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Linker-Based Hemisuccinate Derivatives of Artemisinin: Synthesis and Antimalarial Assessment against Multidrug-Resistant *Plasmodium yoelii nigeriensis* in Mice[1]

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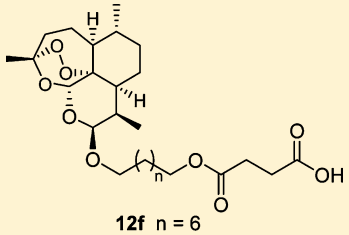
Supporting Information

ABSTRACT: Artesunic acid **5**, the hemisuccinate derivative of dihydroartemisinin **2**, is the only clinically useful water-soluble derivative of artemisinin **1**. However, being a lactol ester, it is rapidly hydrolyzed back to dihydroartemisinin in aqueous alkaline solution, a reaction that seriously limits its utility. A new series of potentially more stable linker-based hemisuccinate derivatives **12a−i** and **14a−c** have been prepared. The process involved acid-catalyzed reaction of dihydroartemisinin with various diols and polyethylene glycols to give hydroxy-functionalized ethers **7a−i** and **10a−c** and their further derivatization to hemisuccinate esters **12a−i** and **14a−c**. Both the hydroxy-functionalized ethers **7a−i** and **10a−c** and their hemisuccinate derivatives **12a−i** and **14a−c** have been assessed for antimalarial activity against multidrug-resistant *Plasmodium yoelii nigeriensis* in Swiss mice. Several of these hemisuccinate derivatives have shown very promising activity. Hemisuccinate derivatives **12f** and **12i**, the two most active compounds of the series, provided 100% protection to malaria-infected mice at 24 mg/kg × 4 days and therefore are twice as potent as artesunic acid, which provides a similar level of protection at 48 mg/kg × 4 days.



12f n = 6
12i n = 10

INTRODUCTION

Malaria is a major parasitic disease of the tropical and subtropical countries including India.[2] Nearly 300−500 million episodes of malaria infections occur annually, killing more than a million people with severe and cerebral malaria. The malaria problem has been further complicated with the emergence of malarial parasites resistant to the commonly used antimalarial drugs.[3] Chloroquine-resistant *Plasmodium falciparum* is present in most of the countries of Asia, Africa, and South America. Resistance to the sulfonamide−pyrimethamine combination is widespread in southeast Asia and South America. Field trials with mefloquine have met with rapid emergence of malarial parasites resistant to the drug. Resistance to quinine is not common, but the duration of the treatment with the drug is long and requires hospitalization. Currently, artemisinin **1** and its derivatives dihydroartemisinin **2**, artemether **3**, arteether **4**, and artesunic acid **5** (Figure 1) are the only class of drugs that are effective against multidrug resistant malaria.[4] Artesunic acid, the hemisuccinate ester of dihydroartemisinin **2**, is the only clinically useful water-soluble derivative of artemisinin.[5] However, being a lactol ester, it is rapidly hydrolyzed back to dihydroartemisinin in aqueous alkaline solution. Furthermore, dihydroartemisinin, being highly sensitive to basic conditions at ambient temperature, degrades into non-peroxide-containing compounds. This rapid hydrolysis of artesunic acid in aqueous solution greatly restricts its use, which reflects the need for more stable and possibly more effective water-soluble substitutes of artesunic acid. To meet these objectives, we have prepared a series of hydroxy-functionalized ether derivatives of dihydroartemisinin **7a−i** and **10a−c** and converted them into their hemisuccinate derivatives **12a−i** and **14a−c**, which readily form water-soluble sodium salts when treated with aqueous sodium bicarbonate.[6] Hemisuccinate derivatives **12f** and **12i**, the two most active compounds of the series, provided 100% protection to malaria-infected mice at 24 mg/kg × 4 days. Artesunic acid provides a similar level of protection at 48 mg/kg × 4 days. Compound **12h** was also assessed for its stability in aqueous bicarbonate and carbonate solution. It did not show any detectable degradation in 48 h at ambient temperature, while artesunic acid was completely degraded under these conditions.

CHEMISTRY

Dihydroartemisinin **2** was prepared from artemisinin **1** using the known procedure.[7] $BF_3{\cdot}OEt_2$ catalyzed reaction of **2** with alkane diols **6a−i** in CH_2Cl_2 at room temperature furnished the corresponding hydroxy-functionalized ether derivatives **7a−i** (β-isomer) and **8a−i** (α-isomer) in 31−67% yields as diastereomeric mixtures (approximately in the ratio of 3:1), with β-isomers as the major products. A similar reaction of **2** with polyethylene glycols **9a−c** furnished **10a−c** and **11a−c** in 49−55% yields (Scheme 1, Table 1). In most of the cases only β-isomers of these ether derivatives could be obtained in pure form and were used for the preparation of

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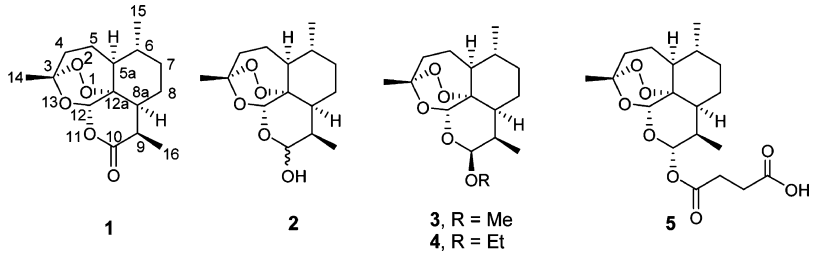
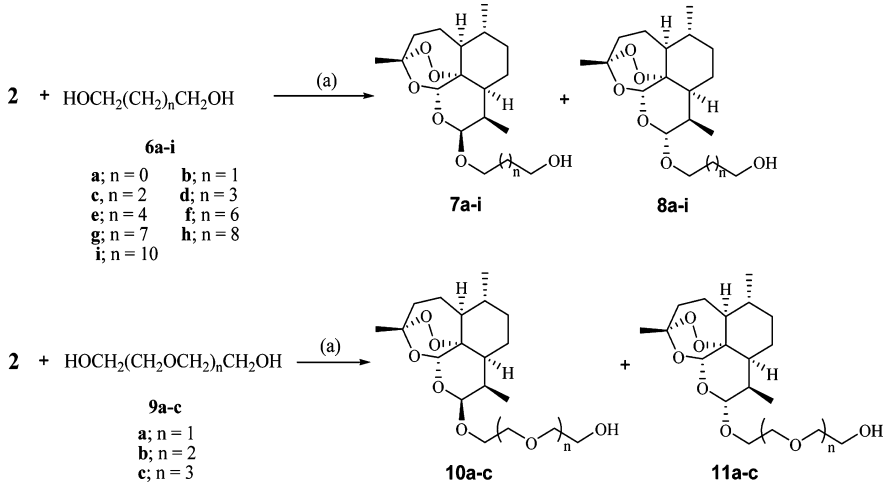


Figure 1. Artemisinin **1** and its clinically useful derivatives **2**−**5**.

Scheme 1[a]



[a]Reagents and conditions: (a) BF_3. OEt_2, CH_2CI_2, room temp, 15 h.

Table 1. Hydroxy-Functionalized Ether Derivatives 7a−i, 8a−i, 10a−c, and 11a−c

Compd. No.	n =	% yield (α+β)
7a + 8a	0	60
7b + 8b	1	67
7c + 8c	2	48
7d + 8d	3	65
7e + 8e	4	47
7f + 8f	6	57
7g + 8g	7	31
7h + 8h	8	58
7i + 8i	10	39

Compd. No.	n =	% yield (α+β)
10a + 11a	1	54
10b + 11b	2	55
10c + 11c	3	49

hemisuccinates.[8] The hemisuccinate derivatives **12a−i** and **14a−c** were prepared by the treatment of hydroxy-functionalized ethers **7a−i** and **10a−c** with succinic anhydride using either pyridine or Et_3N as a base and 4-*N*,

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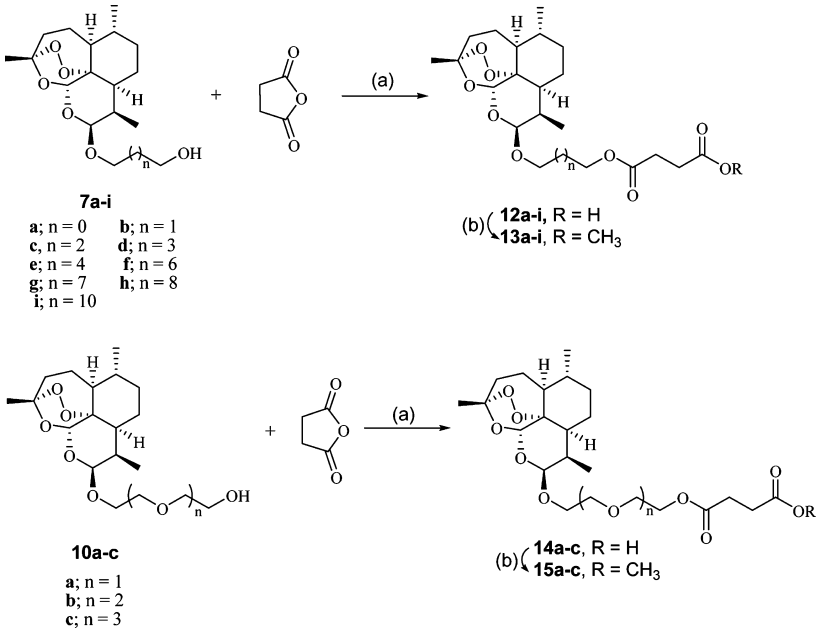
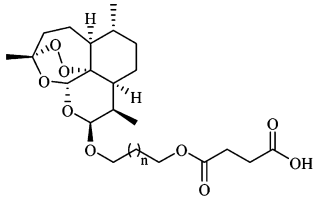
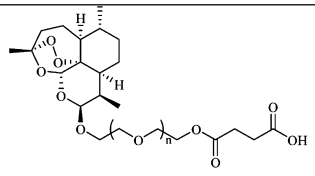
Scheme 2[a]



[a]Reagents and conditions: (a) pyridine or Et_3N, DMAP, CH_2CI_2, 0 °C, 1 h; (b) CH_2N_2, ether, 0 °C.

Table 2. Hemisuccinate Derivatives 12a–i and 14a–c

Compd. No.	 n =	% yield
12a	0	62
12b	1	78
12c	2	68
12d	3	84
12e	4	71
12f	6	70
12g[a]	7	83
12h	8	83
12i	10	83
Compd. No.	 n =	**% yield**
14a	1	51
14b	2	78
14c	3	66

[a]**12g** is a mixture of diastereomers, as it was prepared from a mixture of **7g** and **8g**.

N-dimethylaminopyridine (DMAP) as a catalyst in CH_2Cl_2 at 0 °C to room temperature (Scheme 2, Table 2). The hemisuccinate derivatives **12a–i** and **14a–c** were further converted to the corressponding methyl esters **13a–i** and **15a–c** to determine spectroscopic and analytical data (^{1}H NMR, ^{13}C NMR, mass, and microanalysis).

ANTIMALARIAL ACTIVITY[9]

Artesunic acid, when given intramuscularly at 48 mg/kg × 4 days, provides 100% protection to mice infected with multidrug-resistant *P. yoelli nigeriensis*. At 24 mg/kg × 4 days, it does not provide any protection. Since the objective of the study was to select compounds exhibiting activity profiles

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Table 3. Blood Schizontocidal Activity of Hydroxy Functionalized Ethers 7a−i and 10a−c against Multidrug-Resistant Strain *P. yoelii nigeriensis* in Swiss Mice via im Route[a,9]

compd	log *P*	dose (mg/kg × 4 days)	% suppression of parasitemia on day 4[b,c]	cured/treated
7a	2.99	48	100	12/12
		24	100	12/12
		12	100	9/11
		6	100	3/6
7b	3.10	48	100	5/5
		24	100	5/5
		12	100	9/11
		6	100	6/12
		3	98.3	0/6
7c	3.55	48	100	5/5
		24	100	5/5
		12	100	17/17
		6	100	11/12
		3	99.5	0/6
7d	3.97	48	100	5/5
		24	100	5/5
		12	100	5/5
		6	100	1/5
7e	4.38	48	100	6/6
		24	100	6/6
		12	100	6/6
		6	100	9/12
		3	100	0/6
7f	5.22	48	100	6/6
		24	100	6/6
		12	100	6/6
		6	100	5/6
		3	100	0/6
7g + 8g[d]	5.64	48	100	6/6
		24	100	5/5
		12	100	5/5
		6	100	1/5
		3	99.3	0/5
7h	6.05	48	100	6/6
		24	100	5/12
		12	100	0/6
		6	100	0/6
7i	6.89	48	100	4/12
		24	100	0/6
10a	2.83	48	100	6/6
		24	100	6/6
		12	100	7/12
		6	100	0/6
10b	2.68	48	100	2/6
		24	100	0/6
		12	100	0/6
10c	2.52	48	100	8/10
		24	100	0/5
		12	100	0/5
4	3.84	6	100	6/6
		3	100	0/6
5	3.04	48	100	6/6
		24	100	0/5
		12	96.36	0/5

[a]The drug dilutions of hydroxy funtionalized ethers **7a−i** and **10a−c** were prepared in ground oil and administered to a group of five or six mice at each dose from day 0 to day 3, once daily. [b]Percent suppression = $[(C - T)/C] \times 100$, where C is the parasitemia in control group and T is the parasitemia in treated group. [c]100% suppression of parasitemia means no parasites were detected in 50 oil immersion fields during microscopic observation.[10] [d]Compounds **7g** and **8g** could not be separated and were tested as mixtures.

comparable to or better than that of artesunic acid, all newly prepared hemisuccinate derivatives **12a−i** and **14a−c** were initially screened at 48 mg/kg × 4 days by the im route. Compounds found active at 48 mg/kg × 4 days were further screened at lower doses. The results are shown in Table 4. Similar dose-dependent activity data were generated for hydroxy-functionalized intermediate compounds **7a−i** and **10a−c**. The results are depicted in Table 3.

RESULTS AND DISCUSSION

In the present study, the length of the side chain of the hydroxy-functionalized ethers was systematically increased and its effect on the antimalarial activity was assessed. Simultaneously, each of the hydroxy-functionalized ethers was converted to its hemisuccinate derivative and assessed for its antimalarial activity. Thus, two sets of SAR data were generated (Table 3 and Table 4).

Both **7a** and **7b** showed modest activity compared with arteether; both these compounds showed 100% protection at 24 mg/kg × 4 days, while at 12 mg/kg × 4 days, both compounds showed only partial protection. Arteether in this assay showed 100% protection at 6 mg/kg × 4 days. Thus, these two compounds were significantly less active than arteether. Their respective hemisuccinate derivatives **12a** and **12b** also did not provide any significant protection at 48 mg/kg × 4 days. Compounds **7c−e** showed 100% protection at 12 mg/kg × 4 days and partial protection at 6 mg/kg × 4 days. However, none of their hemisuccinate derivatives **12c−e** provided significant protection at 48 mg/kg. The activity of hydroxy-functionalized ethers did not show any improvement with further increase in the chain length. Both **7f** and **7g** showed similar levels of protection as provided by **7c−e**. However, their hemisuccunate derivatives showed remarkable improvements in activity. While **12f** showed 100% protection at 24 mg/kg, **12g** showed a similar level of protection at 48 mg/kg × 4 days.

Further increase in the chain length resulted in reduced activity of the hydroxy-functionalized ethers. Both **7h** and **7i** were considerably less active than **7c−f**. Their hemisuccinate derivatives, however, did not show similar drops in activity. While **12i** provided 100% protection at 24 mg/kg, **12h** provided similar level of protection at 48 mg/kg × 4 days.

Of the polyethylene glycol derivatives **10a−c**, only **10a** showed 100% protection at 24 mg/kg. Similarly, their hemisuccinate derivatives **14a−c** showed poor activity; none of these compounds showed any significant protection at 48 mg/kg × 4 days.

Hemisuccinate derivative **12h** was also assessed for its stability in aqueous $NaHCO_3$ and aqueous Na_2CO_3 solution. It did not show any detectable degradation within 48 h at ambient

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Table 4. Blood Schizontocidal Activity of Hemisuccinates 12a−i and 14a−c against Multidrug-Resistant Strain *P. yoelii nigeriensis* in Swiss Mice via im Route[a,9]

compd	log *P*	dose mg/kg × 4 days	% suppression of parasitemia on day 4[b,c]	cured/treated
12a	2.89	48	100	0/6
12b	2.99	48	100	0/6
12c	3.45	48	100	5/12
12d	3.86	48	94.91	0/6
		24	92.73	0/6
12e	4.28	48	98.55	0/6
12f	5.12	48	100	6/6
		24	100	6/6
		12	100	0/6
12g[d]	5.53	48	100	6/6
		24	93.09	0/5
		12	67.27	0/5
12h	5.95	48	100	5/5
		24	100	8/11 + 1/5
		12	98.18	0/5
12i	6.78	48	100	5/5
		24	100	5/5
		12	71.27	0/5
		6	57.09	0/5
14a	2.73	48	100	1/11
14b	2.54	48	92	1/6
14c	2.42	48	97	0/6
5	3.04	48	100	6/6
		24	100	0/5
		12	96.36	0/5

[a]The drug dilution of hemisuccinates **12a−i** and **14a−c** were prepared in 5% $NaHCO_3$ and administered to the group of five or six mice at each dose from day 0 to day 3, once daily. [b]Percent suppression = $[(C - T)/C] \times 100$, where C is the parasitemia in control group and T is the parasitemia in treated group. [c]100% suppression of parasitemia means no parasites were detected in 50 oil immersion fields during microscopic observation.[10] [d]Compound **12g** is a mixture of diastereomers, as it is prepared from a mixture of **7g** and **8g**.

temperature, while artesunic acid was completely degraded under these conditions.

Thus, of the hemisuccinate derivatives, both **12f** and **12i** are superior to artesunic acid and both are twice as active as artesunic acid while **12g** and **12h** are comparable to artesunic acid. In addition, these compounds have the advantage of being more stable than artesunic acid in aqueous $NaHCO_3$ solutions.

CONCLUSION

We have prepared a new series of linker-based hemisuccinate derivatives of dihydroartemisinin, several of which have shown a high order of antimalarial activity against multidrug-resistant *P. yoelii nigeriensis* in Swiss mice. Hemisuccinate derivatives **12f** and **12i**, the most active compounds of the series, are twice as active as artesunic acid, the only clinically useful water-soluble derivative of artemisinin. Hemisuccinate **12h**, an active representative of the series, was also found to be stable in aqueous alkaline solution.

EXPERIMENTAL SECTION

General. All glass apparatuses were oven-dried prior to use. Melting points were taken in open capillaries on a Complab melting point apparatus and are presented uncorrected. Infrared spectra were recorded on a Perkin-Elmer FT-IR RXI spectrophotometer. ^1H NMR and ^{13}C NMR spectra were recorded using a Bruker Supercon Magnet DPX-200 or DRX-300 spectrometer operating at 200 and 300 MHz, respectively, for ^1H and at 50 and 75 MHz, respectively, for ^{13}C and at 400 MHz using $CDCl_3$ as solvent. Tetramethylsilane (δ 0 0.00 ppm) served as an internal standard in ^1H NMR, and $CDCl_3$ (δ 77.0 ppm) was the internal standard in ^{13}C NMR. Chemical shifts are reported in parts per million. Splitting patterns are described as singlet (s), doublet (d), triplet (t), and multiplet (m). In NMR, numbering of atoms is presented according to the usual numbering in artemisinin as indicated in the text. Fast atom bombardment mass spectrometry (FABMS) data were obtained on JEOL SX-102/DA-6000 mass spectrometer using argon/xenon (6 kV, 10 mA) as the FAB gas. Glycerol or *m*-nitrobenzyl alcohol was used as matrix. Electrospray mass spectrometry (ES-MS) results were recorded on a MICROMASS QUATTRO II triple quadruple mass spectrometer. Elemental analyses were performed on a Vario EL-III C, H, N, S analyzer (Germany) and Carlo-Erba-1108 C, H, N elemental analyzer (Italian), and values were within ±0.5% of the calculated values; therefore, these compounds meet the criteria of ≥95% purity. Reactions were monitored on silica gel TLC plates (coated with TLC grade silica gel, obtained from Merck). Detecting agents used (for TLC) were iodine vapors, and/or spraying was done with an aqueous solution of vanillin in 10% sulfuric acid followed by heating at 150 °C. Column chromatography was performed over Merck silica gel (particle size, 60−120 mesh) procured from Qualigens (India) and flash silica gel (particle size, 230−400 mesh). All chemicals and reagents were obtained from Aldrich (U.S.), Lancaster (England), or Spectrochem (India) and were used without further purification. The log *P* values of the compounds were calculated using Chem Draw Ultra 10.0 software.

General Procedure for Preparation of Hydroxy-Functionalized Ethers 7a−i and 10a−c (Compound 7d as Representative). To a solution of dihydroartemisinin **2** (1.0 g, 3.52 mmol) and pentane-1,5-diol **6d** (1.10 g, 10.5 mmol) in dry dichloromethane (20 mL) was added $BF_3{\cdot}OEt_2$ (0.25 mL) at room temperature. The reaction mixture was stirred at the same temperature for 15 h. Then the reaction mixture was neutralized with saturated sodium bicarbonate solution (25 mL) and extracted with ether (3 × 25 mL). The combined organic layer was washed with water (2 × 25 mL) and then with brine (2 × 25 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resultant crude product, upon column chromatography over silica gel using ethyl acetate/hexane (15:85) as eluant, gave **7d** (0.122 g) as a solid, a mixture of **7d** and **8d** (0.687 g), and **8d** (0.037 g) as a solid, the combined yield being 65%.

7a. White solid; mp 98−100 °C; FT-IR (KBr, cm^{-1}) 3426.4, 2930.0, 2875.0, 1453.9, 1376.6, 1154.6, 1018.1, 757.5; ^1H NMR (400 MHz, $CDCl_3$) δ 0.93 (d, 3H, J = 7.3 Hz, CH_3), 0.97 (d, 3H, J = 6.7 Hz, CH_3), 1.23−2.05 (m, 10H), 1.44 (s, 3H, CH_3), 2.35−2.42 (m, 1H), 2.65−2.71 (m, 1H), 3.65 (m, 1H), 3.76 (m, 2H, $\underline{CH_2}OH$), 3.91 (m, 1H), 4.86 (d, 1H, J = 3.4 Hz, C_{10}-H), 5.46 (s, 1H, C_{12}-H). FABMS (m/z): 335 $[M + Li]^+$, 267 $[M^+ - OCH_2CH_2OH]$. Anal. Calcd for $C_{17}H_{28}O_6$: C, 62.17; H, 8.59. Found: C, 62.20; H, 8.60.

Ethers **7b−i** and **10a−c** were prepared using the above procedure.

7b. White solid; mp 74−75 °C; FT-IR (KBr, cm^{-1}) 3461.4, 2927.3, 1594.5, 1351.4, 1102.2, 1017.0, 759.2; ^1H NMR (200 MHz, $CDCl_3$) δ 0.91 (d, 3H, J = 7.4 Hz, CH_3), 0.95 (d, 3H, J = 7.3 Hz, CH_3), 1.22−2.12 (m, 12H), 1.44 (s, 3H, CH_3), 2.29−2.45 (s, 1H), 2.61−2.69 (m, 1H), 3.52 (td, 1H, J = 9.8 Hz, 6.0 Hz), 3.76 (t, 2H, J = 5.7 Hz, $\underline{CH_2}OH$), 4.05 (td, 1H, J = 9.9, 5.5 Hz), 4.80 (d, 1H, J = 3.4 Hz, C_{10}-H), 5.40 (s, 1H, C_{12}-H). FABMS (m/z): 343 $[M + H]^+$, 310 $[M^+ - O_2]$, 267 $[M^+ - O(CH_2)_3OH]$. Anal. Calcd for $C_{18}H_{30}O_6$: C, 63.14; H, 8.83. Found: C, 62.94; H, 8.81.

7c. White solid; mp 117−118 °C; FT-IR (KBr, cm^{-1}) 3442.9, 2925.1, 2859.3, 1458.7, 1374.7, 1023.3, 761.0; ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (d, 3H, J = 7.2 Hz, CH_3), 0.94 (d, 3H, J = 6.0 Hz, CH_3), 1.22−2.05 (m, 14H), 1.43 (s, 3H, CH_3), 2.31−2.37 (m, 1H), 2.61−2.63 (m, 1H), 3.37−3.49 (m, 1H), 3.66 (t, 2H, J = 5.4 Hz, $\underline{CH_2}OH$), 3.85−3.90 (m, 1H), 4.78 (d, 1H, J = 3.3 Hz, C_{10}-H), 5.39 (s, 1H, C_{12}-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.22 (CH_3), 20.59 (CH_3), 24.70 (CH_2), 24.89 (CH_2), 26.39 (CH_2), 26.41 (CH_3), 29.96

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(CH_2), 31.14 (CH), 34.85 (CH_2), 36.65 (CH_2), 37.70 (CH), 44.65 (CH), 52.79 (CH), 62.91 (CH_2), 68.52 (CH_2), 81.36 (C), 88.14 (CH), 102.24 (CH), 104.34 (C). FABMS (m/z): 357 $[M + H]^+$, 324 $[M^+ - O_2]$, 267 $[M^+ - O(CH_2)_4OH]$. Anal. Calcd for $C_{19}H_{32}O_6$: C, 64.02; H, 9.05. Found: C, 64.19; H, 9.07.

7d. White solid; mp 64−67 °C; FT-IR (KBr, cm^{-1}) 3432.5, 2932.3, 1594.3, 1459.7, 1381.8, 1351.3, 1103.3, 1026.3, 761.1; ^1H NMR (300 MHz, $CDCl_3$) δ 0.83 (d, 3H, J = 7.3 Hz, CH_3), 0.88 (d, 3H, J = 5.9 Hz, CH_3), 1.15−1.98 (m, 16H), 1.36 (s, 3H, CH_3), 2.29−2.38 (m, 1H), 2.53−2.54 (m, 1H), 3.32 (td, 1H, J = 9.7 Hz, 6.0 Hz), 3.55 (t, 2H, J = 6.3 Hz, $\underline{CH_2}OH$), 3.76 (td, 1H, J = 9.7, 6.2 Hz), 4.69 (d, 1H, J = 3.4 Hz, C_{10}-H), 5.32 (s, 1H, C_{12}-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.67 (CH_3), 19.03 (CH_3), 21.11 (CH_2), 23.12 (CH_2), 23.34 (CH_2), 24.80 (CH_3), 28.10 (CH_2), 29.59 (CH), 30.99 (CH_2), 33.32 (CH_2), 35.10 (CH_2), 36.11 (CH), 43.14 (CH), 51.24 (CH), 61.25 (CH_2), 66.97 (CH_2), 79.79 (C), 86.55 (CH), 100.63 (C), 102.74 (C). ES-MS (m/z): 393 $[M + Na]^+$, 371 $[M + H]^+$, 267 $[M^+ - O(CH_2)_5OH]$. Anal. Calcd for $C_{20}H_{34}O_6$: C, 64.84; H, 9.25. Found: C, 64.73; H, 9.00.

8d. White solid; mp 90−92 °C; FT-IR (KBr, cm^{-1}) 3427.8, 2926.2, 2856.9, 1716.5, 1460.3, 1376.8, 1217.3, 1157.8, 1019.6, 762.0; ^1H NMR (200 MHz, $CDCl_3$) δ 0.88 (d, 3H, J = 7.1 Hz, CH_3), 0.95 (d, 3H, J = 5.5 Hz, CH_3), 1.25−2.09 (m, 16H), 1.43 (s, 3H, CH_3), 2.30−2.45 (m, 2H), 3.37−3.48 (m, 1H), 3.65 (t, 2H, J = 6.2 Hz, $\underline{CH_2}OH$), 3.91 (m, 1H), 4.41 (d, 1H, J = 9.2 Hz, C_{10}-H), 5.33 (s, 1H, C_{12}-H). FABMS (m/z): 371 $[M + H]^+$, 267 $[M^+ - O(CH_2)_5OH]$. Anal. Calcd for $C_{20}H_{34}O_6$: C, 64.84; H, 9.25. Found: C, 64.73; H, 9.10.

7e. Oil; FT-IR (neat, cm^{-1}) 3422.5, 2930.0, 2864.6, 1596.9, 1458.5, 1353.1, 1102.7, 1016.2, 760.9; ^1H NMR (200 MHz, $CDCl_3$) δ 0.89 (d, 3H, J = 7.3 Hz, CH_3), 0.95 (d, 3H, J = 5.9 Hz, CH_3), 1.21−2.07 (m, 18H), 1.44 (s, 3H, CH_3), 2.29−2.38 (m, 1H), 2.59−2.63 (m, 1H), 3.37 (td, 1H, J = 9.6 Hz, 6.3 Hz), 3.64 (t, 2H, J = 6.4 Hz, $\underline{CH_2}OH$), 3.83 (td, 1H, J = 9.6, 6.4 Hz), 4.77 (d, 1H, J = 3.2 Hz, C_{10}-H), 5.39 (s, 1H, C_{12}-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.73 (CH_3), 19.08 (CH_3), 23.19 (CH_2), 23.41 (CH_2), 24.16 (CH_2), 24.77 (CH_2), 24.92 (CH_3), 28.34 (CH_2), 29.66 (CH), 31.44 (CH_2), 33.40 (CH_2), 35.18 (CH_2), 36.21 (CH), 43.22 (CH), 51.33 (CH), 61.64 (CH_2), 67.02 (CH_2), 79.87 (C), 86.63 (CH), 100.68 (CH), 102.78 (C). FABMS (m/z): 385 $[M + H]^+$, 267 $[M^+ - O(CH_2)_6OH]$. Anal. Calcd for $C_{21}H_{36}O_6$: C, 65.60; H, 9.44. Found: C, 65.55; H, 9.41.

7f. Oil; FT-IR (neat, cm^{-1}) 3461.5, 2930.8, 1592.5, 1383.3, 1352.3, 1104.0, 1025.6, 766.2; ^1H NMR (300 MHz, $CDCl_3$) δ 0.91 (d, 3H, J = 7.3 Hz, CH_3), 0.96 (d, 3H, J = 6.1 Hz, CH_3), 1.29−2.06 (m, 22H), 1.45 (s, 3H, CH_3), 2.32−2.38 (m, 1H), 2.61−2.64 (m, 1H), 3.36 (td, 1H, J = 9.5 Hz, 6.5 Hz), 3.65 (t, 2H, J = 6.5 Hz, $\underline{CH_2}OH$), 3.83 (td, 1H, J = 9.5 Hz, 6.5 Hz), 4.78 (d, 1H, J = 3.2 Hz, C_{10}-H) 5.40 (s, 1H, C_{12}-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.19 (CH_3), 20.53 (CH_3), 24.62 (CH_2), 24.86 (CH_2), 25.86 (CH_2), 26.10 (CH_2), 26.13 (CH_3), 29.45 (CH_2), 29.55 (CH_2), 29.79 (CH_2), 31.11 (CH), 32.91 (CH_2), 34.87 (CH_2), 36.63 (CH_2), 37.65 (CH), 44.68 (CH), 52.78 (CH), 63.01 (CH_2), 68.58 (CH_2), 81.32 (C), 88.07 (CH), 102.10 (CH), 104.23 (C). FABMS (m/z): 413 $[M + H]^+$, 267 $[M^+ - O(CH_2)_8OH]$. Anal. Calcd for ($C_{23}H_{40}O_6$): C 66.96; H, 9.77. Found: C, 66.76; H, 9.46.

8f. Oil; FT-IR (neat, cm^{-1}) 3429.1, 2930.8, 2817.5, 1596.3, 1383.3, 1352.3, 1025.3, 766.2; ^1H NMR (200 MHz, $CDCl_3$) δ 0.88 (d, 3H, J = 7.1 Hz, CH_3), 0.95 (d, 3H, J = 5.6 Hz, CH_3), 1.26−2.05 (m, 22H), 1.44 (s, 3H, CH_3), 2.32−2.44 (m, 2H), 3.37−3.42 (m, 1H), 3.63 (t, 2H, J = 6.4 Hz, $\underline{CH_2}OH$), 3.96 (m, 1H), 4.41 (d, 1H, J = 9.2 Hz, C_{10}-H), 5.33 (s, 1H, C_{12}-H). FABMS (m/z): 413 $[M + H]^+$, 267 $[M^+ - O(CH_2)_8OH]$. Anal. Calcd for ($C_{23}H_{40}O_6$): C, 66.96; H, 9.77. Found: C, 66.66; H, 9.56.

7g + 8g. Oil; FT-IR (neat, cm^{-1}) 3434.4, 2929.1, 2860.1, 1456.7, 1376.3, 1230.3, 1195.5, 1102.8, 1026.0, 755.4; ^1H NMR (200 MHz, $CDCl_3$) δ 0.88 and 0.89 (2 × d, 3H, J = 6.6 and 7.3 Hz, respectively, CH_3), 0.95 (d, 3H, J = 5.3 Hz, CH_3), 1.20−2.06 (m, 24H), 1.43 (s, 3H, CH_3), 2.29−2.37 (m, 1H), 2.58−2.62 (m, 1H), 3.35 (td, 1H, J = 9.5 Hz, 6.3 Hz), 3.62 and 4.05 (2 × t, 2H, J = 6.4 and 6.7 Hz, respectively, together integrating for 2H), 3.82 (td, 1H, J = 9.6, 6.4 Hz), 4.41 and 4.76 (2 × d, 1H, J = 9.2 and 3.3 Hz, respectively, together integrating for 1 C_{10}-H), 5.33 and 5.38 (2 × s, 1H, together integrating for 1 C_{12}-H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.97 and 13.38 (2 × CH_3), 20.73 and 21.35 (2 × CH_3), 24.82 and 25.06 (2 × CH_2), 26.10 (CH_2), 26.37 and 26.55 (2 × CH_3), 29.60 and 29.71 (CH_2), 29.89 and 29.98 (CH_2), 31.31 (CH), 33.11 (CH_2), 34.63 and 35.06 (CH_2), 36.82 (CH_2), 37.84 (CH), 44.88 and 45.72 (2 × CH), 52.05 and 52.97 (2 × CH), 63.27 and 65.01 (2 × CH_2), 68.77 and 69.53 (2 × CH_2), 80.72 and 81.53 (2 × C), 88.27 and 91.54 (2 × CH), 100.47 and 102.30 (2 × CH), 104.43 and 104.61 (2 × C). FABMS (m/z): 427 $[M + H]^+$, 267 $[M^+ - O(CH_2)_9OH]$. ESMS (m/z): 449 $[M + Na]^+$. Anal. Calcd for $C_{24}H_{42}O_6$: C, 67.57; H, 9.92. Found: C, 67.26; H, 9.82.

7h. Oil; FT-IR (neat, cm^{-1}) 3429.5, 2927.9, 1596.4, 1459.8, 1380.8, 1351.9, 1157.3, 1025.6, 760.3; ^1H NMR (300 MHz, $CDCl_3$) δ 0.89 (d, 3H, J = 7.5 Hz, CH_3), 0.94 (d, 3H, J = 6.3 Hz, CH_3), 1.21−2.06 (m, 26H), 1.43 (s, 3H, CH_3), 2.31−2.36 (m, 1H), 2.59−2.63 (m, 1H), 3.35 (td, 1H, J = 9.6, 6.6 Hz), 3.62 (t, 2H, J = 6.6 Hz, $\underline{CH_2}OH$), 3.81 (td, 1H, J = 9.6, 6.6 Hz), 4.76 (d, 1H, J = 3.3 Hz, C_{10}-H), 5.38 (s, 1H, C_{12}-H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 12.99 (CH_3), 20.66 (CH_3), 22.59 (CH_2), 25.09 (CH_2), 26.12 (CH_2), 26.59 (CH_3), 29.76 (CH_2), 29.89 (CH_2), 31.34 (CH), 33.01 (CH_2), 33.16 (CH_2), 34.66 (CH_2), 36.74 (CH_2), 37.76 (CH), 45.74 (CH), 52.08 (CH), 63.38 (CH_2), 69.56 (CH_2), 81.52 (C), 88.29 (CH), 102.32 (CH), 104.62 (C). FABMS (m/z): 441 $[M + H]^+$, 267 $[M^+ - O(CH_2)_{10}OH]$. Anal. Calcd for $C_{25}H_{44}O_6$: C, 68.15; H, 10.07. Found: C, 68.24; H, 10.24.

7i. Oil; FT-IR (neat, cm^{-1}) 3420.6, 2928.4, 1595.5, 1382.4, 1351.8, 1104.0, 1026.9, 763.5; ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (d, 3H, J = 7.3 Hz, CH_3), 0.95 (d, 3H, J = 6.1 Hz, CH_3), 1.22−2.05 (m, 30H), 1.43 (s, 3H, CH_3), 2.31−2.37 (m, 1H), 2.60−2.61 (m, 1H), 3.36 (td, 1H, J = 9.6, 6.4 Hz), 3.63 (t, 2H, J = 6.5 Hz, $\underline{CH_2}OH$), 3.82 (td, 1H, J = 9.6, 6.6 Hz), 4.77 (d, 1H, J = 3.3 Hz, C_{10}-H), 5.39 (s, 1H, C_{12}-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.72 (CH_3), 19.07 (CH_3), 23.16 (CH_2), 23.40 (CH_2), 24.45 (CH_2), 24.91 (CH_3), 24.93 (CH_2), 28.02 (CH_2), 28.14 (CH_2), 28.25 (CH_2), 28.28 (CH_2), 28.29 (CH_2), 28.32 (CH_2), 28.35 (CH_2), 29.67 (CH), 31.50 (CH_2), 33.41 (CH_2), 35.18 (CH_2), 36.18 (CH), 43.23 (CH), 51.33 (CH), 61.72 (CH_2), 67.14 (CH_2), 79.87 (C), 86.61 (CH), 100.64 (CH), 102.75 (C). ESMS (m/z): 507 $[M + K]^+$, 469 $[M + H]^+$, 267 $[M^+ - O(CH_2)_{12}OH]$. Anal. Calcd for $C_{27}H_{48}O_6$: C, 69.19; H, 10.32. Found: C, 69.40; H, 10.67.

10a. White solid; mp 94−95 °C; FT-IR (KBr, cm^{-1}) 3411.0, 2930.4, 2876.7, 1455.3, 1377.8, 1220.2, 1128.9, 1023.4, 757.2; ^1H NMR (300 MHz, $CDCl_3$) δ 0.92 (d, 3H, J = 7.3 Hz, CH_3), 0.96 (d, 3H, J = 6.1 Hz, CH_3), 1.20−2.07 (m, 10H), 1.44 (s, 3H, CH_3), 2.32−2.38 (m, 1H), 2.58−2.68 (m, 1H), 3.59−3.77 (m, 7H), 3.90−3.98 (m, 1H), 4.84 (d, 1H, J = 3.3 Hz, C_{10}-H), 5.50 (s, 1H, C_{12}-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.18 (CH_3), 20.58 (CH_3), 24.67 (CH_2), 24.89 (CH_2), 26.31 (CH_3), 31.12 (CH), 34.83 (CH_2), 36.60 (CH_2), 37.69 (CH), 44.62 (CH), 52.75 (CH), 62.06 (CH_2), 67.93 (CH_2), 70.89 (CH_2), 72.47 (CH_2), 81.35 (C), 88.11 (CH), 102.46 (CH), 104.40 (C). FABMS (m/z): 373 $[M + H]^+$, 395 $[M + Na]^+$, 267 $[M^+ - O(CH_2CH_2O)_2H]$. Anal. Calcd for $C_{19}H_{32}O_7$: C, 61.27; H, 8.66. Found: C, 61.62; H, 8.83.

10b. Oil; FT-IR (neat, cm^{-1}) 3432.7, 2928.0, 2876.2, 1454.6, 1454.6, 1379.0, 1218.1, 1104.5, 1026.7, 985.7, 757.0; ^1H NMR (300 MHz, $CDCl_3$) δ 0.87 (d, 3H, J = 7.3 Hz, CH_3), 0.93 (d, 3H, J = 6.2 Hz, CH_3), 1.20−1.84 (m, 10H), 1.41 (s, 3H, CH_3), 2.34−2.35 (m, 1H), 2.59−2.65 (m, 1H), 3.57−3.72 (m, 11H), 3.91−3.94 (m, 1H), 4.80 (d, 1H, J = 3.3 Hz, C_{10}-H), 5.43 (s, 1H, C_{12}-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.66 (CH_3), 19.06 (CH_3), 23.11 (CH_2), 23.40 (CH_2), 24.82 (CH_3), 29.56 (CH), 33.38 (CH_2), 35.12 (CH_2), 36.12 (CH), 43.16 (CH), 51.26 (CH), 60.42 (CH_2), 66.04 (CH_2), 69.27 (CH_2), 71.30 (CH_2), 79.82 (C), 86.58 (CH), 100.77 (CH), 102.77 (C). FABMS (m/z): 417 $[M + H]^+$, 267 $[M^+ - (CH_2CH_2O)_3H]$. ESMS (m/z): 439 $[M + Na]^+$. Anal. Calcd for $C_{21}H_{36}O_8$: C, 60.56; H, 8.71. Found: C, 60.31; H, 8.70.

10c. Oil; FT-IR (neat, cm^{-1}) 3422.5, 2927.1, 1457.7, 1378.3, 1218.8, 1106.0, 1025.8, 985.7, 763.7; ^1H NMR (200 MHz, $CDCl_3$) δ 0.91 (d, 3H, J = 7.3 Hz, CH_3), 0.95 (d, 3H, J = 6.1 Hz, CH_3), 1.20−2.05 (m, 10H), 1.43 (s, 3H, CH_3), 2.36−2.37 (m, 1H), 2.60−2.62 (m, 1H), 3.64−3.74 (m, 15H), 3.91−3.96 (m, 1H), 4.83 (d, 1H, J = 3.3 Hz, C_{10}-H), 5.43 (s, 1H, C_{12}-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.10 (CH_3),

20.51 (CH_3), 24.58 (CH_2), 24.87 (CH_2), 26.26 (CH_3), 31.01 (CH), 34.84 (CH_2), 36.59 (CH_2), 37.61 (CH), 44.62 (CH), 52.73 (CH), 61.67 (CH_2), 67.54 (CH_2), 70.39 (CH_2), 70.59 (CH_2), 70.72 (CH_2), 72.71 (CH_2), 81.27 (C), 88.03 (CH), 102.22 (CH), 104.24 (C). FABMS (m/z): 461 $[M + H]^+$, 267 $[M^+ - (CH_2CH_2O)_4H]$. Anal. Calcd for $C_{23}H_{40}O_9$: C, 59.98; H, 8.75. Found: C, 59.80; H, 8.89.

11c. Oil; FT-IR (neat, cm^{-1}) 3427.0, 2925.7, 1459.3, 1375.5, 1219.7, 1105.2, 1026.5, 769.2; ^1H NMR (200 MHz, $CDCl_3$) δ 0.89 (d, 3H, J = 7.0 Hz, CH_3), 0.98 (d, 3H, J = 6.7 Hz, CH_3), 1.18–2.12 (m, 10H), 1.43 (s, 3H, CH_3), 2.29–2.43 (m, 2H), 3.58–3.75(m, 15H), 4.01–4.10 (m, 1H), 4.50 (d, 1H, J = 9.2 Hz, C_{10}-H), 5.33 (s, 1H, C_{12}-H). FABMS (m/z): 483 $[M + Na]^+$. Anal. Calcd for $C_{23}H_{40}O_9$: C, 59.98; H, 8.75. Found: C, 59.80; H, 8.89.

General Procedure for Formation of Hemisuccinates 12a–i and 14a–c (Compound 12a as Representative). To a solution of hydroxy ether **7a** (0.200 g, 0.6 mmol) and succinic anhydride (0.300 g, 3.0 mmol) in CH_2Cl_2 (30 mL) was added pyridine (0.24 mL, 3.0 mmol). The reaction mixture was stirred at the room temperature for 15 h. Then the reaction mixture was quenched with 10% aqueous HCl solution (20 mL) and extracted with ether (3 × 20 mL). The combined organic layer was washed with water (20 mL) and then with brine (25 mL), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The crude product on column chromatography over silica gel using ethyl acetate/hexane (1:4) as eluant furnished pure **12a** as an oil (0.160 g, 62% yield). FT-IR (neat,cm^{-1}) 2927.5, 2819.8, 1731.5, 1452.5, 1379.2, 1362.3, 1211.4, 1173.4, 1102.5, 1025.9, 760.5; ^1H NMR (200 MHz, $CDCl_3$) δ 0.90 (d, 3H, J = 7.3 Hz, CH_3), 0.95 (d, 3H, J = 5.8 Hz, CH_3), 1.10–2.12 (m, 10H), 1.43 (s, 3H, CH_3), 2.31–2.41 (m, 1H), 2.66 (m, 5H), 3.59–3.76 (m, 1H), 3.65 and 3.98 (2 × m, 1H, $OCH_2CH_2OCO(CH_2)_2COOH$), 3.94–4.05 (m, 1H), 4.26 (m, 1H), 4.81 (d, 1H, J = 3.3 Hz, C_{10}-H), 5.43 (s, 1H, C_{12}-H). FABMS (m/z): 435 $[M + Li]^+$, 397 $[(M^+ - O_2) + H]^+$, 267 $[M^+ - OCH_2CH_2OCO(CH_2)_2COOH]$. **12a** on treatment with CH_2N_2 in ether and subsequent purification by column chromatography furnished ester **13a** as a white solid. Mp 70–71 °C; FT-IR (KBr, cm^{-1}) 1725.0; ^1H NMR (200 MHz, $CDCl_3$) δ 0.83 (d, 3H, J = 7.3 Hz, CH_3), 0.88 (d, 3H, J = 5.8 Hz, CH_3), 1.14–1.99 (m, 10H), 1.36 (s, 3H, CH_3), 2.22–2.36 (m, 1H), 2.57–2.66 (m, 5H), 3.52–3.69 (m, 1H), 3.62 (s, 3H, $O\underline{CH_3}$), 3.87–3.98 (m, 1H), 4.16–4.25 (t, 2H, J = 4.9 Hz, $OCH_2\underline{CH_2}OCO(CH_2)_2COOCH_3$), 4.74 (d, 1H, J = 3.2 Hz, C_{10}-H), 5.35 (s, 1H, C_{12}-H). FABMS (m/z): 443 $[M + H]^+$, 267 $[M^+ - OCH_2CH_2OCO(CH_2)_2COOCH_3]$. Anal. Calcd for $C_{22}H_{34}O_9$: C, 59.71; H, 7.74. Found: C, 60.12; H, 7.85.

Hemisuccinates **12b–i** and **14a–c** were prepared using the above procedure.

12b. Yield 78%; oil; FT-IR (neat, cm^{-1}) 2923.6, 2845.3, 1732.0, 1451.7, 1380.0, 1360.5, 1210.7, 1172.4, 1102.1, 1027.1, 760.3; ^1H NMR (400 MHz, $CDCl_3$) δ 0.90 (d, 3H, J = 7.4 Hz, CH_3), 0.96 (d, 3H, J = 6.0 Hz, CH_3), 1.20–2.07 (m, 12H), 1.44 (s, 3H, CH_3), 2.33–2.43 (m, 1H), 2.77 (m, 5H), 3.41 (td, 1H, J = 10.5, 6.0 Hz), 3.94 (td, 1H, J = 10.5, 6.0 Hz), 4.15 (m, 1H), 4.27 (m, 1H), 4.88 (d, 1H, J = 3.6 Hz, C_{10}-H), 5.44 (s, 1H, C_{12}-H). FABMS (m/z): 449 $[M + Li]^+$, 267 $[M^+ - O(CH_2)_3OCO(CH_2)_2COOH]$. **12b** on treatment with CH_2N_2 in ether and subsequent purification by column chromatography furnished ester **13b** as an oil. FT-IR (neat, cm^{-1}) 1734.0; ^1H NMR (200 MHz, $CDCl_3$) δ 0.89 (d, 3H, J = 7.4 Hz, CH_3), 0.95 (d, 3H, J = 5.6 Hz, CH_3), 1.25–2.06 (m, 12H), 1.43 (s, 3H, CH_3), 2.31–2.43 (s, 1H), 2.63 (m, 5H), 3.38–3.96 (m, 2H), 3.64 (s, 3H, $O\underline{CH_3}$), 4.17 (t, 2H, J = 6.2 Hz, $\underline{CH_2}OCO(CH_2)_2COOCH_3$), 4.77 (d, 1H, J = 3.3 Hz, C_{10}-H), 5.40 (s, 1H, C_{12}-H). ESMS (m/z): 479 $[M + Na]^+$, 267 $[M^+ - O(CH_2)_3OCO(CH_2)_2COOH]$. Anal. Calcd for $C_{23}H_{36}O_9$: C, 60.51; H, 7.95. Found: C, 60.85; H, 7.90.

12c. Yield 68%; oil; FT-IR (neat, cm^{-1}) 2926.8, 2875.1, 1732.4, 1450.1, 1379.2, 1362.2, 1215.8, 1173.3, 1102.8, 1027.3, 769.8; ^1H NMR (200 MHz, $CDCl_3$) δ 0.90 (d, 3H, J = 7.3 Hz, CH_3), 0.95 (d, 3H, J = 5.9 Hz, CH_3), 1.21–2.07 (m, 14H), 1.44 (s, 3H, CH_3), 2.29–2.43 (s, 1H), 2.65 (m, 5H), 3.38–3.46 (m, 1H), 3.80–3.88 (m, 1H), 4.12 (brs, 2H, $\underline{CH_2}OCO(CH_2)_2COOH$), 4.80 (d, 1H, J = 2.8 Hz, C_{10}-H), 5.42 (s, 1H, C_{12}-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.73 (CH_3), 19.06 (CH_3), 23.16 (CH_2), 23.35 (CH_2), 24.23 (CH_2), 24.80 (CH_3), 24.97 (CH_2), 27.69 (CH_2), 28.39 (CH_2), 29.59 (CH), 33.34 (CH_2), 35.11 (CH_2), 36.10 (CH), 43.13 (CH), 51.29 (CH), 63.45 (CH_2), 66.67 (CH_2), 79.85 (C), 86.69 (CH), 100.72 (CH), 102.93 (C), 171.02 (C), 175.95 (C). FABMS (m/z): 457 $[M + H]^+$, 267 $[M^+ - O(CH_2)_4OCO(CH_2)_2COOH]$. **12c** on treatment with CH_2N_2 in ether and subsequent purification by column chromatography furnished ester **13c** as an oil. FT-IR (neat, cm^{-1}) 2923.9, 2873.7, 1737.7, 1436.9, 1361.7, 1161.1, 1103.2, 1029.9, 760.1; ^1H NMR (400 MHz, $CDCl_3$) δ 0.91 (d, 3H, J = 7.3 Hz, CH_3), 0.96 (d, 3H, J = 6.0 Hz, CH_3), 1.21–2.07 (m, 14H), 1.43 (s, 3H, CH_3), 2.33–2.41 (m, 1H), 2.64 (m, 5H), 3.38 (td, 1H, J = 10.1, 5.7 Hz), 3.68 (s, 3H, $O\underline{CH_3}$), 3.87 (td, 1H, J = 10.1, 5.7 Hz), 4.12 (t, 2H, J = 6.0 Hz, $CH_2OCO(CH_2)_2COOCH_3$), 4.78 (d, 1H, J = 3.6 Hz, C_{10}-H), 5.38 (s, 1H, C_{12}-H). FABMS (m/z): 471 $[M + H]^+$. Anal. Calcd for $C_{24}H_{38}O_9$: C, 61.26; H, 8.14. Found: C, 60.81; H, 8.03.

12d. Yield 84%; oil; FT-IR (neat, cm^{-1}) 2931.4, 2373.4, 1732.0, 1591.8, 1351.4, 1164.1, 1105.0, 1027.2, 756.0; ^1H NMR (200 MHz, $CDCl_3$) δ 0.91 (d, 3H, J = 7.3 Hz, CH_3), 0.96 (d, 3H, J = 5.8 Hz, CH_3), 1.23–2.06 (m, 16H), 1.43 (s, 3H, CH_3), 2.36 (m, 1H), 2.60–2.69 (m, 5H), 3.39 (td, 1H, J = 9.7, 6.2 Hz), 3.83 (td, 1H, J = 9.7, 6.2 Hz), 4.12 (t, 2H, J = 6.4 Hz, $\underline{CH_2}OCO(CH_2)_2COOH$), 4.78 (d, 1H, J = 3.4 Hz, C_{10}-H), 5.41 (s, 1H, C_{12}-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.74 (CH_3), 19.07 (CH_3), 21.40 (CH_2), 23.21 (CH_2), 23.42 (CH_2), 24.88 (CH_3), 26.99 (CH_2), 27.68 (CH_2), 27.90 (CH_2), 28.41 (CH_2), 29.66 (CH), 33.41 (CH_2), 35.13 (CH_2), 36.21 (CH), 43.23 (CH), 51.34 CH), 63.46 (CH_2), 66.95 (CH_2), 79.92 (C), 86.67 (CH), 100.66 (CH), 102.89 (C), 170.96 (C), 175.78 (C). ESMS (m/z): 493 $[M + Na]^+$, 488 $[M + NH_4]^+$, 509 $[M + K]^+$. **12d** on treatment with CH_2N_2 in ether and subsequent purification by column chromatography furnished ester **13d** as an oil. FT-IR (neat, cm^{-1}) 1737.0; ^1H NMR (400 MHz, $CDCl_3$) δ 0.89 (d, 3H, J = 7.3 Hz, CH_3), 0.95 (d, 3H, J = 5.7 Hz, CH_3), 1.21–2.11 (m, 16H), 1.43 (s, 3H, CH_3), 2.95–2.45 (m, 1H), 2.62 (m, 5H), 3.37 (td, 1H, J = 9.5, 6.5 Hz), 3.69 (s, 3H, $O\underline{CH_3}$), 3.84 (td, 1H, J = 9.6, 6.5 Hz), 4.09 (t, 2H, J = 6.4 Hz, $CH_2CH_2OCO(CH_2)_2COOCH_3$), 4.77 (d, 1H, J = 3.0 Hz, C_{10}-H), 5.38 (s, 1H, C_{12}-H). FABMS (m/z): 507 $[M + Na]^+$, 523 $[M + K]^+$. Anal. Calcd for $C_{25}H_{40}O_9$: C, 61.96; H, 8.32. Found: C, 62.30; H, 8.63.

12e. Yield 71%; oil; FT-IR (neat, cm^{-1}) 2935.5, 2869.9, 1735.8, 1442.7, 1367.4, 1218.9, 1164.9, 1103.2, 1018.3, 758.0; ^1H NMR (200 MHz, $CDCl_3$) δ 0.90 (d, 3H, J = 7.3 Hz, CH_3), 0.94 (d, 3H, J = 5.7 Hz, CH_3), 1.24–2.11 (m, 18H), 1.43 (s, 3H, CH_3), 2.31–2.43 (m, 1H), 2.62–2.69 (m, 5H), 3.35–3.41 (m, 1H), 3.76–3.87 (m, 1H), 4.12 (t, 2H, J = 6.0 Hz, $\underline{CH_2}OCO(CH_2)_2COOH$), 4.80 (d, 1H, J = 3.2 Hz, C_{10}-H), 5.42 (s, 1H, C_{12}-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.73 (CH_3), 19.11 (CH_3), 23.17 (CH_2), 23.35 (CH_2), 24.23 (CH_2), 24.45 (CH_2), 24.83 (CH_3), 27.27 (CH_2), 27.77 (CH_2), 28.12 (CH_2), 28.40 (CH_2), 29.65 (CH), 33.42 (CH_2), 35.36 (CH_2), 36.17 (CH), 43.31 (CH), 51.46 (CH), 63.91 (CH_2), 67.06 (CH_2), 80.12 (C), 86.87 (CH), 100.82 (CH), 103.07 (C), 171.48 (C), 178.24 (C); ESMS (m/z): 507 $[M + Na]^+$, 267 $[M^+ - O(CH_2)_6OCO(CH_2)_2COOH]^+$. **12e** on treatment with CH_2N_2 in ether and subsequent purification by column chromatography furnished ester **13e** as an oil. FT-IR (neat, cm^{-1}) 2931.6, 2746.4, 1695.3, 1419.5, 1311.5, 1203.5, 920.0, 771.5; ^1H NMR (300 MHz, $CDCl_3$) δ 0.90 (d, 3H, J = 7.2 Hz, CH_3), 0.95 (d, 3H, J = 6.0 Hz, CH_3), 1.23–2.06 (m, 18H), 1.44 (s, 3H, CH_3), 2.37–2.38 (m, 1H), 2.61–2.64 (m, 5H), 3.35–3.38 (m, 1H), 3.70 (s, 3H, $O\underline{CH_3}$), 3.82–3.85 (m, 1H), 4.09 (t, 2H, J = 6.6 Hz, $\underline{CH_2}OCO(CH_2)_2COOCH_3$), 4.78 (d, 1H, J = 3.0 Hz, C_{10}-H), 5.39 (s, 1H, C_{12}-H). FABMS (m/z): 499 $[M + H]^+$, 521 $[M + Na]^+$. Anal. Calcd for $C_{26}H_{42}O_9$: C, 62.63; H, 8.49. Found: C, 62.99; H, 8.77.

12f. Yield 70%; oil; FT-IR (neat, cm^{-1}) 2920.8, 2853.8, 2363.6, 1726.0, 1594.1, 1382.0, 1351.8, 1218.9, 1164.5, 1103.7, 1027.6, 761.4; ^1H NMR (200 MHz, $CDCl_3$) δ 0.91 (d, 3H, J = 7.3 Hz, CH_3), 0.97 (d, 3H, J = 5.8 Hz, CH_3), 1.27–2.12 (m, 22H), 1.45 (s, 3H, CH_3), 2.33–2.46 (m, 1H), 2.59–2.69 (m, 5H), 3.37–3.40 (m, 1H), 3.79–3.85 (m, 1H), 4.11 (t, 2H, J = 6.6 Hz, $\underline{CH_2}OCO(CH_2)_2COOH$), 4.79 (d, 1H, J = 3.2 Hz, C_{10}-H), 5.41 (s, 1H, C_{12}-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.72 (CH_3), 19.08 (CH_3), 23.18 (CH_2), 23.42 (CH_2), 24.47 (CH_2), 24.77 (CH_2), 24.88 (CH_3), 27.25 (CH_2), 27.69 (CH_2), 27.83 (CH_2), 28.29 (CH_2), 28.42 (CH_2), 29.65 (CH), 33.41 (CH_2), 35.19

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(CH_2), 36.23 (CH), 43.20 (CH), 51.33 (CH), 63.67 (CH_2), 67.11 (CH_2), 79.88 (C), 86.68 (CH), 100.65 (CH), 102.84 (C), 170.98 (C), 177.88 (C). ESMS (m/z): 512 $[M + Na]^+$, 267 $[M^+ - O(CH_2)_8OCO(CH_2)_2COOH]^+$. **12f** on treatment with CH_2N_2 in ether and subsequent purification by column chromatography furnished ester **13f** as an oil. FT-IR (neat, cm^{-1}) 2932.4, 2300.4, 1736.4, 1448.7, 1366.3, 1162.8, 1102.3, 1028.1, 874.0; ^1H NMR (200 MHz, $CDCl_3$) δ 0.89 (d, 3H, J = 7.3 Hz, CH_3), 0.95 (d, 3H, J = 5.8 Hz, CH_3), 1.18−2.12 (m, 22H), 1.44 (s, 3H, CH_3), 2.31−2.46 (m, 1H), 2.63 (m, 5H), 3.35 (td, 1H, J = 9.9 Hz, 6.1 Hz), 3.69 (s, 3H, OCH_3), 3.82 (td, 1H, J = 9.7 Hz, 6.4 Hz), 4.08 (t, 2H, J = 6.6 Hz, $CH_2OCO(CH_2)_2COOCH_3$), 4.77 (d, 1H, J = 3.3 Hz, C_{10}-H), 5.39 (s, 1H, C_{12}-H). FABMS (m/z): 527 $[M + H]^+$, 549 $[M + Na]^+$, 267 $[M^+ - O(CH_2)_8OCO(CH_2)_2COOCH_3]^+$. Anal. Calcd for $C_{28}H_{46}O_9$: C, 63.86; H, 8.80. Found: C, 63.96; H, 9.14.

12g. Yield 83%; oil; FT-IR (neat, cm^{-1}) 2930.8, 2374.3, 1722.0, 1596.2, 1352.0, 1026.6, 761.6; ^1H NMR (200 MHz, $CDCl_3$) δ 0.88 and 0.89 (2 × d, together integrating for 3H, J = 6.8 and 7.3 Hz, CH_3), 0.95 (d, 3H, J = 5.7 Hz, CH_3), 1.25−2.04 (m, 24H), 1.43 (s, 3H, CH_3), 2.29−2.43 (m, 1H), 2.62 (m, 5H), 3.31−3.46 and 3.62−3.67 (2 × m, together integrating for 1H), 3.76−3.97 (2 × m, together integrating for 1H), 4.08 (t, 2H, J = 6.4 Hz, $CH_2OCO(CH_2)_2COOH$), 4.42 and 4.78 (2 × d, 1H, J = 9.2 and 3.1 Hz, respectively, together integrating for C_{10}-H), 5.33 and 5.39 (2 × s, 1H, together integrating for C_{12}-H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 13.01 and 13.42 (2 × CH_3), 20.67 and 20.77 (2 × CH_3), 24.85 and 25.09 (2 × CH_2), 26.23 and 26.56 (2 × CH_3), 28.93 (CH_2), 29.55 (CH_2), 30.07 (CH_2), 31.34 (CH), 34.66 and 35.09 (2 × CH_2), 36.85 (CH_2), 37.87 (CH), 44.91 and 45.73 (2 × CH), 51.01 (CH), 65.40 (CH_2), 68.80 and 69.59 (2 × CH_2), 81.56 (C), 88.35 and 91.58 (2 × CH), 100.54 and 102.31 (2 × CH), 104.49 (C), 173.04 (C), 177.40 (C). ESMS (m/z): 527 $[M + H]^+$, 481 $[M^+ - COOH]$, 267 $[M^+ - O(CH_2)_9OCO(CH_2)_2COOH]^+$. **12g** on treatment with CH_2N_2 in ether and subsequent purification by column chromatography furnished ester **13g** as an oil. FT-IR (neat, cm^{-1}) 1732.0; ^1H NMR (200 MHz, $CDCl_3$) δ 0.89 (d, 3H, J = 7.3 Hz, CH_3), 0.95 (d, 3H, J = 5.8 Hz, CH_3), 1.25−2.04 (m, 24H), 1.43 (s, 3H, CH_3), 2.29−2.43 (m, 1H), 2.62 (m, 5H), 3.23−3.41 (m, 1H), 3.69 (s, 3H, OCH_3), 3.76−3.97 (m, 1H), 4.08 (t, 2H, J = 6.5 Hz, $CH_2OCO(CH_2)_2COOCH_3$), 4.41 and 4.77 (d, 1H, J = 9.7 and 2.7 Hz, respectively, together integrating for C_{10}-H), 5.33 and 5.38 (s, 1H, together integrating for C_{12}-H). FABMS (m/z): 539 $[M^+ - H]$, 267 $[M^+ - O(CH_2)_9OCO(CH_2)_2COOCH_3]^+$. Anal. Calcd for $C_{29}H_{48}O_9$: C, 64.42; H, 8.95. Found: C, 64.78; H, 9.16.

12h. Yield 83%; oil; FT-IR (neat, cm^{-1}) 2928.5, 2818.9, 2181.8, 1726.0, 1595.5, 1383.0, 1351.8, 1025.9, 763.5; ^1H NMR (300 MHz, $CDCl_3$) δ 0.91 (d, 3H, J = 7.3 Hz, CH_3), 0.96 (d, 3H, J = 5.8 Hz, CH_3), 1.23−2.07 (m, 26H), 1.45 (s, 3H, CH_3), 2.31−2.41 (m, 1H), 2.63−2.67 (m, 5H), 3.36−3.39 (m, 1H), 3.81−3.85 (m, 1H), 4.10 (t, 2H, J = 6.6 Hz, $CH_2OCO(CH_2)_2COOH$), 4.79 (d, 1H, J = 3.4 Hz, C_{10}-H), 5.41 (s, 1H, C_{12}-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.75 (CH_3), 19.06 (CH_3), 23.20 (CH_2), 23.40 (CH_2), 24.58 (CH_2), 24.90 (CH_3), 27.26 (CH_2), 27.69 (CH_2), 27.94 (CH_2), 28.16 (CH_2), 28.37 (CH_2), 29.68 (CH), 33.46 (CH_2), 35.20 (CH_2), 36.21 (CH), 43.25 (CH), 51.37 (CH), 63.81 (CH_2), 67.20 (CH_2), 79.93 (C), 86.69 (CH), 100.64 (CH), 102.79 (C), 171.00 (C), 175.73 (C). FABMS (m/z): 541 $[M + H]^+$, 267 $[M^+ - O(CH_2)_{10}OCO(CH_2)_2COOH]^+$. **12h** on treatment with CH_2N_2 in ether and subsequent purification by column chromatography furnished ester **13h** as an oil. FT-IR (neat, cm^{-1}) 2929.7, 2860.2, 1737.7, 1461.9, 1164.9, 1024.1, 756.0; ^1H NMR (200 MHz, $CDCl_3$) δ 0.91 (d, 3H, J = 7.3 Hz, CH_3), 0.96 (d, 3H, J = 6.0 Hz, CH_3), 1.22−2.07 (m, 26H), 1.44 (s, 3H, CH_3), 2.33−2.43 (m, 1H), 2.64 (m, 5H), 3.36 (td, 1H, J = 10.1 Hz, 6.1 Hz), 3.71 (s, 3H, OCH_3), 3.83 (td, 1H, J = 10.1 Hz, 6.1 Hz), 4.28 (t, 2H, J = 6.5 Hz, $CH_2OCO(CH_2)_2COOCH_3$), 4.79 (d, 1H, J = 3.2 Hz, C_{10}-H), 5.40 (s, 1H, C_{12}-H). FABMS (m/z): 555 $[M + H]^+$, 267 $[M^+ - O(CH_2)_{10}OCO(CH_2)_2COOCH_3]^+$. Anal. Calcd for $C_{30}H_{50}O_9$: C, 64.96; H, 9.09. Found: C, 64.77; H, 9.13.

12i. Yield 83%; oil; FT-IR (neat, cm^{-1}) 2819.8, 2375.9, 1724.0, 1595.7, 1352.2, 1017.0, 763.4; ^1H NMR (200 MHz, $CDCl_3$) δ 0.89 (d, 3H, J = 7.3 Hz, CH_3), 0.95 (d, 3H, J = 5.8 Hz, CH_3), 1.21−2.07 (m, 30H), 1.44 (s, 3H, CH_3), 2.31−2.43 (m, 1H), 2.61−2.67 (m, 5H), 3.37 (td, 1H, J = 9.5 Hz, 6.2 Hz), 3.80 (td, 1H, J = 9.5 Hz, 6.5 Hz), 4.09 (t, 2H, J = 6.6 Hz, $CH_2OCO(CH_2)_2COOH$), 4.78 (d, 1H, J = 3.4 Hz, C_{10}-H), 5.39 (s, 1H, C_{12}-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.00 (CH_3), 20.67 (CH_3), 24.85 (CH_2), 25.09 (CH_2), 26.24 (CH_2), 26.40 (CH_2), 26.60 (CH_3), 28.94 (CH_2), 29.19 (CH_2), 29.36 (CH_2), 29.92 (CH_2), 30.07 (CH_2), 31.36 (CH), 33.01 (CH_2), 36.87 (CH_2), 37.87 (CH_2), 44.92 (CH), 53.02 (CH), 65.44 (CH_2), 68.85 (CH_2), 81.68 (C), 88.32 (CH), 100.32 (CH), 102.32 (C), 172.63 (C), 177.01 (C). ESMS (m/z): 569 $[M + H]^+$, 591 $[M + Na]^+$, 607 $[M + K]^+$, 267 $[M^+ - O(CH_2)_{12}OCO(CH_2)_2COOH]^+$. **12i** on treatment with CH_2N_2 in ether and subsequent purification by column chromatography furnished ester **13i** as an oil. FT-IR (neat, cm^{-1}) 1740.0; ^1H NMR (200 MHz, $CDCl_3$) δ 0.89 (d, 3H, J = 7.3 Hz, CH_3), 0.95 (d, 3H, J = 5.9 Hz, CH_3), 1.20−2.07 (m, 30H), 1.44 (s, 3H, CH_3), 2.29−2.38 (m, 1H), 2.59−2.63 (m, 5H), 3.36 (td, 1H, J = 9.5 Hz, 6.5 Hz), 3.69 (s, 3H, OCH_3), 3.82 (td, 1H, J = 9.8 Hz, 6.5 Hz), 4.08 (t, 2H, J = 6.6 Hz, $CH_2OCO(CH_2)_2COOCH_3$), 4.77 (d, 1H, J = 3.5 Hz, C_{10}-H), 5.39 (s, 1H, C_{12}-H). ESMS (m/z): 583 $[M + H]^+$, 605 $[M + Na]^+$. Anal. Calcd for $C_{32}H_{54}O_9$: C, 65.95; H, 9.34. Found: C, 65.97; H, 9.44.

14a. Yield 51%; oil; FT-IR (neat, cm^{-1}) 2926.5, 1727.5, 1627.5, 1568.1, 1381.2, 1229.3, 1168.1, 1084.2, 1022.4, 620.2; ^1H NMR (200 MHz, $CDCl_3$) δ 0.91 (d, 3H, J = 7.6 Hz, CH_3), 0.95 (d, 3H, J = 6.0 Hz, CH_3), 1.25−2.13 (m, 10H), 1.43 (s, 3H, CH_3), 2.31−2.38 (m, 1H), 2.67 (m, 5H), 3.60−3.70 (m, 5H), 3.89−3.92 (m, 1H), 4.22−4.26 (m, 2H, $CH_2OCO(CH_2)_2COOH$), 4.86 (d, 1H, J = 2.7 Hz, C_{10}-H), 5.45 (s, 1H, C_{12}-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.64 (CH_3), 19.07 (CH_3), 23.14 (CH_2), 23.39 (CH_2), 24.78 (CH_3), 27.77 (CH_2), 30.83 (CH), 33.40 (CH_2), 35.14 (CH_2), 36.16 (CH), 43.18 (CH), 51.29 (CH), 62.67 (CH_2), 65.81 (CH_2), 67.59 (CH_2), 69.21 (CH_2), 79.89 (C), 88.62 (CH), 100.69 (CH), 102.95 (C), 172.39 (C), 175.85 (C). ESMS (m/z): 473 $[M + H]^+$, 267 $[M^+ - O(CH_2)_2O(CH_2)_2OCO(CH_2)_2COOH]^+$. **14a** on treatment with CH_2N_2 in ether and subsequent purification by column chromatography furnished ester **15a** as an oil. FT-IR (neat, cm^{-1}) 1730.0; ^1H NMR (400 MHz, $CDCl_3$) δ 0.91 (d, 3H, J = 7.6 Hz, CH_3), 0.94 (d, 3H, J = 5.6 Hz, CH_3), 1.21−2.07 (m, 10H), 1.44 (s, 3H, CH_3), 2.33−2.43 (m, 1H), 2.68 (m, 5H), 3.62−3.73 (m, 5H), 3.71 (s, 3H, OCH_3), 3.95 (m, 1H), 4.23 (t, 2H, J = 5.1 Hz, $CH_2OCO(CH_2)_2COOCH_3$), 4.85 (d, 1H, J = 2.8 Hz, C_{10}-H), 5.43 (s, 1H, C_{12}-H). FABMS (m/z): 487 $[M + H]^+$, 267 $[M^+ - O(CH_2CH_2O)_2CO(CH_2)_2COOCH_3]^+$. Anal. Calcd for $C_{24}H_{38}O_{10}$: C, 59.24; H, 7.87. Found: C, 59.29; H, 8.13.

14b. Yield 78%; oil; FT-IR (neat, cm^{-1}) 2929.2, 2877.5, 1733.0, 1452.9, 1380.1, 1218.6, 1167.4, 1136.1, 1107.5, 1025.8, 760.9; ^1H NMR (200 MHz, $CDCl_3$) δ 0.91 (d, 3H, J = 7.6 Hz, CH_3), 0.94 (d, 3H, J = 6.9 Hz, CH_3), 1.21−2.14 (m, 10H), 1.43 (s, 3H, CH_3), 2.31−2.43 (m, 1H), 2.65 (m, 5H), 3.64−3.67 (m, 9H), 3.92−3.99 (m, 1H), 4.27 (t, 2H, J = 4.5 Hz, $CH_2OCO(CH_2)_2COOH$), 4.85 (d, 1H, J = 3.1 Hz, C_{10}-H), 5.43 (s, 1H, C_{12}-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.58 (CH_3), 19.00 (CH_3), 23.12 (CH_2), 23.40 (CH_2), 24.74 (CH_3), 27.19 (CH_2), 27.62 (CH_2), 27.80 (CH_2), 28.37 (CH_2), 29.56 (CH), 33.38 (CH_2), 35.11 (CH_2), 36.15 (CH), 43.14 (CH), 51.26 (CH), 62.57 (CH_2), 66.01 (CH_2), 67.70 (CH_2), 69.19 (CH_2), 79.95 (C), 86.56 (CH), 100.84 (CH), 102.80 (C), 170.98 (C), 174.90 (C). FABMS (m/z): 517 $[M + H]^+$, 267 $[M^+ - O(CH_2CH_2O)_3CO(CH_2)_2COOH]^+$. **14b** on treatment with CH_2N_2 in ether and subsequent purification by column chromatography furnished ester **15b** as an oil. FT-IR (neat, cm^{-1}) 2873.7, 1739.7, 1438.8, 1348.1, 1105.1, 1029.9, 758.0; ^1H NMR (400 MHz, $CDCl_3$) δ 0.90 (d, 3H, J = 7.6 Hz, CH_3), 0.94 (d, 3H, J = 6.0 Hz, CH_3), 1.19−2.05 (m, 10H), 1.42 (s, 3H, CH_3), 2.33−2.41 (m, 1H), 2.61−2.69 (m, 5H), 3.58−3.70 (m, 9H), 3.68 (s, 3H, OCH_3), 3.92−3.97 (m, 1H), 4.25 (t, 2H, J = 5.0 Hz, $CH_2OCO(CH_2)_2COOCH_3$), 4.84 (d, 1H, J = 3.2 Hz, C_{10}-H), 5.42 (s, 1H, C_{12}-H). FABMS (m/z): 531 $[M + H]^+$, 537 $[M + Li]^+$, 553 $[M + Na]^+$. Anal. Calcd for $C_{26}H_{42}O_{11}\cdot 0.2H_2O$: C, 58.85; H, 7.98. Found: C, 58.69; H, 7.97.

14c. Yield 66%; oil; FT-IR (neat, cm^{-1}) 2925.9, 1734.1, 1454.1, 1379.3, 1218.5, 1106.0, 1027.3, 985.6, 758.2; ^1H NMR (200 MHz, $CDCl_3$) δ 0.90 (d, 3H, J = 7.4 Hz, CH_3), 0.94 (d, 3H, J = 6.1 Hz, CH_3), 1.20−2.04 (m, 10H), 1.43 (s, 3H, CH_3), 2.31−2.37 (m, 1H),

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2.63−2.69 (m, 5H), 3.56−3.69 (m, 13H), 3.85−3.98 (m, 1H), 4.24−4.29 (m, 2H, $\underline{CH_2}OCO(CH_2)_2COOCH_3$), 4.83 (d, 1H, J = 3.4 Hz, C_{10}-H), 5.42 (s, 1H, C_{12}-H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.68 (CH_3), 19.09 (CH_3), 23.12 (CH_2), 23.40 (CH_2), 24.83 (CH_3), 27.73 (CH_2), 27.99 (CH_2), 28.39 (CH_2), 29.56 (CH), 33.37 (CH_2), 35.12 (CH_2), 36.13 (CH), 43.14 (CH), 51.25 (CH), 62.53 (CH_2), 66.03 (CH_2), 67.70 (CH_2), 69.16 (CH_2), 69.28 (CH_2), 69.36 (CH_2), 79.84 (C), 86.59 (CH), 100.76 (CH), 102.82 (C), 170.86 (C), 174.50 (C). FABMS (m/z): 585 $[M + Na]^+$, 599 $[M + K]^+$, 267 $[M^+ - O(CH_2CH_2O)_4CO(CH_2)_2COOH]^+$. **14c** on treatment with CH_2N_2 in ether and subsequent purification by column chromatography furnished ester **15c** as an oil. FT-IR (neat, cm^{-1}) 2942.0, 1740.0, 1634.3, 1454.6, 1266.0, 1112.3, 1030.1, 756.2; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.91 (d, 3H, J = 7.2 Hz, CH_3), 0.94 (d, 3H, J = 6.3 Hz, CH_3), 1.21−2.05 (m, 10H), 1.43 (s, 3H, CH_3), 2.31−2.37 (m, 1H), 2.61−2.68 (m, 5H), 3.61−3.71 (m, 13H), 3.69 (s, 3H, $O\underline{CH_3}$), 3.91−3.97 (m, 1H), 4.25 (t, 2H, J = 4.8 Hz, $\underline{CH_2}OCO(CH_2)_2COOCH_3$), 4.82 (d, 1H, J = 3.3 Hz, C_{10}-H), 5.42 (s, 1H, C_{12}-H). FABMS (m/z): 575 $[M + H]^+$, 267 $[M^+ - O(CH_2CH_2O)_4CO(CH_2)_2COOH]^+$. Anal. Calcd for $C_{28}H_{46}O_{12}$: C, 58.52; H, 8.07. Found: C, 58.12; H, 8.24.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Table of purity data, evidence for stability of compound **12h**, table of NMR data of the final products **13a−i** and **15a−c**, and ^{1}H NMR and ^{13}C NMR spectra of compounds **7d**, **7e**, **7h**, **7i**, **10b**, **12d**, **12e**, **12f**, and **12h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) (a) Peters, W. Techniques for the Study of Drug Response in Experimental Malaria. In *Chemotherapy and Drug Resistance in Malaria*; Academic Press: London, 1970; pp 64−136. (b) For the in vivo antimalarial efficacy test, the blood schizontocidal activity of the test compounds was evaluated in rodent model using multidrug-resistant strain of *Plasmodium yoelii nigeriensis*. The colony bred Swiss mice of either sex (20 ± 2 g) were inoculated intraperitoneally with 1×10^5 *P. yoelii* (MDR) parasites on day 0, and treatment was administered to a group of five or six mice at each dose from day 0 to day 3, once daily. The drug dilutions of hydroxy functionalized compounds **7a−i** and **10a−c** were prepared in groundnut oil, while hemisuccinates **12a−i** and **14a−c** were dissolved in 5% $NaHCO_3$ to contain the required amount of the drug (0.6 mg for a dose of 48 mg/kg, 0.3 mg for a dose of 24 mg/kg, 0.15 mg for a dose of 12 mg/kg, 0.075 mg for a dose of 6 mg/kg, 0.003 75 mg for a dose of 3 mg/kg) in 0.1 mL and administered intramuscular for each dose. Parasitemia levels were recorded from thin blood smears on day 4 and subsequently twice a week until day 28.[11] The animals that did not develop patent infection until day 28 were recorded as cured. Multidrug-resistant *Plasmodium yoelii nigeriensis* used in this study is resistant to chloroquine, mefloquine, and halofantrine. Mice treated with β-arteether served as positive controls.
(10) (a) 100% suppression of parasitemia means no parasites were detected in 50 oil immersion microscopic fields (parasites, if at all present, are below the detection limit). The parasites present below the detection limit can multiply and eventually can be detected during observation on subsequent days. In such cases the drug is providing near 100% suppression of the parasitemia on day 4 but will not provide full protection to the treated mice in the 28 day survival assay. (b) 100% protection means none of the treated mice developed patent

infection during the 28 days of observation and hence were recorded as cured. Similarly 60% protection means only 3 out of 5 mice were cured.

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