Design and synthesis of analogues of ionomycin

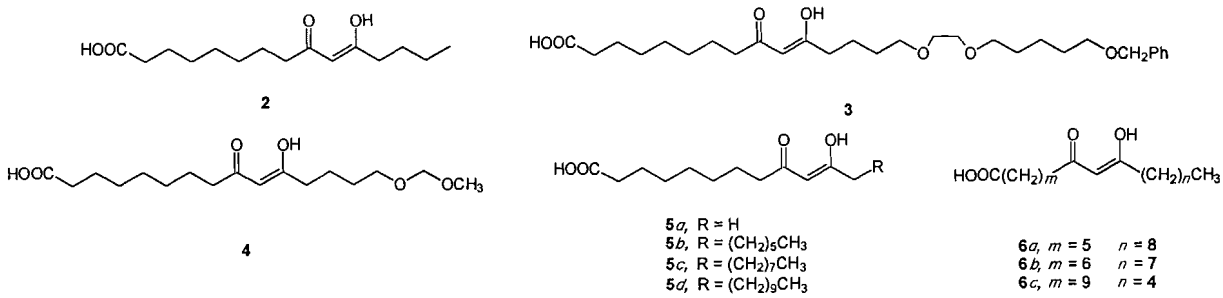
THOMAS Q. HU AND LARRY WEILER[1]

Department of Chemistry, University of British Columbia, 2036 Main Mall, Vancouver, BC V6T 1Z1 Canada

Received June 30, 1993[2]

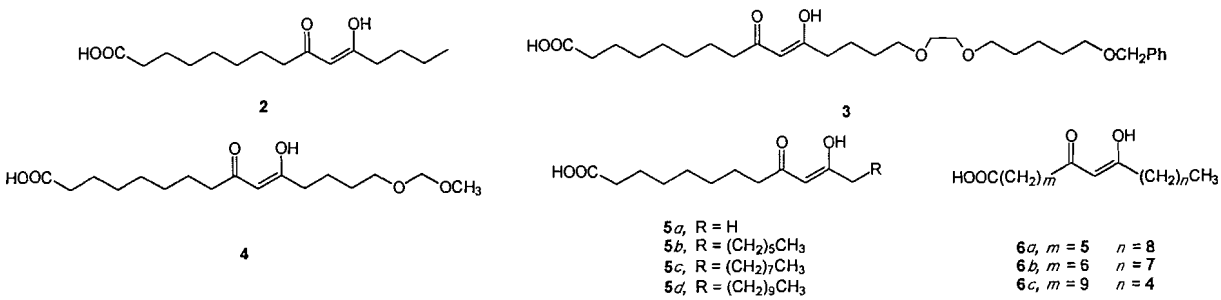
THOMAS Q. HU and LARRY WEILER. Can. J. Chem. **72**, 1500 (1994).

Based on the analysis of the crystal structure of the Ca^{2+} salt of ionomycin and the chemical and physical data on ionomycin, a number of ionomycin analogues have been synthesized to study the structural features affecting the Ca^{2+} binding and transport. Compounds **2**, **3**, and **4** were synthesized to study the effect of additional intramolecular oxygen coordination sites on Ca^{2+} transport. Compounds ***5a–5d*** were prepared to study the effect of lipid solubility on Ca^{2+} binding and transport. Compounds ***6a–6c*** were prepared to study the effect of the distance between the β-diketone and the carboxyl group on Ca^{2+} transport. A general synthetic route to these compounds has been developed. The key reactions in this route are the consecutive regioselective alkylations of the dianion of 2,4-pentanedione with the appropriate bromides.



THOMAS Q. HU et LARRY WEILER. Can. J. Chem. **72**, 1500 (1994).

En se basant sur une analyse de la structure cristalline du sel de Ca^{2+} de l'ionomycine et sur les données chimiques et physiques de l'ionomycine, on a synthétisé une série d'analogues de l'ionomycine dans le but d'étudier leurs caractéristiques structurales affectant leur liaison au Ca^{2+} et son transport. On a synthétisé les composés **2**, **3** et **4** pour étudier l'effet d'une augmentation des sites intramoléculaires de coordination de l'oxygène sur le transport du Ca^{2+}. On a préparé les composés ***5a–5d*** pour étudier l'effet de la solubilité lipidique sur la liaison avec le Ca^{2+} et sur son transport. On a préparé les composés ***6a–6c*** pour étudier l'effet de la distance entre la β-dicétone et le groupe carboxyle sur le transport du Ca^{2+}. On a mis au point une méthode générale de synthèse de ces composés. Les réactions clés de cette voie sont les alcoylations régiosélectives consécutives du dianion de la pentane-2,4-dione avec les bromures appropriés.



[Traduit par la Rédaction]

Introduction

Ionomycin (**1**) is a polyether calcium ionophore isolated from a strain of *Streptomyces conglobatus* (1). Its molecular structure was determined by Toeplitz et al. using ^1H NMR spectroscopy, mass spectrometry, and X-ray crystallographic analysis of three crystalline forms of its cadmium and calcium salts (2).

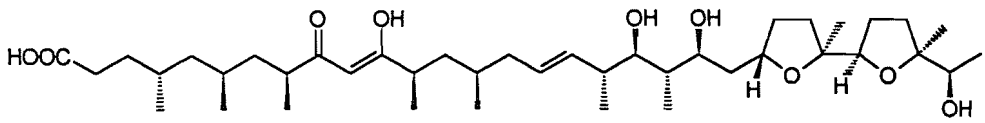
Like other polyether Ca^{2+} ionophores, ionomycin has been found to be a potent antimicrobial agent. It is active against Gram-positive bacteria with no demonstrable effect against Gram-negative bacteria. However, ionomycin was found to have unusual physical, chemical and biological properties. It possesses a β-diketo group that, together with the carboxyl group, confers dibasic character to the ionophore. It has a very high affinity for Ca^{2+} and other divalent cations. In fact, the calcium salt of ionomycin was extracted from an aqueous solution of pH 12 that had been made alkaline with sodium hydroxide (3).

Ionomycin is unique among the polyether ionophores in that it forms a neutral 1:1 Ca^{2+} salt (2). As shown in the crystal structure of this Ca^{2+} salt of ionomycin (Fig. 1), the carboxylate group, the enolate of the β-diketone, two hydroxyl groups, and a tetrahydrofuranyl oxygen form an octahedral complex around the Ca^{2+}. The ligand wraps around the Ca^{2+} ion with the oxygen atoms directed towards the inside of the sphere. The alkyl groups, on the other hand, protrude from the shell, providing the Ca^{2+} salt with its lipophilic properties.

Liu and Hermann investigated the extraction of Ca^{2+} ions

[1]Author to whom correspondence may be addressed.

[2]Revision received January 4, 1994.



1

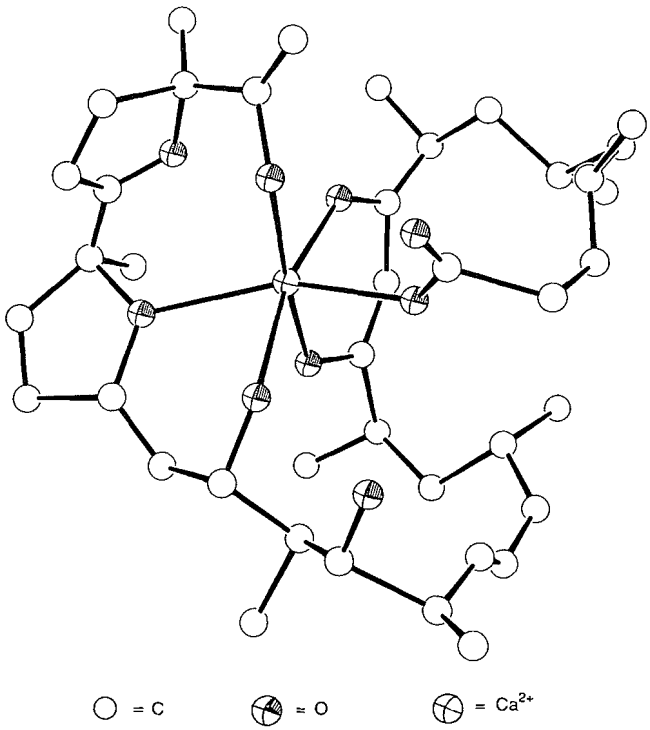


FIG. 1. Crystal structure of the calcium salt of ionomycin (2).

from an aqueous phase into an organic phase and the transport of Ca^{2+} across an organic barrier by ionomycin (4). The selectivity of ionomycin for divalent cations was shown to be $Ca^{2+} > Mg^{2+} \gg Sr^{2+} = Ba^{2+}$. No complexation or transport of monovalent cations by ionomycin could be detected.

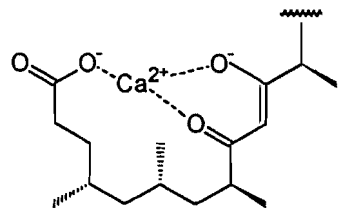
Owing to its ability to selectively bind and transport Ca^{2+} across an organic barrier, ionomycin has been widely used as a tool to investigate the role of calcium ion as a second messenger in biological systems. In studies of rat liver mitochondria, it was shown that ionomycin efficiently catalyzed the exchange of two protons for one Ca^{2+} across the cell membrane (5, 6). Ionomycin has been found to stimulate the release of histamine from mast cells and catecholamine from pheochromocytoma cells by transporting Ca^{2+} across the cell membranes (7). It has also been linked to the activation of human blood platelets by facilitating the transport of Ca^{2+} across the membrane and mobilizing Ca^{2+} stored in organelles (8).

Although the ability of ionomycin to mimic the effects of many physiological cell stimuli has been demonstrated, little is known about the structural features controlling Ca^{2+} binding and transport by ionomycin. This prompted us to design and synthesize a series of simple ionomycin analogues to study the role of the functional groups of ionomycin in Ca^{2+} binding and transport and to study the effect of other structural features, such as lipophilicity and oxygen coordination sites, on Ca^{2+} transport.

Results and discussion

The design of ionomycin analogues was based on the literature data on the mode of action of ionomycin itself. The functional groups thought to be vital to the function of ionomycin would be retained in the synthetic analogues while the numerous stereochemical centers found along the carbon backbone of ionomycin would be omitted to simplify the synthesis of these model compounds. The chemical and physical data on ionomycin suggest that the β-diketone and carboxyl groups are crucial to its ionophoric properties. The crystal structure of the Ca^{2+} salt of ionomycin (Fig. 1) shows that both these groups are ionized and coordinated to the metal cation in the formation of the 1:1 Ca^{2+} salt. It was considered important to retain these two functional groups in the model compounds.

In the natural product, there is a seven-carbon chain separating the β-diketone and the carboxyl groups. The presence of this seven-carbon chain could certainly contribute to the high lipid solubility of the ionophore–Ca^{2+} complex. The distance between these two functional groups is such that a 12-membered ring is formed on chelation of a calcium ion by the carboxylate oxygen and the first oxygen of the β-diketone enolate as shown in **A**. Thus a seven-methylene unit was chosen as the linker for these two functional groups in the initial model compounds.

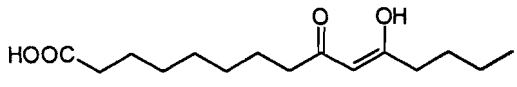


A

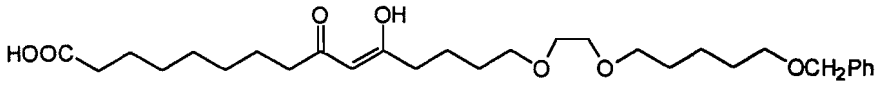
High lipophilicity of the model compounds may be needed for suitable membrane solubility. One of the simplest analogues fulfilling these requirements would be a 9,11-dioxocarboxylic acid such as 9,11-dioxopentadecanoic acid (**2**), which was chosen as one of the first target molecules.

Since one tetrahydrofuranyl and two hydroxyl oxygens of ionomycin are involved in coordination to the Ca^{2+} (Fig. 1), we speculated that it might be necessary to incorporate a side chain that contained appropriately placed oxygen atoms to retain the six Ca^{2+} binding sites found in ionomycin. A side chain that contains an ethylene glycol and an ether function five methylene units away was chosen to mimic the Ca^{2+} coordination sites in ionomycin. An ether function, such as a benzyl ether, could compensate for the decrease of lipophilicity created by the introduction of three oxygen atoms in such a molecule. Therefore, a benzyloxypentyloxyethoxyl unit was incorporated into analogue **2** to give another target analogue, 15-[2-(5-benzyloxy)-pentyloxy]-ethoxy-9,11-dioxopentadecanoic acid (**3**).

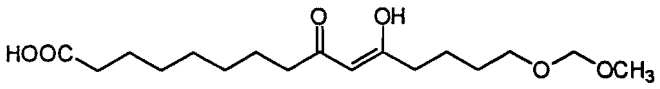
The presence of six oxygen coordination sites may not be necessary for binding and transport of Ca^{2+}. A molecule of water from the aqueous medium could occupy a Ca^{2+} coordina-



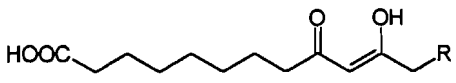
2



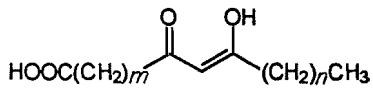
3



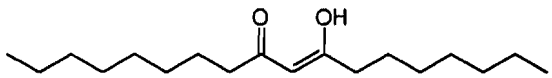
4



5*a*, R = H
5*b*, R = $(CH_2)_5CH_3$
5*c*, R = $(CH_2)_7CH_3$
5*d*, R = $(CH_2)_9CH_3$



6*a*, *m* = 5 *n* = 8
6*b*, *m* = 6 *n* = 7
6*c*, *m* = 9 *n* = 4



7

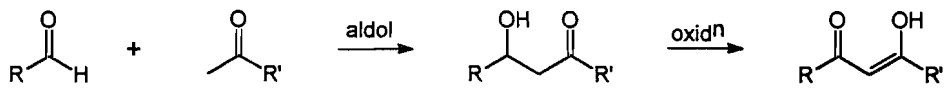
tion site as is often observed in the binding of Ca^{2+} with proteins and other ionophores such as lasalocid A (9, 10). Thus, it may be sufficient to incorporate a side chain that contains only one or two oxygen atoms as potential Ca^{2+} coordination sites. With this in mind we added a methoxymethoxyl unit to analogue **2** to give the target molecule, 15-methoxymethoxy-9,11-dioxopentadecanoic acid (**4**).

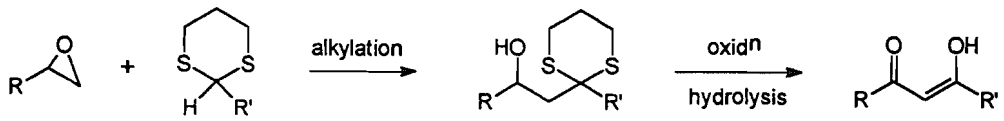
In addition to these three analogues, compounds **5***a*–**5***d* were synthesized as models to study the effect of lipid solubility on Ca^{2+} binding and transport. On the other hand, compounds **6***a*–**6***c*, which should have the same lipid solubility as **5***b* but have a different number of methylene units separating the β-diketone and the carboxyl group, were synthesized to study the effect of the distance between the β-diketone and carboxyl groups on Ca^{2+} binding and transport. Compound **7** possesses only the β-diketo group and was chosen as the final target.

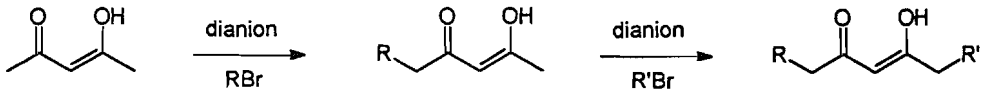
Retrosynthetically, the carboxyl function of each proposed analogue could be made by oxidation of a hydroxyl group. The ether units in analogues **3** and **4** could be prepared using known chemistry (11). Thus the crucial part in the synthesis of the analogues was the introduction of the β-diketone and the construction of the carbon framework. A β-diketone could be prepared by oxidation of a β-hydroxyl ketone, which in turn could be generated by an aldol condensation between a methyl ketone and an aldehyde (eq. [1]). This route was used for the synthesis of the β-diketone in ionomycin (12).

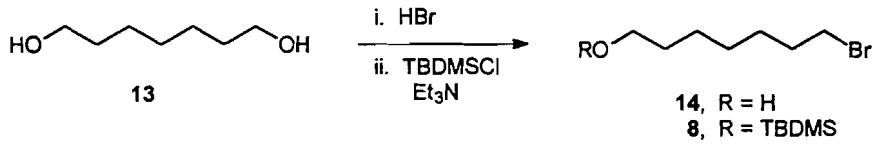
Alternatively, the β-diketone could be generated by alkylation of the anion of a dithiane with an epoxide, followed by oxidation of the hydroxyl group and hydrolysis of the dithiane (eq. [2]). This method was employed in the synthesis of an ionomycin fragment (13).

Either of these two methods could be applied to the synthesis

[1] 

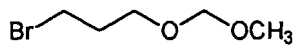
[2] 

[3] 

[4] 

13

14, R = H
8, R = TBDMS



11

of the proposed analogues of ionomycin. However, neither route appeared to be very efficient for the synthesis of simple, unsubstituted compounds. A logical precursor of a β-diketone appeared to be the simplest β-diketone, the commercially available 2,4-pentanedione. Consecutive alkylation of 2,4-pentanedione at the methyl carbons could be achieved using the dianion chemistry (eq. [3]) (14). Thus we require bromides **8–12** for the synthesis of analogues **2–5**.

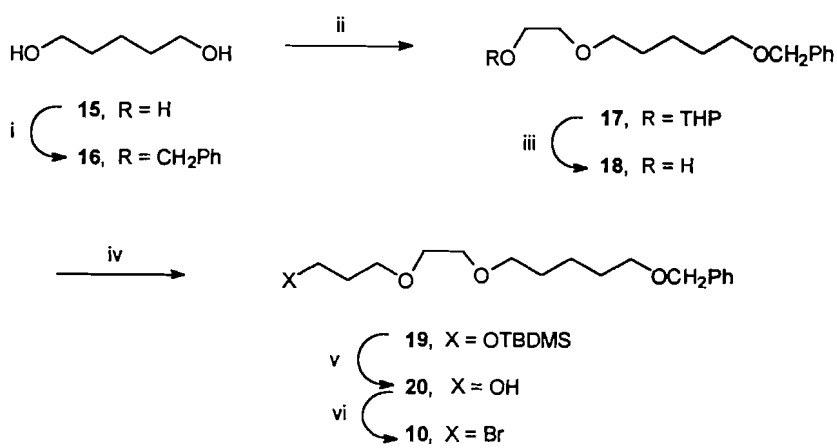
The synthesis of bromide **8**, a common intermediate in the preparation of many of the analogues, is illustrated in eq. [4]. Monobromination of 1,7-heptanediol (**13**) was achieved in 72% yield by continuously extracting a mixture of diol **13** and aqueous hydrobromic acid with heptane (15). The hydroxyl group of bromide **14** was protected as its *tert*-butyldimethylsilyl ether (16) to give bromide **8** in 82% yield. Bromide **11** was prepared in good yield by treatment of 3-bromo-1-propanol with phosphorus pentoxide and dimethoxymethane (17).

The synthesis of bromide **10** is outlined in Scheme 1. It started with the monobenzylation of 1,5-pentanediol (**15**) (18). The resulting mono alcohol **16** was subjected to the modified Williamson ether synthesis (19), which involved the vigorous mixing of a two-phase system containing **16**, 1-bromo-2-tetrahydropyranyloxylethane, and aqueous sodium hydroxide in the presence of a phase transfer catalyst, tetrabutylammonium hydrogen sulfate. The reaction gave the desired ether **17** in 83% yield. In contrast, only a small amount of alcohol **16** could be converted to ether **17** when the reaction was carried out using sodium hydride as a base in polar aprotic solvents such as dimethylformamide. The tetrahydropyranyl ether protecting group in **17** was cleaved to give alcohol **18** (20). The alcohol **18** was subjected to a second modified Williamson ether synthesis using 1-bromo-3-*tert*-butyldimethylsilyloxylpropane to give the ether **19**. Deprotection of the TBDMS ether (21) gave alcohol **20**, which was converted to bromide **10** (22) in good yield.

Next we proceeded to carry out the dianion alkylation reactions on 2,4-pentanedione as shown in Scheme 2 for the synthesis of analogue **2**. The dianion of 2,4-pentanedione was reacted with bromide **8** to give the monoalkylated β-diketone **21** in 81% yield.

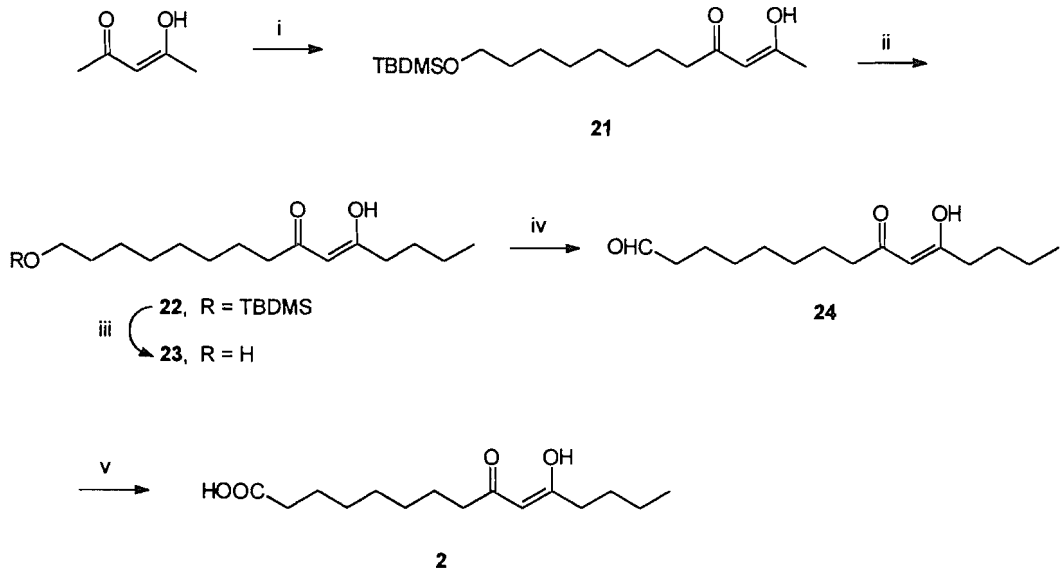
The structure of the monoalkylated β-diketone **21** was confirmed by ^{1}H NMR spectroscopy, which exhibited a triplet at δ 2.51 that integrated to 0.4 proton and a triplet at δ 2.27 that integrated to 1.6 protons ascribable to the methylene protons at C-8 of the keto and enol forms of the β-diketone, respectively. A 0.6-proton singlet at δ 2.24 and a 2.4-proton singlet at δ 2.06 were assigned to the methyl protons at C-12 of the keto and enol forms, respectively. A 0.8-proton singlet at δ 15.50, a 0.8-proton singlet at δ 5.49, and a 0.4-proton singlet at δ 3.58 were assigned to the enol hydroxyl proton, the vinyl proton, and the methylene proton at C-10, respectively (Fig. 2).

The second dianion alkylation reaction was achieved by treat-



SCHEME 1.

i. NaH, $PhCH_2Br$, 54%; ii. NaOH, Bu_4NHSO_4, $THPO(CH_2)_2Br$, 83%; iii. PPTs, 83%; iv. NaOH, Bu_4NHSO_4, $TBDMSO(CH_2)_3Br$, 83%; v. Bu_4NF, 89%, vi. Ph_3P, CBr_4, 91%



SCHEME 2.

i. NaH, *n*-BuLi, TBDMSO$(CH_2)_7$Br (**8**), 81%; ii. 2.0 LDA, $CH_3(CH_2)_2$Br, 81%; iii. Bu_4NF, 91%; iv. DMSO, DCC, Cl_2CHCO_2H; v. $AgNO_3$, NaOH, 69%

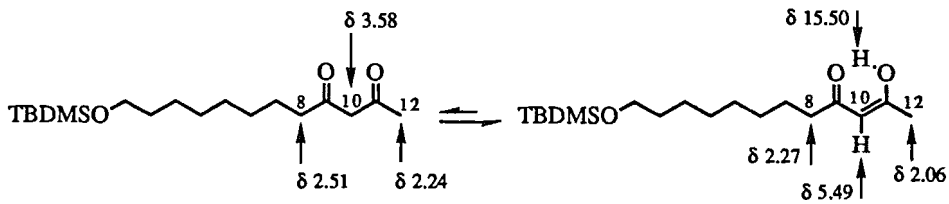


FIG. 2. Partial ^{1}H NMR assignments to the keto and enol forms of **21**.

ing the β-diketone **21** with two equivalents of lithium diisopropylamide to regioselectively generate the primary dianion that subsequently was reacted with one equivalent of 1-bromopropane (**9**) to produce the β-diketone **22** in 81% yield. The regioselectivity in this alkylation was confirmed by ^{1}H NMR and mass spectroscopy. The ^{1}H NMR spectrum of compound **22** showed four triplets at δ 2.50, 2.48, 2.28, and 2.26 integrating to a total of four protons ascribable to the methylene protons at C-8 and C-12 of the keto and enol forms of **22**. In addition, three singlets at δ 15.51, 5.48, and 3.54 integrating to a total of two protons were assigned to the enol hydroxyl proton, the vinyl proton, and the methylene proton at C-10. The mass spectrum of compound **22** showed peaks at *m/z* 313 and 127 corresponding to fragmentation α to the β-diketone group of **22**.

To complete the synthesis of analogue **2**, the silyl ether protecting group of compound **22** was cleaved to give alcohol **23**, which was oxidized to aldehyde **24** under Moffatt conditions (23). Treatment of **24** with silver oxide (24) produced the acid **2** in 69% yield for the two steps.

The synthesis of analogues **3**, **4**, and **5***a*–**5***d* started with the β-diketone **21** and followed a similar path with comparable yields as for **2** (Scheme 3). The syntheses of analogues **6***a*–**6***c* were accomplished in similar yields to those of analogue **5***b* (Scheme 4) and the synthesis of compound **7** was achieved by two consecutive dianion alkylations.

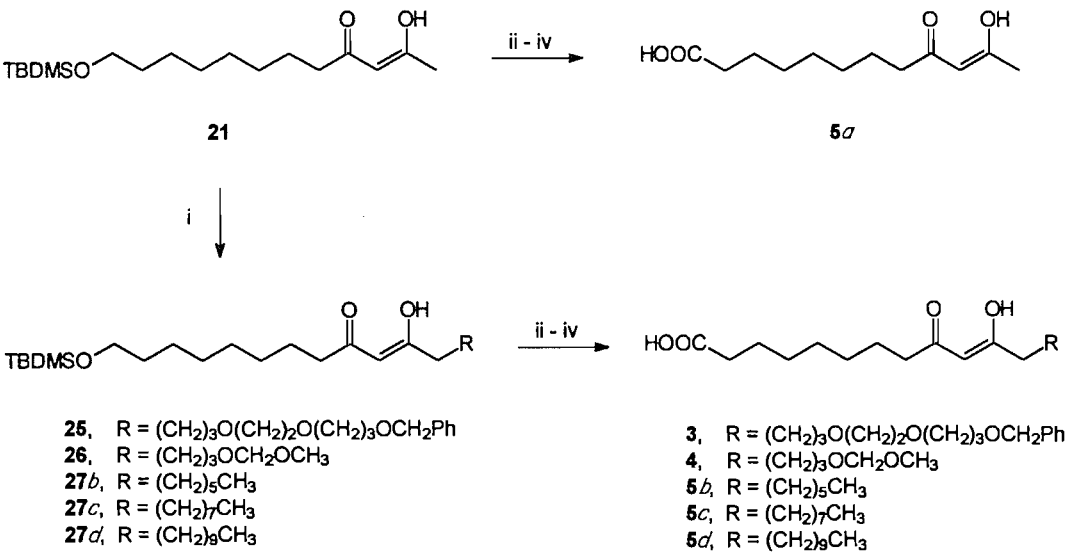
In conclusion, a series of analogues of ionomycin were designed to study the structural features affecting the ability of Ca^{2+} binding and transport by ionomycin. The syntheses of these analogues were achieved by consecutive regioselective alkylation of the dianion of 2,4-pentanedione with the appropriate bromides and subsequent oxidation of the β-diketone ω-alcohols. The results of the studies on the Ca^{2+} binding and transport properties of these ionomycin analogues and their potential as Ca^{2+} ionophores are reported in the following paper in this series (25).

Experimental section

General procedures

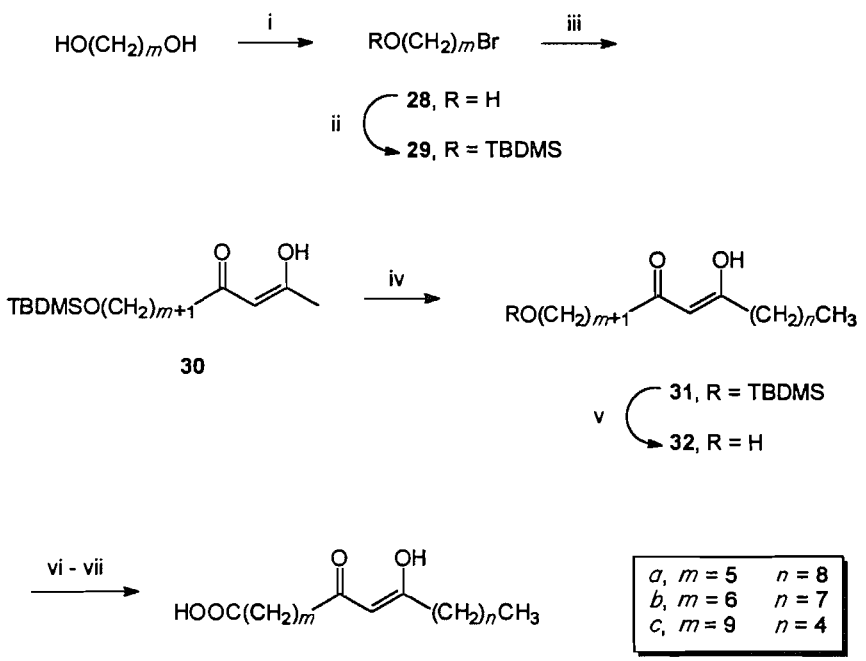
Melting points were determined on a Mel-Temp II melting point apparatus and were not corrected. Infrared spectra were recorded on a Bomem Michelson 100 FT-IR spectrophotometer using internal calibration. Liquid samples were applied directly between two 3-mm NaCl plates, and solid samples were dissolved in chloroform. Proton nuclear magnetic resonance spectra were recorded at 400 MHz on a Bruker WH-400 spectrometer or at 300 MHz on a Varian XL-300 spectrometer. Chemical shifts are reported on the δ scale, with deuterochloroform as solvent and tetramethylsilane as an internal standard. The multiplicity, coupling constants (if observable), and integrated peak area are indicated in parentheses after each signal. High-resolution mass spectra were determined on a Kratos-AEI model MS 50 spectrometer at 70 eV. Elemental analyses were performed by Mr. Peter Borda, Microanalysis Laboratory, University of British Columbia, Vancouver, B.C.

All reactions were monitored by thin-layer chromatography (TLC). Analytical TLC was performed on aluminum backed, precoated silica (SiO_2) gel plates (E. Merck, type 5554). The plates were visualized by ultraviolet fluorescence or by heating the plates after spraying them with a mixture of methanol, acetic acid, sulfuric acid, and anisaldehyde (90:10:5:1 by volume). Silica gel $PF_{254+366}$ supplied by E. Merck was used for both analytical and preparative thin-layer chromatography.



SCHEME 3.

i. 2.0 LDA, RBr; ii. Bu_4NF; iii. DMSO, DCC, Cl_2CHCO_2H; iv. $AgNO_3$, NaOH



SCHEME 4.

i. HBr; ii. Et_3N, DMAP, TBDMSCl; iii. dianion from 2,4-pentanedione; iv. 2.0 LDA, $CH_3(CH_2)_{n-1}Br$; v. Bu_4NF: vi. DMSO, DCC, Cl_2CHCO_2H; vii. $AgNO_3$, NaOH

Flash chromatography (26) was performed using Silica Gel 60, 230–400 mesh ASTM, supplied by E. Merck. All solvent systems are expressed in ratios by volume (v/v).

Materials

The petroleum ether used was of boiling range 30–60°C. Dry solvents and reagents were prepared as follows: diethyl ether and tetrahydrofuran by distillation from sodium benzophenone; dichloromethane by distillation from calcium hydride and methanol by distillation from magnesium methoxide. *n*-Butyllithium (in hexane) was obtained from the Aldrich Chemical Company and was standardized by titration against 2,2-diphenylacetic acid in THF at room temperature to the appearance of a faint yellow colour (27). All other reagents and solvents were either of reagent grade and used directly, or purified according to literature procedures (28). All reactions were run under a dry nitrogen atmosphere. Organic extracts were dried over anhydrous magnesium sulfate.

A. General procedure for the preparation of (1, n) bromo alcohols from (1, n)-diols

A suspension of the diol in 48% HBr was prepared in a 1-L liquid–liquid continuous extractor. The suspension was heated in an oil bath while being continuously extracted with 300 mL of heptane at 90°C for 72 h. The extract was cooled and the organic layer separated, washed

with saturated $NaHCO_3$, brine, and dried over $MgSO_4$. Removal of the solvent under reduced pressure gave the crude bromo alcohol, which was further purified by column chromatography.

*7-Bromo-1-heptanol (**14**)*

This compound was prepared according to procedure A using 1,7-heptanediol (**13**) (5.8 g, 44 mmol) and 48% HBr (7.5 mL, 66 mmol). The crude oil was purified by column chromatography using petroleum ether:ethyl acetate (6:1) as eluent to give 6.2 g (72%) of **14** as a colourless liquid: R_f 0.54 (1:1 petroleum ether:ethyl acetate eluent); IR ν_{max}: 3347, 2930, 2858, 1452, 1254, 1054, and 726 cm^{-1}; ^1H NMR (300 MHz) δ: 3.66 (t, J = 6 Hz, 2H), 3.42 (t, J = 6 Hz, 2H), 1.87 (qn, J = 6 Hz, 2H), 1.57 (m, 2H), and 1.52–1.25 (m, 7H). Exact Mass calcd. for $C_7H_{15}BrO$–H: 195.0204, 193.0224; found: 195.0213, 193.0228.

B. General procedure for the preparation of tert*-butyldimethylsilyl ethers from alcohols*

Freshly distilled triethylamine (2.0 equiv.) was added into a solution of the alcohol (1.0 equiv.) in 100 mL of CH_2Cl_2 at room temperature. A catalytic amount of 4-dimethylaminopyridine and *tert*-butyldimethylsilyl chloride (1.5 equiv.) was added. The reaction was stirred at room temperature for 24 h. The mixture was then quenched with 1 N HCl and extracted with ether three times. The combined organic layers were washed twice with saturated $NaHCO_3$ and once with brine. The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography.

*1-Bromo-7-(*tert*-butyldimethylsilyloxy)-heptane (**8**)*

This compound was prepared according to procedure B, using the alcohol **13** (1.17 g, 6.0 mmol). Purification of the crude product by column chromatography using petroleum ether:ethyl acetate (15:1) as eluent gave 1.50 g (82%) of **8** as a colourless oil: R_f 0.83 (6:1 petroleum ether:ethyl acetate eluent); IR ν_{max}: 2937, 2858, 1466, 1388, 1361, 1254, 1101, 938, 838, and 776 cm^{-1}; ^1H NMR (400 MHz) δ: 3.64 (t, J = 6 Hz, 2H), 3.44 (t, J = 6 Hz, 2H), 1.86 (qn, J = 6 Hz, 2H), 1.53–1.31 (m, 8H), 0.89 (s, 9H), and 0.05 (s, 6H). Exact Mass calcd. for $C_{13}H_{29}SiBrO - C_4H_9$: 253.0438, 251.0458; found: 253.0450, 251.0460.

*1-Bromo-3-methoxymethoxypropane (**11**)*

To a solution of 3-bromo-1-propanol (3.08 g, 22.1 mmol) in 35 mL of CH_2Cl_2 was added dimethoxymethane (30.3 g, 399 mmol). The solution was cooled to 0°C and phosphorus pentoxide (approximately 1.0 g at a time) was added every 10 min until the reaction was completed as shown by TLC. The mixture was poured into 200 mL of an ice-cooled saturated $NaHCO_3$ and the gummy residue remaining in the reaction flask carefully quenched with saturated $NaHCO_3$. The aqueous layer from the combined work-up solutions was extracted with ether. The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. Vacuum distillation of the crude product gave 3.67 g (91%) of **11** as a colourless liquid: bp 85°C/32 Torr (1 Torr = 133.3 Pa); IR ν_{max}: 2931, 2886, 1476, 1449, 1383, 1284, 1258, 1216, 1144, 1045, 919, 880, and 766 cm^{-1}; ^1H NMR (400 MHz) δ: 4.63 (s, 2H), 3.67 (t, J = 6 Hz, 2H), 3.54 (t, J = 6 Hz, 2h), 3.38 (s, 3H), and 2.14 (qn, J = 6 Hz, 2H). Exact Mass calcd. for $C_5H_{11}BrO_2$–H: 182.9841; found: 182.9847.

*5-Benzyloxy-1-pentanol (**16**)*

Sodium hydride (4.58 g, 80% in oil, 153 mmol) was added to a 500-mL, two-neck, round-bottom flask and washed twice with 20 mL of THF. A solution of 1,5-pentanediol (**15**) (7.95 g, 76.4 mmol) in 20 mL of THF and 200 mL of THF was then added. The mixture was stirred at room temperature for 30 min. Benzyl bromide (9.1 mL, 77 mmol) was slowly added and the mixture was refluxed overnight. The reaction mixture was quenched with H_2O. The organic layer was washed once with 1 N HCl and twice with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was chromatographed on a silica gel column using petroleum ether:ethyl acetate (3:1) as eluent to give 7.98 g (54%) of **16** as a colourless oil: R_f 0.38 (1:1 petroleum ether:ethyl acetate eluent); IR ν_{max}: 3372, 3090, 3063, 3030, 2897, 2850, 1496, 1454, 1363, 1206, and 1077 cm^{-1}; ^1H NMR (400 MHz) δ: 7.40–7.24 (m, 5H), 4.52 (s, 2H), 3.65 (t, J = 6 Hz, 2H), 3.52 (t, J = 6 Hz, 2H), and 1.70–1.40 (m, 7H). Exact Mass calcd. for $C_{12}H_{18}O_2$: 194.1302; found: 194.1304.

*5-Benzyloxy-1-(2-tetrahydropyranyloxy)-ethoxypentane (**17**)*

A 25-mL, three-neck round-bottom flask was charged with 50% sodium hydroxide (4.0 mL, 50 mmol), 1-bromo-2-tetrahydropyranyloxyethane (4.18 g, 20.0 mmol), and the alcohol **16** (0.97 g, 5.0 mmol). Tetrabutylammonium hydrogen sulfate (0.15 g, 0.44 mmol) was added. The two-phase mixture was stirred vigorously and heated to 65°C for 72 h. The reaction mixture was cooled to room temperature and taken up into 100 mL of ether. The organic layer was washed with H_2O, brine, dried over $MgSO_4$, and concentrated under reduced pressure. Purification of the crude product by column chromatography using petroleum ether:ethyl acetate (6:1) as eluent gave 1.34 g (83%) of **17** as a light yellow oil: R_f 0.16 (6:1 petroleum ether:ethyl acetate eluent); IR ν_{max}: 3086, 3060, 3029, 2935, 2861, 1495, 1453, 1359, 1269, 1201, 1184, 1106, 1032, 988, 929, 906, 872, 814, and 739 cm^{-1}; ^1H NMR (300 MHz) δ: 7.40–7.24 (m, 5H), 4.64 (t, J = 4 Hz, 1H), 4.50 (s, 2H), 3.94–3.80 (m, 2H), 3.62–3.55 (m, 2H), 3.50–3.46 (m, 6H), and 1.90–1.40 (m, 12H). Exact Mass calcd. for $C_{19}H_{30}O_4$: 322.2136; found: 322.2152.

*2-(5-Benzyloxy)-pentyloxy-1-ethanol (**18**)*

Pyridinium *p*-toluenesulfonate (42 mg, 0.16 mmol) was added to a solution of the tetrahydropyranyl ether **17** (550 mg, 1.60 mmol) in 15 mL of MeOH. The mixture was stirred at room temperature for 12 h. The solvent was removed under reduced pressure and the residue was taken up in ether, washed with saturated $NaHCO_3$ and brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude oil was chromatographed on a silica gel column using petroleum ether:ethyl acetate (6:1) as eluent to give 368 mg (91%) of **18** as a light yellow oil: R_f 0.30 (1:1 petroleum ether:ethyl acetate eluent); IR ν_{max}: 3414, 3082, 3063, 3030, 2932, 2862, 1495, 1454, 1362, 1207, 1086, 893, and 740 cm^{-1}; ^1H NMR (300 MHz) δ: 7.40–7.24 (m, 5H), 4.52 (s, 2H), 3.72 (m, 2H), 3.56–3.44 (m, 2H), 3.44 (t, J = 5 Hz, 4H), 2.04 (t, J = 5 Hz, 1H), and 1.69–1.53 (m, 4H), 1.50–1.40 (m, 2H). Exact Mass calcd. for $C_{14}H_{22}O_3$: 238.1563; found: 238.1559.

*5-Benzyloxy-1-[2-(3-*tert*-butyldimethylsilyloxy)propyloxy]-ethoxypentane (**19**)*

Following the procedure for the preparation of 5-benzyloxy-1-(2-tetrahydropyranyloxy)-ethoxypentane (**17**), the alcohol **18** (300 mg, 1.26 mmol) was reacted with 1-bromo-3-*tert*-butyldimethylsilyloxypropane (1.28 g, 5.04 mmol) to give the ether **19**. The crude product was purified by column chromatography using petroleum ether:ethyl acetate (6:1) as eluent to give 1.34 g (83%) of **19** as a light yellow oil: R_f 0.20 (6:1 petroleum ether:ethyl acetate eluent); IR ν_{max}: 3087, 3064, 3030, 2934, 2862, 1463, 1360, 1253, 1108, 1015, 841, 777, and 737 cm^{-1}; ^1H NMR (300 MHz) δ: 7.36–7.24 (m, 5H), 4.50 (s, 2H), 3.70 (t, J = 6 Hz, 2H), 3.58–3.51 (m, 6H), 3.50–3.42 (m, 4H), 1.79 (qn, J = 6 Hz, 2H), 1.69–1.58 (m, 4H), 1.49–1.40 (m, 2H), 0.89 (s, 9H), and 0.04 (6H, s). Exact Mass calcd. for $C_{23}H_{42}SiO_4$: 410.2841; found: 410.2861.

C. General procedure for the cleavage of tert*-butyldimethylsilyl ethers*

To a solution of the silyl ether (1.0 equiv.) in 40 mL of THF was added a solution of tetrabutylammonium fluoride in THF (2.0 equiv.). The solution was stirred at room temperature for 12 h. The solvent was removed under reduced pressure and the residue was taken up in ether. The organic layer was washed twice with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography.

*3-[2-(5-Benzyloxy)-pentyloxy]-ethoxy-1-propanol (**20**)*

This compound was prepared according to procedure C using the silyl ether **19** (430 mg, 1.05 mmol) and a solution of tetrabutylammo-

nium fluoride in THF (1.0 M, 2.10 mL, 2.1 mmol). Purification of the crude product by column chromatography using petroleum ether:ethyl acetate (3:1) as eluent gave 275 mg (89%) of **20** as a colourless oil: R_f 0.20 (1:1 petroleum ether:ethyl acetate eluent); IR ν_{max}: 3426, 3085, 3063, 3030, 2932, 2863, 1495, 1454, 1361, 1296, 1204, 1091, and 740 cm^{-1}; ^1H NMR (400 MHz) δ: 7.38–7.26 (m, 5H), 4.50 (s, 2H), 3.78 (bt, J = 6 Hz, 2H), 3.69 (t, J = 6 Hz, 2H), 3.62–3.58 (m, 2H), 3.57–3.55 (m, 2H), 3.47 (t, J = Hz, 2H), 3.45 (t, J = 6 Hz, 2H), 2.48 (bs, 1H), 1.83 (qn, J = Hz, 2H), 1.69–1.56 (m, 4H), and 1.49–1.40 (m, 2H). Exact Mass calcd. for $C_{17}H_{28}O_4 - C_3H_8O$: 236.1407; found: 236.1400.

*5-Benzyloxy-1-[2-(3-bromo)-propyloxy]-ethoxyheptane (**10**)*

A 25-mL round-bottom flask was charged with the alcohol **21** (296 mg, 1.00 mmol) in 12 mL of CH_2Cl_2. The solution was cooled to 0°C. Freshly recrystallized triphenylphosphine (340 mg, 1.30 mmol) and carbon tetrabromide (415 mg, 1.25 mmol) were added. The mixture was stirred at 0°C for 30 min, allowed to warm up to room temperature, and then diluted with ether. The organic layer was washed with H_2O, brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography using petroleum ether:ethyl acetate (9:1) as eluent to give 315 mg (88%) of **10** as a colourless oil: R_f 0.14 (9:1 petroleum ether:ethyl acetate eluent); IR ν_{max}: 3080, 3063, 3030, 2930, 2862, 1495, 1454, 1360, 1256, 1209, and 1110 cm^{-1}; ^1H NMR (400 MHz) δ: 7.38–7.25 (m, 5H), 4.50 (s, 2H), 3.66–3.36 (m, 6H), 3.54–3.44 (m, 6H), 2.12 (qn, J = 6 Hz, 2H), 1.69–1.56 (m, 4H), and 1.49–1.40 (m, 2H). Exact Mass calcd. for $C_{17}H_{27}BrO_3$: 360.1116, 358.1136; found: 360.1109, 358.1139.

D. General procedure for the alkylation of the dianion from 2,4-pentanedione

Sodium hydride (1.2 equiv.) was added to a 100-mL, two-neck round-bottom flask and washed twice with 20 mL of THF. Then 20 mL of THF was added and the resulting suspension was cooled to 0°C. A solution of 2,4-pentanedione (1.2 equiv.) in 15 mL of THF was added through an addition funnel. The resulting white suspension was stirred for 30 min and treated with *n*-BuLi (1.2 equiv.). The orange solution was stirred for 20 min. A solution of the bromide (1.0 equiv.) in 10 mL of THF was slowly added through the addition funnel and the mixture was stirred at 0°C for 1 h and at room temperature for 20 min. The mixture was quenched with saturated NH_4Cl, acidified with 1 N HCl, and extracted with ether three times. The combined organic layers were washed twice with saturated $NaHCO_3$ and once with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography.

*12-(tert-Butyldimethylsilyloxy)-2,4-dodecanedione (**21**)*

This compound was prepared according to procedure D using sodium hydride (610 mg, 50% in oil, 12.7 mmol), 2,4-pentanedione (1.36 mL, 12.7 mmol), *n*-BuLi (7.84 mL, 1.62 M, 12.7 mmol), and the bromide **8** (3.26 g, 10.6 mmol). Purification of the crude product by column chromatography using a mixture of petroleum ether and ethyl acetate (15:1) as eluent gave 2.20 g of **21** and 700 mg of **8**. The yield, based on the recovered bromide, was 81%: R_f 0.61 (6:1 petroleum ether:ethyl acetate eluent); IR ν_{max}: 2934, 2857, 1709, 1614, 1465, 1253, 1100, 1006, 939, 838, and 776 cm^{-1}; ^1H NMR (400 MHz) δ: 15.50 (bs, 0.8 H), 5.49 (s, 0.8 H), 3.61 (t, J = 7 Hz, 2H), 3.58 (s, 0.4 H), 2.51 (t, J = 8 Hz, 0.4 H), 2.27 (t, J = 8 Hz, 1.6 H), 2.24 (s, 0.6 H), 2.06 (s, 2.4 H), 1.65–1.46 (m, 6H), 1.36–1.26 (m, 6H), 0.89 (s, 9H), and 0.04 (s, 6H). Exact Mass calcd. for $C_{18}H_{36}SiO_3 - CH_3$: 313.2190; found: 313.2208.

E. General procedure for the regioselective alkylation of β-diketone dianions

Lithium diisopropylamide (2.0 equiv.) was prepared at –78°C by addition of *n*-BuLi (2.0 equiv.) to a solution of diisopropylamine (2.0 equiv.) in 20 mL of THF and stirring of the mixture for 30 min. It was then cannulated into an addition funnel and added to a solution of the β-diketone (1.0 equiv.) in 20 mL of THF at –78°C over a period of 1 h. The mixture was stirred at –78°C for 24 h and allowed to warm up to 0°C. The bromide (1.0 equiv.) in 10 mL of THF was slowly added and the mixture was stirred at 0°C for 12 h. The mixture was then quenched with saturated NH_4Cl, acidified with 1 N HCl, and extracted with ether three times. The combined organic phases were washed with saturated $NaHCO_3$, brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by column chromatography.

*15-(tert-Butyldimethylsilyloxy)-5,7-pentadecanedione (**22**)*

This compound was prepared according to procedure E using *n*-Buli (1.70 mL, 1.53 M, 2.60 mmol), diisopropylamine (0.36 mL, 2.6 mmol), the β-diketone **21** (426 mg, 1.30 mmol), and 1-bromopropane (**9**) (160 mg, 1.30 mmol). Purification of the crude product by column chromatography using petroleum ether:ethyl acetate (20:1) gave 294 mg of **22** and 294 mg of the starting β-diketone **21**. The yield, based on the recovered β-diketone **21**, was 81%: R_f 0.74 (6:1 petroleum ether:ethyl acetate eluent); IR ν_{max}: 2936, 2858, 1707, 1611, 1463, 1253, 1100, 949, 838, 776, and 704 cm^{-1}; ^1H NMR (400 MHz) δ: 15.50 (bs, 0.8H), 5.48 (s, 0.8H), 3.61 (t, J = 7 Hz, 2H), 3.54 (s, 0.4H), 2.50 (t, J = 8 Hz, 0.4H), 2.48 (t, J = 8 Hz, 0.4H), 2.28 (t, J = 8 Hz, 1.6H), 2.26 (t, J = 8 Hz, 1.6H), 1.66–1.48 (m, 6H), 1.40–1.24 (m, 10H), 0.93 (t, J = 7 Hz, 3H), 0.90 (s, 9H), 0.06 (s, 6H). Exact Mass calcd. for $C_{21}H_{42}SiO_3 - CH_3$: 355.2658; found: 355.2662.

*15-Hydroxy-5,7-pentadecanedione (**23**)*

This compound was prepared according to procedure C using the silyl ether **22** (444 mg, 1.20 mmol) and tetrabutylammonium fluoride in THF (2.40 mL, 1.0 M, 2.4 mmol). Purification of the crude product by column chromatography using petroleum ether:ethyl acetate (6:1) as eluent gave 277 mg of **23** as a colourless solid: R_f 0.58 (1:1 petroleum ether:ethyl acetate eluent); mp 41.5°C; IR ν_{max}: 3621, 3462, 2934, 2859, 1723, 1700, 1605, 1460, 1355, 1307, 1149, 1098, 1005, 957, and 916 cm^{-1}; ^1H NMR (400 MHz) δ: 15.50 (bs, 0.7H), 5.48 (s, 0.7H), 3.65 (t, J = 7 Hz, 2H), 3.53 (s, 0.6H), 2.51 (t, J = 8 Hz, 0.6H), 2.50 (t, J = 8 Hz, 0.6 H), 2.28 (5, J = 8 Hz, 1.4 H), 2.27 (t, J = 8 Hz, 1.4H), 1.67–1.50 (m, 8H), 1.40–1.12 (m, 9H), and 0.93 (5, J = 7 Hz, 3H). Exact Mass calcd. for $C_{15}H_{28}O_3$: 256.2031, found: 256.2031.

F. General procedure for the oxidation of alcohols to acids

To the alcohol (1.0 equiv.) in 15 mL of CH_2Cl_2 and 15 mL of dimethyl sulfoxide was added 1,3-dicyclohexylcarbodiimide (6.0 equiv.) and dichloroacetic acid (0.5 equiv.). This mixture was stirred for 2 h, diluted with ethyl acetate, and treated with oxalic acid (6.0 equiv.). The mixture was poured into brine, filtered to remove the urea precipitate, and extracted with ethyl acetate. The organic layer was concentrated under reduced pressure. The resulting oil was dissolved in 24 mL 50% THF–H_2O. Silver nitrate (8.0 equiv.) and NaOH (16 equiv.) were added and the mixture was stirred for 4 h. The precipitate was filtered and washed with ethyl acetate and water. The aqueous layer was acidified with 1 N HCl and was then extracted with ethyl acetate. The organic extract was washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The crude product was purified by recrystallization from hexanes or by column chromatography.

*9,11-Dioxopentadecanoic acid (**2**)*

This compound was prepared according to F using the alcohol **23** (384 mg, 1.34 mmol), 1,3-dicyclohexylcarbodiimide (1.67 g, 7.95 mmol), and dichloroacetic acid (53 mL, 0.69 mmol). The crude aldehyde **24** was subsequently treated with silver nitrate (1.85 g, 10.8 mmol) and NaOH (0.86 g, 22 mmol). The crude product was purified by recrystallization from hexanes to give 270 mg (69%) of **2** as colourless crystals: R_f 0.54 (5% HOAc in 3:1 petroleum ether:ethyl acetate eluent); mp 43.0°C; IR ν_{max}: 3346-2480, 2937, 2861, 1713, 1601, 1459, 1286, 1116, 968, and 903 cm^{-1}; ^1H NMR (300 MHz) δ: 15.50 (bs, 0.7H), 5.48 (s, 0.7H), 3.53 (s, 0.6H), 2.51 (t, J = 8 Hz, 0.6H), 2.50 (t, J = 8Hz, 0.6H), 2.33 (t, J = 7 Hz, 2H), 2.28 (t, J = 8 Hz, 1.4H), 2.27 (t, J = 8 Hz, 1.4H), 1.70–1.56 (m, 7H), 1.40–1.27 (m, 8H), and 0.93 (t, J = 7 Hz, 3H). Exact Mass calcd. for $C_{15}H_{26}O_4$: 270.1824; found: 270.1828. Anal. calcd. for $C_{15}H_{26}O_4$: C 66.67, H 9.63; found: C 66.60, H 9.65.

*1-[2-(5-Benzyloxy)pentyloxy]-ethoxy-15-(*tert*-butyldimethylsilyloxy)-5,7-pentadecanedione (**25**)*

This compound was prepared according to E using the β-diketone **21** (426 mg, 1.30 mmol) and the bromide **10** (359 mg, 1.00 mmol). The crude product was purified by column chromatography using silica gel and petroleum ether:ethyl acetate (9:1) to give 270 mg of **25** and 104 mg of **10**. The yield, based on the recovered bromide, was 85%: R_f 0.12 (9:1 petroleum ether:ethyl acetate eluent); IR ν_{max}: 3080, 3060, 3026, 1710, 1703, 1609, 1460, 1360, 1252, 1110, and 840 cm^{-1}; ^1H NMR (400 MHz) δ: 15.48 (bs, 0.8H), 7.38–7.26 (m, 5H), 5.47 (s, 0.8H), 4.51 (s, 2H), 3.65–3.53 (m, 6.4H), 3.50–3.44 (m, 6H), 2.53 (t, J = 8 Hz, 0.4H), 2.48 (t, J = 8 Hz, 0.4H), 2.30 (t, J = 8 Hz, 1.6H), 2.26 (t, J = 8 Hz, 1.6H), 1.72–1.38 (m, 14H), 1.36–1.25 (m, 8H), 0.90 (s, 9H), and 0.50 (s, 6H). Exact Mass calcd. for $C_{35}H_{62}SiO_6$: 606.4299; found: 606.4313.

1-[2-(5-Benzyloxy)pentyloxy]-ethoxy-15-hydroxy-5,7-pentadecanedione

This compound was prepared according to procedure C using the silyl ether **25** (1.40 g, 2.58 mmol). The crude product was purified by column chromatography using petroleum ether:ethyl (6:1) as eluent to give 993 mg (87%) of the desired alcohol from **25** as a colourless oil: R_f 0.30 (1:1 petroleum ether:ethyl acetate eluent); IR ν_{max}: 3437, 3080, 3060, 3030, 2930, 2863, 1710, 1702, 1606, 1453, 1361, 1096, and 739 cm^{-1}; ^1H NMR (400 MHz) δ: 15.50 (bs, 0.8H), 7.38–7.24 (m, 5H), 5.48 (s, 0.8H), 4.50 (s, 2H), 3.64 (t, J = 7 Hz, 2H), 3.57 (s, 2H), 3.56 (s, 2H), 3.53 (s, 0.4H), 3.50–3.43 (m, 6H), 2.53 (t, J = 8Hz, 0.4H), 2.49 (t, J = 8 Hz, 0.4H), 2.30 (t, J = 8 Hz, 1.6H), 2.26 (t, J = 8Hz, 1.6H), 1.72–1.50 (m, 13H), 1.46–1.38 (m, 2H), and 1.38–1.25 (m, 8H). Exact Mass calcd. for $C_{29}H_{48}O_6$: 492.3438; found: 492.3445.

*15-[2-(5-Benzyloxy)-pentyloxy)-ethoxy-9,11-dioxopentadecanoic acid (**3**)*

This compound was prepared according to procedure F using the above alcohol (2.11 g, 4.29 mmol). The crude product was purified by column chromatography using petroleum ether:ethyl acetate (6:1) that also contained 5% acetic acid as eluent to give 1.58 g (74%) of **3** as a colourless oil: R_f 0.30 (5% HOAc in 3:1 petroleum ether:ethyl acetate eluent); IR ν_{max}: 3120, 3080, 3060, 3028, 2933, 2859, 1726, 1604, 1455, 1360, 1246, 1105, 928, and 738 cm^{-1}; ^1H NMR (400 MHz) δ: 15.50 (bs, 0.8H), 7.38–7.24 (m, 5H), 5.47 (s, 0.8H), 4.50 (s, 2H), 3.60–3.55 (m, 4H), 3.53 (s, 0.4H), 3.50–3.42 (m, 6H), 2.53 (t, J = 8 Hz, 0.4H), 2.48 (t, J = 8 Hz, 0.4H), 2.34 (t, J = 8 Hz, 2H), 2.30 (t, J = 8 Hz, 1.6H), 2.26 (t, J = 8 Hz, 1.6H), 1.72–1.52 (m, 13H), 1.46–1.38 (m, 2H), and 1.38–1.25 (m, 8H). Exact Mass calcd. for $C_{29}H_{46}O_7$: 506.3231; found: 506.3237.

*1-Methoxymethoxy-15-(*tert*-butyldimethylsilyloxy)-5,7-pentadecanedione (**26**)*

This compound was prepared according to procedure E using the β-diketone **21** (2.16 g, 6.59 mmol) and the bromide **11** (1.08 g, 5.93 mmol). The crude product was purified by column chromatography using petroleum ether:ethyl acetate (15:1) as eluent to give 1.56 g (73%) of **26** as a colourless oil: R_f 0.24 (6:1 petroleum ether:ethyl acetate eluent); IR ν_{max}: 2936, 2858, 1708, 1611, 1463, 1387, 1253, 1148, 1103, 1044, and 924 cm^{-1}; ^1H NMR (400 MHz) δ: 15.50 (bs, 0.8H), 5.48 (s, 0.8H), 4.62 (s, 1.6H), 4.61 (s, 0.4H), 3.61 (t, J = 7 Hz, 2H), 3.57 (s, 0.4H), 3.56 (t, J = 7 Hz, 2H), 3.38 (s, 3H), 2.56 (t, J = 8 Hz, 0.4H), 2.51 (t, J = 8 Hz, 0.4H), 2.32 (t, J = 8 Hz, 1.6H), 2.26 (t, J = 8 Hz, 1.6H), 1.78–1.45 (m, 8H), 1.38–1.25 (m, 8H), 0.90 (s, 9H), and 0.50 (s, 6H). Exact Mass calcd. for $C_{23}H_{46}SiO_5 - CH_3$: 415.2868; found: 415.2875.

1-Methoxymethoxy-15-hydroxy-5,7-pentadecanedione

This compound was prepared according to procedure C using the silyl ether **26** (215 mg, 0.50 mmol). The crude product was purified by column chromatography using petroleum ether:ethyl acetate (6:1) as eluent to give 136 mg (86%) of the desired alcohol from **26** as a white solid: R_f 0.36 (1:1 petroleum ether:ethyl acetate eluent); mp 42.0°C; IR ν_{max}: 3635, 3458, 2932, 2860, 1704, 1610, 1452, 1217, 1148, 1112, 1039, and 923 cm^{-1}; ^1H NMR (400 MHz) δ: 15.50 (bs, 0.8H), 5.48 (s, 0.8H), 4.62 (s, 1.6H), 4.61 (s, 0.4H), 3.65 (t, J = 7 Hz, 2H), 3.56 (s, 0.4H), 3.55 (t, J = 7 Hz, 2H), 3.37 (s, 3H), 2.57 (t, J = 8 Hz, 0.4H), 2.50 (t, J = 8 Hz, 0.4H), 2.32 (t, J = 8 Hz, 1.6H), 2.27 (t, J = 8 Hz, 1.6H), 1.77–1.50 (m, 9H), and 1.42–1.25 (m, 8H). Exact Mass calcd. for $C_{17}H_{32}O_5$: 316.2241; found: 316.2247.

*15-Methoxymethoxy-9,11-dioxopentadecanoic acid (**4**)*

This compound was prepared according to procedure F using the above alcohol (128 mg, 0.40 mmol). The crude product was purified by recrystallization from hexanes to give 94 mg (73%) of **4** as a white solid R_f 0.34 (5% HOAc in 3:1 petroleum ether:ethyl acetate eluent); mp 43.0°C; IR ν_{max}: 3116, 2932, 2860, 1717, 1611, 1461, 1416, 1221, 1148, 1111, 1039, and 923 cm^{-1}; ^1H NMR (300 MHz) δ: 15.50 (bs, 0.8H), 5.49 (s, 0.8H), 4.63 (s, 1.6H), 4.62 (s, 0.4H), 3.57–3.52 (m, 2.4H), 3.38 (s, 2.4H), 3.37 (s, 0.6H), 2.56 (t, J = 8 Hz, 0.4H), 2.50 (t, J = 8 Hz, 0.4H), 2.35 (t, J = 8 Hz, 2H), 2.32 (t, J = 8 Hz, 1.6H), 2.27 (t, J = 8 Hz, 1.6H), 1.77–1.52 (m, 8H), and 1.42–1.25 (m, 6H). Exact Mass calcd. for $C_{17}H_{30}O_6$: 330.2034; found: 330.2036. Anal. calcd. for $C_{17}H_{30}O_6$: C 61.78, H 9.09; found: C 61.72, H 9.08.

12-Hydroxy-2,4-dodecanedione

This compound was prepared according to procedure C using the silyl ether **21** (2.01 g, 6.13 mmol). The crude product was purified by column chromatography using petroleum ether:ethyl acetate (6:1) as eluent to give 1.23 g (94%) of the desired alcohol from **21** as a white solid: R_f 0.50 (1:1 petroleum ether:ethyl acetate eluent); mp 40.5°C; IR ν_{max}: 3621, 3460, 2932, 2858, 1720, 1702, 1610, 1440, 1362, 1304, 1157, 1074, 1011, 956, and 915 cm^{-1}; ^1H NMR (400 MHz) δ: 15.48 (bs, 0.8H), 5.48 (s, 0.8H), 3.65 (t, J = 7 Hz, 2H), 3.57 (s, 0.4H), 2.50 (t, J = 8 Hz, 0.4H), 2.27 (t, J = 8 Hz, 1.6H), 2.22 (s, 0.6H), 2.05 (s, 2.4H), 1.66–1.52 (m, 5H), and 1.42–1.28 (m, 8H). Exact Mass calcd. for $C_{12}H_{22}O_3$: 214.1563; found: 214.1569.

*9,11-Dioxododecanoic acid (**5a**)*

This compound was prepared according to procedure F using the above alcohol (750 mg, 3.50 mmol). The crude product was purified by recrystallization from hexanes to give 480 mg (60%) of **5a** as a white solid: R_f 0.48 (5% HOAc in 3:1 petroleum ether:ethyl acetate eluent); mp 41.5°C; IR ν_{max}: 3340–2500, 2935, 2860, 1712, 1607, 1460, 1410, 1364, 1290, 1135, 1097, 954, and 915 cm^{-1}; ^1H NMR (400 MHz) δ: 15.48 (bs, 0.8H), 5.48 (s, 0.8H), 3.57 (s, 0.4H), 2.48 (t, J = 8 Hz, 0.4H), 2.39 (t, J = 7 Hz, 0.8H), 2.32 (t, J = 8 Hz, 2H), 2.23 (t, J = 8 Hz, 0.8H), 2.21 (s, 0.6H), 2.11 (s, 1.2H), 2.03 (s, 1.2H), 1.66–1.50 (m, 4H), and 1.40–1.22 (m, 6H). Exact Mass calcd. for $C_{12}H_{20}O_4$: 228.1356; found: 228.1362.

*18-(*tert*-Butyldimethylsilyloxy)-8,10-octadecanedione (**27**b)*

This compound was prepared according to procedure E using the β-diketone **21** (4.00 g, 12.2 mmol) and 1-bromohexane (1.81 g, 11.0 mmol). The crude product was purified by column chromatography using petroleum ether: ethyl acetate (20:1) as eluent to give 3.50 g (85%) of **27***b* as a colourless oil: R_f 0.76 (6:1 petroleum ether:ethyl acetate eluent); IR ν_{max}: 2931, 2857, 1711, 1612, 1463, 1392, 1365, 1252, 1101, 837, and 776 cm^{-1}; ^1H NMR (400 MHz) δ: 15.50 (bs, 0.8H) 5.48 (s, 0.8H), 3.61 (t, J = 7 Hz, 2H), 3.53 (s, 0.4H), 2.50 (t, J = 8 Hz, 0.8H), 2.27 (t, J = 8 Hz, 3.2H), 1.66–1.46 (m, 8H), 1.38–1.22 (m, 14H), 0.90 (s, 9H), 0.88 (t, J = 7 Hz, 3H), and 0.06 (s, 6H). Exact Mass calcd. for $C_{24}H_{48}SiO_3 - CH_3$: 397.3126; found: 397.3137.

18-Hydroxy-8,10-octadecanedione

This compound was prepared according to procedure C using the silyl ether **27***b* (2.66 g, 6.46 mmol). The crude product was purified by recrystallization from hexanes to give 1.68 g (87%) of the desired alcohol from **27***b* as a white solid: R_f 0.62 (1:1 petroleum ether:ethyl acetate eluent); mp 56.0°C; IR ν_{max}: 3623, 3460, 2932, 2857, 1724, 1708, 1604, 1460, 1372, 1294, 1146, 1112, and 917 cm^{-1}; ^1H NMR (400 MHz) δ: 15.50 (bs, 0.8H), 5.48 (s, 0.8H), 3.66 (t, J = 7 Hz, 2H), 3.53 (s, 0.4H), 2.51 (t, J = 8 Hz, 0.8H), 2.27 (t, J = 8 Hz, 3.2H), 1.66–1.50 (m, 9H), 1.42–1.20 (m, 14H), and 0.88 (t, J = 7 Hz, 3H). Exact Mass calcd. for $C_{18}H_{34}O_3$: 298.2499; found: 298.2499.

9,11-Dioxooctadecanoic acid (5b)

This compound was prepared according to procedure F using the above alcohol (850 mg, 2.85 mmol). The crude product was purified by recrystallization from hexanes to give 500 mg (56%) of **5*b*** as a white solid: R_f 0.55 (5% HOAc in 3:1 petroleum ether:ethyl acetate eluent); mp 57.0°C; IR ν_{max}: 3310–2480, 2932, 2859, 1707, 1609, 14,66, 1407, 1290, 1132, 951, and 916 cm^{-1}; IR (KBr) ν_{max}: 3543, 3483, 2931, 2849, 1719, 1688, 1642, 1461, 1440, 1421, 1310, 1237, 1188, 1138, and 903 cm^{-1}; ^1H NMR (300 MHz) δ: 15.50 (bs, 0.8H), 5.48 (s, 0.8H), 3.53 (s, 0.4H), 2.50 (t, J = 8 Hz, 0.8H), 2.36 (t, J = 7 Hz, 2H), 2.28 (t, J = 8 Hz, 3.2 H), 1.70–1.50 (m, 8H), 1.40–1.24 (m, 12H), and 0.90 (t, J = 7 Hz, 3H). Exact Mass calcd. for $C_{18}H_{32}O_4$: 312.2292; found: 312.2293. Anal. calcd. for $C_{18}H_{32}O_4$: C 69.23, H 10.33; found: C 69.22, H 10.33.

*1-(*tert*-Butyldimethylsilyloxy)-9,11-eicosanedione (27c)*

This compound was prepared according to procedure E using the β-diketone **21** (1.97 g, 6.0 mmol) and 1-bromooctane (1.04 g, 5.4 mmol). The crude product was purified by column chromatography using petroleum ether:ethyl acetate (20:1) as eluent to give 1.52 g (73%) of **27*c*** as a colourless oil: R_f 0.78 (6:1 petroleum ether:ethyl acetate eluent); IR ν_{max}: 2930, 2856, 1707, 1611, 1463, 1366, 1253, 1100, 1044, 943, 837, and 776 cm^{-1}; ^1H NMR (400 MHz) δ: 15.50 (bs, 0.8H), 5.48 (s, 0.8H), 3.61 (t, J = 7 Hz, 2H), 3.54 (s, 0.4H), 2.50 (t, J = 8 Hz, 0.8H), 2.27 (t, J = 8 Hz, 3.2H), 1.66–1.48 (m, 8H), 1.36–1.24 (m, 18H), 0.90 (s, 9H), 0.88 (t, J = 7 Hz, 3H), and 0.07 (s, 6H). Exact Mass calcd. for $C_{26}H_{52}SiO_3$: 440.3672; found: 440.3654.

1-Hydroxy-9,11-eicosanedione

This compound was prepared according to procedure C using the silyl ether **27*c*** (1.40 g, 3.2 mmol). The crude product was purified by recrystallization from hexanes to give 940 mg (91%) of the desired alcohol from **27*c*** as a white solid: R_f 0.65 (1:1 petroleum ether:ethyl acetate eluent); mp 65.5°C; IR ν_{max}: 3622, 2930, 2857, 1724, 1700, 1608, 1460, 1364, 1308, 1047, and 905 cm^{-1}; ^1H NMR (400 MHz) δ: 15.50 (bs, 0.8H), 5.48 (s, 0.8H), 3.66 (t, J = 7 Hz, 2H), 3.54 (s, 0.4H), 2.50 (t, J = 8 Hz, 0.8H), 2.27 (t, J = 8 Hz, 3.2H), 1.64–1.50 (m, 11H), 1.49–1.22 (m, 16H), and 0.88 (t, J = 7 Hz, 3H). Exact Mass calcd. for $C_{20}H_{38}O_3$: 326.2811; found: 326.2814.

9,11-Dioxoeicosanoic acid (5c)

This compound was prepared according to procedure F using the above alcohol (630 mg, 2.11 mmol). The crude product was purified by recrystallization from hexanes to give 520 mg (79%) of **5*c*** as a white solid: R_f 0.56 (5% HOAc in 3:1 petroleum ether:ethyl acetate eluent); mp 64.0°C; IR ν_{max}: 3355–2490, 2931, 2858, 1708, 1606, 1459, 1413, 1292, 1134, 1104, and 953 cm^{-1}; ^1H NMR (300 MHz) δ: 15.50 (bs, 0.8H), 5.48 (s, 0.8H), 3.53 (s, 0.4H), 2.49 (t, J = 8 Hz, 0.8H), 2.36 (t, J = 7 Hz, 2H), 2.28 (t, J = 8 Hz, 3.2H), 1.70–1.50 (m, 8H), 1.40–1.22 (m, 16H), and 0.90 (t, J = 7 Hz, 3H). Exact Mass calcd. for $C_{20}H_{36}O_4$: 340.2604; found: 340.2620. Anal. calcd. for $C_{20}H_{36}O_4$: C 70.59, H 10.58; found: C 70.32, H 10.66.

*1-(*tert*-Butyldimethylsilyloxy)-9,11-doeicosanedione (27d)*

This compound was prepared according to procedure E using the β-diketone **21** (1.67 g, 5.1 mmol) and 1-bromodecane (1.12 g, 5.1 mmol). The crude product was purified by column chromatography using petroleum ether:ethyl acetate (20:1) as eluent to give 0.95 g (70%) of **27*d*** as a colourless oil: R_f 0.80 (6:1 petroleum ether:ethyl acetate eluent); IR ν_{max}: 2928, 2856, 1711, 1611, 1463, 1390, 1365, 1252, 1101, 1011, 944, and 837 cm^{-1}; ^1H NMR (400 MHz) δ: 15.50 (bs, 0.8H), 5.48 (s, 0.8H), 3.60 (t, J = 7 Hz, 2H), 3.54 (s, 0.4H), 2.50 (t, J = 8 Hz, 0.8H), 2.27 (t, J = 8 Hz, 3.2H), 1.66–1.46 (m, 8H), 1.36–1.22 (m, 22H), 0.90 (s, 9H), 0.89 (t, J = 7 Hz, 3H), and 0.07 (s, 6H). Exact Mass calcd. for $C_{28}H_{56}SiO_3$: 467.3906; found: 467.3960.

1-Hydroxy-9,11-doeicosanedione

This compound was prepared according to procedure C using the silyl ether **27*d*** (870 mg, 1.86 mmol). The crude product was purified by recrystallization from hexanes to give 560 mg (85%) of the desired alcohol from **27*d*** as a white solid: R_f 0.68 (1:1 petroleum ether:ethyl acetate eluent); mp 70.5°C; IR ν_{max}: 3623, 3458, 2929, 2857, 1607, 1459, 1380, 1285, 1148, 1053, 947, and 898 cm^{-1}; ^1H NMR (400 MHz) δ: 15.50 (bs, 0.8H), 5.47 (s, 0.8H), 3.64 (t, J = 7 Hz, 2H), 3.54 (s, 0.4H), 2.50 (t, J = 8 Hz, 0.8H), 2.24 (t, J = 8 Hz, 3.2H), 1.64–1.50 (m, 11H), 1.42–1.22 (m, 20H), and 0.89 (t, J = 7 Hz, 3H). Exact Mass calcd. for $C_{22}H_{42}O_3$: 354.3123; found: 354.3132.

9,11-Dioxodoeicosanoic acid (5d)

This compound was prepared according to procedure F using the above alcohol (450 mg, 1.27 mmol). The crude product was purified by recrystallization from hexanes to give 140 mg (34%) of **5*d*** as a white solid: R_f 0.57 (5% HOAc in 3:1 petroleum ether:ethyl acetate eluent); mp 69.5°C; IR ν_{max}: 3370–2510, 2929, 2857, 1718, 1607, 1460, 1408, 1292, 1135, 1090, and 952 cm^{-1}; ^1H NMR (300 MHz) δ: 15.50 (bs, 0.8H), 5.48 (s, 0.8H), 3.54 (s, 0.4H), 2.50 (t, J = 8 Hz, 0.8H), 2.36 (t, J = 7 Hz, 2H), 2.26 (t, J = 8 Hz, 3.2 H), 1.72–1.52 (m, 8H), 1.42–1.22 (m, 20H), and 0.89 (t, J = 7 Hz, 3H). Exact Mass calcd. for $C_{22}H_{40}O_4$: 368.2916; found: 368.2935. Anal. calcd. for $C_{22}H_{40}O_4$: C 71.74, H 10.87; found: C 71.20, H 10.94.

5-Bromo-1-pentanol (28a)

This compound was prepared according to procedure A using 1,5-pentanediol (15.0 g, 140 mmol) and 48% HBr (24 mL, 211 mmol). The crude product was purified by column chromatography using petroleum ether:ethyl acetate (6:1) as eluent to give 12.4 g (52%) of **28*a*** as a colourless liquid: R_f 0.46 (1:1 petroleum ether:ethyl acetate); IR ν_{max}: 3346, 2936, 2865, 1456, 1434, 1274, 1238, 1137, 1061, 1014, 984, 950, and 734 cm^{-1}; ^1H NMR (400 MHz) δ: 3.70 (t, J = 8 Hz, 2H), 3.42 (t, J = 8 Hz, 2H), 1.92 (qn, J = 8 Hz, 2H), 1.72 (s, 1H), and 1.64–1.48 (m, 4H). Exact Mass calcd. for $C_5H_{11}BrO$ – H: 166.9892, 164.9912; found: 166.9902, 164.9911.

*1-Bromo-5-(*tert*-butyldimethylsilyloxy)-pentane (29a)*

This compound was prepared according to procedure B using the alcohol **28*a*** (2.90 g, 17.4 mmol). The crude product was purified by column chromatography using petroleum ether:ethyl acetate (15:1) as eluent to give 3.81 g (81%) of **29*a*** as a colourless oil: R_f 0.80 (6:1 petroleum ether:ethyl acetate); IR ν_{max}: 2950, 2940, 2890, 2858, 1467, 1388, 1361, 1254, 1102, 1006, 835, and 775 cm^{-1}; ^1H NMR (400 MHz) δ: 3.61 (t, J = 8 Hz, 2H), 3.41 (t, J = 8 Hz, 2H), 1.88 (qn, J = 8 Hz, 2H), 1.58–1.45 (m, 4H), 0.90 (s, 9H), and 0.07 (s, 6H). Exact Mass calcd. for $C_{11}H_{25}SiBrO$ – H: 281.0753, 279.0771; found: 281.0527, 2879.0772.

*10-(*tert*-Butyldimethylsilyloxy)-2,4-decanedione (30a)*

Following procedure D, the β-diketone **30*a*** was prepared using 2,4-pentanedione (1.72 g, 17.2 mmol) and bromide **29*a*** (4.83 g, 17.2 mmol). The crude product was purified by column chromatography using petroleum ether:ethyl acetate (15:1) as eluent to give 2.12 g (60%) of **30*a*** as a colourless oil: R_f 0.56 (6:1 petroleum ether:ethyl acetate); IR ν_{max}: 2936, 2858, 1716, 1614, 1465, 1361, 1252, 1100, 1005, 936, 837, and 775 cm^{-1}; ^1H NMR (400 MHz) δ: 15.50 (bs, 0.8 H), 5.49 (s, 0.8 H), 3.60 (t, J = 8 Hz, 2H), 3.59 (s, 0.4 H), 2.52 (t, J = 8 Hz, 0.4 H), 2.26 (t, J = 8 Hz, 1.6 H), 2.24 (s, 0.6 H), 2.07 (s, 2.4 H), 1.68–1.56 (m, 2H), 1.55–1.46 (m, 2H), 1.38–1.25 (m, 4H), 0.90 (s, 9H), and 0.06 (s, 6H). Exact Mass calcd. for $C_{16}H_{32}SiO_3$ – CH_3: 285.1879; found: 285.1884.

*1-(*tert*-Butyldimethylsilyloxy)-7,9-octadecanedione (31a)*

This compound was prepared according to procedure E using the β-diketone **30**a (1.2 g, 4.2 mmol) and 1-bromooctane (**12*b***) (0.77 g, 4.0 mmol). The crude product was purified by column chromatography using petroleum ether:ethyl acetate (20:1) as eluent to give 0.77 g (75%) of **31*a*** as a colourless oil: R_f 0.74 (6:1 petroleum ether:ethyl acetate); IR ν_{max}: 2930, 2856, 1722, 1707, 1611, 1463, 1387, 1360, 1252, 1101, 1006, 937, 836, 812, and 775 cm^{-1}; ^1H NMR (400 MHz) δ: 15.50 (bs, 0.8H), 5.48 (s, 0.8H), 3.61 (t, J = 8 Hz, 2H), 3.53 (s, 0.4H), 2.51 (t, J = 8 Hz, 0.4H), 2.50 (t, J = 8 Hz, 0.4H), 2.28 (t, J = 8 Hz, 1.6H), 2.27

(t, J = 8 Hz, 1.6H), 1.66–1.48 (m, 8H), 1.38–1.22 (m, 14H), 0.90 (s, 9H), 0.89 (t, J = 8 Hz, 3H), and 0.06 (s, 6H). Exact Mass calcd. for $C_{24}H_{48}SiO_3$: 412.3360; found: 412.3367.

*1-Hydroxy-7,9-octadecanedione (**32**a)*

This compound was prepared according to procedure C using the silyl ether **31***a* (640 mg, 1.55 mmol). The crude product was purified by recrystallization from hexanes to give 410 mg (89%) of **32***a* as a white solid: R_f 0.56 (1:1 petroleum ether:ethyl acetate); mp 57.5°C; IR ν_{max}: 3623, 2930, 2858, 1607, 1459, 1329, 1141, 1052, 965, and 904 cm^{-1}; ^1H NMR (400 MHz) δ: 15.50 (bs, 0.8H), 5.48 (s, 0.8H), 3.64 (t, J = 8 Hz, 2H), 3.55 (s, 0.4H), 2.52 (t, J = 8 Hz, 0.4H), 2.50 (t, J = 8 Hz, 0.4H), 2.29 (t, J = 8 Hz, 1.6H), 2.27 (t, J = 8 Hz, 1.6H), 1.70–1.50 (m, 9H), 1.42–1.18 (m, 14H), and 0.89 (t, J = 7 Hz, 3H). Exact Mass calcd. for $C_{18}H_{34}O_3$: 298.2499; found: 298.2505.

*7,9-Dioxooctadecanoic acid (**6**a)*

This compound was prepared according to procedure F using the alcohol 32*a* (298 mg, 1.00 mmol). The crude product was purified by recrystallization from hexanes to give 210 mg (67%) of **6***a* as a solid: R_f 0.52 (5% HOAc in 3:1 petroleum ether:ethyl acetate); mp 58.0°C; IR ν_{max}: 3340–2490, 2930, 2858, 1709, 1607, 1460, 1409, 1291, 1131, 950, and 907 cm^{-1}; ^1H NMR (300 MHz) δ: 15.50 (bs, 0.8H), 5.49 (s, 0.8H), 3.53 (s, 0.4H), 2.53 (t, J = 8 Hz, 0.4H), 2.49 (t, J = 8 Hz, 0.4H), 2.36 (t, J = 7 Hz, 2H), 2.30 (t, J = 8 Hz, 1.6H), 2.27 (t, J = 8 Hz, 1.6H), 1.72–1.52 (m, 6H), 1.46–1.22 (m, 14H), and 0.90 (t, J = 7 Hz, 3H). Exact Mass calcd. for $C_{18}H_{32}O_4$: 312.2292; found: 312.2291. Anal. calcd. for $C_{18}H_{32}O_4$: C 69.23, H 10.33; found: C 69.24, H 10.33.

*6-Bromo-1-hexanol (**28**b)*

This compound was prepared according to procedure A using 1,6-hexanediol (5.9 g, 50 mmol) and 48% HBr (8.2 mL, 73 mmol). The crude product was purified by column chromatography using petroleum ether:ethyl acetate (6:1) as eluent to give 4.2 g (46%) of **28***b* as a colourless liquid: R_f 0.48 (1:1 petroleum ether:ethyl acetate); IR ν_{max}: 3335, 2932, 2860, 1447, 1260, and 1055 cm^{-1}; ^1H NMR (400 MHz) δ: 3.68 (t, J = 8 Hz, 2H), 3.43 (t, J = 8 Hz, 2H), 1.88 (qn, J = 8 Hz, 2H), 1.62 (m, 2H), and 1.52–1.34 (m, 5H). Exact Mass calcd. for $C_6H_{13}BrO$ – H: 181.0048, 179.0068; found: 181.0043, 179.0063.

*1-Bromo-6-(*tert*-butyldimethylsilyloxy)-hexane (**29**b)*

This compound was prepared according to procedure B using the alcohol **28***b* (2.86 g, 15.8 mmol). The crude product was purified by column chromatography using petroleum ether:ethyl acetate (15:1) as eluent to give 4.12 g (88%) of **29***b* as a colourless oil: R_f 0.82 (6:1 petroleum ether:ethyl acetate); IR ν_{max}: 2936, 2858, 1466, 1253, 1101, 837, and 775 cm^{-1}; ^1H NMR (400 MHz) δ: 3.61 (t, J = 8 Hz, 2H), 3.41 (t, J = 8 Hz, 2H), 1.87 (qn, J = 8 Hz, 2H), 1.58–1.50 (m, 2H), 1.48–1.41 (m, 2H), 1.40–1.33 (m, 2H), 0.90 (s, 9H), and 0.06 (s, 6H). Exact Mass calcd. for $C_{12}H_{27}SiBrO$ – H: 295.2000, 293.2020; found: 295.0917, 293.0928.

2,4-Dodecanedione

Following procedure D, this β-diketone was prepared from 2,4-pentanedione (3.00 g, 30.0 mmol) and 1-bromoheptane (5.37 g, 30.0 mmol). The crude product was purified by column chromatography using petroleum ether:ethyl acetate (15:1) as eluent to give 2.70 g (63%) of 2,4-dodecanedione as a colourless oil: R_f 0.64 (6:1 petroleum ether:ethyl acetate); IR ν_{max}: 2931, 2856, 1713, 1614, 1449, 1363, 1241, 946, and 777 cm^{-1}; ^1H NMR (400 MHz) δ: 15.50 (bs, 0.8H), 5.49 (s, 0.8H), 3.58 (s, 0.4H), 2.50 (t, J = 8 Hz, 0.4H), 2.27 (t, J = 8 Hz, 1.6H), 2.24 (s, 0.6H), 2.07 (s, 2.4H), 1.68–1.52 (m, 2H), 1.40–1.20 (m, 10H), and 0.89 (t, J = 7 Hz, 3H). Exact Mass calcd. for $C_{12}H_{22}O_2$: 198.1614; found: 198.1626.

*1-(*tert*-Butyldimethylsilyloxy)-8,10-octadecanedione (**31**b)*

This compound was prepared according to procedure E using 2,4-dodecanedione (2.50 g, 12.6 mmol) and the bromide **29***b* (3.10 g, 10.5 mmol). The crude product was purified by column chromatography using petroleum ether:ethyl acetate (20:1) as eluent to give 2.30 g (75%) of **31***b* as a colourless oil: R_f 0.76 (6:1 petroleum ether:ethyl acetate); IR ν_{max}: 2909, 2856, 1704, 1615, 1459, 1360, 1251, 1100, 945, 838, and 775 cm^{-1}; ^1H NMR (400 MHz) δ: 15.50 (bs, 0.8H), 5.48 (s, 0.8H), 3.61 (t, J = 8 Hz, 2H), 3.53 (s, 0.4H), 2.50 (t, J = 8 Hz, 0.8H), 2.27 (t, J = 8 Hz, 3.2H), 1.66–1.42 (m, 8H), 1.40–1.22 (m, 14H), 0.90 (s, 9H), 0.89 (t, J = 7 Hz, 3H), and 0.06 (s, 6H). Exact Mass calcd. for $C_{24}H_{48}SiO_3$: 412.3360; found: 412.3377.

*1-Hydroxy-8,10-octadecanedione (**32**b)*

This compound was prepared according to procedure C using the silyl ether **31***b* (2.00 g, 4.85 mmol). The crude product was purified by recrystallization from hexanes to give 1.26 g (87%) of **32***b* as a white solid: R_f 0.64 (1:1 petroleum ether:ethyl acetate); mp 57.0°C; IR ν_{max}: 3622, 3460, 2931, 2857, 1703, 1607, 1458, 1335, 1051, and 902 cm^{-1}; ^1H NMR (400 MHz) δ: 15.50 (bs, 0.8H), 5.48 (s, 0.8H), 3.64 (t, J = 8 Hz, 2H), 3.54 (s, 0.4H), 2.51 (t, J = 8 Hz, 0.4H), 250 (t, J = 8 Hz, 0.4H), 2.26 (t, J = 8 Hz, 1.6H), 2.25 (t, J = 8 Hz, 1.6H), 1.70–1.20 (m, 23H), and 0.89 (t, J = 7 Hz, 3H). Exact Mass calcd. for $C_{18}H_{34}O_3$: 298.2499; found: 298.2514.

*8,10-Dioxooctadecanoic acid (**6**b)*

This compound was prepared according to procedure F using the alcohol **32***b* (596 mg, 2.00 mmol). The crude product was purified by recrystallization from hexanes to give 306 mg (50%) of **6***b* as a white solid: R_f 0.53 (5% HOAc in 3:1 petroleum ether:ethyl acetate); mp 58.5°C; IR ν_{max}: 3340–2480, 2931, 2858, 1708, 1608, 1459, 1300, and 1127 cm^{-1}; ^1H NMR (400 MHz) δ: 15.50 (bs, 0.8H), 5.49 (s, 0.8H), 3.54 (s, 0.4H), 2.51 (t, J = 8 Hz, 0.4H), 2.50 (t, J = 8 Hz, 0.4H), 2.36 (t, J = 8 Hz, 2H), 2.27 (t, J = 8 Hz, 1.6H), 2.26 (t, J = 8 Hz, 1.6H), 1.72–1.50 (m, 6H), 1.48–1.20 (m, 14H), and 0.90 (t, J = 7 Hz, 3H). Exact Mass calcd. for $C_{18}H_{32}O_4$: 312.2292; found: 312.2307. Anal. calcd. for $C_{18}H_{32}O_4$: C 69.23, H 10.33; found: C 68.94, H 10.38.

*9-Bromo-1-nonanol (**28**c)*

This compound was prepared according to procedure A using 1,9-nonanediol (10.0 g, 62.5 mmol) and 48% HBr (10.5 mL, 93.8 mmol). The crude product was purified by column chromatography using petroleum ether:ethyl acetate (6:1) as eluent to give 9.78 g (70%) of **28***c* as a white solid: R_f 0.58 (1:1 petroleum ether:ethyl acetate); mp 34.0°C; IR ν_{max}: 3622, 3460, 2929, 2857, 1459, 1386, 1352, 1274, 1111, 1044, and 889 cm^{-1}; ^1H NMR (400 MHz) δ: 3.64 (t, J = 7 Hz, 2H), 3.42 (t, J = 7 Hz, 2H), 1.83 (qn, J = 8 Hz, 2H), 1.58 (m, 2H), and 1.48–1.30 (m, 11H). Exact Mass calcd. for $C_9H_{19}BrO$ – H_2O: 206.0489, 204.0514; found: 206.0494, 204.0509.

*1-Bromo-9-(*tert*-butyldimethylsilyloxy)-nonane (**29**c)*

This compound was prepared according to procedure B using the alcohol **28***c* (2.66 g, 11.9 mmol). The crude product was purified by column chromatography using petroleum ether:ethyl acetate (15:1) as eluent to give 3.60 g (90%) of **29***c* (3.60 g, 90%) as a colourless oil: R_f 0.84 (6:1 petroleum ether:ethyl); IR ν_{max}: 2933, 2856, 1466, 1387, 1360, 1252, 1101, 1006, 839, 775, and 717 cm^{-1}; ^1H NMR (400 MHz) δ: 3.60 (t, J = 7 Hz, 2H), 3.41 (t, J = 7 Hz, 2H), 1.86 (qn, J = 7 Hz, 2H), 1.54–1.48 (m, 2H), 1.46–1.37 (m, 2H), 1.35–1.26 (m, 8H), 0.89 (s, 9H), and 0.05 (s, 6H). Exact Mass calcd. for $C_{15}H_{33}SiBrO$ – C_4H_9: 281.0173, 279.0193; found: 281.0748, 279.0786.

*14-(*tert*-Butyldimethylsilyloxy)-2,4-tetradecanedione (**30**c)*

Following procedure D, the β-diketone **30***c* was prepared from 2,4-pentanedione (0.98 g, 9.4 mmol) and bromide **29***c*. The crude product was purified by column chromatography using petroleum ether:ethyl acetate (15:1) as eluent to give 2.12 g (79%) of **30***c* as a colourless oil: R_f 0.66 (6:1 petroleum ether:ethyl acetate); IR ν_{max}: 2932, 2856, 1709, 1616, 1465, 1387, 1361, 1251, 1100, 1006, 940, 838, 813, and 776 cm^{-1}; ^1H NMR (400 MHz) δ: 15.50 (bs, 0.8H), 5.49 (s, 0.8H), 3.59 (t, J = 7 Hz, 2H), 3.57 (s, 0.4H), 2.49 (t, J = 8 Hz, 0.4H), 2.27 (t, J = 8 Hz, 1.6H), 2.24 (s, 0.6H), 2.06 (s, 2.4H), 1.65–1.46 (m, 6H), 1.40–1.24 (m, 10H), 0.89 (s, 9H), and 0.06 (s, 6H). Exact Mass calcd. for $C_{20}H_{40}SiO_3$ – H: 355.2658; found: 355.2676.

*18-(*tert*-Butyldimethylsilyloxy)-6,8-octadecanedione (**31**c)*

This compound was prepared according to procedure E using the β-diketone **30***c* (1.2 g, 3.2 mmol) and 1-bromobutane (0.60 g, 3.2 mmol). The crude product was purified by column chromatography using petroleum ether:ethyl acetate (20:1) as eluent to give 0.65 g (77%) of **31***c* as a colourless oil: R_f 0.77 (6:1 petroleum ether:ethyl acetate); IR ν_{max}: 2934, 2856, 1730, 1707, 1612, 1463, 1386, 1361, 1252, 1100, 1006, 940, and 838 cm^{-1}; ^1H NMR (400 MHz) δ: 15.66 (bs, 0.1H), 15.54 (bs, 0.7H), 5.48 (s, 0.7H), 5.47 (s, 0.1H), 3.61 (t, J = 7 Hz, 2H), 3.54 (s, 0.4H), 2.49 (t, J = 8 Hz, 0.8H), 2.27 (m, 3.2H), 1.66–1.46 (m, 8H), 1.38–1.22 (m, 14H), 0.90 (s, 12H), and 0.06 (s, 6H). Exact Mass calcd. for $C_{24}H_{48}SiO_3$ – H: 411.3282; found: 411.3287.

*18-Hydroxy-6,8-octadecanedione (**32**c)*

This compound was prepared according to procedure C using the silyl ether **31***c* (360 mg, 0.87 mmol). The crude product was purified by recrystallization from hexanes to give 250 mg (96%) of **32***c* as a white solid: R_f 0.66 (1:1 petroleum ether:ethyl acetate); mp 56.0°C; IR ν_{max}: 3621, 3456, 2974, 2931, 1700, 1608, 1455, 1390, and 1047 cm^{-1}; ^1H NMR (400 MHz) δ: 15.50 (bs, 0.8H), 5.48 (s, 0.8H), 3.64 (t, J = 7 Hz, 2H), 3.53 (s, 0.4H), 2.51 (t, J = 8 Hz, 0.8H), 2.27 (t, J = 8 Hz, 3.2H), 1.64–1.50 (m, 9H), 1.42–1.22 (m, 14H), and 0.92–0.86 (m, 3H). Exact Mass calcd. for $C_{18}H_{34}O_3$: 298.2499; found: 298.2504.

*11,13-Dioxooctadecanoic acid (**6**c)*

This compound was prepared according to procedure F using the alcohol **32***c* (200 mg, 0.67 mmol). The crude product was purified by recrystallization from hexanes to give 130 mg (64%) of **6***c* as a white solid: R_f 0.56 (5% HOAc in 3:1 petroleum ether:ethyl acetate); mp 56.5°C; IR ν_{max}: 3350–2500, 2933, 2859, 1710, 1605, 1458, 1395, 1281, 1138, 1047, 951, and 879 cm^{-1}; ^1H NMR (300 MHz) δ: 15.50 (bs, 0.8H), 5.48 (s, 0.8H), 3.55 (s, 0.4H), 2.50 (t, J = 8 Hz, 0.8H), 2.35 (t, J = 7 Hz, 2H), 2.27 (t, J = 8 Hz, 3.2H), 1.70–1.52 (m, 6H), 1.40–1.22 (m, 14H), and 0.94–0.86 (m, 3H). Exact Mass calcd. for $C_{18}H_{32}O_4$: 312.2292; found: 312.2294. Anal. calcd. for $C_{18}H_{32}O_4$: C 69.23, H 10.33; found: C68.94, H 10.25.

*2,4-Undecanedione (**33**)*

This compound was prepared according to procedure D using 1-bromohexane (**12***a*) (4.50 mL, 32.0 mmol) and 2,4-pentanedione (4.10 mL, 40.0 mmol). Distillation of the crude product under reduced pressure (155°C/50 Torr) gave 3.70 g (63%) of **33** as a colourless oil: R_f 0.60 (6:1 petroleum ether:ethyl acetate eluent); IR ν_{max}: 2930, 2858, 1711, 1613, 1446, 1364, 1254, and 947 cm^{-1}; ^1H NMR (400 MHz) δ: 15.50 (bs, 0.8H), 5.49 (s, 0.8H), 3.58 (s, 0.4H), 2.51 (t, J = 8 Hz, 0.4H), 2.27 (t, J = 8 Hz, 1.6H), 2.25 (s, 0.6H), 2.06 (s, 2.4H), 1.65–1.52 (m, 2H), 1.38–1.22 (m, 8H), and 0.89 (t, J = 7 Hz, 3H). Exact Mass calcd. for $C_{11}H_{20}O_2$: 184.1458; found: 184.1459.

*8,10-Octadecanedione (**7**)*

This compound was prepared according to procedure E using the β-diketone **33** (756 mg, 4.11 mmol) and 1-bromoheptane (660 mg, 3.69 mmol). Purification of the crude product by column chromatography using petroleum ether:ethyl acetate (20:1) gave 803 mg (77%) of **7** as a colourless oil: R_f 0.78 (6:1 petroleum ether:ethyl acetate eluent); IR ν_{max}: 2934, 2857, 1704, 1613, 1455, 1276, 1142, 1102, and 942 cm^{-1}; ^1H NMR (400 MHz) δ: 15.50 (bs, 0.8H), 5.48 (s, 0.8H), 3.53 (s, 0.4H), 2.50 (t, J = 8 Hz, 0.8H), 2.26 (t, J = 8 Hz, 3.2H), 1.64–1.50 (m, 4H), 1.48–1.22 (m, 18H), and 0.89 (t, J = 7 Hz, 6H). Exact Mass calcd. for $C_{18}H_{34}O_2$: 282.2550; found: 282.2565. Anal. calcd. for $C_{18}H_{34}O_2$: C 76.52, H 12.14; found: C 76.80, H 12.16.

Acknowledgements

We are grateful to the Natural Sciences and Engineering Research Council of Canada and Merck Frosst Canada for financial support of this work.

1. E. Meyers, D.S. Slusarchyk, and W.C. Liu. U.S. Patent 3 873 693 (1975); Chem. Abstr. **83**, 41512a (1975).
2. B.K. Toeplitz, A.I. Cohen, R.T. Funke, W.L. Parker, and J.Z. Gougoutas. J. Am. Chem. Soc. **101**, 3344 (1979).
3. E. Meyers, D.S. Slusarchyk, W.C. Liu, G. Astle, W.H. Trejo, and W.E. Brown. J. Antibiot. **31**, 815 (1978).
4. C.M. Liu and T.E. Hermann. J. Biol. Chem. **253**, 5892 (1978).
5. R.F. Kauffman, R.W. Taylor, and D.R. Pfeiffer. J. Biol. Chem. **253**, 5892 (1978).
6. R.F. Kauffman, R.W. Taylor, and D.R. Pfeiffer. J. Biol. Chem. **255**, 2735 (1980).
7. J.P. Bennett, S. Cockcroft, and B.D. Gomperts. Nature, **282**, 851 (1979).
8. S.E. Rittenhouse and W.C. Horne. Biochem. Biophys. Res. Commun. **123**, 393 (1984).
9. (*a*) B.W. Dijkstra, K.H. Kalk, W.G.J. Hol, and J. Drenth. J. Mol. Biol. **147**, 97 (1981); (*b*) R.H. Kretsinger. Annu. Rev. Biochem. **45**, 239 (1976); (*c*) R.H. Kretsinger. Crit. Rev. Biochem. 114 (1980).
10. S.M. Johnson, J. Jerrin. S.J. Liu, and I.C. Paul. J. Am. Chem. Soc. **92**, 4428 (1970).
11. (*a*) A.F. Gallaugher and H. Hibbert. J. Am Chem. Soc. **58**, 813 (1936); (*b*) C.G. Krespan. J. Org. Chem. **39**, 2351 (1974); (*c*) M. Newcomb, S.S. Moore, and D.J. Cram. J. Am Chem. Soc. **99**, 6405 (1977).
12. (*a*) S. Hanessian, N.G. Cooke, B. Dehoff, and Y. Sakito. J. Am. Chem. Soc. **112**, 5276 (1990); (*b*) D.A. Evans, R.L. Dow, T.L. Shih, J.M. Takacs, and R. Zahler. J. Am. Chem. Soc. **112**, 5290 (1990).
13. L. Weiler and K. Shelly. Can. J. Chem. **66**, 1359 (1988).
14. (*a*) A.H. Alberts and D.J. Cram. J. Am. Chem. Soc. **101**, 3545 (1979); (*b*) C.M. Thompson and D.L.C. Green, Tetrahedron, **47**, 4223 (1991).
15. C.A. Hendrich. Tetrahedron, **33**, 1845 (1977).
16. S.K. Chandhary and O. Hernandez. Tetrahedron Lett. 99 (1979).
17. K. Fuji, S. Nakano, and E. Fujita. Synthesis, 276 (1975).
18. T. Gibson. J. Org. Chem. **45**, 1095 (1980).
19. H.H. Freedman and R.A. Dubois. Tetrahedron Lett. **38**, 3251 (1975).
20. E.J. Corey, H. Niwa, and J. Knolle. J. Am. Chem. Soc. **100**, 1942 (1978).
21. E.J. Corey, and B.B. Snider. J. Am. Chem. Soc. **94**, 2549 (1972).
22. R. Appel. Angew. Chem. Int. Ed. Engl. **14**, 801 (1975).
23. J.G. Moffatt. J. Org. Chem. **36**, 1909 (1971).
24. E.J. Corey and J.J. Das. J. Am. Chem. Soc. **104**, 5551 (1982).
25. T.Q. Hu and L. Weiler. Can. J. Chem. **72**, 1512 (1994).
26. W.C. Still, M. Kahn, and A. Mitra. J. Org. Chem. **43**, 2923 (1978).
27. M.F. Lipton, C.M. Sorensen, A.C. Saddler, and R.H. Shapiro. J. Organomet. Chem. **186**, 155 (1980).
28. D.D. Perrin, W.L.F. Armarego, and D.R. Perrin. *In* Purification of laboratory chemicals. Pergamon Press, Oxford. 1966.