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A [1.1.1]Propellane with an Unprotected Hydroxy Group in the Side Chain

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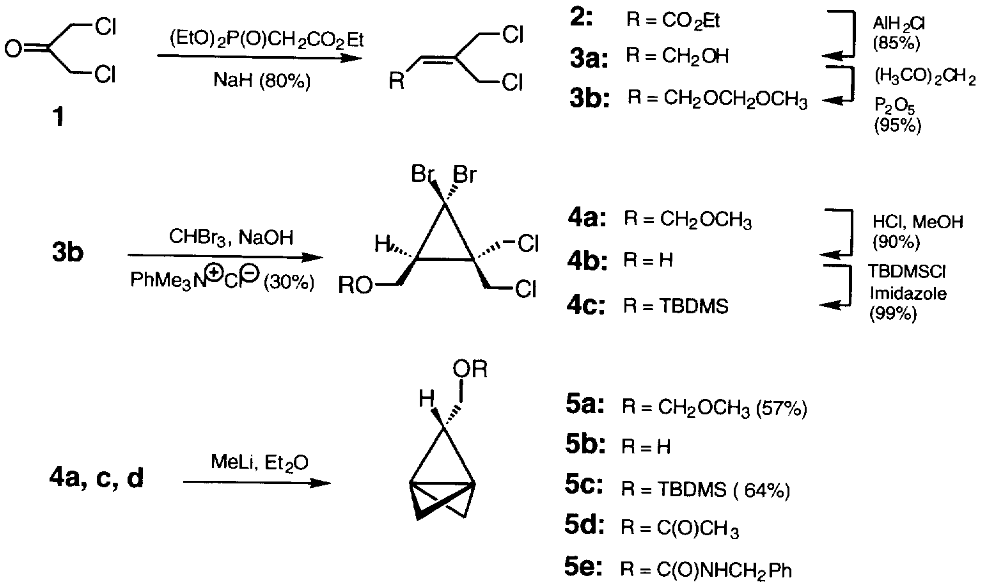
Abstract: A synthesis of hydroxymethyl[1.1.1]propellane is reported which is the first hydrocarbon of this sort with an unprotected functional group. The hydroxy group can be used for further modifications which should make available a variety of functionalized propellanes. These otherwise not accessible compounds would be of great interest, for example, as monomers in the area of rigid-rod polymers.

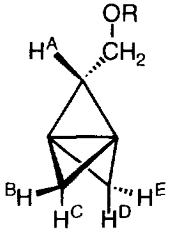
The most efficient protocol for the synthesis of [1.1.1]propellanes involves carbene additions and halogen/lithium exchange reactions.[1] The introduction of other substituents than alkyl or methoxyalkyl to these highly strained hydrocarbons is therefore a somewhat tricky matter and generally requires the use of protective groups.[2] A good example for this is the recently achieved synthesis of a propellane with a methoxy methyl (MOM) protected hydroxy group in the side chain.[3] Because of the high sensitivity of [1.1.1]propellanes towards traces of electrophiles, the MOM group cannot be removed from this compound but only from the corresponding bicyclo[1.1.1]pentane derivative, which in this case is the homopolymer. We are involved in a project aiming at a structural modification of poly[1.1.1]propellanes by adding, e.g., dendritic fragments to every repeat unit.[4] In principal this can be done either by modifying the preformed polymer with dendritic fragments or by polymerizing the modified (dendrimerized) monomer. The latter way has some advantages for general polymer chemical considerations. This led us to synthesize a propellane with hydroxy groups in the side chain carrying a protective group, which may be removed under reaction conditions the propellane moiety can still withstand.

The synthetic route uses a modified Szeimies procedure[1] and involves the Horner olefination of **1** to give ester **2**, reduction of **2** to furnish alcohol **3a**, and protection of the alcohol with the methoxymethyl (MOM) protective group to yield **3b** (Scheme 1). The protected allyl alcohol **3b** is then converted into **4a** using standard carbene chemistry and the MOM group is replaced by the tert.-butyldimethylsilyl group (TBDMS) to give **4c**. This compound upon treatment with two equivalents of methyllithium furnishes propellane **5c**. The TBDMS group can easily be cleaved off by exposing **5c** to "naked" fluoride, tetrabutyl ammonium fluoride (TBAF). **5b** is obtained on the 0.5 g-scale as a solution in THF/ether (1:5). Because of the similar boiling points of **5b**, THF, and TBDMSF, **5b** was generally not isolated but characterized (^1H, ^{13}C NMR spectroscopy, see Tables 1, 2) and derivatized in situ. For other studies, the whole synthesis was also carried through with the MOM group to give propellane **5a**.



Scheme 1. Synthesis of [1.1.1]propellane, **5b**, with an unprotected functional group and its derivatization with acetic acid anhydride and benzyl isocyanate to give **5 d** and **5e**.

The high sensitivity of **5b** towards traces of electrophiles allows derivatization only under non-acidic and low temperature (20° C) conditions and should proceed with high rates.[5] Anhydrides and isocyanates are known to react with alcohols under mild conditions and at high rates. In model studies using acetic acid anhydride and benzyl isocyanate this was proved to be the case also for **5b**. Within a few minutes at room temperature, it reacted with these reagents and cleanly furnished ester **5d** and urethane **5e**. All propellanes **5a - e** were analyzed by NMR spectroscopy (Tables 1, 2).



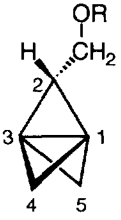


Table 1. Selected ^1H NMR chemical shifts (coupling pattern) of propellanes **5a** - **5e** in C_6D_6 at 20° C.

	H^A(m)	H^B(dd)	H^C(d)	H^D(dd)	H^E(dd)	CH_2O(d)
5 a	2.71	1.58	1.53	1.88	2.48	3.31
5 b	2.70	1.55	1.45	1.85	2.45	3.25
5 c	2.73	1.55	1.49	1.88	2.43	3.43
5 d	2.65	1.50	1.45	1.83	2.48	3.83
5e$^\alpha$	2.85	1.90	1.85	2.27	2.80	4.00

α) in CD_2Cl_2.

Table 2. Selected ^{13}C NMR chemical shifts of propellanes **5a** - **5e** in C_6D_6 at 20° C.

	C-1(C-3)	C-2	C-4$^\beta$	C-5$^\beta$	CH_2-O
5 a	4.7	88.7	70.3	72.3	60.9
5 b	5.0	92.4	70.1	72.1	56.4
5 c	5.1	92.0	70.0	72.3	57.7
5 d	4.6	86.8	70.0	72.1	57.7
5e$^\alpha$	4.9	87.7	70.7	78.8	59.0

α) in CD_2Cl_2, β) an assignment of the signals to C-4 and C-5 has only been proven (COSY) for **5a** and **5c**.

Table 3. m/z values (intensity in %) of **5a, c, d, e** obtained from EI mass spectral analysis (70 eV).

5 a	140 (1.6)$^\alpha$	**5 d**	138 (7.5)
5 c	210 (0.6)	**5 e**	229 (2.7)

α) HRMS clcd 140.08373 found 140.08378.

Experimental: **3-(Chloromethyl)-4-chloro-2-butenic Acid Ethylester (2)**: To a suspension of sodium hydride in THF (300 mL) a solution of triethyl phosphono acetate (182 g, 0.811 mol) in THF (300 mL) is added at 0° C and the mixture is stirred until the sodium hydride has disappeared. The reaction mixture is then cooled to -78° C and a solution of **1** (100 g, 0.787 mol) in THF (400 mL) is quickly added so that the temperature does not increase above -50° C. The cooling bath is removed and the mixture allowed to warm to 20 °C, when it is quenched with water (10 mL). After filtration and removal of the solvent an oily product is obtained which is further purified by column chromatography (silicagel) using hexane as the solvent. Yield: 149 g (83%). ^{1}H NMR ($CDCl_3$, 270 MHz): δ = 1.26 (t, 3 H, $-CH_3$), 4.18 (q, 2 H, $-CH_2O$), 4.23 (s, 2 H, $-CH_2Cl$), 4.77 (s, 2 H, $-CH_2Cl$), 6.03 (s, 1 H, -C=C-H); ^{13}C NMR ($CDCl_3$, 67 MHz): δ = 14.0 ($-CH_3$), 37.9 ($-CH_2Cl$), 45.4 ($-CH_2Cl$), 60.7 ($-CH_2O$), 122.1 (=C-H), 149.1 ($\underline{C}$=C-H), 164.6 (C=O); mass spectrum (EI), *m/z* = 196 (M^+; 30.5), HRMS clcd 196.00579, found 196.00521.

3-(Chloromethyl)-4-chloro-2-butenol (3a): To a suspension of LAH (20.2 g, 0.535 mol) in diethyl ether (200 mL) is added a solution of $AlCl_3$ (71.4 g, 0.535 mol) in diethyl mether (250 mL). After stirring for 30 min the mixture is cooled to -78° C and a solution of **2** in diethyl ether (150 mL) is added dropwise. Stirring is continued for 8 h, during which period the temperature is allowed to slowly reach 20 °C. The resulting mixture is quenched with ice-cooled 10% hydrochloric acid (200 ml). Standard work-up including high vacuum distillation affords compound **3a** as a colorless oil. Yield: 99g (90% yield). ^{1}H NMR ($CDCl_3$, 270 MHz): δ = 3.42 (s, broad, 1 H, -OH), 4.13 (s, 2H, $-CH_2Cl$), 4.18 (s, 2H, $-CH_2Cl$), 4.21 (d, 2 H, $-CH_2O$), 5.84 (t, 1 H, =C-H); ^{13}C NMR ($CDCl_3$, 67 MHz): δ = 38.5 ($-CH_2Cl$), 46.5 ($-CH_2Cl$), 58.1 ($-CH_2O$), 133.6 (=C-H), 134.1 ($\underline{C}$=C-H); mass spectrum (FAB), *m/z* = 189 (M^+Cl^-; 87.9).

1-Chloro-2-(chloromethyl)-4-[(methyloxy)methoxy]-2-butene (3b): In a three-necked flask with mechanical stirrer are placed $CHCl_3$ (500 mL) and phosphoruspentoxide (80 g). Dimethoxymethane (DMM, 400 mL) is added under ice cooling. To this vigorously stirred mixture is added a solution of **3a** in DMM (100 mL). After the addition the reaction mixture is allowed to react to completion for 8-12 h (TLC). Addition to a saturated $NaHCO_3$ solution, followed by standard work-up including high vacuum distillation, gives **3b** as a colorless oil. Yield: 115 g (90%). ^{1}H NMR($CDCl_3$, 270 MHz): δ = 3.33 (s, 3 H, $-CH_3$), 4.15 (d, 2 H, $-CH_2$-C=), 4.17 (s, 2 H, $-CH_2$-Cl), 4.21 (s, 2 H, $-CH_2Cl$), 4.60 (s, 2 H, O-CH_2-O), 5.88 (t, 1 H, =C-H); ^{13}C NMR ($CDCl_3$, 67 MHz): δ = 38.6 ($-CH_2Cl$), 46.5 ($-CH_2Cl$), 55.3 ($-CH_3$), 62.5 ($-CH_2$-C=), 95.8 (O-CH_2-O), 131.2 (=C-H), 135.4 ($\underline{C}$=C-H); mass spectrum (EI), *m/z* = 166 (M+ -H $-CH_3OH$; 3.0) 136 (M+ -H $-CH_3OH$ $-CH_2O$; 7.3).

[1,1-Dibromo-2,2-bis(chloromethyl)cyclopropyl]methanol (4b): A solution of **4a** 29.0 g (78.2 mmol) and hydrochloric acid (5.7 ml, 25%) in methanol (200 mL) is heated to reflux for 2 h, then cooled to room temperature and neutralized with

$NaHCO_3$. After removal of the solvent, the remaining residue is dissolved in ether and washed with water. After drying the organic layer ($MgSO_4$) the solvent is removed in vacuo and the product is purified by column chromatography (silicagel) using toluene, toluene/CH_2Cl_2 (3:1) and toluene/CH_2Cl_2 (1:1) as eluent. Yield: 23.1 g (90%). ^{1}H NMR ($CDCl_3$): δ = 1.90 (t, 1 H, H-3), 2.10 (s (broad), 1 H, OH), 3.70-3.85 (m, 4 H, -CH_2Cl, -CH_2OH), 4.05 (d, 1 H, -CH_2Cl), 4.08 (d, 1 H, -CH_2Cl); ^{13}C NMR ($CDCl_3$): δ = 36.5, 37.6 (C-1,2), 41.4 (C-3), 43.8 (-CH_2Cl), 48.9(-CH_2Cl), 60.7 (-CH_2OH); mass spectrum (EI), *m/z* = 260 (M^+-H_2CO,-HCl; 100). Anal. calcd for $C_6H_8Br_2Cl_2O$: C, 22.05; H, 2.47. Found: C, 22.12; H, 2.44.

1,1-Dibromo-2,2-bis(chloromethyl)-3-[[[(1,1-dimethylethyl)dimethyl silyl]oxy]methyl]cyclopropane (4c): To a solution of **4b** (6.25 g, 19.1 mmol) in dry CH_2Cl_2 is added imidazole (4.5 g, 66 mmol) and t-butyldimethylsilyl chloride (TBDMSCl) (3.46 g, 22 mmol). The mixture is allowed to react for 10 h and is then filtered through silicagel. The solvent is removed and the crude product recrystallized from methanol at -20° C. Yield: 8.0 g (95%). ^{1}H NMR($CDCl_3$): δ = 0.10 (s, 6 H, -$Si(CH_3)_2$), 0.80 (s, 9 H, -$C(CH_3)_3$), 1.90 (t, 1 H, H-3), 3.75 (t, 2 H, -CH_2OH), 3.90 (s, 2 H, -CH_2Cl), 4.00 (s, 2 H, -CH_2Cl); ^{13}C NMR($CDCl_3$): δ = -4.2 (-Si-CH_3), 19.1 (-$\underline{C}(CH_3)_3$), 26.8 (-$C(\underline{C}H_3)_3$), 38.1, 38.5 (C-1,2), 43.1 (C-3), 45.1(-CH_2Cl), 50.1 (-CH_2Cl), 62.0 (-CH_2OH); mass spectrum (EI), *m/z* = 383 (M^+ -*t*-Bu, 0.76). Anal. calcd for $C_{12}H_{22}Br_2Cl_2OSi$: C, 32.68; H, 5.03. Found: C, 32.62; H, 4.80.

[[(Methyloxy)methoxy]methyl][1.1.1]propellane (5a): To a solution of **4a** (21.1 g, 0.057 mol) in 200 ml diethyl ether 80 ml of a 1.5 M solution of MeLi in diethyl ether is added dropwise at -78° C. The reaction mixture is allowed to warm to RT slowly until a white precipitation occurs. The mixture is stirred for an additional 30 min and then quenched with degassed water under ice cooling. The water is removed with a syringe and the organic layer is dried with $MgSO_4$. After filtration and evaporation of the solvent, the propellane is purified by high vacuum transfer. Yield 4.6 g (57%). (Analytical data see Tables 1, 2, and 3.)

([1.1.1]Propellanyl)methanol (5b): A mixture of **5c** (0.20 ml, 1.14 mmol) and a 1M solution of tetrabutylammonium fluoride (2 mmol) in THF (2 mL) is stirred for 15-20 min. 1 mL of dilute NaOH is added and the resulting mixture is extracted with ether (four times). The combined organic layers are dried over CaO to furnish (after filtration) a solution of **5b** which was used for the further experiments. (Analytical data see Tables 1, 2 and 3.).

[[[(1,1-Dimethylethyl)dimethylsilyl]oxy]methyl][1.1.1]propellane (5c): To a solution of **4c** (16.2 g, 36.7 mmol) in ether (250 mL) is added dropwise at -80°C a 1.7 M solution of methyllithium in ether (48 mL). The mixture is allowed to warm slowly to room temperature and degassed water is added. The organic layer is dried over $MgSO_4$, filtered under nitrogen and the solvent is evaporated in vacuo. The remaining residue is further purified by high vacuum transfer. Propellane **5c** is obtained as a colorless oil with characteristic smell. Yield: 4.2 g (55%). (Analytical data see Tables 1, 2, and 3.)

([1.1.1]Propellanyl)methyl acetate (5d): To a solution of **5b** (2.4 mmol) in ether is added a mixture of acetic acid anhydride (0.22 ml 3.5 mmol), triethylamine (0.82 ml 5.9 mmol), and DMAP (0.06 g, 0.5 mmol) at 0° C. After warming to 20° C (15 - 20 min) the reaction mixture is washed twice with water, dried over $MgSO_4$ and after filtration, solvent is removed in vacuo. Propellane **5d** is isolated after fractional high vacuum transfer at RT as colorless liquid. (Analytical data see Tables 1, 2, and 3.)

N-Benzyl-[([1.1.1]propellanyl)methyl]carbamate (5e): To a solution of **5b** (1.41 mmol) in ether is added a mixture of benzyl isocyanate (0.12 ml, 1 mmol) and triethylamine (one drop). After 2 h the solvent is removed in vacuo and the white crystalline residue is lyophilized. (Analytical data see Tables 1, 2, and 3.)

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5. The sensitivity of propellanes **5** is illustrated by the fact that rearrangements cannot be completely suppressed if (re)crystallizations are attempted in protic solvents like MeOH, even if this is done at -78° C and in the presence of NEt_3.

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