Selective Synthesis of Halogeno Derivatives from 5-Acetoxytropolone

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5-Acetoxytropolone was successfully halogenated by means of benzyltrimethylammonium tribromide and sulfuryl chloride to give 3-halotropolones and 3,7-dihalotropolones which were converted to the corresponding halogenated *p*-tropoquinone derivatives. From 3,7-dihalo-*p*-tropoquinones, 3,4,7-trichloro-5-hydroxytropolone was prepared in good yields via a Thiele-type addition reaction with hydrochloric acid. By a similar treatment, 5-hydroxytropolone gave a complex mixture.

Recently, we have shown that tropolones polysubstituted with acetoxyl group and/or halogens undergo reductive dehydrohalogenation during acetyl trifluoroacetate (ATA)-mediated acetolysis.[1] This was particularly interesting in connection to the reduction of *p*-tropoquinones to 5-hydroxytropolones by heating in acetic acid which suffered an oxidative decarboxylation.[2,3] Previous attempts of electrophilic bromination of 5-hydroxytropolone (**1**)[4] have so far been unsuccessful: a treatment of **1** with bromine has been known to give an intractable material.[5] Refluxing acetic acid of **1** with bromine,[2] however, gave 2,10-dihydroxydicyclohepta[*b*,*d*]furan-3,9-dione and its dibromo derivatives and dibromo-5-hydroxytropolones, which were a mixture of 3,6-, 3,7-, and 4,6-dibromo derivatives, indicating the operation of an oxidation-addition mechanism via tropoquinones.[6]

Herein, we discuss the electrophilic substitution reactions of the derivatives of **1** with benzyltrimethylammonium tribromide (**2**)[7] and sulfuryl chloride (**3**) halogenations to selectively form 3-halo or 3,7-dihalotropolones.

First of all, **1** was acetylated to 5-acetoxytropolone (**4**)[4] and treated with two molar equivalents of **2** to form product (**5**) in quantitative yield. The structure of **5** was deduced to be 5-acetoxy-3,7-dibromotropolone by conversion to known 3,7-dibromo-5-hydroxytropolone (**6**).[6]

The reaction was mild and selective. The present procedure gave 3,7-dibromo derivatives selectively. However, an excess amount of **2** resulted in the formation of cyclohexadienones; probably, the product, **5**, was oxidized with **2** to 3,7-dibromo-*p*-tropoquinone (**7**) or its equivalent which further ring-contracted via a benzil-benzilic acid rearrangement, in a protic solvent to 3,5-dibromo-4-hydroxy-4-methoxycarbonyl-2,5-cyclohexadienone (**8**).[6] On the other hand, a monobromo derivative, 5-acetoxy-3-bromotropolone (**9**), was obtained in good yield by the use of a controlled amount of **2**. A mild acid hydrolysis of **9** in aqueous acetic acid gave 3-bromo-5-hydroxytropolone (**10**).

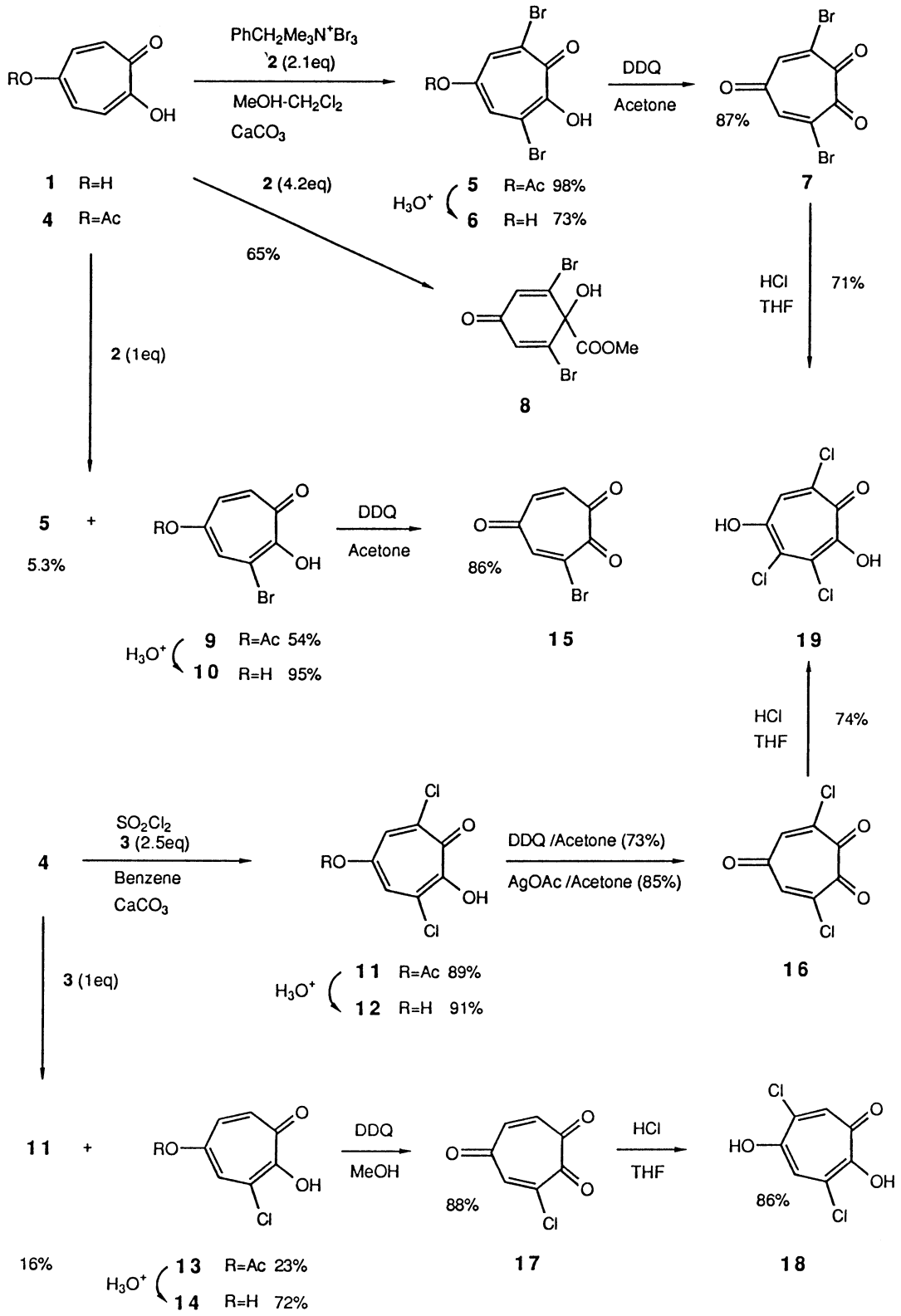
In parallel, chlorination of **4** was also successful by use of **3**: A treatment of **4** with **3** in benzene gave 5-acetoxy-3,7-dichlorotropolone (**11**), which could be quantitatively hydrolyzed to 3,7-dichloro-5-hydroxytropolone (**12**). The controlled chlorination of **4** yielded 5-acetoxy-3-chlorotropolone (**13**) together with an accompanied formation of 16% of **11**. An acid hydrolysis of **13** gave 3-chloro-5-hydroxytropolone (**14**).

The DDQ (2,3-dichloro-5,6-dicyano-*p*-benzoquinone)-oxidation of these halogenated compounds, **6**,[6] **10**, **12**, and **14**, afforded the corresponding *p*-tropoquinone derivatives (**7**,[6] **15**, **16**, and **17**) in high yields. A comparable result could be obtained by silver acetate-oxidation[6] of the 5-hydroxytropolones, as verified, in the case of **6** to **7**. As predicted, concd hydrochloric acid treatment of **17** and **16** in tetrahydrofuran (THF) gave 3,6-dichloro-5-hydroxytropolone (**18**) and 3,4,7-trichloro-5-hydroxytropolone (**19**). The **7** also gave **19** via a halogen exchange. Interestingly, **6** or **10** did not react with concd hydrochloric acid to **12** or **14**; the exchange should be operative only with quinones, prior to the Thiele-type addition step. Further, DDQ-oxidation of **19** was unsuccessful.

In conclusion, we have now obtained products of electrophilic substitution reactions of the derivative of **1** with halogens. Related studies concerning the development of the functional materials starting these troponoids are progressing.

Experimental

Bromination of 4 to 5-Acetoxy-3,7-dibromotropolone (5). A 1 : 1-mixture of MeOH and CH_2Cl_2 (10 cm^3) containing **4** (100 mg) was treated with **2** (476 mg) and $CaCO_3$ (120 mg) at room temperature for 1 h. The mixture was then treated with 1 M HCl (1 M=1 mol dm^{-3}), extracted with EtOAc, and dried over $MgSO_4$. Silica-gel column chromatography of the organic material obtained by removal of the solvent afforded **5** [greenish-yellow needles, mp 188—190 °C, 187 mg; 98%. Found: C, 31.85; H, 2.00%. Calcd for $C_9H_6O_4Br_2$: C, 31.99; H, 1.79%. ^1H NMR[8] δ=2.27 (3H, s) and 7.95 (2H, s). ^{13}C NMR δ=21.1, 123.9 (2C), 135.5 (2C), 139.4, 172.4 (2C), and 175.1. IR ν: 3155, 1760, 1615, 1595, 1565, 1330, 1195, 1155, 915, 810, and 760 cm^{-1}. UV λ_{max}^{MeOH}: 267 nm (ε=29300), 335 (9000, sh), 346 (12200), 418 (9400, sh), and 438 (14400)].



Hydrolysis of 5 to 3,7-Dibromo-5-hydroxytropolone (6). An aqueous AcOH solution (50%, 9 cm^3) of **5** (75 mg) was heated at 100 °C for 6 h. The mixture was then heated in vacuo to remove the solvent and the separated crystals were collected by filtration to give **6** [yellow needles, mp 232—234 °C (decomp) (lit,[6] 166—167 °C), 49 mg; 73%] together with the recovered **5** (17 mg; 23%).

Formation of 3,5-Dibromo-4-hydroxy-4-methoxycarbonyl-2,5-cyclohexadienone (8) by Treatment of 4 with Excess of 2. A 1 : 1-mixed solution consisted of MeOH and CH_2Cl_2 (5 cm^3) of **4** (50 mg) was treated with **2** (458 mg, 4.2 mol equiv) in the presence of $CaCO_3$ (60 mg) at room temperature for 1 h. The same work-up of the mixture gave **8** [colorless prisms, mp 161—162 °C, 59 mg; 65%. Found: C, 29.72; H,

2.05%. Calcd for $C_8H_6O_4Br_2$: C, 29.48; H, 1.86%. ^{1}H NMR δ=3.90 (3H, s) and 6.78 (2H, s). ^{13}C NMR δ=55.6, 77.4, 131.1 (2C), 142.8 (2C), 168.8, and 181.1. IR ν: 3350, 1750, 1650, 1600, 1300, 1225, 1115, 900, and 705 cm^{-1}. UV λ_{max}^{MeOH}: 249 nm (ε=14400) and 280 (4100)].

Controlled Bromination of 4 to 5-Acetoxy-3-bromotropolone (9). To an MeOH solution (20 cm^3) of **4** (200 mg) and $CaCO_3$ (60 mg), a CH_2Cl_2 solution (20 cm^3) of **2** (433 mg) was added drop by drop at room temperature for 2 h. After being stirred for another 2 h, the mixture was acidified with dil HCl, extracted with EtOAc, and dried over $MgSO_4$. Silica-gel column chromatography of the organic material afforded **9** [pale-yellow needles, mp 152—154 °C, 155 mg; 54%. Found: C, 41.86; H, 2.66%. Calcd for $C_9H_7O_4Br$: C, 41.73; H, 2.72%. ^{1}H NMR δ=2.33 (3H, s), 7.15 (1H, dd, J=11.4, 2.6 Hz), 7.30 (1H, d, J=11.4 Hz), and 7.96 (1H, d, J=2.6 Hz), ^{13}C NMR δ=20.9, 118.5, 128.3, 130.2, 137.5, 146.7, 164.3, 169.3, and 169.9. IR ν: 3245, 1765, 1610, 1565, 1210, 1150, 915, and 810 cm^{-1}. UV λ_{max}^{MeOH}: 258 nm (ε=29300), 318 (6200, sh), 335 (9700), 342 (9500, sh), 373 (4600, sh), 391 (5500), and 420 (4800)] together with **5** (20 mg; 5.3%) and the recovered **4** (35 mg; 18%).

Hydrolysis of 9 to 3-Bromo-5-hydroxytropolone (10). Similarly, **9** (93 mg) was treated with aqueous AcOH (33%, 10 cm^3) at 100 °C for 6 h to afford **10** [yellow needles, mp 226—228 °C (decomp), 74 mg; 95%. Found: C, 38.52; H, 2.30%. Calcd for $C_7H_5O_3Br$: C, 38.74; H, 2.32%. ^{1}H NMR δ=7.37 (1H, dd, J=11.7, 2.9 Hz), 7.67 (1H, d, J=11.7 Hz), and 8.15 (1H, d, J=2.9 Hz). ^{13}C NMR δ=127.6, 128.2, 134.2, 134.4, 161.7, 162.1, and 164.9. IR ν: 3300—2300, 1605, 1510, 1465, 1315, 1215, 1080, 870, and 760 cm^{-1}. UV λ_{max}^{MeOH}: 253 nm (ε=14700), 346 (6800), 389 (4900, sh), 401 (5100), and 431 (2800, sh)].

Chlorination of 4. Formation of 5-Acetoxy-3,7-dichlorotropolone (11). An anhydrous benzene suspension (10 cm^3) of **4** (2.0 g) and $CaCO_3$ (560 mg) was treated with SO_2Cl_2 (3.75 g) and refluxed for 2 h. After removing the solvent, the residue was acidified with dil HCl and extracted with $CHCl_3$. Silica-gel column chromatography of the organic material afforded **11** [greenish-yellow crystals, mp 168—170 °C, 2.46 g; 89%. Found: C, 43.12; H, 2.40%. Calcd for $C_9H_6O_4Cl_2$: C, 43.40; H, 2.43%. ^{1}H NMR δ=2.29 (3H, s) and 7.77 (2H, s). ^{13}C NMR δ=20.7, 133.9 (2C), 134.2 (2C), 144.9, 165.7 (2C), and 171.0. IR ν: 3200, 1765, 1600, 1575, 1340, 1200, 1155, and 855 cm^{-1}. UV λ_{max}^{MeOH}: 251 nm (ε=22400, sh), 262 (32600), 333 (9500, sh), 344 (12300), 396 (4100, sh), 412 (6800, sh), and 436 (10000)].

Hydrolysis of 11 to 3,7-Dichloro-5-hydroxytropolone (12). An aqueous acetone solution (33%, 15 cm^3) of **11** (1.84 g) was refluxed for 4 h. Silica-gel column chromatography of the residue, obtained from the mixture, afforded **12** [yellow crystals, mp 253—255 °C (decomp), 1.39 g; 91%. Found: C, 40.91; H, 2.06%. Calcd for $C_7H_4O_3Cl_2$: C, 40.61; H, 1.95%. ^{1}H NMR δ=7.50 (2H, s). ^{13}C NMR δ=127.4 (2C), 136.9 (2C), 154.8, and 162.8 (2C). IR ν: 3400—2400, 1605, 1575, 1530, 1420, 1360, 1220, 1110, 860, and 760 cm^{-1}. UV λ_{max}^{MeOH}: 255 nm (ε=25500), 349 (8800), 395 (6400, sh), 412 (7300), and 438 (4800, sh)].

Controlled Chlorination of 4. Formation of 5-Acetoxy-3-chlorotropolone (13). To an anhydrous benzene suspension (100 cm^3) of **4** (3.0 g), an anhydrous benzene solution (20 cm^3) of SO_2Cl_2 (2.24 g) was added drop by drop for 1 h. After being refluxed for another 2 h, the mixture was heated in vacuo to remove the solvent. The residue was chromatographed on a silica-gel column to give recovered **4** (1.05 g; 35%), **11** (645 mg; 16%), and **13** [pale-yellow needles, mp 148—150 °C, 834 mg; 23%. Found: C, 50.49; H, 3.25%. Calcd for $C_9H_7O_4Cl$: C, 50.37; H, 3.29%. ^{1}H NMR δ=2.33 (3H, s), 7.13 (1H, dd, J=11.4, 2.6 Hz), 7.32 (1H, d, J=11.4 Hz), and 7.73 (1H, d, J=2.6 Hz). ^{13}C NMR δ=20.9, 118.3, 129.9, 134.5, 136.8, 146.6, 164.7, 169.2, and 169.5. IR ν: 3270, 1750, 1610, 1575, 1220, 1155, 920, 845, and 775 cm^{-1}. UV λ_{max}^{MeOH}: 215 nm (ε=29900), 314 (6200, sh), 332 (10000), 342 (9200, sh), 373 (4700, sh), 390 (5500), and 415 (3700)].

Hydrolysis of 13 to 14. An aqueous acetone solution (33%, 15 cm^3) of **13** (300 mg) was refluxed for 4 h. The mixture was then heated in vacuo to remove the solvent; the residue was crystallized from EtOH to give **14** [pale-yellow crystals, mp 218—220 °C (decomp) (lit,[6] 221—223 °C (decomp)). ^{1}H NMR δ=7.03 (1H, d, J=11.4, 2.6 Hz), 7.35 (1H, d, J=11.4 Hz), and 7.70 (1H, d, J=2.6 Hz)].

DDQ-Oxidation of 6. Formation of 3,7-Dibromo-*p*-tropoquinone (7). An acetone suspension (2 cm^3) of **6** (100 mg) was treated with DDQ (93 mg) at room temperature for 30 min. The mixture was then heated in vacuo to remove the solvent; the residue was chromatographed on a silica-gel column to give **7** [yellow crystals, mp 93—95 °C (lit,[6] 96—97 °C (decomp)), 86 mg; 87%].

DDQ-Oxidation of 10 to 3-Bromo-*p*-tropoquinone (15). Similarly, an acetone solution (5 cm^3) of **10** (40 mg) was treated with DDQ (42 mg) at room temperature for 30 min. The mixture was then heated in vacuo to remove the solvent; the residue was chromatographed to give **15** [yellow crystals, mp 59—61 °C, 34 mg; 86%. Found: C, 39.25; H, 1.53%. Calcd for $C_7H_3O_3Br$: C, 39.10; H, 1.41%. ^{1}H NMR δ=6.78 (2H, d, J=0.7 Hz) and 7.53 (1H, t, J=0.7 Hz). ^{13}C NMR δ=133.8, 136.5, 138.5, 141.1, 181.9, 184.6, and 185.2. IR ν: 3045, 1670, 1640, 1610, 1595, 1320, and 1160 cm^{-1}].

DDQ-Oxidation of 12. Formation of 3,7-Dichloro-*p*-tropoquinone (16). An acetone suspension of **12** (200 mg) was treated with DDQ (200 mg) at room temperature for 1 h. After removing the solvent, the residue was chromatographed on a silica-gel column to give **16** [yellow crystals, mp 53—55 °C, 145 mg; 73%. Found: C, 41.50; H, 1.15%; M$^+$, 203.9414. Calcd for $C_7H_4O_3Cl_2$: C, 41.01; H, 0.98%; M, 203.9381. ^{1}H NMR δ=7.30 (2H, s). ^{13}C NMR δ=136.9 (2C), 142.5 (2C), 180.3, and 181.5 (2C). IR ν: 1695, 1630, 1610, 1330, 1190, and 895 cm^{-1}].

AgOAc-Oxidation of 12. An acetone suspension (5 cm^3) of **12** (100 mg) was treated with AgOAc (160 mg) at room temperature for 1 h with stirring. After removing the solvent in vacuo, the residue was passed through a short Celite column and chromatographed on a silica-gel column to give **16** (84 mg; 85%).

Concentrated HCl-Treatment of 16 to 3,4,7-Trichloro-5-hydroxytropolone (19). A THF solution (5 cm^3) of **16** (145 mg) and concd HCl (0.03 cm^3) was stirred at room temperature for 30 min. After removing the solvent in vacuo, the residue was washed with $CHCl_3$ and recrystallized from MeOH to give **19** [greenish-yellow crystals, mp 190 °C (decomp), 126 mg; 74%. Found: C, 34.98; H, 1.25; Cl, 43.90%. Calcd for $C_7H_3O_3Cl_3$: C, 34.82; H, 1.25; Cl, 44.06%. ^{1}H NMR δ=7.59 (1H, s). ^{13}C NMR δ=123.7, 133.3, 135.9, 137.8, 151.4, 161.2, and 163.3. IR ν: 3200—2400, 1510, 1430, 1310, 1190, 1140, 870, and 835 cm^{-1}. UV λ_{max}^{MeOH}: 263 nm (ε=23600), 329 (2900, sh), 355 (6200), 370 (6300), 397 (6400, sh), 416 (7500), and 440 (5800, sh)].

Concentrated HCl-Treatment of 7. Formation of 19. Similarly, a THF solution (5 cm^3) of **7** (195 mg) was treated with concd HCl (0.03 cm^3) at room temperature for 30 min. After removing the solvent, the residue was washed with $CHCl_3$ and recrystallized from MeOH to give **19** (114 mg; 71%). Its identity with the sample obtained from **12** was confirmed by a direct comparison.

DDQ-Treatment of 14. Formation of 3-Chloro-*p*-tropoquinone (17). An MeOH solution (4 cm^3) of **14** (150 mg) was treated with DDQ (200 mg) at room temperature for 30 min. The mixture was then chromatographed on a silica-gel column to give **17** [yellow crystals, mp 68—69 °C (lit,[6] 73—74 °C), 130 mg; 88%].

Concentrated HCl-Treatment of 17 to 3,6-Dichloro-5-hydroxytropolone (18). A THF solution (5 cm^3) containing concd HCl (0.03 cm^3) of **17** (130 mg) was stirred at room temperature for 1 h. After removing the solvent, the residue was recrystallized from EtOH to give **18** [pale-yellow crystals, mp 181—183 °C (decomp), 136 mg; 86%. Found: C, 40.52; H, 2.02%. Calcd for $C_7H_4O_3Cl_2$: C, 40.61; H, 1.95%. ^1H NMR δ=7.70 (1H, s) and 7.96 (1H, s). ^{13}C NMR δ=124.6, 129.6, 130.9, 139.7, 153.5, 159.2, and 168.1. IR ν: 3400—2800, 1525, 1450, 1335, 1220, 1130, and 830 cm^{-1}. UV λ_{max}^{MeOH}: 255 nm (ε=27000), 351 (8100), 365 (8200), 391 (8900, sh), 408 (9800), and 434 (6400, sh)].

Attempted DDQ-Oxidation of 19. An anhydrous acetone solution (5 cm^3) of **19** (100 mg) was treated with DDQ(85 mg) at room temperature for 1 h. After removing the solvent in vacuo, the residue was chromatographed on a silica-gel column to give 14 mg of solid material, whose ^1H NMR spectrum indicated a mixture. Despite the intensive effort, no compound was isolable, and the absence of starting **19** in the mixture was assured by mass spectrometry.

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8) The NMR spectra were measured in $CDCl_3$ solutions, and the chemical shifts were expressed in δ unit (internal Me_4Si).