B

Synthesis of 2,2,5,5-Tetramethylcyclopentanecarboxylic Acid – A Building Block of an Amino Acid Based Sweetener

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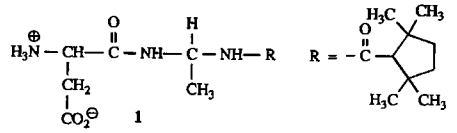
The title compound **2** is synthesized in three steps from readily available 2,5-dichloro-2,5-dimethylhexane (**8**) and vinylidene chloride (**9**). The key steps are carbocationic addition and cyclization reactions.

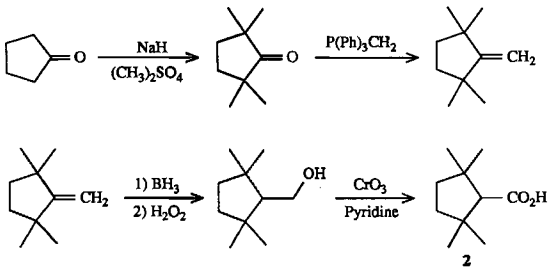
N-L-Aspartyl-*N'*-(alkylcarbonyl)-1,1-diaminoethanes **1** have been reported to be thermally stable, water-soluble sweeteners without bitter after-taste[1]. The sweetness of **1** strongly depends on the nature of the acyl group R, and among 14 tested compounds (**1**), the maximal taste intensity has been found for R = 2,2,5,5-tetramethylcyclopentylcarbonyl (1000-fold sweetness relative to sucrose).



1

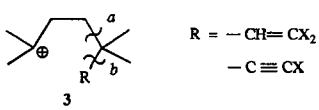
The incorporated carboxylic acid **2** has previously been synthesized by permethylation of the α positions of cyclopentanone, Wittig reaction, hydroboration, and Cr(VI) oxidation as shown in Scheme 1[1a].

Scheme 1



2

Since compounds with quaternary carbons are often readily accessible via carbocationic addition reactions[2], we have attempted to improve the synthesis of **2** by employing the carbocationic cyclization of **3** as the key step[3].

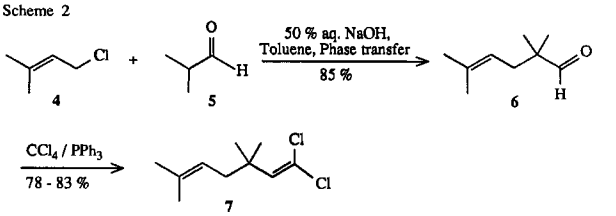


3

For the synthesis of precursors of **3**, two different approaches, indicated by the disconnections *a* and *b* in formula **3**, have been considered.

Disconnection a: The aldehyde **6** has previously been prepared in 88% yield from the anion of isobutyraldehyde (**5**) and prenyl bromide[4]. Since in this procedure, the enolate anion is generated with potassium hydride in THF, we have preferred to combine compounds **4** and **5** under phase-transfer conditions as shown in Scheme 2, making use of a procedure previously described for the synthesis of similar compounds[5]. Treatment of **6** with triphenylphosphine/tetrachloromethane[6] gives the diene **7** in good yield.

Scheme 2



Disconnection b yields a C_8 fragment, which is technically produced from acetylene and acetone. The commercially available 2,5-dimethyl-2,5-hexanediol is quantitatively converted into the dichloride **8**[7] by treatment with hydrochloric acid. Attempts to produce the five-membered ring in a one-pot reaction from **8** have not been successful. While reactions of **8** with vinylsilanes have not been considered for economic reasons, the reaction of **8** with propyne gives complex mixtures of products under a variety of conditions[3b]. When **8** and **9** are combined in sulfuric acid (Bott-Hellmann conditions[8]), a diacid is formed from **8** and two equivalents of vinylidene chloride **9**.

Since **8** incorporates two isolated equivalent functional groups, we have not succeeded in selectively engaging a single C–Cl bond in the reaction with vinylidene chloride. Mild Lewis acids ($ZnCl_2$) do not initiate the reaction of **8** with **9**, while $AlCl_3$, $EtAlCl_2$, or $FeCl_3$ produce mixtures of

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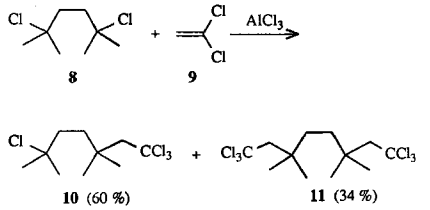
the 1:1 adduct **10** and the 2:1 adduct **11**. Among these Lewis acids, $AlCl_3$ gives rise to the highest yields of **10**.



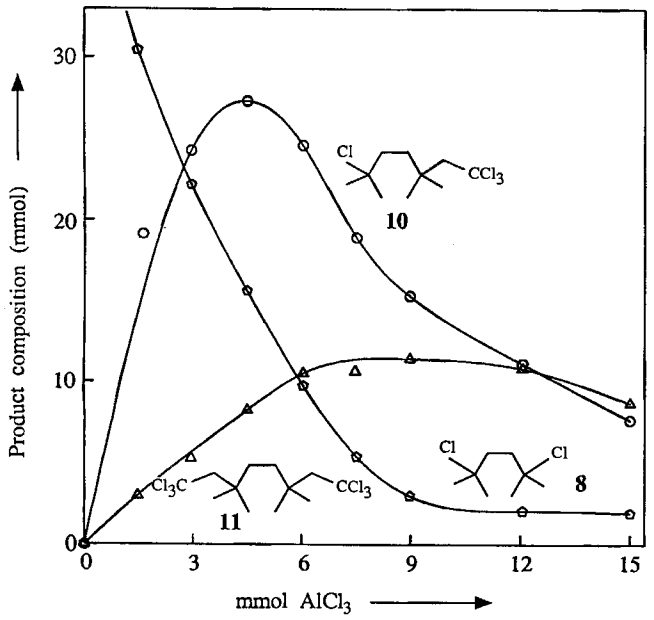
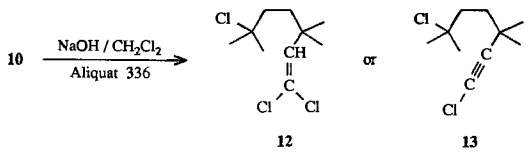


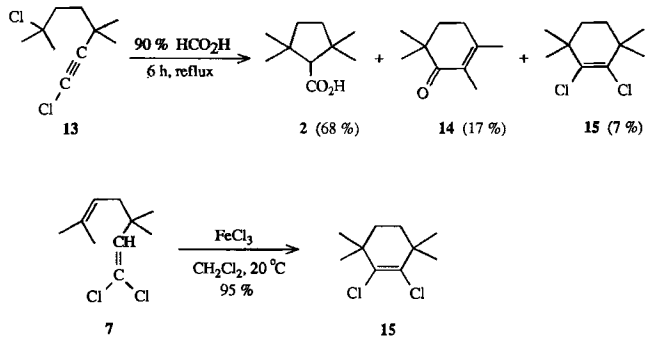
Figure 1. Product composition during the $AlCl_3$-promoted reaction of **8** (50.0 mmol) with **9** (325 mmol) at 0°C. Since the reaction takes place only within the first few minutes after the addition of the catalyst, this figure refers to a single experiment, in which the $AlCl_3$ portions have been added at 30-min intervals.

Though vinylidene chloride is usually employed as the solvent, the $AlCl_3$-initiated reactions terminate after a certain degree of conversion due to deactivation of the Lewis acid. In accord with this rationalization, a progress of the reactions can be achieved by adding more aluminum chloride. The degree of conversion thus depends on the percentage of Lewis acid, and Figure 1 shows that optimal yields of **10** are obtained with 8–10% of $AlCl_3$. Larger amounts of the Lewis acid give rise to the formation of a higher percentage of **11** and of unidentified nonvolatile compounds. Since the ratio of **10**/**11** decreases with increasing degree of conversion, one can improve the yield of the process by using a smaller amount of Lewis acid and recovering the nonconverted reactants **8** and **9**.



Treatment of **10** with a base under phase-transfer conditions ($NaOH/CH_2Cl_2$) gives mixtures of **12** and **13**; on heating, pure **13** is formed in 79% yield. Since the cyclization of **13** appears to be easier than the cyclization of **12**, no efforts have been made to selectively produce **12**.

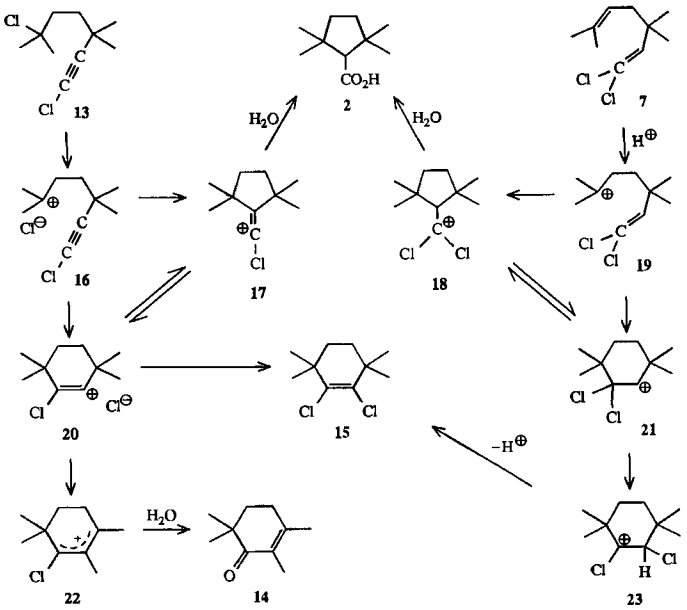
Cyclizations: In analogy to investigations by Bott[9] and Gallo[10], we tried to achieve the conversion of **13** into **2** in sulfuric acid. Compound **2** is obtained under these conditions, but generally only in low yield (<30%). Therefore, the cyclization has been carried out in boiling formic acid, conditions previously employed by Lansbury for analogous conversions[11]. In this medium, like in 70–95% aqueous acetic acid, **7** as well as **13** are cyclized to give 50–60% of **2**, but we have not found conditions which avoid the concomitant formation of the six-membered ring compounds **14** and/or **15**.



Compound **15** is formed in 95% yield, however, when **7** is treated with $FeCl_3$ in CH_2Cl_2. Possibly, this conversion is due to proton catalysis (traces of moisture) since the selective rearrangement of **7** to **15** is also catalyzed by FSO_3H.

The mechanism of these reactions has not been elucidated, and Scheme 3, which is self-explanatory, only represents a rationalization of the isolated products. Probably, thermodynamic product control is responsible for the exclusive formation of **15** from **7** in the absence of water: Under these

Scheme 3



conditions, irreversible trapping of the cyclopentyl-substituted carbenium ion **18** is not possible, so that the less strained six-membered ring compound **15** is produced selectively. It is remarkable that compound **15** is also generated from **13** in formic acid; thus, one has to assume the presence of an ion pair [**20** $Cl^{\ominus}$] which collapses to give the dichloride **15**.

The dependence of the product composition on the reaction conditions indicates the occurrence of mutual rearrangements of the intermediate carbenium ions, so that the product ratio **2**/(**14** + **15**) does not provide information on the relative rates of the cyclization steps (6-*endo* or 5-*exo*[12]).

Conclusion: The sequence **8** → **10** → **13** → **2** leads to the title compound **2** in a three-step synthesis in 32% overall yield. Since only inexpensive reagents are needed, which are combined under convenient reaction conditions, the carbocationic approach to **2** is superior to the carbanionic route described in Scheme 1. Alternative routes[13], which have been published after the submission of our first report[3a], also employ 2,2,5,5-tetramethylcyclopentanone as starting compound and, in our opinion, are less straightforward than the procedures reported in this article.

Experimental

NMR: XL 200 (Varian), internal standard TMS. – Mass spectra: 70–250 E (VG-Instruments). – IR: IR-435 (Shimadzu).

2,2,5-Trimethyl-4-hexenal (**6**): A solution of **4** (13.6 g, 130 mmol) and **5** (7.21 g, 100 mmol) in toluene (10 ml) is added dropwise (10 min) to a vigorously stirred mixture of 50% aqueous NaOH (30 g), toluene (70 ml), and tetrabutylammonium iodide (1.4 g, 3.8 mmol) at 80°C. The mixture is stirred for 4.5 h (80°C), cooled and poured onto water. The product is extracted with ether, and the ethereal extract dried with Na_2SO_4. Distillation over a Vigreux column yields **6** (11.9 g, 85%) as a colorless liquid with b.p. 89–92°C/71 mbar (ref.[14]: 65–66°C/20 Torr; purity 94% by GC). Spectral data are given in ref.[14].

1,1-Dichloro-3,3,6-trimethyl-1,5-heptadiene (**7**): A solution of **6** (5.00 g, 35.7 mmol) in CCl_4 (5 ml) is added dropwise (5 min) with stirring to a mixture of triphenylphosphine (21.0 g, 80.0 mmol) in CCl_4 (40 ml) at 80°C (N_2 atmosphere). After 3.5 h, the mixture is cooled and poured onto 300 ml of hexane to precipitate triphenylphosphine and triphenylphosphine oxide. The suspension is filtered over silica gel and the resulting solution evaporated to give **7** (6.12 g, 83%), as a colorless oil, which is used without further purification. Bulb-to-bulb distillation [34–37°C (bath)/0.15 mbar] yields an analytically pure product. – ^{1}H NMR ($CDCl_3$): δ = 1.16 (s, 6H, 3-CH_3), 1.62, 1.73 (2 br. s, 6H, 6-CH_3, 7-H), 2.14 (br. d, *J* = 7.6 Hz, 2H, 4-H), 5.13 (br. t, *J* = 7.6 Hz, 1H, 5-H), 5.87 (s, 1H, 2-H). – ^{13}C NMR ($CDCl_3$): δ = 17.95, 26.04 (2 q, 6-CH_3, C-7), 26.70 (q, 3-CH_3), 37.66 (s, C-3), 40.52 (t, C-4), 118.83 (s, C-1), 120.21 (d, C-5), 134.10 (s, C-6), 137.93 (d, C-2). – IR (neat): $\tilde{\nu}$ = 2956, 2917, 1606, 1466, 1450, 1383, 1376, 879 cm^{-1}. – MS (70 eV): *m*/*z* (%) = 208, 206 (0.1, 0.15) [M^+], 141, 139, 137 (3, 17, 26), 118, 116 (6, 8), 69 (100), 41 (47).

$C_{10}H_{16}Cl_2$ (207.1) Calcd. C 57.98 H 7.79
Found C 57.97 H 7.84

2,5-Dichloro-2,5-dimethylhexane (**8**): 2,5-Dimethyl-2,5-hexanediol (73.1 g, 0.500 mol) is stirred with 37% aqueous HCl (250 ml) for 1 h. The initially biphasic mixture first becomes homogeneous, and later on the precipitation of crystalline **8** takes place. The product is extracted with 600 ml of petroleum ether (b.p. 40–60°C) and dried with $CaCl_2$. Evaporation of the solvent yields 81.9 g (89%) of an NMR-spectroscopically pure solid, which is recrystallized from petroleum ether: m.p. 68–68.5°C (ref.[7]: 64°C). – ^{1}H NMR (CCl_4): δ = 1.55 (s, 12H, CH_3), 1.86 (s, 4H, CH_2). – ^{13}C NMR ($CDCl_3$): δ = 32.51 (q), 41.11 (t), 70.22 (s).

Reaction of **8** *with Vinylidene Chloride* (**9**): Aluminum chloride (3.75 g, 28.0 mmol) is added in portions during 45 min to a well-stirred suspension of **8** (54.9 g, 300 mmol) in **9** (135 ml, 1.70 mol) at 0°C. After stirring for another 100 min at 0°C, 10 ml of water and 20 g of $CaCl_2$ are added successively, and the mixture is filtered. Evaporation of **9** leaves 88.4 g of a dark viscous residue from which 17.5 g (95.6 mmol) of **8** are recovered by distillation. Distillation of the residue yields 34.3 g of **10** (60% with respect to consumed **8**) and 26.2 g of **11** (34% with respect to consumed **8**) which solidifies at −20°C.

1,1,1,6-Tetrachloro-3,3,6-trimethylheptane (**10**): B.p. 79–80°C/0.5 mbar. – ^{1}H NMR ($CDCl_3$): δ = 1.20 (s, 6H, CH_3), 1.59 (s, 6H, CH_3), 1.59–1.83 (m, 4H, CH_2-CH_2), 2.81 (s, 2H, CH_2-CCl_3). – ^{13}C NMR ($CDCl_3$): δ = 27.80 (q), 32.43 (q), 35.69 (s), 38.38 (t), 39.97 (t), 63.25 (t), 70.74 (s), 98.60 (s). – IR (neat): $\tilde{\nu}$ = 2961, 2931, 2870, 1470, 1452, 1387, 1370, 1100, 896, 790, 726, 703, 605 cm^{-1}. – MS (70 eV): *m*/*z* (%) = 229, 227 (0.9, 1.3) [M^+ – HCl – CH_3], 171 (4), 147 (7), 137 (13), 123 (10), 111 (50), 77 (64), 69 (83), 31 (100).

$C_{10}H_{18}Cl_4$ (280.1) Calcd. C 42.89 H 6.48
Found C 43.06 H 6.54

1,1,1,8,8,8-Hexachloro-3,3,6,6-tetramethyloctane (**11**): Colorless needles with m.p. 52.5–53.5°C (petroleum ether). – ^{1}H NMR ($CDCl_3$): δ = 1.18 (s, 12H, CH_3), 1.46 (s, 4H, CH_2-CH_2), 2.81 (s, 4H, CH_2-CCl_3). – ^{13}C NMR ($CDCl_3$): δ = 27.79 (q), 35.91 (s), 37.16 (t), 63.32 (t), 98.67 (s). – IR (KBr): $\tilde{\nu}$ = 2976, 2953, 2904, 2870, 1472, 1465, 1390, 1373, 1337, 1255, 1188, 1154, 1123, 1042, 903, 784, 717, 608 cm^{-1}. – MS (70 eV): *m*/*z* (%) = 344, 342, 340, 338, (0.07, 0.18, 0.29, 0.18) [M^+ – HCl], 229, (1.3), 227 (1.4), 193 (1.0), 191 (1.2), 173 (3), 171 (7), 149 (23), 147 (70), 137 (19), 111 (81), 77 (100), 69 (36).

$C_{12}H_{20}Cl_6$ (377.0) Calcd. C 38.23 H 5.35
Found C 38.38 H 5.37

1,6-Dichloro-3,3,6-trimethyl-1-heptyne (**13**): Compound **10** (25.2 g, 90.0 mmol) and 0.60 g of tricaprylmethylammonium chloride (Aliquat 336) are stirred vigorously with 40% aqueous NaOH (50 ml) at 80°C for 22 h. After cooling, 60 ml of CH_2Cl_2 is added, and the organic layer is dried with $CaCl_2$. The solvent is evaporated, and the residue is distilled to give 14.7 g (79%) of **13** with b.p. 39–43°C/1 mbar. – ^{1}H NMR ($CDCl_3$): δ = 1.21 (s, 6H, CH_3), 1.59 (s, CH_3), 1.53–1.93 (m, 10H including the s at δ 1.59, CH_2-CH_2). – ^{13}C NMR ($CDCl_3$): δ = 28.98 (q), 31.26 (s), 32.49 (q), 38.25 (t), 41.48 (t), 57.90 (s), 70.66 (s), 75.80 (s). – IR (neat): $\tilde{\nu}$ = 2967, 2920, 2864, 2220, 1465, 1450, 1385, 1370, 1267, 1098, 989, 788 cm^{-1}. – MS (70 eV): *m*/*z* (%) = 208, 206 (0.4, 0.6) [M^+], 155 (28), 135 (20), 115 (15), 103 (33), 101 (100), 77 (16), 69 (74), 65 (28).

$C_{10}H_{16}Cl_2$ (207.1) Calcd. C 57.98 H 7.79
Found C 58.29 H 7.67

Cyclization of **13**: Compound **13** (8.29 g, 40.0 mmol) is added dropwise with stirring to 80 ml of refluxing 90% aqueous formic acid (30 min) and heated under reflux for 6 h. Water (300 ml) is added after cooling, and the mixture is extracted with two 50-ml portions of petroleum ether. The combined organic layers are extracted with five 30-ml portions of 10% aqueous Na_2CO_3 solution. The aqueous layers are combined and acidified with conc. HCl to precipitate 4.63 g (68%) of spectroscopically (^{1}H NMR) pure **2**.

The remaining petroleum ether solution is dried with $CaCl_2$, and the solvent is evaporated to give 2.07 g of a brown liquid residue which is separated by chromatography (silica gel, petroleum ether/CH_2Cl_2) to give 574 mg (7%) of **15** and 1.02 g (17%) of **14**.

2,2,5,5-Tetramethylcyclopentanecarboxylic Acid (**2**): M.p. 128–129°C (petroleum ether). – ^{1}H NMR ($CDCl_3$): δ = 1.15 (s, 6H, 2,5-CH_3), 1.16 (s, 6H, 2,5-CH_3), 1.51–1.63 (m_c, 4H, 3,4-H), 2.26 (s, 1H, 1-H). – ^{13}C NMR ($CDCl_3$): δ = 25.42, 31.41, (2 q, CH_3), 40.80 (t, C-3,4), 42.56 (s, C-2,5), 64.20 (d, C-1), 179.26 (s, CO_2H). – IR (KBr): $\tilde{\nu}$ = 2938, 2860, 2724, 2325, 1691, 1459, 1409, 1379, 1362, 1274, 1253, 1230, 1204, 935, 730 cm^{-1}. – MS (70 eV): *m/z* (%) = 170 (0.21) [M^+], 155 (1.8), 137 (1.5), 114 (2.4), 110 (4), 109 (10), 102 (5), 101 (100), 83 (8), 70 (32), 55 (17).

$C_{10}H_{18}O_2$ (170.3) Calcd. C 70.55 H 10.66
Found C 70.32 H 10.51

2,3,6,6-Tetramethyl-2-cyclohexen-1-one (**14**): B.p. 30–40°C (bath)/0.6 mbar. – ^{1}H NMR ($CDCl_3$): δ = 1.04 (s, 6H, 6-CH_3), 1.69 (t, *J* = 7.4 Hz, 2H, 5-H), 1.85 (br. s, 3H, 2-CH_3), 2.24 (t, *J* = 2 Hz, 3H, 3-CH_3), 2.50 (m_c, 2H, 4-H). – ^{13}C NMR ($CDCl_3$): δ = 20.41 (q), 24.07 (q, 6-CH_3), 24.43 (q), 25.27, 34.77 (2 t, C-4,5), 46.48 (s, C-6), 130.12, 148.28 (2s, C-2,3), 211.22 (s, C-1). – IR (neat): $\tilde{\nu}$ = 2951, 2850, 1706 (s, C=O), 1631 (s, C=C), 1450, 1378, 1364, 1270, 1192, 1114, 989, 849, 786, 762 cm^{-1}. – MS (70 eV): *m/z* (%) = 152 (78) [M^+], 137 (93), 109 (25), 96 (31), 81 (12), 68 (100), 67 (36).

$C_{10}H_{16}O$ (152.2) Calcd. C 78.90 H 10.59
Found C 79.50 H 10.75

Cyclization of 7 *in Formic Acid:* Compound 7 (1.0 g, 4.8 mmol) is added dropwise within 10 min to a refluxing mixture of 98% formic acid (10 ml) and BF_3–ether (1 ml). The mixture is heated under reflux for 6 h and worked up as described above to yield 0.40 g (49%) of **2** and 0.20 g (20%) of **15**.

1,2-Dichloro-3,3,6,6-tetramethyl-1-cyclohexene (**15**): A solution of 7 (210 mg, 1.01 mmol) in 3 ml of anhydrous CH_2Cl_2 is added to a suspension of $FeCl_3$ (40 mg, 0.25 mmol) in 5 ml of CH_2Cl_2. During stirring, the mixture adopts a deep red color after approximately 5 min. Pentane (20 ml) is added after 2.5 h, and the mixture is passed through 2.0 g of silica gel. After elution with pentane (ca. 50 ml), the pentane solutions are concentrated to give 200 mg (95%) of spectroscopically (^{1}H NMR) pure **15**; b.p. 20–30°C (bath)/0.5 mbar. – ^{1}H NMR ($CDCl_3$): δ = 1.27 (s, 12H, CH_3), 1.63 (s, 4H, CH_2). – ^{13}C NMR ($CDCl_3$): δ = 26.13 (q, 3,6-CH_3), 41.00 (t, C-4,5), 47.00 (s, C-3,6), 155.06 (s, C-1,2). – IR (neat): $\tilde{\nu}$ = 2987, 2950, 2864, 1604, 1588, 1458, 1363, 1216, 1145, 1007, 907, 866, 847, 778 cm^{-1}. – MS (70 eV): *m/z* (%) = 208, 206 (9, 14) [M^+], 193 (8), 191 (13), 173 (17), 171 (52), 150 (58), 135 (18), 115 (59), 91 (12), 83 (100), 77 (21), 55 (18).

$C_{10}H_{16}Cl_2$ (207.1) Calcd. C 57.98 H 7.79
Found C 58.14 H 7.78

CAS Registry Numbers

2: 96188-82-8 / **4**: 503-60-6 / **5**: 78-84-2 / **6**: 1000-30-2 / 7: 128600-84-0 / **8**: 6223-78-5 / **9**: 75-35-4 / **10**: 109749-69-1 / **11**: 128600-85-1 / **13**: 109749-70-4 / **14**: 53343-33-2 / **15**: 128600-86-2 / 2,5-dimethyl-2,5-hexanediol: 110-03-2

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