Syntheses of 2-oxabicyclo[4.10.0]hexadec-1(6)-ene from cyclododecanone

*L. I. Zakharkin** and *I. M. Churilova*

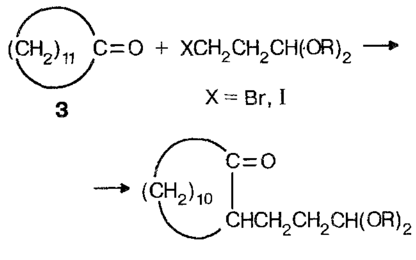
A. N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences,
28 ul.Vavilova, 117813 Moscow, Russian Federation.
Fax: +7 (095) 135 5085

Two methods for the synthesis of 2-oxabicyclo[4.10.0]hexadec-1(6)-ene from cyclododecanone have been suggested. The most convenient method involves the preparation of 2-(3-*tert*-butoxypropyl)cyclododecanone by phase-transfer catalyzed alkylation of cyclododecanone with 1-bromo-3-*tert*-butoxypropane followed by removal of the protecting *tert*-butyl group and elimination of water.

Key words: cyclododecanone, phase-transfer catalysis, alkylation, 2-(3,3-diethoxypropyl)cyclododecanone, 2-(3,3-ethylenedioxypropyl)cyclododecanone, 12-hydroxybicyclo[9.3.1]pentadecane-15-one, 3-ethoxy-2-oxabicyclo[4.10.0]hexadec-1(6)-ene, 2-(3-chloropropen-3-yl)cyclododecanone, 2-(3-benzyloxypropyl)cyclododecanone, 2-(3-*tert*-butoxypropyl)cyclododecanone, 2-(3-acetoxypropyl)cyclododecanone, 2-(3-hydroxypropyl)cyclododecanone.

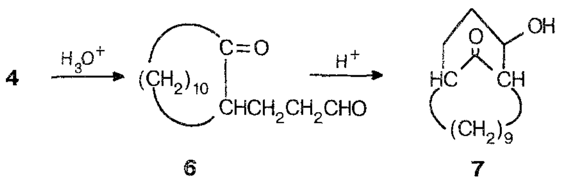
The synthesis of 2-oxabicyclo[4.10.0]hexadec-1(6)-ene (**1**), which is the key material in the production of pentadecanolide (tibetolide), a valuable fragrant macrocyclic lactone with a fine musk odor, has been reported previously.[1—3] In one of these works,[3] the reaction of lithium cyclododecanone enolate with 3-alkoxy-1-iodopropane was used for the synthesis of compound **1** or its precursor, 2-(3-hydroxypropyl)cyclododecanone (**2**). However, a disadvantage of this method is the difficulty of obtaining the enolate.

We have shown previously[4] that cyclododecanone (**3**) is easily alkylated with alkyl halides under phase-transfer catalysis conditions to give 2-alkylcyclododecanones. In the present work aimed at the synthesis of **1**, we have studied the behavior of 1-halopropanes containing functional substituents at position 3. In particular, it has been found that β-halopropionic aldehyde acetals readily undergo this reaction to give the respective 2-(3-oxopropyl)cyclododecanone acetals (**4**, **5**).



4: R = Et
5: 2R = $—CH_2CH_2—$

We assumed that mild acidic hydrolysis of these acetals would give 2-(3-oxopropyl)cyclododecanone (**6**) which can easily be reduced similarly to the transformation of 2-carbethoxy-2-(3-oxopropyl)cyclododecanone into 2-carbethoxy-2-(3-hydroxypropyl)cyclododecanone.[1,5] Treatment of compound **4** with 2,4-dinitrophenylhydrazine (2,4-DPH) in EtOH in the presence of H_2SO_4 afforded the bis-(2,4-dinitrophenylhydrazone) of ketoaldehyde **6**. However, hydrolysis of acetal **4** with AcOH in the presence of HCl gave 12-hydroxybicyclo[9.3.1]pentadecan-15-one (**7**) probably formed due to intramolecular aldol condensation of ketoaldehyde **6**.



The structure of compound **7** was confirmed by a comparison with an authentic sample and by IR and mass-spectra. A similar example of intramolecular aldol condensation during acidic hydrolysis has been reported for 2-nitro-(3-oxopropyl)cyclododecanone.[6] Treatment of acetal **5** with 2,4-DPH under the same conditions as those for acetal **4** gave 2-(3,3-ethylenedioxypropyl)-cyclododecanone 2,4-dinitrophenylhydrazone. Acidic hydrolysis of acetal **5** also resulted in alcohol **7**. An attempt to synthesize aldehyde **6** by acidic hydrolysis of 3-alkoxy-2-oxabicyclo[4.10.0]hexadeca-1(6)enes

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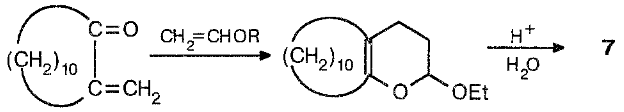
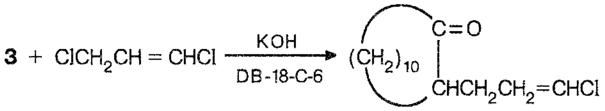
8 and **9**, the adducts of 2-methylenecyclododecanone with ethyl-vinyl ether and butyl-vinyl ether also failed: compound **7** was obtained, like in the case of the hydrolysis of **4** and **5**.



8: R = Et
9: R = Bu

Like acetal **4**, ether **8** treated with 2,4-DPH affords a bis-hydrazone. It is known that ketone **3** undergoes intramolecular condensation in an acidic medium under more drastic conditions[7] than cyclopentanone and cyclohexanone.[8] Unlike the reaction involving compound **3**, intramolecular condensation of ketoaldehyde **6** under acidic conditions occurs very readily, but it does not occur in a weakly-alkaline medium in the case of 2-carbethoxy-2-(3-oxopropyl)cyclododecanone.[1,5] One more precursor of ketoaldehyde **6**, 2-(3-chloropropen-3-yl)cyclododecanone (**10**), was obtained in the present work by the alkylation of compound **3** with 1,3-dichloropropene under phase-transfer catalysis conditions:



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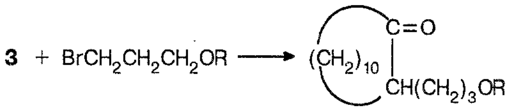
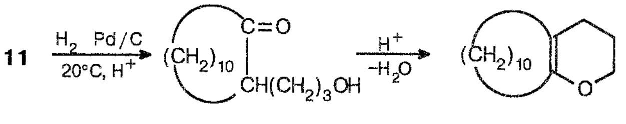
DB-18-C-6 = dibenzo-18-crown-6 ether

In a continuation of the search for a more convenient and simple approach to oxabicyclohexadecene **1** and its precursor **2**, we found that alkylation of ketone **3** with 3-*tert*-butoxy- and 3-benzyloxypropyl bromides under phase-transfer catalysis conditions in the presence of an alkali, which makes it possible to obtain 2-(3-alkoxypropyl)cyclododecanones (**11**, **12**), can serve as the desired method. An attempt to use 2-benzyloxyethyl bromide as an alkylating reagent under the same conditions resulted in the dehydrobromination of the latter into benzyl-vinyl ether.



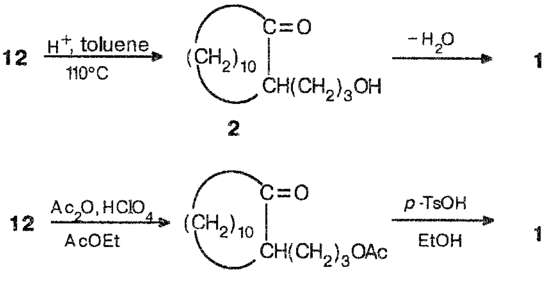
11: R = Bn
12: R = Bu^t

The catalytic hydrogenation of 2-(3-benzyloxypropy-l)cyclododecanone **11** on Pd/C in the presence of an acid smoothly results in debenzylation into compound **2**. The latter gives compound **1** on treatment with a catalytic amount of *p*-TsOH:[1]



2 **1**

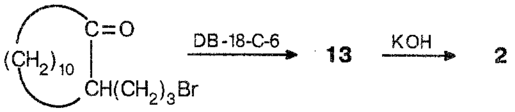
The removal of the protective *tert*-butyl group from substituted cyclododecanone **12** by the known procedures[9,10] also affords compound **1**.



2

13

The structure of 2-(3-acetoxypropyl)cyclododecanone (**13**) was confirmed by an independent synthesis from 2-(3-bromopropyl)cyclododecanone (**14**) and potassium acetate, followed by transformation of compound **13** into hydroxyketone **2** by alkaline hydrolysis:



14

We believe that the two-stage method for the synthesis of oxabicyclohexadecene **1** *via* compound **12** is the most simple.

Experimental

GLC analyses were performed on a LKhM-8MD chromatograph in a stream of He, column 2 m × 4 mm, 5 % SKTF-5Kh. Mass spectra were recorded on a Kratos MS-890 instrument.

2-(2-Bromoethyl)-1,3-dioxolane was obtained by the known procedure.[11] 2-Methylenecyclododecanone was obtained by a reported procedure.[12] 1-Bromo-3-*tert*-butoxypropane was synthesized from 3-bromopropanol,[13] b.p. 60—62 °C (8 Torr), n_D^{20} 1.4412. 2-(3-Bromopropyl)cyclododecanone (**14**) was obtained from 2-allylcyclododecanone.[14]

2-(3,3-Diethoxypropyl)cyclododecanone (4). Compound **3** (10 g, 0.055 mol), 3-bromopropanal diethylacetal (12 g, 0.056

mol), powdered KOH (7 g, 0.125 mol) and dibenzo-18-crown-6 ether (DB-18-C-6) (0.5 g) in toluene (50 mL) were heated with stirring for 5 h at 50—60 °C. After cooling, the mixture was poured into water. The toluene solution was separated and dried with Na_2SO_4. Distillation *in vacuo* gave 2 g of compound **3** and 10 g (60 %) of **4**, b.p. 170—175 °C (1 Torr). Found (%): C, 73.23; H, 11.59. $C_{19}H_{36}O_3$. Calculated (%): C, 73.08; H, 11.53. Bis-(2,4-dinitrophenylhydrazone), m.p. 145—147 °C (EtOH). Found (%): C, 54.12; H, 5.76; N, 18.64. $C_{27}H_{34}N_8O_8$. Calculated (%): C, 54.18; H, 5.09; N, 18.73.

2-(3,3-Ethylenedioxypropyl)cyclododecanone (5) was obtained similarly to **4** from compound **3** and 2-(2-bromoethyl)-1,3-dioxolane, yield 65 %, b.p. 162—164 °C (1 Torr). Found (%): C, 71.93; H, 10.40. $C_{17}H_{30}O_3$. Calculated (%): C, 72.34; H, 10.64. 2,4-Dinitrophenylhydrazone, m.p. 128—130 °C (AcOH). Found (%): C, 59.85; H, 7.57; N, 12.42. $C_{29}H_{34}N_4O_6$. Calculated (%): C, 59.74; H, 7.34; N, 12.12.

12-Hydrobicyclo[9.3.1]pentadecan-15-one (7). A mixture of compound **4**, AcOH (50 mL), HCl (6 mL), and H_2O (6 mL) was stirred for 10 h at 20 °C. The course of the reaction was monitored by GLC. The mixture was poured into water and extracted with ether. The ethereal extracts were washed with water and a $NaHCO_3$ solution and then dried with Na_2SO_4. The ether was removed, and the residue was distilled *in vacuo* to give 2.9 g (76 %) of compound **7**, b.p. 160—165 °C (1 Torr), m.p. 126—128 °C (EtOH) (*cf.* Ref. 15). IR, ν/cm^{-1}: 1710 (C=O), 3400 (OH). MS (*m/z*): 238 $[M]^+$. Found (%): C, 75.53; H, 11.07. $C_{15}H_{26}O_2$. Calculated (%): C, 75.63; H, 10.92.

3-Ethoxy-2-oxabicyclo[10.4.0]hexadec-1(6)-ene (8). A mixture of 2-methylenecyclododecanone (5 g, 25 mmol), ethylvinyl ether (7.5 g, 0.1 mol) stabilized by hydroquinone, and Na_2CO_3 (0.1 g) placed in a sealed tube was heated for 12 h in an autoclave at 180 °C. Distillation gave 3.6 g (52 %) **8**, b.p. 130—132 °C (1 Torr). IR, ν/cm^{-1}: 1650. Found (%): C, 76.88; H, 11.48. $C_{17}H_{30}O_2$. Calculated (%): C, 76.69; H, 11.28. Bis-(2,4-dinitrophenylhydrazone), m.p. 145—146 °C (EtOH). It does not give m.p. depression with the bis-hydrazone obtained from **4**.

Hydrolysis of compound 8 under the conditions of acetal **4** hydrolysis resulted in alcohol **7** (yield 88 %) identical to that obtained from acetal **4**.

3-Butoxy-2-oxabicyclo[10.4.0]hexadec-1(6)-ene (9) was obtained similarly to compound **8** from 2-methylenecyclododecanone and butyl vinyl ether. The yield of product **9** was 45 %, b.p. 150—155 °C (0.5 Torr). Found (%): C, 77.09; H, 11.44. $C_{19}H_{34}O_2$. Calculated (%): C, 77.55; H, 11.56.

2-(Chloropropen-3-yl)cyclododecanone (10). A mixture of compound **3** (5 g, 0.028 mol), 1,3-dichloropropene (2.6 g, 0.023 g), KOH (4 g, 0.07 g), and DB-18-C-6 (0.1 g) in benzene (20 mL) was heated for 10 h at 70—75 °C. The usual treatment gave 1 g of compound **3** and 5 g (70 %) of compound **10**, b.p. 165—170 °C (0.9 Torr), m.p. 53—54 °C (hexane). Found (%): C, 70.25; H, 9.97; Cl, 13.54. $C_{15}H_{25}ClO$. Calculated (%): C, 70.15; H, 9.81; Cl, 13.80.

2-(Benzyloxypropyl)cyclododecanone (11). A mixture of compound **3** (10 g, 0.055 mol), 3-benzyloxy-1-bromopropane (12.6 g, 0.056 mol), KOH (10 g, 0.17 mol), and DB-18-C-6 (0.15 g) in toluene (50 mL) was heated for 20 h at 100 °C. Usual work-up gave 4 g of compound **3** and 9 g (50 %) of compound **11**, b.p. 225—230 °C (1 Torr), m.p. 36—37 °C (hexane). Found (%): C, 80.03; H, 10.34. $C_{22}H_{34}O_2$. Calculated (%): C, 80.00; H, 10.31.

2-(3-*tert*-Butoxypropyl)cyclododecanone (12). A mixture of compound **3** (7 g, 0.038 mol), 1-bromo-3-propane (7.5 g, 0.038 mol), and KOH (8 g, 0.14 mol) was heated for 10 h at 80—90 °C to give 8 g (70 %) of compound **12**, b.p. 165—167 °C (1 Torr), m.p. 32—34 °C (pentane). Found (%): C, 77.10; H, 12.30. $C_{19}H_{36}O_2$. Calculated (%): C, 77.03; H, 12.16.

2-(3-Hydroxypropyl)cyclododecanone (2). Compound **11** (4 g, 0.012 mol) in ethyl acetate (20 mL) containing $HClO_4$ (0.01 mL) was hydrogenated under atmospheric pressure (20 °C, 6 h) in the presence of Pd/C (0.5 g). The catalyst was filtered off from the solution, which was then washed with aqueous Na_2SO_4 and water and then dried with Na_2SO_4. The solvent was removed to leave 2.5 g (86 %) of compound **2**, m.p. 36—37 °C (pentane) (*cf.* Ref. 1). Distillation of **2** with *p*-TsOH *in vacuo* gave compound **1**, b.p. 145—148 °C (1 Torr) (*cf.* Ref. 1).

2-Oxabicyclo[4.10.0]hexadec-1(6)-ene (1). Compound **12** (3 g, 0.01 mol) and *p*-TsOH (0.5 g) in toluene (15 mL) were boiled for 3 h with a Dean—Stark trap. After cooling the mixture was poured into water, extracted with ether, washed with water, and dried with Na_2SO_4. The solvent was removed, and the residue was distilled *in vacuo* to give 2 g (89 %) of compound **1** identical to that obtained from **2**.

2-(3-Acetoxypropyl)cyclododecanone (13). 1) Compound **12** (3 g, 0.01 mol) was added to 12 mL of a solution obtained from EtOAc (10 mL), $HClO_4$ (0.01 mL), and Ac_2O (1.2 mL) by the procedure reported previously.[10] The mixture was kept for 12 h at 20 °C, poured into water, washed with a Na_2CO_3 solution, and dried with Na_2SO_4. The solvent was removed, and the residue was distilled *in vacuo* to give 2.3 g (80 %) of compound **13**, b.p. 160—165 °C (1 Torr), m.p. 38—40 °C (hexane). Found (%): C, 71.86; H, 10.71. $C_{17}H_{30}O_3$. Calculated (%): C, 72.34; H, 10.64.

2) A mixture of compound **14** (2.4 g, 0.008 mol), AcOK (0.8 g, 0.008 mol), and DB-18-C-6 (0.12 g) in dioxane (30 mL) was stirred under reflux for 7 h, cooled, poured into water, and extracted with ether. The extract was washed with water and dried with Na_2SO_4. The solvent was removed to give 1.6 g (72 %) of compound **13**, m.p. 39—40 °C (hexane). Found (%): C, 72.35; H, 10.64. $C_{17}H_{30}C_3$. Calculated (%): C, 72.34; H, 10.64.

Alkaline hydrolysis of compound 13. A mixture of compound **13** (3 g, 0.01 mol) and KOH (0.9 g, 1.5 mmol) in ethanol (15 mL) was heated for 0.5 h at 50 °C and cooled to ~20 °C. The excess EtOH was removed, then the residue was poured into water, and the mixture was extracted with ether. The extract was washed with water and dried with Na_2SO_4. The solvent was removed to give 2.3 g (90 %) of compound **2**, m.p. 35—37 °C (pentane).

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