2-BROMO-3,4,4-TRICHLOROBUT-3-ENOATES OF CERTAIN NATURAL ALCOHOLS, PHENOLS, AND OXIMES OF CARBONYL COMPOUNDS

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*Previously undescribed 2-bromo-3,4,4-trichlorobut-3-enoates **1b-23b** were synthesized in 84-91% yield from natural alcohols including terpenes and steroids, plant phenols, and oximes of natural carbonyl compounds **1a-23a** by reaction of 2-bromo-3,4,4-trichlorobut-3-enoyl chloride in the presence of pyridine.*

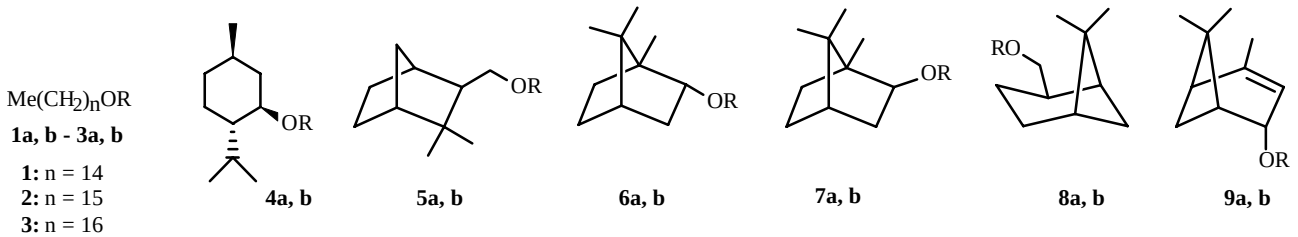
Key words: 2-bromo-3,4,4-trichlorobut-3-enoyl chloride, 2-bromo-3,4,4-trichlorobut-3-enoates, esters, terpene alcohols, steroidal alcohols, plant phenols, oximes, chemical modification.

Research on the addition of pharmacophores to natural physiologically active compounds has been developing vigorously recently owing to the probability that using such modifications will selectively transport medicines to certain types of cells [1]. Natural alcohols and phenols can act as convenient vectors for supplying pharmacophores, in particular those containing halogens, to the targeted cellular receptors [2].

Our goal was to prepare a series of new derivatives of natural compounds as esters of 2-bromo-3,4,4-trichlorobut-3-enoic acid (**1b-23b**). We selected the following compounds for the chemical modification: pentadecanol (**1a**), hexadecanol (cetyl alcohol) (**2a**), heptadecanol (**3a**), (-)-(1*R*,2*S*,5*R*)-menthol (**4a**), 10-hydroxymethylcamphene (**5a**), borneol (**6a**), isoborneol (**7a**), nopol (**8a**), *trans*-verbenol (**9a**), cholesterol (**10a**), ergosterol (**11a**), β-sitosterol (**12a**), lanosterol (**13a**), diosgenin (**14a**), solasodin (**15a**), androsterone (**16a**), pregnenolone (**17a**), 5α-androstan-17β-ol-3-one (**18a**), testosterone (**19a**), vanillin (**20a**), vanillal (**21a**), (-)-(2*S*,5*R*)-methone oxime (**22a**), and D,L-camphar oxime (**23a**).

Esters of 2-bromo-3,4,4,-trichlorobut-3-enoic acid (**1b-23b**) were prepared by reaction of the appropriate hydroxylated compounds (**1a-23a**) with 2-bromo-3,4,4-trichlorobut-3-enyl chloride in absolute benzene in the presence of pyridine. A stoichiometric 1:1:1 ratio of reagents was found to be optimal. An excess of pyridine led to polymerization of the mixture and lowered the yield of the esters. The yields of the esters (**1b-23b**) were 84-91%.

The structures of the synthesized esters (**1b-23b**) were confirmed by elemental analysis; PMR, IR, and UV spectra; and cryoscopic determination of the molecular weight. According to PMR spectroscopy, the purity of the prepared compounds was 98 ± 1%. The analytical results and molecular weights of all compounds agreed with those calculated.



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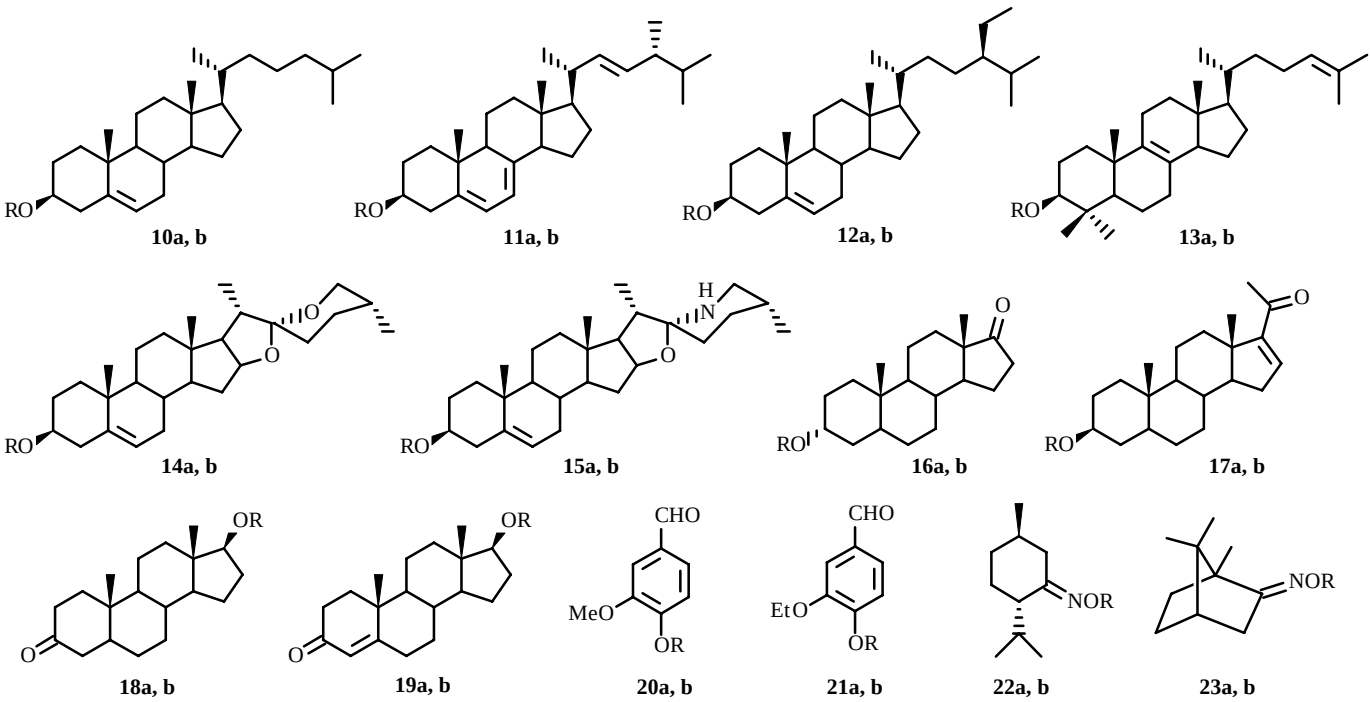

a: R = H; **b**: R = Cl_2C=CClCHBrC(O)-

EXPERIMENTAL

IR spectra were recorded on a Protege-460 IR-Fourier spectrophotometer (Nicolet) as thin layers or in KBr; UV spectra, on a Specord UV-Vis instrument as $1 \cdot 10^{-4}$ solutions in CH_3OH. PMR spectra were obtained on a BS-587A spectrometer (100 MHz, Tesla) as solutions (5%) in $CDCl_3$. Chemical shifts were measured relative to TMS internal standard. Molecular weights were measured by cryoscopy in benzene. Column chromatography used neutral aluminum oxide L 40/250 μm of Brockmann activity II.

2-Bromo-3,4,4-trichloro-3-butenoic acid was synthesized by bromination of available [3] 3,4,4-trichloro-3-butenoic acid using elemental bromine in CCl_4 solution with boiling (72 h). Yield 57%, mp 83-85°C. IR spectrum (ν, cm^{-1}): 3300-2500 (COOH), 1738 (C=O), 1589 (C=C), 722, 814 (C–Cl), 648 (C–Br). PMR spectrum (δ, ppm): 5.93 (CHBr, s), 10.97 (COOH, br.s).

The acid chloride was prepared by boiling 2-bromo-3,4,4-trichloro-3-butenoic acid with a 2.5-fold excess of thionyl chloride [3]. Yield 81%, bp 76-77°C (2 mm Hg). IR spectrum (ν, cm^{-1}): 1801 (C=O), 1584 (C=C), 728, 825 (C–Cl), 671 (C–Br). PMR spectrum (δ, ppm): 6.13 (CHBr, s).

2-Bromo-3,4,4-trichlorobut-3-enyl Esters (1b-23b) (general method). A solution of the appropriate compound (**1a-23a**, 10 mmol) in absolute benzene (50 mL) was treated with 2-bromo-3,4,4-trichlorobut-3-enyl chloride (10 mmol). The resulting solution was stirred, treated over 3-5 min dropwise with a solution of absolute pyridine (10 mmol) in benzene (10 mL) and left for 10-12 h at 20-23°C. The precipitate of pyridine hydrochloride was filtered off. The filtrate was thoroughly washed with water and aqueous sodium bicarbonate (5%) and dried over $CaCl_2$. The solvent was distilled off. The solid was purified by low-temperature crystallization from ethanol (96%) (**3b**, **6b**, **7b**, **10b**-**21b**, **23b**) or column chromatography over aluminum oxide (**1b**, **2b**, **4b**, **5b**, **8b**, **9b**, **22b**) using hexane eluent.

This method produced the following compounds.

1-Pentadecyl 2-bromo-3,4,4-trichlorobut-3-enoate (1b). Yield 90%, d_{20}^{20} 1.1613, n_D^{20} 1.4960. $C_{19}H_{32}BrCl_3O_2$. IR spectrum (ν, cm^{-1}): 2960, 2924, 2853 (CH_{Alk}); 1765 (C=O); 1590 (C=C); 1466 (CH_2).

UV spectrum (λ_{max}, nm, ε): 219 (8000), 238 (8000).

PMR spectrum (δ, ppm): 0.92 (CH_3, t), 1.27 [$(CH_2)_{12}$, br.s], 1.68 (CH_2, q), 4.23 (CH_2O, t), 5.84 (CHBr, s).

1-Hexadecyl 2-bromo-3,4,4-trichlorobut-3-enoate (2b). Yield 91%, d_{20}^{20} 1.0774, n_D^{20} 1.4830. $C_{20}H_{34}BrCl_3O_2$. IR spectrum (ν, cm^{-1}): 2963, 2924, 2853 (CH_{Alk}); 1767 (C=O); 1588 (C=C); 1467 (CH_2).

UV spectrum (λ_{max}, nm, ε): 218 (8000), 238 (8000).

PMR spectrum (δ, ppm): 0.89 (CH_3, t), 1.27 [$(CH_2)_{13}$, br.s], 1.68 (CH_2, q), 4.25 (CH_2O, t), 5.84 (CHBr, s).

1-Heptadecyl 2-bromo-3,4,4-trichlorobut-3-enoate 3b. Yield 88%, mp 33-34°C. $C_{21}H_{36}BrCl_3O_2$.

IR spectrum (ν, cm^{-1}): 2954, 2920, 2851 (CH_{Alk}); 1763 (C=O); 1588 (C=C); 1465 (CH_2).

UV spectrum (λ_{max}, nm, ε): 219 (8000), 238 (8000).

PMR spectrum (δ, ppm): 0.92 (CH_3, t), 1.26 [$(CH_2)_{12}$, br.s], 1.70 (CH_2, q), 4.24 (CH_2O, t), 5.84 (CHBr, s).

(–)-(1*R*,2*S*,5*R*)-Menthyl 2-bromo-3,4,4-trichlorobut-3-enoate 4b. Yield 84%, d_{20}^{20} 1.2299, n_D^{20} 1.5100. $C_{14}H_{20}BrCl_3O_2$.

IR spectrum (ν, cm^{-1}): 2957, 2928, 2870 (CH_{Alk}); 1762 (C=O); 1587 (C=C); 1456 (CH_2).

UV spectrum (λ_{max}, nm, ε): 220 (8000), 238 (9000).

PMR spectrum (δ, ppm): 0.83 (CH_3 on C-5, d), 0.94 [$(CH_3)_2C$, d], 4.74 (CHO, m), 5.82 (CHBr, m).

10-Methylcamphenyl 2-bromo-3,4,4-trichlorobut-3-enoate 5b. Yield 87%, d_{20}^{20} 1.2324, n_D^{20} 1.5370. $C_{14}H_{18}BrCl_3O_2$.

IR spectrum (ν, cm^{-1}): 2958, 2879 (CH_{Alk}); 1761 (C=O); 1586 (C=C); 1459 (CH_2).

UV spectrum (λ_{max}, nm, ε): 220 (8000), 237 (8000).

PMR spectrum (δ, ppm): 1.01 and 1.03 ($2CH_3$ on C-2, 2s), 4.70 (CH_2O, d), 5.83 (CHBr, m).

Borneolyl 2-bromo-3,4,4-trichlorobut-3-enoate 6b. Yield 89%, mp 33-34°C. $C_{14}H_{18}BrCl_3O_2$.

IR spectrum (ν, cm^{-1}): 2958, 2876 (CH_{Alk}); 1747 (C=O); 1589 (C=C); 1454 (CH_2).

UV spectrum (λ_{max}, nm, ε): 220 (8000), 238 (8000).

PMR spectrum (δ, ppm): 0.87 (CH_3 on C-1, s), 0.90 (CH_3 on C-7, s), 0.91 (CH_3 on C-7, s), 4.95 (CHO, m), 5.87 (CHBr, m).

Isoborneolyl 2-bromo-3,4,4-trichlorobut-3-enoate 7b. Yield 87%, mp 103-104°C, $C_{14}H_{18}BrCl_3O_2$.

IR spectrum (ν, cm^{-1}): 2961, 2930, 2877 (CH_{Alk}); 1744 (C=O); 1593 (C=C); 1455 (CH_2).

UV spectrum (λ_{max}, nm, ε): 219 (8000), 238 (8000).

PMR spectrum (δ, ppm): 0.85 (CH_3 on C-1, s), 0.87 (CH_3 on C-7, s), 0.94 (CH_3 on C-7, s), 4.68 (CHO, m), 5.86 (CHBr, m).

Nopolyl 2-bromo-3,4,4-trichlorobut-3-enoate 8b. Yield 84%, d_{20}^{20} 1.3367, n_D^{20} 1.5375. $C_{14}H_{18}BrCl_3O_2$.

IR spectrum (ν, cm^{-1}): 2984, 2950, 2917, 2876, 2830 (CH_{Alk}); 1765 (C=O); 1591 (C=C), 1470 (CH_2).

UV spectrum (λ_{max}, nm, ε): 218 (8000), 240 (9000).

PMR spectrum (δ, ppm): 0.80 (CH_3, s), 1.29 (CH_3, s), 4.25 (CH_2O, m), 5.86 (CHBr, s).

***trans*-Verbenolyl 2-bromo-3,4,4-trichlorobut-3-enoate 9b.** Yield 86%, d_{20}^{20} 1.3420, n_D^{20} 1.5355. $C_{14}H_{16}BrCl_3O_2$.

IR spectrum (ν, cm^{-1}): 3040 (C=CH); 2975, 2957, 2936, 2871 (CH_{Alk}); 1758 (C=O); 1636, 1590 (C=C); 1470, 1440 (CH_2).

UV spectrum (λ_{max}, nm, ε): 205 (6000), 220 (10000), 240 (8000).

PMR spectrum (δ, ppm): 0.91 (CH_3, s), 1.35 (CH_3, s), 2.04 (CH_3, d), 4.80 (CHO, m), 5.40 (C=CH, m), 5.88 (CHBr, m).

Cholesterolyl 2-bromo-3,4,4-trichlorobut-3-enoate 10b. Yield 90%, mp 95-96°C. $C_{31}H_{46}BrCl_3O_2$.

IR spectrum (ν, cm^{-1}): 3035 (C=CH); 2965, 2932, 2867, 2850, 2800 (CH_{Alk}); 1760 (C=O); 1634, 1591 (C=C); 1467, 1440 (CH_2).

UV spectrum (λ_{max}, nm, ε): 204 (6000), 221 (11000), 240 (8000).

PMR spectrum (δ, ppm): 0.68 (CH_3-18, s), 1.03 (CH_3-19, s), 4.70 (H-3, m), 5.38 (H-6, m), 5.82 (CHBr, s).

Ergosterolyl 2-bromo-3,4,4-trichlorobut-3-enoate 11b. Yield 85%, mp 110-111°C. $C_{32}H_{44}BrCl_3O_2$.

IR spectrum (ν, cm^{-1}): 3045 (C=CH); 2970, 2956, 2928, 2853 (CH_{Alk}); 1759 (C=O); 1660, 1640, 1592 (C=C); 1468 (CH_2).

UV spectrum (λ_{max}, nm, ε): 205 (18000), 222 (12000), 242 (12000), 265 (10000).

PMR spectrum (δ, ppm): 0.63 (CH_3-18, s), 1.03 (CH_3-19, s), 4.75 (H-3, m), 5.05-5.75 (H-6, H-7, H-22, H-23, m), 5.82 (CHBr, s).

***β*-Sitosterolyl 2-bromo-3,4,4-trichlorobut-3-enoate 12b.** Yield 88%, mp 103-104°C. $C_{33}H_{50}BrCl_3O_2$.

IR spectrum (ν, cm^{-1}): 3035 (C=CH); 2959, 2934, 2867, 2851 (CH_{Alk}); 1758 (C=O); 1636, 1592 (C=C); 1466, 1450 (CH_2).

UV spectrum (λ_{max}, nm, ε): 205 (6000), 222 (11000), 240 (8000).

PMR spectrum (δ, ppm): 0.68 (CH_3-18, s), 1.04 (CH_3-19, s), 4.70 (H-3, m), 5.36 (H-6, m), 5.82 (CHBr, s).

Lanosterolyl 2-bromo-3,4,4-trichlorobut-3-enoate 13b. Yield 87%, mp 97-98°C. $C_{34}H_{50}BrCl_3O_2$.

IR spectrum (ν, cm^{-1}): 3030 (C=CH); 2949, 2928, 2872, 2840 (CH_{Alk}); 1761 (C=O); 1645, 1630, 1590 (C=C); 1466, 1453 (CH_2).

UV spectrum (λ_{max}, nm, ε): 205 (10000), 221 (12000), 240 (8000).

PMR spectrum (δ, ppm): 0.70 (CH_3-18, s), 1.04 (CH_3-19, s), 4.47 (H-3, m), 5.17 (H-24, m), 5.86 (CHBr, s).

Diosgeninyl 2-bromo-3,4,4-trichlorobut-3-enoate 14b. Yield 86%, mp 175-176°C. $C_{31}H_{42}BrCl_3O_4$.

IR spectrum (ν, cm^{-1}): 3040 (C=CH); 2950, 2935, 2905, 2871, 2852 (CH_{Alk}); 1760 (C=O); 1630, 1590 (C=C); 1455 (CH_2).

UV spectrum (λ_{max}, nm, ε): 204 (6000), 221 (11000), 240 (8000).

PMR spectrum (δ, ppm): 0.78 (CH_3-18, s), 1.04 (CH_3-19, s), 4.36 (H-3, m), 5.38 (H-6, m), 5.82 (CHBr, s).

Solasodinyl 2-bromo-3,4,4-trichlorobut-3-enoate 15b. Yield 84%, mp 231-232°C. $C_{31}H_{43}BrCl_3NO_3$.

IR spectrum (ν, cm^{-1}): 3040 (C=CH); 2960, 2930, 2872, 2852 (CH_{Alk}); 1762 (C=O); 1632, 1580 (C=C); 1455 (CH_2).

UV spectrum (λ_{max}, nm, ε): 205 (7000), 222 (12000), 240 (8000).

PMR spectrum (δ, ppm): 0.79 (CH_3-18, s), 1.04 (CH_3-19, s), 4.40 (H-3, m), 5.30 (H-6, m), 5.80 (CHBr, s).

Androsteronyl 2-bromo-3,4,4-trichlorobut-3-enoate 16b. Yield 90%, mp 129-130°C. $C_{23}H_{30}BrCl_3O_3$.

IR spectrum (ν, cm^{-1}): 2976, 2933, 2857 (CH_{Alk}); 1757, 1741 (C=O); 1589 (C=C); 1470, 1451 (CH_2).

UV spectrum (λ_{max}, nm, ε): 217 (9000), 236 (9000).

PMR spectrum (δ, ppm): 0.86 (CH_3-18, s), 1.26 (CH_3-19, s), 4.80 (H-3, m), 5.82 (CHBr, s).

Pregnenolonyl 2-bromo-3,4,4-trichlorobut-3-enoate 17b. Yield 91%, mp 131-132°C. $C_{25}H_{32}BrCl_3O_3$.

IR spectrum (ν, cm^{-1}): 3074 (C=CH); 2968, 2933, 2914, 2854 (CH_{Alk}); 1758, 1660 (C=O); 1630, 1590 (C=C); 1470, 1452 (CH_2).

UV spectrum (λ_{max}, nm, ε): 225 (15000), 240 (10000).

PMR spectrum (δ, ppm): 0.89 (CH_3-18, s), 1.25 (CH_3-19, s), 2.26 (CH_3-21, s), 4.80 (H-3, m), 5.82 (CHBr, s), 6.70 (H-16, m).

5α-Androstan-17β-(2-bromo-3,4,4-trichlorobut-3-enoate 18b. Yield 84%, mp 81-82°C. $C_{23}H_{30}BrCl_3O_3$.

IR spectrum (ν, cm^{-1}): 2978, 2935, 2860 (CH_{Alk}); 1760, 1660 (C=O); 1589 (C=C); 1470, 1455 (CH_2).

UV spectrum (λ_{max}, nm, ε): 218 (9000), 238 (9000).

PMR spectrum (δ, ppm): 0.87 (CH_3-18, s), 1.22 (CH_3-19, s), 4.70 (H-17, m), 5.86 (CHBr, s).

Testosteronyl 2-bromo-3,4,4-trichlorobut-3-enoate 19b. Yield 90%, mp 53-54°C. $C_{23}H_{28}BrCl_3O_3$.

IR spectrum (ν, cm^{-1}): 3033 (C=CH); 2965, 2941, 2890, 2875, 2854 (CH_{Alk}); 1761, 1673 (C=O); 1617, 1589 (C=C); 1478, 1449, 1435 (CH_2).

UV spectrum (λ_{max}, nm, ε): 219 (10000), 242 (20000).

PMR spectrum (δ, ppm): 0.88 (CH_3-18, s), 1.20 (CH_3-19, s), 4.70 (H-17, m), 7.72 (H-4, m), 5.91 (CHBr, s).

Vanillinyl 2-bromo-3,4,4-trichlorobut-3-enoate 20b. Yield 92%, mp 103-104°C. $C_{12}H_8BrCl_3O_4$.

IR spectrum (ν, cm^{-1}): 3085, 3060, 3010 (CH_{Ar}); 2985, 2955, 2923, 2885, 2854, 2745 (CH_{Alk}); 1786, 1697 (C=O); 1601, 1504, 1423, 1396 (Ar).

UV spectrum (λ_{max}, nm, ε): 207 (8000), 222 (20000), 240 (12000), 260 (8000), 310 (3000).

PMR spectrum (δ, ppm): 3.91 (CH_3O, s), 6.15 (CHBr, s), 7.15-7.60 (C_6H_3, m), 9.97 (CHO, s).

Vanillalyl 2-bromo-3,4,4-trichlorobut-3-enoate 21b. Yield 91%, mp 84-85°C. $C_{13}H_{10}BrCl_3O_4$.

IR spectrum (ν, cm^{-1}): 3080, 3060, 3010 (CH_{Ar}); 2987, 2925, 2900, 2860, 2850, 2745 (CH_{Alk}); 1785, 1693 (C=O); 1599, 1504, 1439, 1392 (Ar).

UV spectrum (λ_{max}, nm, ε): 208 (9000), 223 (20000), 240 (11000), 260 (8000), 310 (3000).

PMR spectrum (δ, ppm): 1.44 (CH_3, t), 4.18 (CH_2, q), 6.14 (CHBr, s), 7.20-7.64 (C_6H_3, m), 9.96 (CHO, s).

(–)-1-(2-Bromo-3,4,4-trichlorobut-3-enylhydroxyimino)menthane 22b. Yield 89%, d_{20}^{20} 1.3938, n_D^{20} 1.5405. $C_{14}H_{16}BrCl_3NO_2$.

IR spectrum (ν, cm^{-1}): 2959, 2928, 2870 (CH_{Alk}); 1778 (C=O); 1635 (C=N); 1587 (C=C); 1456 (CH_2).

UV spectrum (λ_{max}, nm, ε): 209 (5000), 219 (9000), 238 (8000).

PMR spectrum (δ, ppm): 0.98 (CH_3-5, d), 1.04 [$(CH_3)_2C$, d], 5.99 (CHBr, s).

(*E*)-2-(2-Bromo-3,4,4-trichlorobut-3-enylhydroxyimino)-1,7,7-trimethylbicyclo[2.2.1]heptane 23b. Yield 88%, mp 94-95°C. $C_{14}H_{17}BrCl_3NO_2$.

IR spectrum (ν, cm^{-1}): 2980, 2960, 2942, 2888, 2872 (CH_{Alk}); 1774 (C=O); 1664 (C=N); 1590 (C=C); 1451 (CH_2).

UV spectrum (λ_{max}, nm, ε): 210 (5000), 220 (9000), 240 (9000).

PMR spectrum (δ, ppm): 0.83 (CH_3-1, s), 0.95 (CH_3-7, s), 1.11 (CH_3-7, s), 5.97 (CHBr, m).

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