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Synthesis of 2,8-Dioxaspiro[4.5]decane-1,3,7,9-tetrone and the Reactions with Amines

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For the studies of highly-sophisticated utilization of itaconic anhydride, some compounds of polybasic carboxylic acids having a quaternary or a spiro carbon atom were prepared, starting from itaconic anhydride and isoprene. Aliphatic tetracarboxylic dianhydride having a spiro carbon atom with five- and six-membered rings, 2,8-dioxaspiro[4.5]decane-1,3,7,9-tetrone (TCDA), was also obtained. The reaction of TCDA with primary amines and subsequent dehydration gave two types of products, either diimides or imide (with five-membered ring)-anhydrides (with six-membered ring), depending on the hydrocarbon moiety of the amines used. It was suggested that each imide-anhydride was formed by the intramolecular ring transformation of the intermediate amic acid-anhydride.

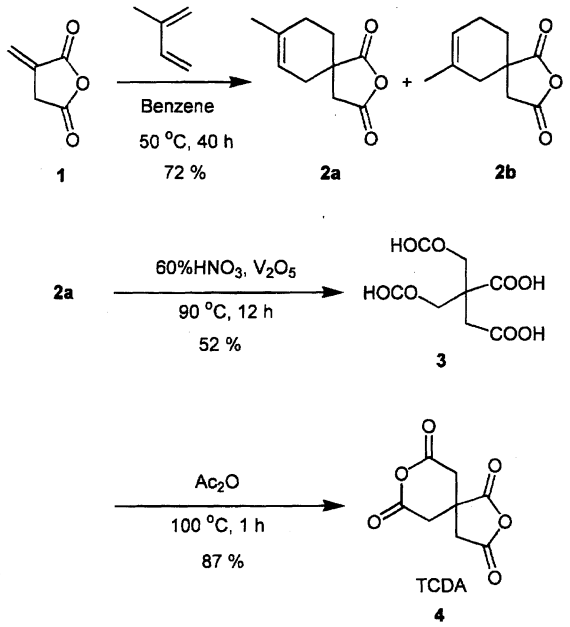
In the syntheses of compounds possessing complex molecular architecture such as natural products, it is often significant to create a quaternary or a spiro carbon atom containing differentiated functionality and substituents.[1—4] Especially, the polybasic carboxylic acids containing a quaternary center or a spirocycle are important as the building blocks for chiral compounds[5,6] and dendrimers.[7—10] Therefore, a simple and efficient procedure for the generation of such quaternary centers or spirocycles from readily available starting materials is required.

Itaconic anhydride (**1**) has a unique structure which may fit various chemical conversions. Nevertheless, because of the isomerization of itaconic anhydride (**1**) to citraconic anhydride by heating or with bases, which was accelerated in polar solvents,[11—14] there have been very few reports on the highly-sophisticated utilization of this compound **1**. We have started to synthesize the compounds having a quaternary or a spiro carbon atom by a convenient method starting from commercially available itaconic anhydride. Previously, we reported on the preparations of an unsymmetric tetracarboxylic acid, 3-carboxy-3-(carboxymethyl)hexanedioic acid, and the derivatives thereof.[15]

In this article, we describe the facile synthesis of some novel aliphatic polybasic carboxylic acids having a quaternary or a spiro carbon atom, and the interesting intramolecular ring transformation in the reaction of the resulting aliphatic tetracarboxylic dianhydride, 2,8-dioxaspiro[4.5]-decane-1,3,7,9-tetrone (TCDA), with amines.

Results and Discussion

Some novel aliphatic polybasic carboxylic acids having a quaternary or a spiro carbon atom were prepared by a simple and easy procedure as shown in Scheme 1. Diels–Alder reaction of itaconic anhydride with isoprene was carried out under mild conditions in order to prevent the isomerization of



Scheme 1.

itaconic anhydride to citraconic anhydride.[11—15] The reaction period necessary to complete the reaction was 9 d at room temperature and 40 h at 50 °C. In order to determine the ratio of 8-methyl-2-oxaspiro[4.5]dec-7-ene-1,3-dione (**2a**) to its regio isomer (**2b**), derivation to dimethyl esters from the crude products, a mixture of **2a** and **2b**, and GC/MS and GC analyses of the dimethyl esters were carried out to show that the regio isomer ratios of **2a/2b** were 4.2 : 1 at room temperature and 3.8 : 1 at 50 °C in the resulting products. In either condition, the "para" product (**2a**) was favored over the "meta"[16—18] and neither citraconic anhydride nor the adduct derived from citraconic anhydride was observed.

The regioselectivity of a Diels–Alder adduct can be gen-

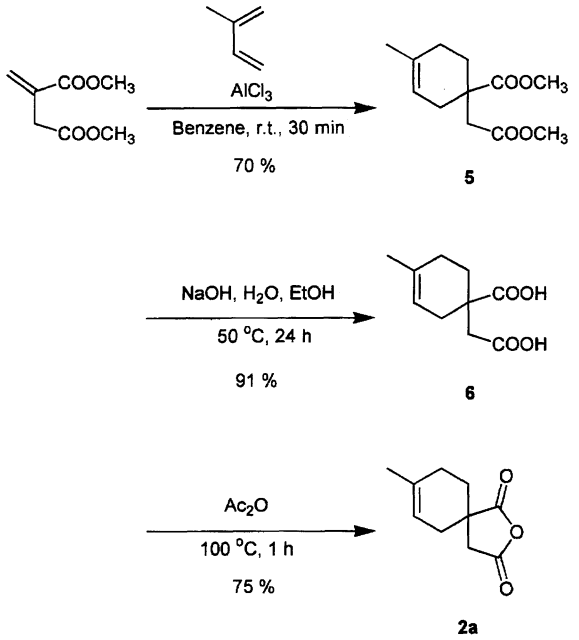
erally enhanced by the use of a Lewis acid as a catalyst.[19,20] The reaction of itaconic anhydride with a Lewis acid might be tedious. The reaction of dimethyl itaconate with isoprene in the presence of aluminum chloride gave only methyl 1-(methoxycarbonyl)-4-methyl-3-cyclohexene-1-acetate (**5**) in a shorter reaction time and no regio isomer was detected (Scheme 2). Hydrolysis of the dimethyl ester **5** and subsequent dehydration gave the major "para" product **2a** mentioned above.

Nitric acid oxidation of the adduct **2a** or its hydrolyzed product **6** with vanadium pentaoxide as a catalyst at 90 °C gave an unsymmetric tetracarboxylic acid, 3-carboxy-3-(carboxymethyl)pentanedioic acid (**3**) (Scheme 1). The reaction was considered to take place via oxidative scission of ketone intermediate to give the product which has two fewer carbon atoms than the starting Diels–Alder adduct **2a** (Scheme 3).

The tetracarboxylic acid **3** gave a novel aliphatic tetracarboxylic dianhydride, 2,8-dioxaspiro[4.5]decane-1,3,7,9-tetrone (TCDA) (**4**), by dehydration with acetic anhydride (Scheme 1). The TCDA (**4**) has a unique noncoplanar structure, that is, having a spiro carbon atom with two different ring sizes (five- and six-membered ring anhydrides).

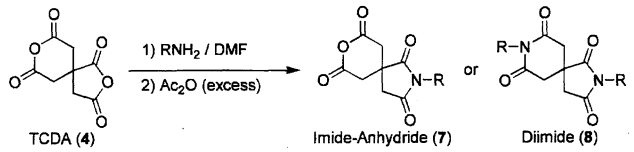
The reaction of TCDA (**4**) with various amines was investigated. The reaction with two-fold molar amounts of primary amines and subsequent dehydration gave two types of products depending on the hydrocarbon moiety of the amines used (Table 1). In the cases of aliphatic amines with primary alkyl group linked to amino group, such as butylamine and benzylamine, the diimides (with five- and six-membered rings) **8a** and **8b** were obtained as expected. On the other hand, in the cases of aromatic amines or aliphatic amines with secondary or tertiary alkyl group linked to amino group, such as aniline, *p*-anisidine, *p*-aminobenzonitrile, *t*-butylamine, isopropylamine, and cyclohexylamine, the imide (with a five-membered ring)-anhydrides (with a six-membered ring) **7c—h** were exclusively obtained, contrary to our expectations. The structure of the products **7c—h** was proved by infrared absorption bands at 1816—1805 and 1771—1759 cm^{-1}, which were characteristic of a six-membered ring anhydride. We previously reported the intramolecular ring transformation in the reaction of anhydride (with five-membered ring)-bis(carbonyl chloride) with aniline.[15] The imide-anhydrides are considered to be formed via a similar type of intramolecular imide formation from initially formed amic acid-anhydride and subsequent dehydration. There were a few reports on the intramolecular ring transformation of spirocycle analogues with reactive groups which possessed the potential to form five-membered rings.[21—24]

In order to confirm the validity of this hypothesis, some model reactions were carried out (Schemes 4 and 5). The reaction of TCDA (**4**) with even two-fold molar amounts of aniline gave imide (with five-membered ring)-di(carboxyl-



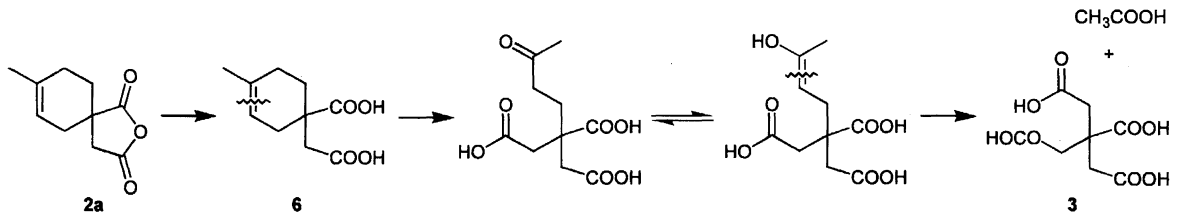
Scheme 2.

Table 1. Reaction[a] of TCDA (**4**) with Primary Amines and Subsequent Dehydration[b]

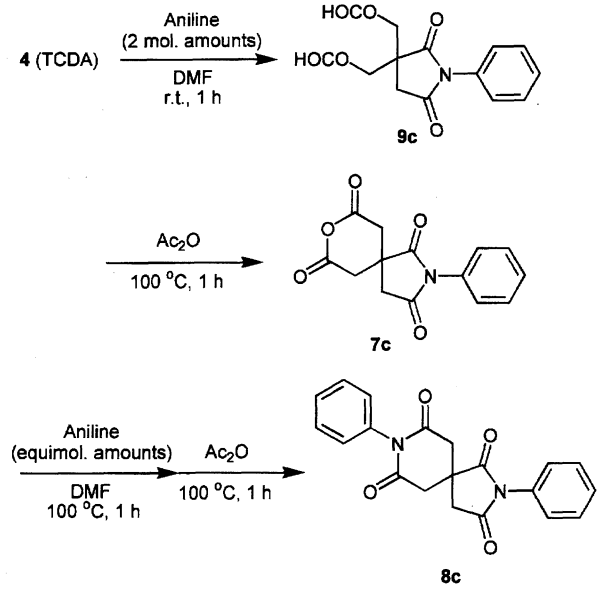


Entry	Amine	mmol	Product	Yield[c]/%
1	$PhNH_2$	2.0	**7c**	70
2	*p*-$MeOC_6H_4NH_2$	2.0	**7d**	66
3	*p*-NC $C_6H_4NH_2$	2.0	**7e**	67
4	*t*-$BuNH_2$	2.0	**7f**	59
5	*i*-$PrNH_2$	2.0	**7g**	67
6	*cyclo*-$HexNH_2$	2.0	**7h**	68
7	$PhCH_2NH_2$	2.0	**8b**	82
8	*n*-$BuNH_2$	2.0	**8a**	84
9		1.0	**7a**	87

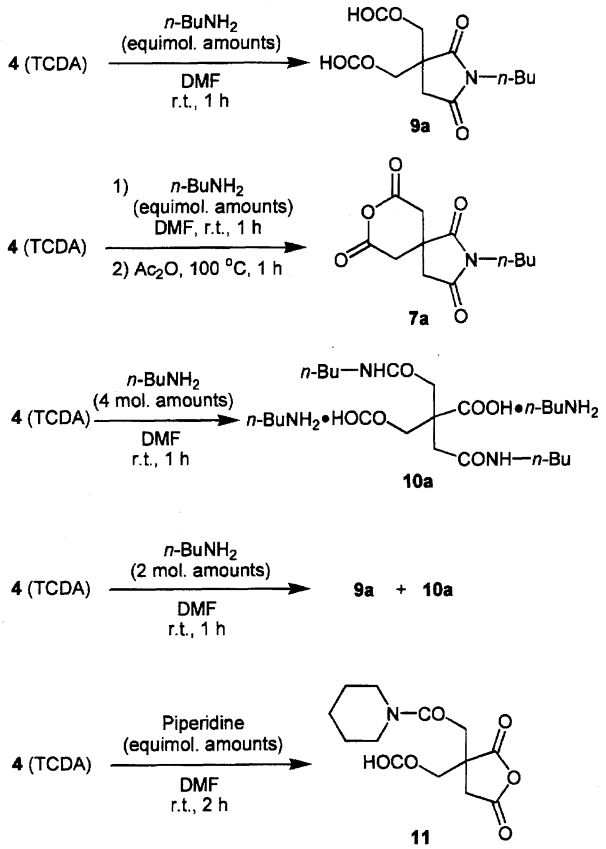
a) Reaction conditions: TCDA (**4**) (1.0 mmol) in DMF at room temperature for 1 h. b) Dehydration conditions: in Ac_2O at 100 °C for 1 h. c) Isolated yields based on TCDA (**4**) after purification by recrystallization.



Scheme 3.



Scheme 4.

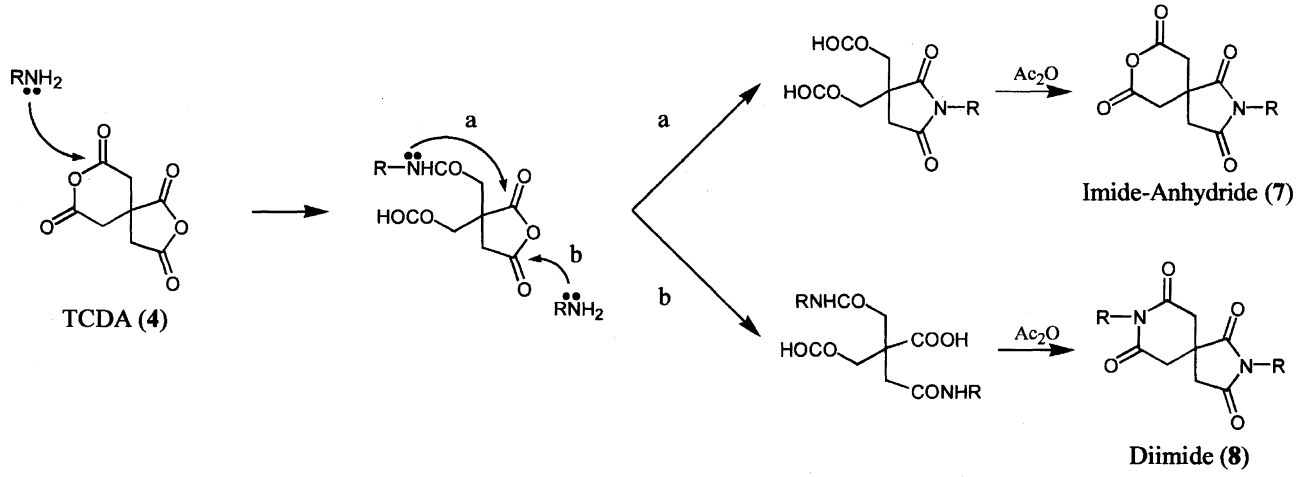


Scheme 5.

ic acid) **9c**, which gave imide-anhydride **7c** by subsequent dehydration with acetic anhydride (Scheme 4). The further reaction of **7c** with aniline and subsequent dehydration gave the diimide (with five- and six-membered rings) **8c**. The reaction of TCDA (**4**) with equimolar amounts of butylamine gave imide (with five-membered ring)-di(carboxylic acid) **9a** and subsequent dehydration gave imide-anhydride **7a** (Scheme 5). These results suggest that the reaction of TCDA (**4**) with amines is accompanied by the intramolecular ring transformation. The reaction of TCDA (**4**) with piperidine, which is considered not to undergo the intramolecular ring transformation, gave amic acid-anhydride (with five-membered ring) **11** (Scheme 5). The IR spectrum of this compound **11** showed absorption bands at 1847 and 1779 cm^{-1}, which were characteristic of a five-membered ring anhydride. Additional support for the structure of **11** was obtained from the ^{13}C NMR spectrum, which exhibited four peaks due to carbonyl carbons, four peaks due to sp^3 carbons derived from TCDA (**4**), and five peaks due to sp^3 carbons derived from piperidine. The result indicates that the carbonyl carbon in six-membered anhydride of TCDA (**4**) might be more reactive than the five-membered anhydride. The reaction of TCDA (**4**) with four-fold molar amounts of butylamine gave diamide-bis(alkylammonium carboxylate) **10a** (Scheme 5). The reaction of TCDA (**4**) with two-fold molar amounts of butylamine gave a mixture of **9a** and **10a**. These results suggest that the nucleophilic attack of another amine to the other five-membered ring anhydride takes place prior to the intramolecular ring transformation in the reaction of TCDA (**4**) with the aliphatic amines with primary alkyl group linked to amino group such as butylamine.

The two types of products designated in Table 1, imide-anhydrides **7** or diimides **8**, can be considered to be exclusively formed by the mechanism shown in Scheme 6. In the reactions with less reactive amines such as aromatic amines or aliphatic amines with secondary or tertiary alkyl group linked to amino group, amic acid-anhydride (with five-membered ring) is formed by the nucleophilic attack of amine at the carbonyl carbon in six-membered anhydride of TCDA (**4**) at the initial stage of the reaction. And then, the intramolecular ring transformation of amic acid-anhydride takes place to form five-membered ring imide before another amine attacks to five-membered anhydride to give imide (with five-membered ring)-di(carboxylic acid) exclusively, which will give imide (with five-membered ring)-anhydride (with six-membered ring) by subsequent dehydration. In the reactions with more reactive amines such as aliphatic amines with primary alkyl group linked to amino group, another amine attacks the five-membered anhydride prior to the intramolecular ring transformation after the same initial stage. And then, diimide (with five- and six-membered rings) is formed by subsequent dehydration. The difference in the products depending on the amines used may be due to the difference in the nucleophilic reactivity of the amines. Aliphatic amines with primary alkyl group linked to amino group are reactive enough to attack the remaining anhydride before intramolecular ring transformation takes place, or the intramolecular imidization and intermolecular amic acid formation might be competitive.

The aliphatic polybasic carboxylic acids having a quaternary or a spiro carbon atom such as reported here may be applicable to the synthesis of polyimides, dendrimers, chiral compounds, or natural products. In addition, the intramolecular ring transformation may make it possible for one to design and to produce structurally-controlled com-



Scheme 6.

plex molecules such as strictly alternating copolyimides.

In conclusion, some compounds of polybasic carboxylic acids having a quaternary or a spiro carbon atom were prepared starting from itaconic anhydride. Nitric acid oxidation of the Diels–Alder adduct from itaconic anhydride and isoprene gave an unsymmetric tetracarboxylic acid. Dehydration of the tetracarboxylic acid with acetic anhydride gave the tetracarboxylic dianhydride having a spiro carbon atom with five- and six-membered rings, 2,8-dioxaspiro[4.5]decane-1, 3,7,9-tetrone (TCDA) (**4**). The reaction of TCDA (**4**) with primary amines and subsequent dehydration gave two types of products, either diimides or imide (with five-membered ring)-anhydrides (with six-membered ring), depending on the hydrocarbon moiety of the amines used. It was suggested that each imide-anhydride was exclusively formed by the intramolecular ring transformation of the intermediate amic acid-anhydride.

Experimental

Itaconic anhydride and dimethyl itaconate was commercially obtained from Tokyo Chemical Industry Co., Ltd. The anhydride was used after purification by recrystallization from chloroform/hexane. Aniline was distilled in vacuo. *p*-Anisidine was purified by sublimation in vacuo. *N,N*-Dimethylformamide (DMF) was purified by distillation under reduced pressure over calcium hydride and stored over molecular sieves 4A. Other organic solvents were purified by standard procedures. Reagents used were of commercial quality unless otherwise stated.

Melting points were measured on the Yazawa Chemical BY-1 apparatus and are uncorrected. The elemental analyses were performed on Yanaco MT-3 or FISONS Instruments EA1108 CHN analyzer. The ^{1}H NMR and ^{13}C NMR spectra were recorded on JEOL JNM-LA400 (^{1}H: 399.65 MHz; ^{13}C: 100.40 MHz) or JEOL JNM-LA500 (^{1}H: 500.00 MHz; ^{13}C: 125.65 MHz) spectrometer with TMS or dioxane as internal standard. IR spectra were obtained using a JASCO IR-700 spectrometer. Mass spectra were measured on JEOL JMS-DX303 spectrometer. GC analysis was carried out with Shimadzu GC-14B gas chromatograph and ULBON HR-20M capillary column. GC/MS analysis was carried out with Shimadzu GCMS-QP5000 gas chromatograph/mass spectrometer. Analytical TLC plates Silica Gel 60 F_{254} were purchased from Merck.

Preparation of 8-Methyl-2-oxaspiro[4.5]dec-7-ene-1,3-dione (2a). Method (A) for 2a: To a stirred solution of itaconic anhydride (20.0 g, 178 mmol) in dry benzene (200 mL) at 50 °C was added dropwise isoprene (100 g, 1.47 mol) for 30 min. The mixture was stirred at 50 °C for 40 h. At the end of the reaction time, no starting anhydride was confirmed to remain (TLC analysis). After cooling, evaporation of the solvent in vacuo left the remaining crude product, a mixture of **2a** and the regio isomer **2b**, which was repeatedly recrystallized from dry benzene to give the Diels–Alder adduct **2a** as white needles (23.1 g, 72%): Mp 111—112 °C; MS (EI) *m/z* 180 (M^+); IR (KBr) 1845, 1785 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 5.39—5.38 (m, 1H, =CH–), 2.81 (d, J = 19 Hz, 1H, $-CH_2CO-$), 2.73 (d, J = 19 Hz, 1H, $-CH_2CO-$), 2.62—1.78 (m, 6H, $-CH_2-$), 1.71 (s, 3H, $-CH_3$); ^{13}C NMR ($CDCl_3$) δ = 176.81, 169.88, 134.14, 116.68, 44.23, 39.57, 33.99, 29.14, 26.35, 23.25. Found: C, 66.63; H, 6.74%. Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71%.

The regio isomer **2b** could not be isolated by fractional recrystallization.

Method (B) for 2a: Methyl 1-(Methoxycarbonyl)-4-methyl-3-cyclohexene-1-acetate (5): To a vigorously stirred suspension of aluminum chloride (25.3 g, 190 mmol) in dry benzene (300 mL) was added dropwise a solution of dimethyl itaconate (30.0 g, 190 mmol) in dry benzene (15 mL) with vigorous stirring. Into the resulting solution, isoprene (40.0 g, 587 mmol) was added slowly. After 30 min, no starting ester remained (TLC analysis). After cooling, dilute aqueous HCl (50 mL) was added and the mixture was extracted with ether (3×150 mL). The organic layer was washed with brine (2×300 mL) and dried ($MgSO_4$). The solvent was removed under reduced pressure and the crude product was distilled through a Vigreux column to give the Diels–Alder adduct **5** as a colorless oil (30.2 g, 70%): Bp 102—105 °C (5 mmHg, 1 mmHg = 133.322 Pa); MS (EI) *m/z* 226 (M^+); IR (film) 1738 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ = 5.32—5.31 (m, 1H, =CH–), 3.70 (s, 3H, $-OCH_3$), 3.65 (s, 3H, $-OCH_3$), 2.67 (d, J = 16 Hz, 1H, $-CH_2CO-$), 2.61 (d, J = 16 Hz, 1H, $-CH_2CO-$), 2.53—1.75 (m, 6H, $-CH_2-$), 1.65 (s, 3H, $-CH_3$); ^{13}C NMR ($CDCl_3$) δ = 176.64, 171.86, 132.84, 118.31, 52.03, 51.57, 42.62, 40.10, 32.91, 29.63, 26.99, 23.24. Found: C, 63.76; H, 8.16%. Calcd for $C_{12}H_{18}O_4$: C, 63.70; H, 8.02%.

1-Carboxy-4-methyl-3-cyclohexene-1-acetic Acid (6): The dimethyl ester **5** (76.1 g, 336 mmol) prepared above was hydrolyzed in a solution of sodium hydroxide (50.0 g, 1.25 mol) in 50% aqueous ethanol (400 mL) at 50 °C for 24 h. The mixture was

allowed to cool down, ethanol was evaporated off, and the aqueous phase was washed with ether (2×500 mL). After acidification of the aqueous phase with dilute aqueous HCl to a pH of 3, the mixture was extracted with ether (5×300 mL), and the combined extracts was dried over magnesium sulfate. The solvent was removed in vacuo and recrystallization from 2-butanone (MEK) afforded dicarboxylic acid **6** as colorless crystals (60.8 g, 91%): Mp 189—190 °C; MS (CI) *m/z* 199 (MH^+); IR (KBr) 3300—2500 (br), 1711 cm^{-1}; ^1H NMR (Methanol-d_4) δ = 5.33—5.31 (m, 1H, =CH–), 2.64 (d, J = 16 Hz, 1H, $-CH_2CO-$), 2.56 (d, J = 16 Hz, 1H, $-CH_2CO-$), 2.52—1.83 (m, 6H, $-CH_2-$), 1.65 (s, 3H, $-CH_3$); ^{13}C NMR (Methanol-d_4) δ = 180.25, 175.06, 133.90, 119.70, 43.34, 40.88, 34.09, 30.88, 28.01, 23.41. Found: C, 60.48; H, 7.30%. Calcd for $C_{10}H_{14}O_4$: C, 60.59; H, 7.12%.

8-Methyl-2-oxaspiro[4.5]dec-7-ene-1,3-dione (2a): Dicarboxylic acid **6** (24.4 g, 123 mmol) was dissolved and heated in acetic anhydride (20 mL) at 100 °C for 1 h. Evaporation of acetic anhydride in vacuo left a solid, which was purified by sublimation under vacuum (100 °C, 1.5 mmHg) to give **2a** as a white powder (16.6 g, 75 %). The total yield for the three steps was 48 %.

3-Carboxy-3-(carboxymethyl)pentanedioic Acid (3). To a stirred solution of vanadium pentaoxide (0.050 g, 0.27 mmol) in 60% nitric acid (17.2 g, 164 mmol) was added the compound **2a** (5.00 g, 27.7 mmol, 15 portions) portion by portion every 5 min at 90 °C. On each addition of **2a**, evolution of nitrogen dioxide gas was observed. After addition, stirring was continued at 90 °C for 12 h. After approximately two-thirds of the nitric acid was removed by evaporation from the reaction mixture, the solution was allowed to stand overnight at room temperature to precipitate a solid. This was collected by filtration and dried overnight in vacuo. The crude product was recrystallized from dioxane/hexane to give tetracarboxylic acid **3** as a white powder (3.37 g, 52%): Mp 194—196 °C; MS (FAB) *m/z* 235 (MH^+); IR (KBr) 3300—2500 (br), 1760, 1711 cm^{-1}; ^1H NMR (D_2O, Dioxane) δ = 2.93 (s, 4H, $-CH_2CO-$), 2.91 (s, 2H, $-CH_2CO-$); ^{13}C NMR (D_2O, Dioxane) δ = 178.48, 175.28, 44.62, 39.76. Found: C, 41.08; H, 4.36%. Calcd for $C_8H_{10}O_8$: C, 41.03; H, 4.30%.

2,8-Dioxaspiro[4.5]decane-1,3,7,9-tetrone (TCDA) (4). Tetracarboxylic acid **3** (7.15 g, 30.5 mmol) was heated at 100 °C with stirring in acetic anhydride (20 mL). After a few minutes, the reaction mixture once turned into a clear solution and immediately separated as a solid again. Heating was continued at 100 °C for another hour before recrystallization from acetic anhydride/toluene to give tetracarboxylic dianhydride (TCDA) **4** as a white powder (5.27 g, 87%): Mp 183—185 °C; MS (EI) *m/z* 199 (MH^+); IR (KBr) 1866, 1785, 1764 cm^{-1}; ^1H NMR (Acetone-d_6) δ = 3.54 (d, J = 17 Hz, 2H, $-CH_2CO-$), 3.43 (d, J = 17 Hz, 2H, $-CH_2CO-$), 3.35 (s, 2H, $-CH_2CO-$); ^{13}C NMR (Acetone-d_6) δ = 175.99, 169.00, 165.32, 42.94, 39.65, 37.58. Found: C, 48.53; H, 3.16%. Calcd for $C_8H_6O_6$: C, 48.50; H, 3.05%.

Syntheses of Imide-Anhydride 7c—h and Diimide 8a,b. A typical procedure is as follows. To a stirred solution of TCDA (**4**) (0.20 g, 1.0 mmol) in dry DMF (5 mL) was added an amine (2.0 mmol) at room temperature, and the mixture was let stand at ambient temperature for 1 h. The reaction mixture was concentrated in vacuo. The remaining solid or semisolid was dissolved in acetic anhydride (10 mL) and heated at 100 °C for 1 h, and then the solvent was removed in vacuo to give the corresponding crude product. Each product was purified and characterized as follows.

2-Phenyl-8-oxa-2-azaspiro[4.5]decane-1,3,7,9-tetrone (7c): A white powder (0.19 g, 70%): Mp 219—220 °C (from acetic anhydride); MS (FAB) *m/z* 274 (MH^+); IR (KBr) 1807, 1788, 1760, 1715 cm^{-1}; ^1H NMR (Acetone-d_6) δ = 7.50—7.34 (m, 5H, ArH), 3.42 (d, J = 17 Hz, 2H, $-CH_2CO-$), 3.33 (d, J = 17 Hz, 2H, $-CH_2CO-$), 3.07 (s, 2H, $-CH_2CO-$); ^{13}C NMR (Acetone-d_6) δ = 179.56, 173.76, 166.18, 133.25, 129.59, 129.32, 127.74, 41.16, 40.35, 37.94. Found: C, 61.60; H, 4.05; N, 5.17%. Calcd for $C_{14}H_{11}NO_5$: C, 61.54; H, 4.06; N, 5.13%.

2-(*p*-Methoxyphenyl)-8-oxa-2-azaspiro[4.5]decane-1,3,7,9-tetrone (7d): A white powder (0.20 g, 66 %): Mp 205—207 °C (from acetic anhydride); MS (FAB) *m/z* 304 (MH^+); IR (KBr) 1805, 1763, 1709 cm^{-1}; ^1H NMR (Acetone-d_6) δ = 7.25 (d, J = 9 Hz, 2H, ArH), 7.01 (d, J = 9 Hz, 2H, ArH), 3.82 (s, 3H, $-OCH_3$), 3.40 (d, J = 17 Hz, 2H, $-CH_2CO-$), 3.31 (d, J = 17 Hz, 2H, $-CH_2CO-$), 3.04 (s, 2H, $-CH_2CO-$); ^{13}C NMR (Acetone-d_6) δ = 179.75, 174.00, 166.23, 160.49, 128.97, 125.75, 114.80, 55.81, 41.05, 40.28, 37.95. Found: C, 59.58; H, 4.26; N, 4.64%. Calcd for $C_{15}H_{13}NO_6$: C, 59.41; H, 4.32; N, 4.62%.

2-(*p*-Cyanophenyl)-8-oxa-2-azaspiro[4.5]decane-1,3,7,9-tetrone (7e): A white powder (0.20 g, 67%): Mp 248—250 °C (from acetone/hexane); MS (FAB) *m/z* 299 (MH^+); IR (KBr) 2238, 1812, 1788, 1764, 1712 cm^{-1}; ^1H NMR (DMSO-d_6) δ = 8.01 (d, J = 8.4 Hz, 2H, ArH), 7.57 (d, J = 8.4 Hz, 2H, ArH), 3.37 (d, J = 17 Hz, 2H, $-CH_2CO-$), 3.23 (d, J = 17 Hz, 2H, $-CH_2CO-$), 2.90 (s, 2H, $-CH_2CO-$); ^{13}C NMR (DMSO-d_6) δ = 178.48, 173.04, 165.96, 135.93, 132.85, 127.83, 118.18, 111.03, 39.77, 39.18, 36.43. Found: C, 60.14; H, 3.47; N, 9.37%. Calcd for $C_{15}H_{10}N_2O_5$: C, 60.41; H, 3.38; N, 9.39%.

2-*t*-Butyl-8-oxa-2-azaspiro[4.5]decane-1,3,7,9-tetrone (7f): A white powder (0.15 g, 59%): Mp 211—215 °C (from acetone/hexane); MS (FAB) *m/z* 254 (MH^+); IR (KBr) 1808, 1759, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 3.02 (d, J = 17 Hz, 2H, $-CH_2CO-$), 2.77 (d, J = 17 Hz, 2H, $-CH_2CO-$), 2.61 (s, 2H, $-CH_2CO-$), 1.58 (s, 9H, $-CH_3$); ^{13}C NMR ($CDCl_3$) δ = 178.56, 173.26, 163.49, 59.87, 39.89, 39.79, 38.27, 28.19. Found: C, 57.09; H, 6.06; N, 5.81%. Calcd for $C_{12}H_{15}NO_5$: C, 56.91; H, 5.97; N, 5.53%.

2-Isopropyl-8-oxa-2-azaspiro[4.5]decane-1,3,7,9-tetrone (7g): A white powder (0.16 g, 67%): Mp 235—238 °C (from acetone/hexane); MS (FAB) *m/z* 240 (MH^+); IR (KBr) 1806, 1759, 1694 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 4.42—4.35 (m, J = 7 Hz, 1H, –CHN–), 3.05 (d, J = 17 Hz, 2H, $-CH_2CO-$), 2.80 (d, J = 17 Hz, 2H, $-CH_2CO-$), 2.67 (s, 2H, $-CH_2CO-$), 1.40 (d, J = 7 Hz, 6H, $-CH_3$); ^{13}C NMR (Acetone-d_6) δ = 180.28, 174.40, 166.18, 44.57, 40.49, 39.99, 37.80, 19.13. Found: C, 55.30; H, 5.46; N, 5.78%. Calcd for $C_{11}H_{13}NO_5$: C, 55.23; H, 5.48; N, 5.85%.

2-Cyclohexyl-8-oxa-2-azaspiro[4.5]decane-1,3,7,9-tetrone (7h): A white powder (0.19 g, 68%): Mp 196—199 °C (from benzene); MS (FAB) *m/z* 280 (MH^+); IR (KBr) 1816, 1771, 1697 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 4.00—3.93 (m, 1H, –CHN–), 3.04 (d, J = 17 Hz, 2H, $-CH_2CO-$), 2.82 (d, J = 17 Hz, 2H, $-CH_2CO-$), 2.68 (s, 2H, $-CH_2CO-$), 2.14—1.10 (m, 10H, $-CH_2-$); ^{13}C NMR (Acetone-d_6) δ = 180.36, 174.42, 166.16, 52.50, 40.45, 39.94, 37.88, 29.27, 26.42, 25.86. Found: C, 60.08; H, 6.20; N, 4.80%. Calcd for $C_{14}H_{17}NO_5$: C, 60.21; H, 6.13; N, 5.02%.

2,8-Dibutyl-2,8-diazaspiro[4.5]decane-1,3,7,9-tetrone (8a): A white powder (0.26 g, 84%): Mp 104—109 °C (from acetonitrile/water); MS (FAB) *m/z* 309 (MH^+); IR (KBr) 1778, 1700, 1667 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 3.81 (t, J = 7 Hz, 2H, $-CH_2N-$), 3.52 (t, J = 7 Hz, 2H, $-CH_2N-$), 3.04 (d, J = 17 Hz, 2H, $-CH_2CO-$), 2.69 (d, J = 17 Hz, 2H, $-CH_2CO-$), 2.63 (s, 2H, $-CH_2CO-$), 1.60—1.48 (m, 4H, $-CH_2-$), 1.35—1.27 (m, 4H, $-CH_2-$), 0.93 (t, J = 7 Hz, 6H, $-CH_3$); ^{13}C NMR ($CDCl_3$) δ = 178.07, 173.12, 168.81, 40.61, 40.58, 39.94, 39.79, 39.20, 29.92, 29.57, 20.15, 19.96, 13.72, 13.53.

Found: C, 62.09; H, 7.84; N, 9.04%. Calcd for $C_{16}H_{24}N_2O_4$: C, 62.32; H, 7.84; N, 9.08%.

2,8-Dibenzyl-2,8-diazaspiro[4.5]decane-1,3,7,9-tetrone (8b): A white powder (0.31 g, 82%): Mp 168—169 °C (from acetonitrile/water); MS (FAB) *m/z* 377 (MH^+); IR (KBr) 1780, 1703, 1675 cm^{-1}; ^1H NMR (DMSO-d_6) δ = 7.33—7.20 (m, 10H, ArH), 4.84 (s, 2H, $-CH_2Ar$), 4.55 (s, 2H, $-CH_2Ar$), 3.08 (d, J = 17 Hz, 2H, $-CH_2CO-$), 3.03 (d, J = 17 Hz, 2H, $-CH_2CO-$), 2.77 (s, 2H, $-CH_2CO-$); ^{13}C NMR (DMSO-d_6) δ = 179.54, 174.41, 170.27, 137.19, 135.74, 128.49, 128.16, 127.38, 127.22, 127.08, 126.80, 42.21, 41.68, 40.03, 39.58, 39.34. Found: C, 70.13; H, 5.54; N, 7.36%. Calcd for $C_{22}H_{20}N_2O_4$: C, 70.20; H, 5.36; N, 7.44%.

Stepwise Imidization. *N*-Phenyl-2,5-dioxopyrrolidine-3,3-diacetic Acid (9c): To a stirred solution of TCDA (**4**) (0.20 g, 1.0 mmol) in dry DMF (5 mL) was added aniline (0.20 g, 2.1 mmol) at room temperature, and the reaction was then continued at ambient temperature for 1 h. The reaction mixture was concentrated in vacuo. The remaining solid was recrystallized from acetone/hexane to give the imide-di(carboxylic acid) **9c** as a white powder (0.22 g, 76%): Mp 208—211 °C; MS (FAB) *m/z* 292 (MH^+); IR (KBr) 3300—2500 (br), 1779, 1709 cm^{-1}; ^1H NMR (Acetone-d_6) δ = 7.49—7.29 (m, 5H, ArH), 2.948 (s, 2H, $-CH_2CO-$), 2.944 (s, 2H, $-CH_2CO-$), 2.942 (s, 2H, $-CH_2CO-$); ^{13}C NMR (Acetone-d_6) δ = 180.87, 175.78, 172.26, 134.44, 129.48, 128.92, 127.92, 43.03, 41.35, 39.71. Found: C, 57.45; H, 4.21; N, 5.04%. Calcd for $C_{14}H_{13}NO_6$: C, 57.73; H, 4.50; N, 4.81%.

Dehydration of **9c** with acetic anhydride was confirmed to give **7c**.

2,8-Diphenyl-2,8-diazaspiro[4.5]decane-1,3,7,9-tetrone (8c): To a stirred solution of the imide-anhydride **7c** (0.20 g, 0.73 mmol) in dry DMF (5 mL) was added aniline (0.08 g, 0.86 mmol) at room temperature. The solution was stirred at 100 °C for 1 h. After cooling, the reaction mixture was concentrated in vacuo. The remaining product was dissolved in acetic anhydride (10 mL) and heated at 100 °C for 1 h. After cooling at room temperature, the solvent was removed in vacuo. The crude product was recrystallized from acetonitrile/water to give diimide **8c** as a white powder (0.18 g, 71%): Mp > 315 °C; MS (EI) *m/z* 348 (M^+); IR (KBr) 1785, 1734, 1712, 1686 cm^{-1}; ^1H NMR (DMSO-d_6) δ = 7.52—7.12 (m, 10H, ArH), 3.28 (d, J = 16.5 Hz, 2H, $-CH_2CO-$), 3.22 (d, J = 16.5 Hz, 2H, $-CH_2CO-$), 2.93 (s, 2H, $-CH_2CO-$); ^{13}C NMR (DMSO-d_6) δ = 179.14, 173.82, 170.45, 135.66, 132.20, 128.78, 128.64, 128.49, 128.04, 127.25, 40.21, 39.82, 39.65. Found: C, 69.02; H, 4.64; N, 8.25%. Calcd for $C_{20}H_{16}N_2O_4$: C, 68.96; H, 4.63; N, 8.04%.

Reactions of TCDA with Butylamine. Reaction with Equimolar Amounts of Butylamine: To a stirred solution of TCDA (**4**) (0.20 g, 1.0 mmol) in dry DMF (5 mL) was added butylamine (0.074 g, 1.0 mmol) at room temperature, and the reaction was then continued at ambient temperature for 1 h. The reaction mixture was concentrated in vacuo. The remaining product was dissolved in 10% aqueous NaOH and the aqueous phase was washed with ethyl acetate (3×30 mL). After acidification of the aqueous phase with dilute aqueous HCl, the mixture was extracted with ether (3×30 mL), and the combined extracts was dried over sodium sulfate. The solvent was removed in vacuo and the crude product was recrystallized from ethyl acetate to give *N*-butyl-2,5-dioxopyrrolidine-3,3-diacetic acid (**9a**) as a colorless solid (0.18 g, 68%): Mp 106—110 °C; MS (EI) *m/z* 271 (M^+); IR (KBr) 3300—2500 (br), 1777, 1730, 1699 cm^{-1}; ^1H NMR (DMSO-d_6) δ = 3.33 (t, J = 7 Hz, 2H, $-CH_2N-$), 2.67 (s, 2H, $-CH_2CO-$), 2.66 (s, 4H, $-CH_2CO-$), 1.47—1.41 (m, J = 7 Hz, 2H, $-CH_2-$), 1.31—1.25 (m, J = 7 Hz, 2H, $-CH_2-$), 0.85 (t, J = 7 Hz, 3H, $-CH_3$); ^{13}C NMR (DMSO-d_6) δ = 180.72, 176.09, 171.55, 41.63, 40.36, 38.38, 37.76, 28.85, 19.32, 13.52. Found: C, 52.98; H, 6.43; N, 4.91%. Calcd for $C_{12}H_{17}NO_6$: C, 53.13; H, 6.32; N, 5.16%.

Reaction with Equimolar Amounts of Butylamine and Subsequent Dehydration: To a stirred solution of TCDA (**4**) (0.10 g, 0.50 mmol) in dry DMF (5 mL) was added butylamine (0.037 g, 0.50 mmol) at room temperature. The mixture was stirred at ambient temperature for 1 h and then concentrated in vacuo. The remaining product was dissolved in acetic anhydride (10 mL) and heated at 100 °C for 1 h. The solvent was removed in vacuo. The crude product was recrystallized from benzene to give 2-butyl-8-oxa-2-azaspiro[4.5]decane-1,3,7,9-tetrone (**7a**) as a white powder (0.11 g, 87%): Mp 127—130 °C; MS (EI) *m/z* 253 (M^+); IR (KBr) 1805, 1762, 1695 cm^{-1}; ^1H NMR ($CDCl_3$) δ = 3.54 (t, J = 7 Hz, 2H, $-CH_2N-$), 3.07 (d, J = 17 Hz, 2H, $-CH_2CO-$), 2.84 (d, J = 17 Hz, 2H, $-CH_2CO-$), 2.73 (s, 2H, $-CH_2CO-$), 1.60—1.53 (m, J = 7 Hz, 2H, $-CH_2-$), 1.35—1.26 (m, J = 7 Hz, 2H, $-CH_2-$), 0.94 (t, J = 7 Hz, 3H, $-CH_3$); ^{13}C NMR ($CDCl_3$) δ = 177.52, 172.44, 163.33, 40.08, 39.56, 39.47, 38.08, 29.54, 19.97, 13.52. Found: C, 56.64; H, 5.82; N, 5.31%. Calcd for $C_{12}H_{15}NO_5$: C, 56.91; H, 5.97; N, 5.53%.

Reaction with Four-Fold Molar Amounts of Butylamine: To a stirred solution of TCDA (**4**) (0.20 g, 1.0 mmol) in dry DMF (5 mL) was added butylamine (0.30 g, 4.1 mmol) at room temperature. After a few minutes, white solid gradually precipitated. After stirring was continued for another hour, the precipitate was separated by filtration and dried overnight in vacuo to give bis(butylammonium) 2,2-bis(*N*-butylcarbamoylmethyl)butanedioate (**10a**) as a white solid (0.25 g, 51%): Mp 141—145 °C; MS (FAB) *m/z* 345 ($MH^+ - 2\times BuNH_2$); IR (KBr) 3258, 1667, 1639, 1585 cm^{-1}; ^1H NMR (DMSO-d_6) δ = 7.93 (t, J = 5 Hz, 2H, $-CONH-$), 3.05—2.95 (m, 4H, $-CH_2N-$), 2.66 (t, J = 7 Hz, 4H, $-CH_2N-$), 2.47 (s, 2H, $-CH_2CO-$), 2.39 (d, 2H, J = 14 Hz, $-CH_2CO-$), 2.33 (d, 2H, J = 14 Hz, $-CH_2CO-$), 1.45—1.22 (m, 16H, $-CH_2-$), 0.87 (t, J = 7 Hz, 6H, $-CH_3$), 0.86 (t, J = 7 Hz, 6H, $-CH_3$); ^{13}C NMR (DMF-d_7) δ = 178.97, 174.80, 171.11, 46.90, 44.35, 43.69, 41.05, 39.11, 32.85, 32.24, 20.56, 20.26, 13.97. Found: C, 58.53; H, 10.57; N, 11.13%. Calcd for $C_{24}H_{50}N_4O_6$: C, 58.75; H, 10.27; N, 11.42%.

Acidification of the product was confirmed to give 2,2-bis(*N*-butylcarbamoylmethyl)butanedioic acid.

Reaction with Two-Fold Molar Amounts of Butylamine: To a stirred solution of TCDA (**4**) (0.198 g, 1.0 mmol) in dry DMF (5 mL) was added butylamine (0.146 g, 2.0 mmol) at room temperature. After stirring was continued for another hour, the solvent was removed and dried overnight in vacuo to give the mixture of **9a** and **10a** as a white solid (0.344 g).

Reaction of TCDA with Piperidine. 3-(Piperidylcarbonylmethyl)-3-carboxypentanedioic 1,3-Anhydride (11): The reaction was conducted using TCDA (**4**) (0.198 g, 1.0 mmol) and piperidine (0.0871 g, 1.0 mmol) in dry DMF (5 mL) at room temperature for 2 h, and then the reaction mixture was concentrated in vacuo. The remaining crude product was washed with acetone and dried overnight in vacuo to give **11** as a white powder (0.214 g, 76%): Mp 246—248 °C; MS (EI) *m/z* 283 (M^+); IR (KBr) 3300—2500 (br), 1847, 1779, 1722, 1610 cm^{-1}; ^1H NMR (DMF-d_7) δ = 3.43—3.41 (m, 4H, $-CH_2N-$), 3.21—2.98 (m, 6H, $-CH_2CO-$), 1.62—1.51 (m, 4H, $-CH_2-$), 1.46—1.41 (m, 2H, $-CH_2-$); ^{13}C NMR (DMF-d_7) δ = 178.65, 172.87, 172.43, 168.29, 46.63, 44.93, 42.78, 42.12, 42.01, 39.65, 26.63, 26.07, 24.72. Found: C, 54.98; H, 6.13; N, 4.65%. Calcd for $C_{13}H_{17}NO_6$: C, 55.12; H, 6.05; N, 4.94%.

Esterification of Diels–Alder Adducts for Determination of

the Regio Isomer Ratio of 2a/2b by GC/MS and GC Analyses. Diels–Alder reaction of itaconic anhydride with isoprene was carried out at room temperature and at 50 °C on the basis of Method (A) for **2a**. Evaporation of solvent in vacuo left a solid, a mixture of **2a** and **2b**, into which an excess amount of dry methanol was added. The mixture was heated to reflux for 1 h, and was concentrated in vacuo. Into the concentrate was added dimethoxy-*N*,*N*-dimethylmethylamine and the mixture was stirred at 80 °C for 20 min. After cooling, the reaction mixture was concentrated in vacuo. The remaining product was diluted with methanol for GC/MS and GC analyses. GC/MS analysis gave well separated peaks (retention times were 20.2 min for the dimethyl esters from **2a**, and 20.0 min for the dimethyl esters from **2b**) of the regio isomeric dimethyl esters with same molecular weight (M^+ = 226). Retention time and molecular weight of dimethyl ester from **2a** agreed with those of **5**. The regio isomer ratios of **2a/2b** were determined from the peak area ratios of GC (FID).

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