Synthesis of Tercyclohexanones

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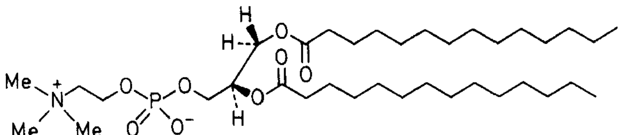
A synthetic route to tercyclohexanones is described in which alkylation of 4-cyclohexylcyclohexanone with the dianion of 4,4-(ethylenedioxy)cyclohexanecarboxylic acid gives 1-carboxy-1′-hydroxyl-1,1′:4′,1″-tercyclohexan-4-one ethylene ketal. Decarboxylative dehydration of the latter followed by hydrolysis of the ketal gives 4-(4′-cyclohexylcyclohexylidene)cyclohexanone. Hydrogenation of this compound gives *cis*- and *trans*-1,1′:4′,1″-tecyclohexan-4-one, the latter of which is correlated with authentic *trans*-1,1′:4′,1″-tercyclohexane.

Two of the most abundant chemical components of mammalian cell membranes are the phospholipids, e.g., 1,2-dimyristoyl-*sn*-glycero-3-phosphoryl-choline (**1**), and cholesterol (**2**).[1]



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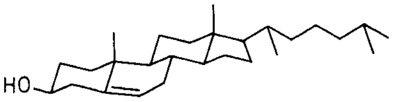

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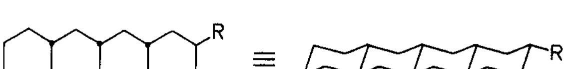
X-ray crystallographic studies of phospholipids reveal that the long hydrocarbon side chains are ordered in parallel patterns as illustrated for **1**.[2-5] This parallel orientation of side chains is preserved to a considerable extent in the cell membrane, wherein the polar head group of the phospholipid is found at the membrane–medium interface and the hydrocarbon side chains are found projecting into the membrane interior. The polar hydroxyl group and lipophilic hydrocarbon nucleus of cholesterol are complementary to the phospholipids in the membrane matrix which is held together primarily by noncovalent forces.

We were interested in devising a synthetic hybrid structure combining the parallel hydrocarbon chains of phospholipids with the rigid polycyclic steroid nucleus, the idea being that such a structure may be useful as the lipophilic portion of amphiphilic molecules having the potential for use as membrane probes and/or drugs. We first envisioned a linear polycyclic system such as **3** in which the rigid hydrocarbon structure of the *trans-syn-trans-syn-trans* isomer (shown) should be compatible with the other components of the cell membrane. Another ring system having structural features related to **3** is the tercyclohexyl system illustrated by **4**. The tercyclohexyl nucleus is conformationally less rigid than **3**, but may be more accessible to synthesis. In both **3** and **4**, R represents a group suitable for elaboration of functional side chains.



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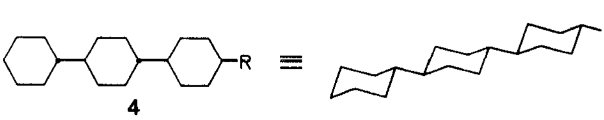

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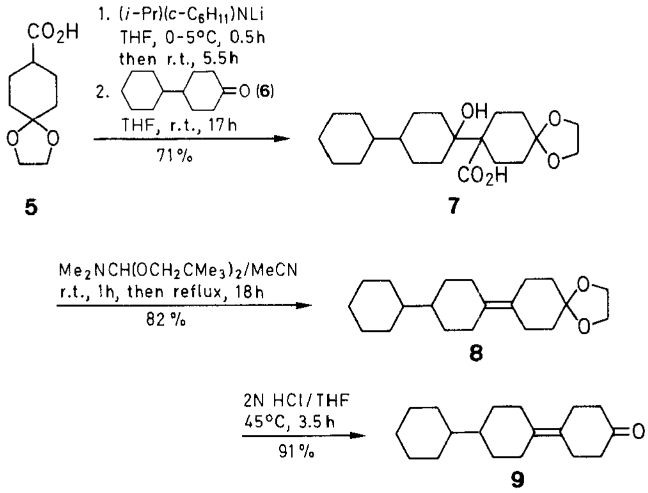
In this report, we describe the synthesis and characterization of three tercyclohexanones which are suitable for combination with various side chains. The first of these is structure **9** (see Scheme **A**), a compound in which the double bond between cyclohexanone and cyclohexyl rings imparts additional conformational rigidity to the structure. Reduction of the double bond in **9** produces the completely saturated tercyclohexanones **12** and **13** (see Scheme **B**) whose stereochemistry we define by correlation with compounds of known structure.

The route (Scheme **A**) we have used to prepare ketone **9** is based on methodology described by Humphreys and Newall[6] and has proven amenable to large scale preparation of **9**. Alkylation of 4-cyclohexylcyclohexanone[7] (**6**) with the dianion of 4,4-(ethylenedioxy)cyclohexanecarboxylic acid[6] (**5**) gave the hydroxy acid **7** as a mixture of isomers. Decarboxylative dehydration[8,9] of **7** with dimethylformamide dineopentyl acetal[10] gave the olefin **8** which upon hydrolysis of the ketal produced ketone **9**.[11] A yield of 53 % was realized for the three step conversion of **6** to **9**.

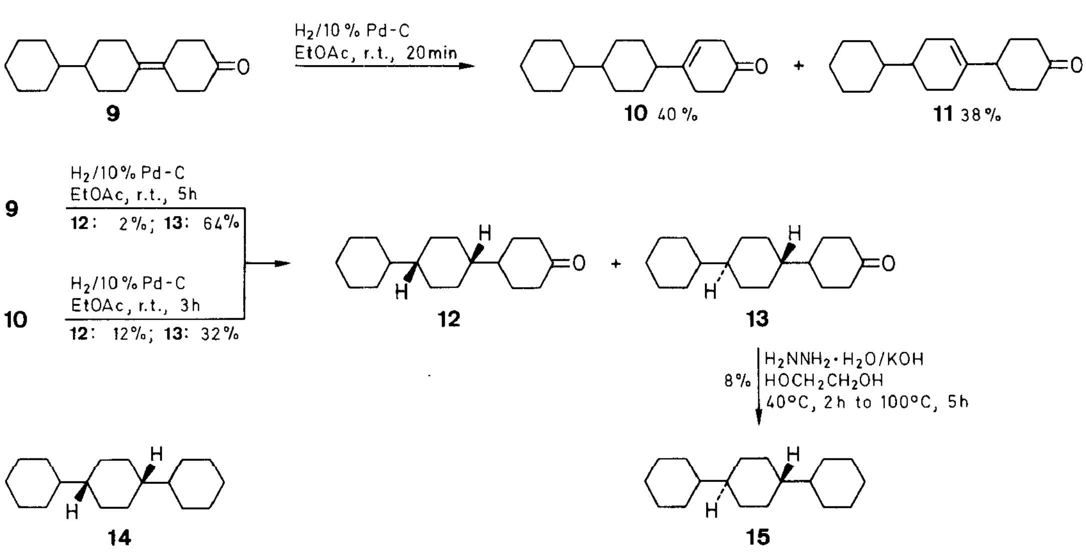


Scheme A

Catalytic hydrogenation of **9** (see Scheme **B**) over 10% palladium on carbon gave a mixture of the tercyclohexyl ketones **12** and **13** in which isomer **13** predominated in a ratio of 9:1. The predominant ketone **13** was obtained in pure form by crystallization from the mixture and has mp 121–122 °C. The mixture of isomers remaining after crystallization of the major component was separated by semipreparative HPLC using a C-18 reversed phase column. From this, the minor ketone **12** was obtained and has mp 60.5–61.5 °C. Capillary GC proves useful for determining both the ratio of products in the mixture and the purity of the two isomers following separation procedures.

Upon brief exposure (20 minutes) to 10% palladium on carbon, ketone **9** was converted to an approximately equal mixture of the isomeric structures **10** and **11** in which the double bond has isomerized into either of the adjacent rings. Isomers **10** and **11** are separable by chromatography and the less polar isomer was assigned structure **10** since it has a signal in the ^{1}H-NMR spectrum at $\delta = 2.85$ for one of the protons on the carbon located between the carbonyl and double bond. Such a downfield signal, relative to the region in which protons on saturated carbon resonate, is absent in the other isomer **11**. The possibility that *cis* and *trans* isomers of **10** were formed during the isomerization reaction seems likely but no evidence for this was seen in the chromatographic and spectral data for **10**. However, when **10** was subjected to catalytic reduction for a longer period of time, saturated ketones **12** and **13** were formed in a ratio of about 1:3. From this result we conclude that **10** also is a mixture of *cis* and *trans* isomers in the same ratio.

The assignment of stereochemistry to ketones **12** and **13** was achieved by correlation with *cis*- and *trans*-tercyclohexane. *cis*-Tercyclohexane (**14**, mp 51–52 °C) and *trans*-tercyclohexane (**15**, mp 161–162 °C) have been described previously and their stereochemistry has been assigned on the basis of X-ray crystallographic studies.[12–15] To aid the correlation, we repeated the



Scheme B

preparation of these two hydrocarbons by reduction of *p*-terphenyl using platinum in acetic acid in place of the previously reported[12] Raney nickel. The ^{13}C-NMR spectra of hydrocarbons **14** and **15**, previously unreported, are very distinctive, **15** having only four resolved signals and **14** having five signals. Wolff–Kishner reduction of the predominant ketone **13** gave a tercyclohexane with mp 161–162 °C and having ^{1}H-NMR and ^{13}C-NMR identical to those of *trans*-tercyclohexane **(15)**. The predominant ketone **13** mp 121–122 °C, therefore has the *trans* configuration and the minor ketone, mp 60.5–61.5 °C, has the *cis* configuration.

Reactions were monitored by thin layer chromatography (TLC) using plates purchased from Analtech, Inc. (silica gel GF, 250 microns in thickness, 1″ × 4″) with solvent systems made up of mixtures of common laboratory solvents. The compounds were visualized on the plates with UV-light and/or spraying with a solution of 5% HNO_3 in 50% H_2SO_4/H_2O followed by charring of the plate on a hotplate. Melting points were obtained with either a Fisher–Johns or a Thomas–Hoover melting point apparatus and are uncorrected IR spectra were recorded with either a Perkin–Elmer Model 137 or a Digilab Model FTS-15E spectrophotometer; mulls were in Nujol and liquids and oils were films between salt plates. The ^{1}H-NMR were obtained either with a Bruker AM 300 or a Varian EM 390 spectrometer as solutions in $CDCl_3$ with TMS as an internal reference. ^{13}C-NMR were obtained with a Bruker AM 300 spectrometer. Mass spectra were obtained with a Finnigan MAT CH7 spectrometer. Capillary GC was performed on a Hewlett–Packard 5880A chromatograph with a flame ionization detector.

4-(4′-Cyclohexylcyclohexylidene)cyclohexanone Ethylene Ketal (8):

1-Carboxy-1′-hydroxy-1,1′:4′,1″-tercyclohexan-4-one Ethylene Ketal (**7**): *N*-Isopropylcyclohexylamine (19.57 g, 0.139 mol) is added dropwise to a magnetically stirred solution of butyllithium (94.2 mL, 1.35 M in hexane, 0.127 mol) in THF (350 mL) under a N_2 atmosphere and cooled in an ice bath at 0–5 °C. After maintaining the solution at 0–5 °C for an additional 30 min, the solid acid **5**[6] 10.76 g, 0.0578 mol) is added at once. The cooling bath is removed and the reaction solution is allowed to stir at r.t. for 5.5 h. A solution of 4-cyclohexylcyclohexanone[7] (**6**; 10.41 g, 0.0578 mol) in THF (25 mL) is added at once and is followed with a rinse of THF (25 mL). After stirring at r.t. for 17 h, the milky white suspension is poured into ice water (500 mL), washed once with Et_2O (500 mL), acidified to pH 1 with conc HCl (ca. 19 mL), and extracted with $CHCl_3$/MeOH (9:1, 2 × 400 mL). The combined extracts are dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The colorless solid residue is triturated with a solvent mixture consisting of EtOAc (50 mL), Et_2O (250 mL), and hexane (250 mL), collected by filtration, and dried to give hydroxy acid **7** which is sufficiently pure for the subsequent reaction; yield: 15.04 g (71%); R_f on silica gel TLC (1″ × 4″ plates, acetone/$CHCl_3$/HOAc (5:94:1) was 0.14.

4-(4′-Cyclohexylcyclohexylidene)cyclohexanone Ethylene Ketal (8): Dimethylformamide dineopentyl acetal (18.99 g, 0.0822 mol) is added at once to a magnetically stirred slurry of hydroxy acid **7** (15.04 g, 0.041 mole) in MeCN (500 mL) at r.t. The mixture is stirred at r.t. for 1 h and then is heated overnight at gentle reflux. The mixture is cooled, diluted with Et_2O, washed successively with ice water (3 × 100 mL), brine (1 × 100 mL), and the organic layer dried (Na_2SO_4). The solution is filtered and concentrated *in vacuo*, giving a residue which is chromatographed (flash, 225 g of silica gel, 5% EtOAc in hexane). The olefin-ketal **8** is obtained as a colorless solid; yield: 10.22 g (82%); mp 110–115 °C.

$C_{20}H_{32}O_2$ calc. C 78.95 H 10.53
(304.5) found 79.13 10.84

IR: ν = 3 strongest peaks in order of intensity, 2942, 2915, 1450 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 3.98 (s, 4 H), 2.88–2.53 (m, 2 H), 2.44–2.01 (m, 4 H), 1.93–1.35 (m, 12 H), 1.35–0.33 (m, 10 H).

MS: *m/z* = 304 (M$^+$).

4-′-Cyclohexylcyclohexylidene)cyclohexanone (9):

A solution of **8** (13.5 g, 0.0444 mol) in THF (475 mL) and aq 2 N HCl (175 mL) is stirred and warmed to 45 °C in an oil bath for 3.5 h. The reaction is cooled to r.t. and diluted with Et_2O. The solution is washed with ice water (2 × 200 mL), brine (125 mL), dried (Na_2SO_4), filtered, and concentrated to yield 13.1 g of colorless solid. Crystallization from MeOH/H_2O gives **9** as a colorless crystalline solid; yield: 10.50 g (91%); recrystallization from hexane gives colorless crystals, mp 81–81.5 °C.

$C_{18}H_{28}O$ calc. C 83.02 H 10.84
(260.4) found 82.99 10.71

IR (Nujol): ν = 1731, 1720 cm^{-1}.

^{1}H-NMR ($CDCl_3$/TMS): δ = 2.68 (m, 8 H), 1.78 (m, 9 H), 1.15 (m, 11 H).

***cis*- (12) and *trans*-1,1′:4′1″-Tercyclohexan-4-one (13):**

A solution of the keto olefin **9** (0.100 g, 0.38 mmol) in EtOAc (25 mL) is shaken with 10% Pd-C (50 mg) in a H_2 atmosphere on a semi-micro hydrogenation apparatus for 5 h. The mixture is filtered and the filtrate is concentrated under reduced pressure leaving a colorless solid. Chromatographic analysis of the solid by capillary GC (15 meter DB-1 capillary column) reveals a ratio of about 9:1 for two reduction products. The crude solid is passed through a gravity chromatography column (9.5 g silica gel, 10% EtOAc/hexane, 5 mL fractions) which gives in fractions 3–5 the two products mixed with some less polar impurities (11 mg) and in fractions 6–10 a mixture of the two products free of impurities. Two recrystallizations of the material in fractions 6–10 from MeOH give pure **13** (0.040 g), mp 121–122 °C.

The material from the filtrates of these recrystallizations is combined with fractions 3–5 and chromatographed by semi-preparative HPLC on a reversed phase C_{18} column using MeOH/H_2O (96:4) as the elution solvent. The flow rate is 2 mL/min and the UV detector is set at 205 nm. Repeated injections of the mixture on the column are required to achieve the separation and give the following results.

Eluted first at 20.4 min is **12**; yield: 2 mg (2%), a colorless solid with mp 59–60 °C. Capillary GC analysis on the above mentioned column gives a retention time of 2.94 min at an oven temperature of 220 °C and shows the sample to be homogeneous within the limits of detection. Recrystallization from MeOH/H_2O gives colorless crystals, mp 60.5–61.5 °C.

HRMS: *m/z*, $C_{18}H_{30}O$ calc.: 262.2297; found: 262.2309.

^{1}H-NMR ($CDCl_3$, TMS): δ = 2.32 (m, 4 H), 2.10 (m, 2 H), 1.73 (m, 6 H), 1.43 (m, 11 H), 1.19 (m, 5 H), 0.87 (m, 2 H).

^{13}C-NMR ($CDCl_3$/TMS): δ = 40.96, 40.84, 39.61, 39.08, 37.69, 30.70, 30.39, 26.71, 26.28.

MS: *m/z* = 262 (M$^+$), 244, 233, 215, 206, 179, 161, 138, 124, 109, 98, 83, 67.

Eluted second at 24.3 min is **13**; yield: 24 mg, total 64 mg (64%). Capillary GC analysis (as described above) of this fraction gives a retention time of 3.21 min and shows the sample to be homogeneous within the limits of detection.

HRMS: *m/z*, $C_{18}H_{30}O$ calc.: 262.2297; found: 262.2307.

^{1}H-NMR ($CDCl_3$, TMS): δ = 2.33 (m, 4 H), 2.03 (m, 2 H), 1.69 (m, 9 H), 1.47 (m, 3 H), 1.18 (m, 4 H), 0.99 (m, 8 H).

^{13}C-NMR ($CDCl_3$/TMS): δ = 50.85, 43.40, 43.28, 42.07, 41.71, 41.17, 30.53, 30.27, 30.08, 29.89, 26.86.

MS: *m/z* = 262 (M$^+$), 244, 233, 206, 179, 161, 151, 138, 124, 109, 97, 89, 67.

Isomerization of [1,1′:4′,1″-Tercyclohex-1(1′)en]-4-one (9) to [1,1′:4′,1″-Tercyclohex-1(2)-en]-4-one (10) and [1,1′:4′,1″-Tercyclohex-1′(2′)-en]-4-one (11):

A solution of olefinic ketone **9** (2.00 g, 7.69 mmol) in EtOAc (200 mL) is treated with 10% Pd-C (200 mg) and is shaken in a H_2

atmosphere (16 psi) at r.t. for 20 min. The mixture is vacuum filtered through a pad of Celite and the filtrate is concentrated at reduced pressure. The residue is chromatographed (flash, 180 g of silica gel; EtOAc/hexane, 5:95) to provide the isomeric products **10** and **11**. Isomer **10** is eluted first and is a waxy colorless solid; yield: 0.808 g (40%).

HRMS: *m/z*, $C_{18}H_{28}O$ calc.: 260.2140; found: 260.2140.

^{1}H-NMR ($CDCl_3$/TMS): $\delta = 5.43$ (m, 1 H, C-2 olefinic proton), 2.85 (d, 1 H, =CHC$\underline{H}$HCO–), 2.75–2.23 (m, 5 H), 2.19–1.56 (m, 10 H), 1.56–1.35 (m, 1 H), 1.35–0.71 (m, 10 H).

^{13}C-NMR ($CDCl_3$/TMS): $\delta = 211.16$, 143.91, 115.69.

Eluted next is a mixture of **10** and **11** (0.360 g, 1.38 mmol, 18%). Eluted last is isomer **11** as a colorless solid; yield: 0.762 g (38%).

HRMS: *m/z*, $C_{18}H_{28}O$ calc.: 260.2140; found: 260.2147.

^{1}H-NMR ($CDCl_3$/TMS): $\delta = 5.47$ (s, 1 H, C-2′ proton), 2.51–2.18 (m, 5 H), 2.18–1.92 (m, 5 H), 2.18–1.92 (m, 4 H), 1.92–1.38 (m, 10 H), 1.38–0.85 (m, 8 H).

^{13}C-NMR ($CDCl_3$/TMS): $\delta = 211.90$, 139.87, 120.45.

Catalytic Hydrogenation of 10; Ketones 12 and 13:
A solution of **10** (0.808 g, 3.11 mmol) in EtOAc (100 mL) is charged with 10% Pd-C (140 mg) and is shaken with H_2 (23 psi) at r.t. for 3 h. Removal of the catalyst by filtration through Celite and evaporation of the filtrate gives a crude product which, when examined by ^{1}H-NMR, is found to be a mixture of reduced and unreduced olefins. This product is further reduced over 10% Pd-C (400 mg) with H_2 (36 psi) for 2 h at r.t. Filtration through Celite and evaporation under reduced pressure gives a crue product which is chromatographed over silica gel (180 g, flash, EtOAc/hexane, 4:96). Eluted first is the ketone **12**; yield: 0.102 g (12%), followed by a mixture of **12** and **13**; yield: 0.272 g (33%), and then by ketone **13**; yield: 0.264 g (32%). The spectral properties (^{1}H- and ^{13}C-NMR, MS) of **12** and **13** are identical to those of the above described ketones **12** and **13**.

Wolff–Kishner Reduction of 13; *trans*-1,1′:4′,1″-Tercyclohexane (15):
Ketone **13** (0.052 g, 0.20 mmol), KOH (0.112 g, 0.20 mmol), diethylene glycol (5 mL), and hydrazine hydrate (120 μL, 2.5 mmol) are placed in a round-bottomed flask equipped with a reflux condenser and under a N_2 atmosphere. The mixture is heated at a bath temperature of 40 °C for 2 h and then at a temperature of 100 °C for 5 h after which time all starting material is consumed. Toluene (20 mL) is added to the mixture and then is removed by distillation, the purpose being to azeotrope H_2O from the mixture. The temperature of the oil bath is then raised to 220 °C and maintained at this temperature for 24 h. The reaction is cooled, poured into half sat. brine, and the resulting mixture is extracted with Et_2O (4 × 25 mL). The Et_2O extracts are washed with 0.1 N HCl and with brine and dried (Na_2SO_4). After filtration, the Et_2O is removed under reduced pressure leaving a residue which is crystallized from MeOH. A colorless solid (0.012 g) is collected and has mp 148–152 °C; HRMS ($C_{18}H_{32}$ calc.: 248.2504; found: 248.2511). Further recrystallization fails to improve the melting point of the solid. The remaining material is chromatographed over a size A Merck Lobar® column (silica gel, 3 mL fractions). Elution of the column with hexane gives pure **15** in fractions 4–6; yield: 4 mg (8%). Crystallization from acetone gives colorles crystals, mp 61–162 °C (capillary), Lit.[15] mp 161–162 °C; ^{1}H- and ^{13}C-NMR spectra are identical to those of an authentic sample of *trans*-1,1′:4′,1″-tercyclohexane prepared as described below.

Hydrogenation of *p*-Terphenyl; *cis*-(14) and *trans*-1,1′:4′,1″-Tercyclohexane (15):
A solution of *p*-terphenyl (0.500 g, 2.17 mmol) in HOAc (200 mL, warming required to attain solution) is hydrogenated over Pt (0.500 g) on the Parr apparatus at a temperature of 60 °C. Measurable uptake of H_2 stops after 30 min and the reaction is removed from the hydrogenator after 2.5 h. The mixture is filtered to remove the catalyst while still warm. The HOAc is removed under reduced pressure leaving a colorless, solid residue. MeOH is added to the residue and the mixture is heated on a steam bath. Material insoluble in the hot MeOH is separated (0.048 g) and recrystallized twice from acetone to give colorless crystals of *trans*-1,1′:4′,1″-tercyclohexane; yield: 0.015 g (3%) mp 161–162 °C.

^{13}C-NMR ($CDCl_3$/TMS): $\delta = 43.61$, 43.40, 30.28, 26.89.

From the hot MeOH filtrate, crystals (0.20 g) are obtained upon cooling, mp 50–52 °C. Repeated recrystallizations from MeOH give *cis*-1,1′:4′,1″-tercyclohexane which contains ~5% of the *trans* isomer as judged from the ^{13}C-NMR spectrum; yield: 0.10 g (18%); mp 50–52 °C (Lit.[15] mp 51–52 °C).

^{13}C-NMR ($CDCl_3$/TMS): $\delta = 41.10$, 39.19, 30.73, 26.78, 26.40.

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