Pergamon

Tetrahedron Vol. 50, No. 29, pp. 8597-8602, 1994
Copyright © 1994 Elsevier Science Ltd
Printed in Great Britain. All rights reserved
0040-4020/94 $7.00+0.00

0040-4020(94)00482-X

New Route to 4,4,6,7-Tetrasubstituted Pentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecanes

Alexander M. Aleksandrov,*[a] Susan A. Bourne,[b] Mariusz Krawiec,[b] Tonis J. Pehk,[c]

Alexander E. Petrenko,[a] William H. Watson*[,b]

[a]Institute of Bioorganic Chemistry, Ukrainian Academy of Sciences, 252094 Kiev, Ukraine
[b]Department of Chemistry, Texas Christian University, Fort Worth, TX 76129 USA
[c]Institute of Chemical and Biological Physics, Estonian Academy of Sciences, 200001 Tallinn, Estonia

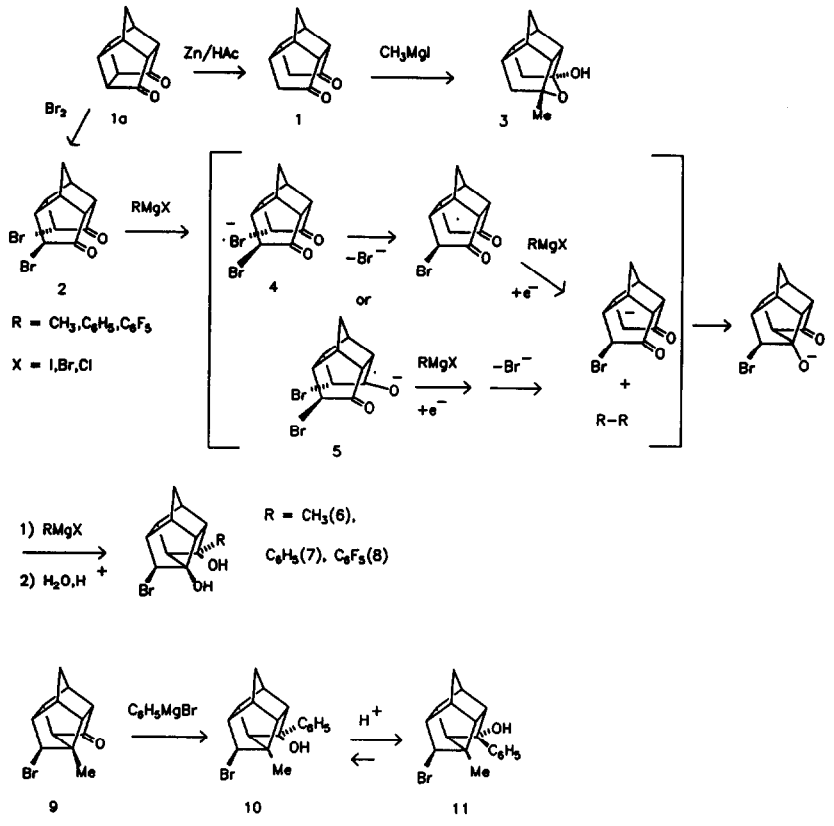
Abstract: The reactions of 3,6-dibromo-2,7-dioxotetracyclo[6.3.0.0^{4,11}.0^{5,9}]undecane with organomagnesium halides are investigated as a method of preparing unusual tetrasubstituted pentacycloundecanes (D_3-trishomocubanes). The tetrasubstituted pentacycloundecanes have been characterized and product geometries confirmed by NMR and X-ray crystal structure analysis. Rel-(1R,2R,3S,4S,5R,6R,7S,8S,9R,10R)-4-hydroxy-4-phenyl-6-methyl-7-bromo-(D_3)-trishomocubane (11) exhibits a sterically locked phenyl group with a rotation barrier > 17 kcal/mol which should make possible the preparation of stable rotational isomers with o- or m-substituted phenyl groups.

INTRODUCTION

The synthesis of the strained polyfunctionalized pentacycloundecane (PCUD) series of molecules by photochemical methods has been investigated extensively.[1] Some derivatives of the PCUD system may not be directly available from photochemical synthesis and direct modification of the cage; however, they may be prepared by opening and reclosing the cage by chemical procedures. Among the possible precursors for the chemical closure to the PCUD system, derivatives of the tetracyclo-[6.3.0.0^{4,11}.0^{5,9}]undecane-2,7-dione moiety (1) appear most promising. The 2,7-dioxotetracyclo-(1)[2] and 3,6-dibromo-2,7-dioxotetracycloundecane (2)[3] derivatives can be prepared from the readily available parent, e.g. pentacyclo[5.4.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane-8,11-dione **1a**, by treatment with Zn in acetic acid[2,3] (1) and by bromination (2).[3] Compound **1** in an analogous manner to the parent **1a** undergoes transannular cyclization to form **3** upon treatment with methylmagnesium iodide. The dibromo compound **2** does not react in an analogous manner, and in this paper we discuss the use of **2** to synthesize new D_3-trishomocubane (pentacyclo[6.3.0.0^{2,6}.0^{3,10}.0^{5,9}]undecane) derivatives.

DISCUSSION

The reaction of **1** with methylmagnesium iodide gives **3** which can be characterized by loss of the C=O absorption in the IR spectrum and the disappearance of the C=O resonance in the ^{13}C NMR



spectrum while the remaining cage ^{1}H and ^{13}C NMR resonances change only slightly. The presence of the bromine atoms α to the carbonyls in compound **2** alters the direction of the reaction with organomagnesium compounds. The reaction can be rationalized as either an attack of RMgX on the carbonyl group to produce an intermediate of type **5**[4-6] or by the attack of RMgX on the bromine atom to give an intermediate of type **4**.[7] Intermediate **5** is reduced by an additional molecule of RMgX and loses bromide ion to give the enolate while **4** loses bromide ion then reacts with a second molecule of RMgX to give the enolate. The enolate rearranges to the D_3-trishomocubane isomer which reacts with an additional molecule of RMgX. Upon normal hydrolysis the products **6**, **7** and **8** are obtained. Both pathways give R-R as a product.

The reaction of **2** with RMgX leads to the stereospecific formation of isomers **6**, **7** and **8**. The structures of **6** and **7** were determined by X-ray diffraction, while the structure of **8** was established by

comparing the NMR with that of **7**. Neither the nature of the organic radical nor of the halogen appears to have any affect upon the course of the reaction. In order to evaluate the stereospecificity of the reaction with phenylmagnesium bromide the reaction of compound **9** was investigated. Only isomer **10** was formed by the reaction. The stereochemistry of D_3-trishomocubane and derivatives has been thoroughly described. [8-10]

An attempt to replace the hydroxyl group in **10** with a bromine atom by refluxing in concentrated hydrobromic acid for five minutes produced a mixture of **10** and its isomer **11** in a 1:3 ratio. The structures were confirmed by an X-ray analysis. Heating for longer periods of time leads to the formation of tars without the ratio of **10** to **11** changing. When compound **11** was refluxed with HBr under the same conditions a 1:3 mixture of **10** and **11** were again obtained indicating an equilibrium mixture of the two isomers. The two isomers were separated by silica gel chromatography. Acylation of compound **10** with acetic anhydride (H_2SO_4 as catalyst) gives a mixture of the acetates of **10** and **11**. The mixture could not be separated by chromatography, and the acetates were hydrolyzed with KOH in methanol. This gave approximately the same isomeric ratio as the aqueous treatment with aqueous HBr. Molecular mechanics[11] calculations predict the heats of formation and the steric strains in the two molecules differ by less than 1 kcal/mol, and the 1:3 equilibrium ratio is difficult to rationalize without imposing electronic effects not reproduced by molecular mechanics. The NMR spectra of compounds **10** and **11** are quite unique with the methyl group of **11** shifted upfield by 1.23 ppm (δ, 0.36 ppm) from that in **10** due to the shielding effect of the aromatic ring and deshielding effect of the OH group. In addition, the phenyl group in **11** is locked due to steric hindrance and the chemically equivalent protons are no longer magnetically equivalent. When **11** was heated from room temperature to 100 °C in 1,1,2,2-tetrachloroethane the typical exchange broadening was observed, but full coalescence was not achieved. Full coalescence at 100 °C would correspond to a rotational barrier of 17 kcal/mol implying the barrier is slightly greater than 17 kcal/mol. A molecular mechanics[11] study of **11** predicts a rotation barrier of about 17.5 kcal/mol. From these data we would suggest the existence of stable sterically locked isomers when ortho or metaphenyl Grignard reagents are used.

EXPERIMENTAL

All ^1H and ^{13}C NMR spectra were recorded at 200 or 500 MHz using TMS in $CDCl_3$. Chromatography was performed on Silica gel columns. Melting points are uncorrected.

General Procedure for preparation of 6, 7, and 8. To a precooled (ice bath) solution of alkyl- or arylmagnesium halide (32 mmol) in ether (80 mL) was added dropwise with stirring a solution of 3.34 g (10 mmol) dibromodiketone (**2**) in THF (60 mL). After stirring for 2 h at 20 °C the reaction mixture

was treated with water, saturated aqueous NH_4Cl and the water layer extracted with ether (100 mL). The solvent was distilled off and the residue crystallized from ethyl acetate.

Compound 3, 1-Hydroxy-7-methyl-12-oxapentacyclo[5.4.1.$0^{2,6}$.$0^{3,10}$.$0^{5,9}$]dodecane. To a solution of CH_3MgI, prepared from 1.2 g (50 mmol) Mg and 7.0 g (50 mmol) CH_3I in 75 mL ether, was added dropwise with stirring a solution of 3.5 g (20 mmol) diketone 1 in 50 mL THF. After 5 h the reaction mixture containing excess organomagnesium reagent was treated with water followed by a 10% solution of HCl. The organic layer was separated and the water layer extracted with additional ether, and the combined ether layers were washed with sodium bisulfite, and then water. The ether was removed and the reaction product purified by chromatography. Yield 2.73 g (57%) , b.p. 104-105 °C (0.1 mm); ^{1}H NMR($CDCl_3$), δ, 1.34 (s,CH_3), 1.50 and 1.87 (AB ddd,J_{AB} = 13.9 Hz, J = 4.5 Hz,C(8)H_2),1.52 and 1.64 (AB dmdm,J_{AB} = 10.6 Hz,C(4)H_2). 1.86 and 2.06 (AB ddd, J_{AB} = 13.4 Hz, J = 5.0 Hz, C(11)H_2), 2.10 (m,1H), 2.11 (m,1H), 2.21 (m,1H), 2.37 (ddd, J = 11.0 Hz, J - 4.5 Hz, J = 1.6 Hz, C(6)H), 2.39 (m,1H), 2.44 (ddd, J = 11.0 Hz, J = 4.8 Hz, J = 2.2 Hz, C(2)H), 2.89 (1H,OH), ^{13}C NMR($CDCl_3$), δ, 25.4(CH_3), 37.4(4), 41.5(10), 42.9(9), 43.2(11), 43.4(8), 47.3(3), 48.7(5),59.3(6), 59.4(2), 88.2(8), 114.9(1). Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.96; H, 8.39. Found: C, 74.85; H, 8.29.

Compound 6, Rel-(4R,7S)-4-hydroxy-4-methyl-6-hydroxy-7-bromo-D_3-trishomocubane. Yield 1.93 g (71%), m.p. 150-151 °C; ^{1}H NMR($CDCl_3$), δ, 1.35 and 1.46 (AB dd,J_{AB} = 11.4 Hz,CH_2), 1.39 (s,CH_3), 1.74 (dt,J = 6 and 1.8 Hz,1H), 2.07 (m,1H) 2.17 (m,1H), 2.29 (m,2H), 2.44 (m,1H), 3.07 (dm,J = 4.5 Hz,1H), 3.39 (br.s,OH), 4.10 (br.s,OH), 4.18 (dm,J = 2 Hz,CHBr); ^{13}C NMR($CDCl_3$): δ, 23.0 (q,CH_3), 34.5 (t,CH_2), 41.0 (d), 44.1(d), 47.8(d), 48.2(d), 50.1(d), 52.1(d), 58.1(d), 59.1(d), 84.5(s), 91.0(s). Anal. Calcd for $C_{12}H_{15}O_2Br$: C, 53.15; H, 5.58; Br, 29.47. Found: C, 53.12; H, 5.56; Br, 29.48.

Compound 7, Rel-(4R,7S)-4-Hydroxy-4-phenyl-6-hydroxy-7-bromo-D_3-trishomocubane. Yield 2.27 g (68%), m.p. 156-157 °C; ^{1}H NMR($CDCl_3$), δ, 1.26 and 1.43 (AB dmdm,J_{AB} = 10.9 Hz,C(11)H_2), 1.91 (m,1H), 2.18 (dm,J = 6.0 Hz,1H), 2.34 (m,1H), 2.35 (m,1H), 2.43 (ddm,J = 5.5, J = 6.0 Hz,1H), 2.56 (dm,J = 6.0 Hz,1H), 3.15 (dm,J = 5.5 Hz,1H), 3.24 (s,OH), 4.28 (dm,J = 2.0 Hz,CHBr), 4.47 (s,OH), 7.31 (m,p-Ph), 7.37 (m,2H,m-Ph), 7.39 (m,2H,o-Ph). ^{13}C NMR($CDCl_3$): δ, 34.3(11), 41.4(9), 43.8(10), 48.3(8), 48.5(1), 49.8(2), 50.4(5), 57.4(3), 58.5(7), 88.3(4), 90.5(6), 126.3(o-Ph), 127.9(p-Ph), 128.7(m-Ph), 142.5(s). Anal. Calcd for $C_{17}H_{17}O_2Br$: C, 61.27; H, 5.14; Br, 23.98. Found: C, 61.19; H, 5.17; Br, 23.93.

Compound 8, Rel-(4R,7S)-4-Hydroxy-4-pentafluorophenyl-6-hydroxy-7-bromo-D_3-trishomocubane. Yield 2.20 g (52%), m.p. 164-165 °C; ^{1}H, NMR(CDC_3), δ, 1.36 and 1.52 (AB dd,J_{AB} = 10.5 Hz,CH_2), 2.05 (m,1H), 2.25 (m,1H), 2.39 (m,2H), 2.75 (m,1H), 2.91 (m,1H), 3.16 (dm,J = 5 Hz,1H), 3.63 (s,OH), 4.27 (dm,J = 2 Hz,CHBr), 4.43 (s,OH). Anal. Calcd for $C_{17}H_{12}O_2BrF_5$: C, 48.25; H, 2.86; Br, 18.88.

Found: C, 48.21; H, 2.88; Br, 19.01.

Compound **9** was prepared as described in the literature.[12]

Compound **10**, Rel-(1R,2R,3S,4R,6R,7S)-4-hydroxy-4-phenyl-6-methyl-7-bromo-D_3-trishomocubane. To a precooled (ice bath) solution of phenylmagnesium bromide (from 3.15 g PhBr and 0.5 g Mg in 75 mL ether) was added dropwise with stirring a solution of 2.53 g (10 mmol) compound **9** in ether (40 mL). After stirring for 2 h at 20 °C the reaction mixture was treated with water, saturated aqueous NH_4Cl and the water layer extracted with ether (100 mL). The solvent was distilled off and the residue crystallized from ethyl acetate. Yield 2.76 g (83%), m.p. 124-125 °C; ^{1}H NMR($CDCl_3$), δ, 1.26 and 1.32 (AB dmdm,J_{AB} = 10.5 Hz,C(11)H_2), 1.59 (s,CH_3), 1.80 (m,1H), 2.05 (s,OH), 2.12 (dm,J = 5.6 Hz,1H), 2.19 (tm,J = 5.7 Hz,1H), 2.23 (qm,J = 5.8 Hz,1H), 2.29 (dm,J = 6.0 Hz,1H),2.34 (dm,J = 6.0 Hz,1H), 3.05 (dm,J = 5.5 Hz,1H), 4.05 (dm,J = 1.8,CHBr), 7.28 (m,p-Ph), 7.34 (m,m-Ph), 7.35 (m,o-Ph). ^{13}C NMR($CDCl_3$): δ, 19.3(CH_3), 32.9(11), 42.8(9), 44.1(10), 48.4(2), 49.2(1), 52.3(8), 53.1(5), 57.4(3), 58.1(6), 65.2(7), 86.7(4), 126.1(o-Ph), 127.3(p-Ph), 128.4(m-Ph), 144.8(s). Anal. Calcd for $C_{18}H_{19}OBr$: C, 65.26; H, 5.78; Br, 24.12. Found: C, 65.10; H, 5.77; Br, 24.23.

Compound**11**,Rel-(1R,2R,3S,4S,5R,6R,7S,8S,9R,10R)-4-hydroxy-4-phenyl-6-methyl-7-bromo-D_3-trishomocubane. A mixture of 1.0 g (3 mmol) of compound **10** and hydrobromic acid (12 mL) was refluxed for 5 min then cooled and diluted with water (50 mL) and extracted with ethyl acetate. The solvent was distilled off, and the residue separated on silica gel. Yield 0.34 g (34%), m.p. 108-109 °C; ^{1}H NMR($CDCl_3$): δ, 0.36 (s,CH_3), 1.47 and 1.53 (AB,dmdm,J_{AB} = 10.6 Hz,C(11)H_2), 1.89 (tm,J=5.8 Hz,1H), 1.93 (br,s,OH), 2.01 (dm,J = 5.7 Hz,1H), 2.36 (dm,J = 6.2 Hz,1H), 2.56 (m,1H), 2.57 (m,1H), 2.99 (m,1H), 3.04 (dm,J = 5.5 Hz,1H), 3.90 (dm,J = 2.0 Hz,CHBr), 7.31 (m,2H,0-Ph and m-Ph), 7.32 (m,p-Ph), 7.39 (m,1H,m-Ph), 7.52 (m,1H,o-Ph). ^{13}C NMR($CDCl_3$): δ, 17.9(CH_3), 32.6(11), 43.7(9), 45.3(10), 47.8(2), 49.3(1), 51.9(8), 54.7(3), 55.1(6), 56.4(5), 65.5(7), 86.2(4), 125.7(-o-Ph), 128.0(p-Ph), 128.2(m-Ph), 128.6(o-Ph), 128.7(m-Ph), 143.5(s). Anal. Calcd for $C_{18}H_{19}OBr$: C, 65.26; H, 5.78; Br, 24.12. Found: C, 65.32; H, 5.87; Br, 23.74.

X-ray Diffraction Studies. All data were collected on a Rigaku AFC-6S diffractometer using the ω-2θ mode at a fixed scan rate with multiple scans for weak reflections. The data were collected with Cu Kα radiation (λ = 1.54178 Å). Lorentz-polarization, Ψ-scan empirical absorption corrections and isotropic extinction corrections were applied. The structures were solved by direct methods,[13] and parameters were refined by a full-matrix least-squares technique. Compound **6**, monoclinic $P2_1/c$, a = 6.983(2), b = 6.928(2), c = 22.748(2), β = 92.43(2)°, V = 1099.6(7) Å^3; d_c = 1.638 gcm^{-3}; μ = 49.42 cm^{-1}; R = 0.047 for 1456 reflections with I $\geq 3\sigma$(I). Compound **7**, monoclinic $P2_1$, a = 8.691(2), b = 8.451(2), c =

10.468(2) Å, ß = 111.97(1)°, V = 713.1(5) Å^3; d_c = 1.552 gcm^{-3}; μ = 39.28 cm^{-1}; R = 0.028 for 1107 reflections with I ≥ 3σ(I). Compound **10**, tetragonal P4nc, a = 17.530(2), c = 9.861(3) Å, V = 3031(2) Å^3; d_c = 1.452 gcm^{-3}; μ = 36.43 cm^{-1}; R = 0.036 for 1174 reflections with I ≥ 3σ(I). Compound **11**, tetragonal P4/n; a = 17.8422(8), c = 10.601(2) Å, V = 3374.9(8) Å^3; d_c = 1.304 gcm^{-3}; μ = 32.71 cm^{-1}; R = 0.106 for 1928 reflections with I ≥ 3σ(I). The crystal structure contains a molecule of toluene lying disordered along the 4-fold axis in a cavity of 392 Å^3. When this solvate molecule is included the calculated density is 1.43 g cm^{-3}. A molecule of adamantane can be fitted into the cavity.

ACKNOWLEDGEMENT

We thank the Robert A. Welch Foundation (P-074) and the National Science Foundation (CHE-9017654) for financial support.

REFERENCES

1. Marchand, A.P. In Advances in Theoretically Interesting Molecules; Thummel, R.P., Ed.; JAI: Greenwich, CT, **1989**; Vol. 1, pp. 357-399.
2. Wenkert, E.; Yoder, J.E. J. Org. Chem., **1970**, 35, 2986.
3. Sorochinskii, A.E.; Aleksandrov, A.M.; Kukhar, V.P. Zh. Org. Khim., **1985**, 21, 681. Chem. Abstr., **1985**, 103, 160130r.
4. Walling, C. J. Am. Chem. Soc., **1988**, 110, 6846.
5. a) Ashby, E.C.; Laemmle, J.; Neumann, H.M. Acc. Chem. Res., **1974**, 7, 272. b.) Ashby, E.C. Pure Appl. Chem., **1980**, 52, 545.
6. Holm, T. Acta Chem. Scand. Ser. B., **1983**, B37, 569.
7. Narasimhan, N.S.; Sunder, N.M.; Ammanamanchi, R.; Bonde, B.D. J. Am. Chem. Soc., **1990**, 112, 4431.
8. Helmchen, G.; Staiger, G. Angew. Chem. Int. Ed. Engl., **1977**, 16, 116.
9. Nakazaki, M.; Naemura, K.; Arashiba, N. J. Org. Chem., **1978**, 43, 689.
10. Oliver, D.. W.; Dekker, T.G. South Afr. J. Sci., **1988**, 84, 407.
11. PCMODEL 386 V4.0, **1992**. Serena Software, Bloomington, IN.
12. Aleksandrov, A.M.; Turov, A.V.; Kornilov, M. Yu.; Kukhar, V.P. Zh. Org. Khim., **1991**, 27, 2566. Chem. Abstr. **1992**, 117, 69487r.
13. Sheldrick, G.M. SHELXS86. Program for the Solution of Crystal Structures. **1986**, Univ. of Göttingen, Germany.

(*Received in USA* 3 *January* 1994; *accepted* 20 *May* 1994)