical AM1 calculations we used these structures as the starting point for the optimization jobs. Energy minimizations were performed until the absolute value of the largest partial derivative of energy with respect to the coordinates was below 0.01 kcal mol^{-1} Å^{-1}. Calculated data of structures **6a–f** are as follows:

a. cis-skew conformer

a-1. MM+—Bond stretching=3.33851, Angle strain =13.2337, Dihedral=3.5564, Vdw energy=4.22826, Stretch-bend energy=0.447529, Electrostatic energy= −0.801628 kcal/mol.

a-2. AM1—Total Energy=−138379.0835242, Binding Energy=−7520.5459522, Isolated Atomic Energy= −130858.5375720, Electronic Energy=−1445037.3816034, Core–Core Interaction=1306658.2980791, Heat of Formation=−314.9879522 kcal/mol.

b. cis-twist boat conformer

b-1. MM+—Bond stretching=3.34686, Angle strain= 14.1988, Dihedral=6.36952, Vdw energy=1.52549, Stretch-bend energy=0.541038, Electrostatic energy= −1.12608 kcal/mol.

b-2. AM1—Total Energy=−138385.2877156, Binding Energy=−7526.7501436, Isolated Atomic Energy= −130858.5375720, Electronic Energy=−1474589.5008138, Core–Core Interaction=1336204.2130981, Heat of Formation=−321.1921436 kcal/mol.

c. cis-twist boat conformer

c-1. MM+—Bond stretching=3.33851, Angle strain= 13.2337, Dihedral=3.5564, Vdw energy=4.22826, Stretch-bend energy=0.447529, Electrostatic energy= −0.801628 kcal/mol.

c-2. AM1—Total Energy=−138387.2956649, Binding Energy=−7528.7580929, Isolated Atomic Energy= −130858.5375720, Electronic Energy=−1473547.7900084, Core–Core Interaction=1335160.4943435, Heat of Formation=−323.2000929 kcal/mol.

d. trans-twist chair conformer

d-1. MM+—Bond stretching=3.33851, Angle strain= 13.2337, Dihedral=3.5564, Vdw energy=4.22826, Stretch-bend energy=0.447529, Electrostatic energy= −0.801628 kcal/mol.

d-2. AM1—Total Energy=−138385.4748943, Binding Energy=−7526.9373223, Isolated Atomic Energy= −130858.5375720, Electronic Energy=−1456740.8932233, Core–Core Interaction=1318355.4183290, Heat of Formation=−321.3793223 kcal/mol.

e. trans-twist boat conformer

e-1. MM+—Bond stretching=3.31088, Angle strain= 13.3497, Dihedral=5.28457, Vdw energy=1.81986, Stretch-bend energy=0.546829, Electrostatic energy= −1.25593 kcal/mol.

e-2. AM1—Total Energy=−138387.6145492, Binding Energy=−7529.0769772, Isolated Atomic Energy= −130858.5375720, Electronic Energy=−1473632.3917278, Core–Core Interaction=1335244.7771786, Heat of Formation=−323.5189772 kcal/mol.

f. cis-twist chair conformer

f-1 MM+—Bond stretching=3.16996, Angle strain=14.4689, Dihedral=4.40099, Vdw energy= 3.86709, Stretch-bend energy=0.380132, Electrostatic energy=−1.95244 kcal/mol.

f-2. AM1—Total Energy=−138380.7652243, Binding Energy=−7522.2276523, Isolated Atomic Energy= −130858.5375720, Electronic Energy=−1468430.8959513, Core–Core Interaction=1330050.1307270, Heat of Formation=−316.6696523 kcal/mol.

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