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An Aldol - Bislactonization Route to α-Methylene Bis-γ-butyrolactones

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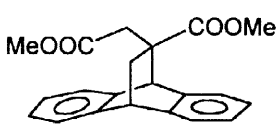
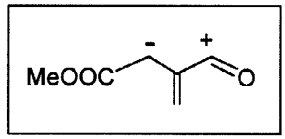
Abstract: The syntheses of α-methylene γ-butyrolactones and α-methylene bis-γ-butyrolactones are made simple through the use of the versatile dimethyl itaconate - anthracene adduct, **1**.

INTRODUCTION

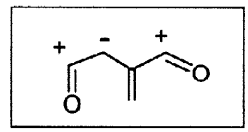
We have been employing the itaconate - anthracene adduct **1** as a starting block in the synthesis of various important bioactive natural products,[1] for example, **1** has served as the methylene carbonyl equivalent, ***A***, in the syntheses of sarkomycin,[2] methylenomycin A and deepoxy-4,5-didehydromethylenomycin A.[3] Here we further disclose that **1** behaves as an excellent methylene dicarbonyl equivalent, ***B***, which offers an ideal route to the fused bis-γ-butyrolactone skeleton, **2**. The α-methylene bis-γ-butyrolactone skeleton comprises the structure of various biologically active mold metabolites such as canadensolide, **2*d***,[4] sporothriolide, **2*f***[5] and the recently discovered phytotoxin, xylobovide, **2*b***.[6]



1



A



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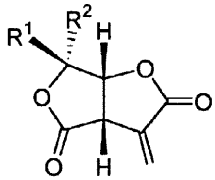
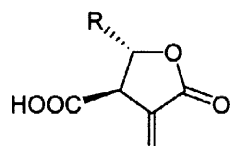


2 ***a***, $R^1 = R^2 = H$
b, $R^1 = H$, $R^2 = C_2H_5$
c, $R^1 = C_2H_5$, $R^2 = H$
d, $R^1 = H$, $R^2 = n\text{-}C_4H_9$
e, $R^1 = n\text{-}C_4H_9$, $R^2 = H$
f, $R^1 = H$, $R^2 = n\text{-}C_6H_{13}$
g, $R^1 = n\text{-}C_6H_{13}$, $R^2 = H$



3 ***a***, $R = n\text{-}C_5H_{11}$
b, $R = n\text{-}C_{11}H_{23}$
c, $R = n\text{-}C_{13}H_{27}$

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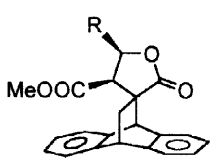
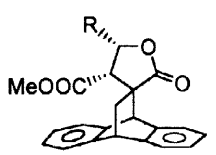
RESULTS AND DISCUSSION

In our pursuit of the synthesis of naturally occurring α-methylene γ-butyrolactones, *e.g.* methylenolactocin, **3*a***,[7] nephrosterinic acid, **3*b***, and protolichesterinic acid, **3*c***,[8] we discovered that **1** preferentially cyclized when its anion was allowed to react with an aldehyde to yield mainly the *cis*- diastereomeric lactones which thus necessitate a further isomerization step to obtain the desired compound.

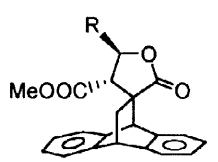
LDA (1.2 eq.) treatment of **1** in THF at 0°C generated the corresponding ester enolate, **4** (Scheme 1), which readily reacted with carpronaldehyde (-78° - 0°C, 2 hr.) to yield, after standard aqueous saturated ammonium chloride work-up followed by flash column chromatographic separation (silica gel, ethyl acetate : acetone : hexane = 1 : 0.5 : 8.5 as eluent), diastereomeric spiro-lactones **5*a-i*** - **5*a-iv*** respectively in 24%, 46%, 3% and 1% isolated yields. Similar reaction of the same ester enolate with laurinaldehyde provided **5*b-i*** - **5*b-iv*** in 13%, 45%, 7% and 5% yields and, likewise, compounds **5*c-i*** - **5*c-iv*** were obtained in 15%, 45%, 3% and 2% respectively when tetradecanal was allowed to react with the enolate **4** (Table 1). The stereochemical assignment to products, *i* - *iv*, were made according to their nmr data, *i.e.* the H_m - H_n coupling constants indicated the relative stereochemistry of the adjacent R and COOMe groups while the orientation of the latter was determined by the interaction of H_n to either H_x or H_a in the NOE experiments (see Figures).



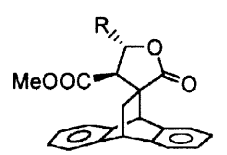
5-*i*



5-*ii*



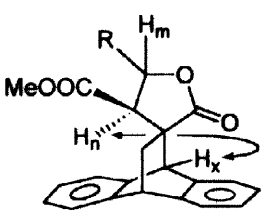
5-*iii*



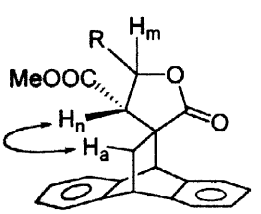
5-*iv*

Table 1 : % Yields of products **5**(*i-iv*)

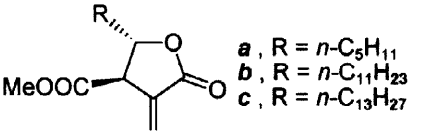
Product **5**	% Yield			
	i	*ii*	*iii*	*iv*
a , R = *n*-C_5H_{11}	24	46	3	1
b , R = *n*-$C_{11}H_{23}$	13	45	7	5
c , R = *n*-$C_{13}H_{27}$	15	45	3	2



5-*i* and 5-*iv*



5-*ii* and **5-*iii***



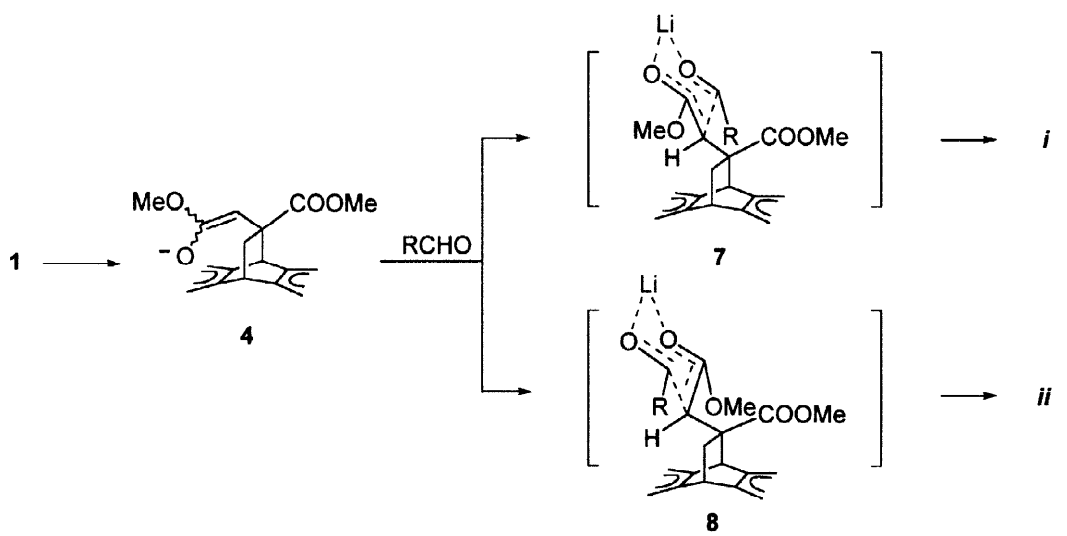
6

Isomerization of **5*a*-*i*** and **5*a*-*ii*** (0.5 eq. NaOMe, MeOH : THF = 1 : 5, room temp., 2 days) yielded the thermodynamically more stable *trans*- isomers, **5*a*-*iii*** and **5*a*-*iv***, respectively, in almost quantitative yields. Under similar reaction conditions **5*b*-*iii*** and **5*b*-*iv*** were obtained from **5*b*-*i*** and **5*b*-*ii*,** and **5*c*-*iii*** and **5*c*-*iv*** from **5*c*-*i*** and **5*c*-*ii*** respectively. In practice we found that it was more convenient to treat crude mixtures of lactones (*i* - *iv*) with base and then use chromatography (silica gel, ethyl acetate : acetone : hexane = 1 : 0.5 : 8.5 as eluent) to separate the isomerized products, *iii* and *iv*.

Flash vacuum pyrolysis of **5*a*-*iii*** and **5*a*-*iv*,** either in pure forms or as a mixture, gave rise to the methylene lactone **6*a*** (>90% purified yield in each run) which could be hydrolyzed under acidic conditions by the established method to yield methylenolactocin, **3*a***.[7] In a similar manner, compounds **5*b*-*iii*** and **5*b*-*iv*** almost quantitatively provided the ester **6*b*** thence nephrosterinic acid, **3*b***.[8c] Pyrolysis of **5*c*-*iii*** and **5*c*-*iv*** followed by hydrolysis yielded protolichesterinic acid, **3*c***.[8]

The stereochemical outcome of the tandem aldol - lactonization reactions between the ester enolate, **4**, and the aldehyde to provide mainly the *cis*- lactones, *i* and *ii*, can be explained by evoking the chair-like transition states, **7** and **8**, for the aldol reaction wherein large substituents occupy the less sterically demanding equatorial orientations as shown in Scheme 1.[9] This seemingly unfavorable situation in the synthesis of **3*a***, **3*b*** and **3*c***, however, was perceived to ideally lend itself to the construction of the *cis*- fused bis-γ-lactone skeleton, **2**.

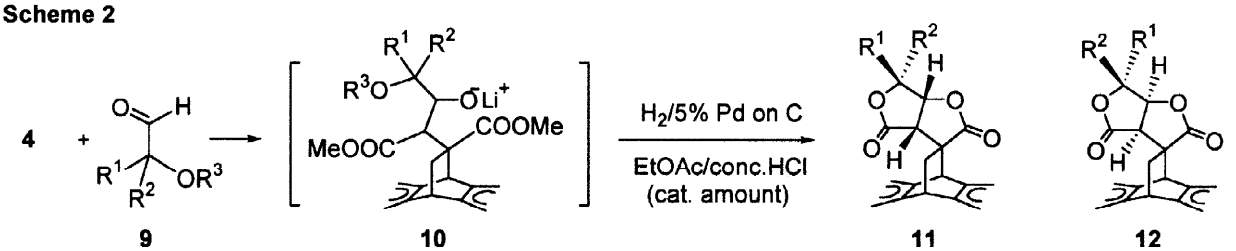
Scheme 1



When the anion **4** was allowed to react (THF, -78°- room temp., overnight) with the lithium alkoxide of glycolaldehyde monomer, **9*a***, generated *in situ* by the previously published method,[10] four products, separated (silica gel PLC using acetone : ethyl acetate : hexane = 1.5 : 1 : 7.5 as eluent) and identified as bislactones **11*a*** (19%) and **12*a*** (13%), and the *trans*-monolactones **13** (12%) and **14** (15%), were obtained (Table 2). The bislactones, **11*a*** and **12*a***, smoothly underwent flash vacuum pyrolysis to quantitatively give the corresponding methylene bislactone, **2*a***.

Manipulation of the aldol - bislactonization reaction eventually provided better yields of the bislactones **11** and **12** when **4** was allowed to react under the conditions described above with the *O*-benzyl protected hydroxy aldehyde **9*b*** followed by hydrogenolysis (H_2/5% Pd on C, EtOAc, catalytic amount of conc. HCl) of the crude reaction mixture. Silica gel PLC separation (hexane : dichloromethane = 1 : 1.5 as eluent) provided three stereomeric bislactones **11*b***, **11*c*** and **12*c*** in 1%, 33% and 34% yields respectively. Reaction of **4** with **9*c*** yielded the butyl substituted bislactones **11*d***, **11*e*** and **12*e*** in 2%, 34%, and 29% isolated yields and, lastly, compounds **11*f***, **11*g*** and **12*g*** (6%, 52% and 16% respectively) were obtained when the aldehyde **9*d*** was employed. It is interesting to note that none of the *trans*- monolactone, *i.e.* **13** or **14**, could be detected in these three experiments, and none of compound **12*b***, **12*d*** or **12*f*** was isolated from these reactions. As previously described, the stereochemistry of all products were deduced by extensive NOE experiments.

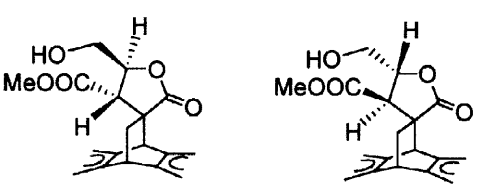
Scheme 2



9 **10** **11** **12**

a, $R^1 = R^2 = H$; $R^3 = Li$
b, R^1, $R^2 = C_2H_5$, H ; $R^3 = CH_2Ph$
c, R^1, $R^2 = n\text{-}C_4H_9$, H ; $R^3 = CH_2Ph$
d, R^1, $R^2 = n\text{-}C_6H_{13}$, H ; $R^3 = CH_2Ph$

a, $R^1 = R^2 = H$
b, $R^1 = H$, $R^2 = C_2H_5$
c, $R^1 = C_2H_5$, $R^2 = H$
d, $R^1 = H$, $R^2 = n\text{-}C_4H_9$
e, $R^1 = n\text{-}C_4H_9$, $R^2 = H$
f, $R^1 = H$, $R^2 = n\text{-}C_6H_{13}$
g, $R^1 = n\text{-}C_6H_{13}$, $R^2 = H$



13 **14**

Table 2 : % Yields of products **11-14**

Products	%Yield			
	11	**12**	**13**	**14**
a, $R^1 = R^2 = H$	19	13	12	15
b, $R^1 = H$, $R^2 = C_2H_5$	1	-	-	-
c, $R^1 = C_2H_5$, $R^2 = H$	33	34	-	-
d, $R^1 = H$, $R^2 = n\text{-}C_4H_9$	2	-	-	-
e, $R^1 = n\text{-}C_4H_9$, $R^2 = H$	34	29	-	-
f, $R^1 = H$, $R^2 = n\text{-}C_6H_{13}$	6	-	-	-
g, $R^1 = n\text{-}C_6H_{13}$, $R^2 = H$	52	16	-	-

Flash vacuum pyrolysis of **11*b*** furnished racemic xylobovide, **2*b***,[6] while compounds **11*c*** and **12*c*** provided *epi*-xylobovide, **2*c***. Likewise, **11*d*** gave canadensolide, **2*d***,[4] and *epi*-canadensolide, **2*e***,[4c] was obtained from **11*e*** and **12*e*** and, finally, **11*f*** provided sporothriolide, **2*f***,[5] while **11*g*** and **12*g*** gave epi-sporothriolide, **2*g***, all in almost quantitative yields.

CONCLUSIONS

Although the syntheses of the α-methylene bis-γ-butyrolactones described above have provided mainly compounds with opposite stereochemistry to that of the natural products (at the stereogenic center bearing the alkyl substituent) the work nevertheless offers the most direct and convenient route to the α-methylene bis-γ-butyrolactone skeleton through the versatile dimethyl itaconate - anthracene adduct, **1**.

EXPERIMENTAL†

General methods

Melting points were determined by Electrothermal Melting Point apparatus and were uncorrected. ^{1}H NMR spectra were recorded on Bruker DPX 300 and 400 MHz spectrometers in $CDCl_3$ using TMS as internal standard. Infrared spectra were recorded on a FT-IR system 2000 (Perkin-Elmer) spectrometer. Elemental analyses were performed on a Perkin Elmer Elemental Analyzer 2400 CHN and mass spectra were recorded on Bruker Esquire and Finnigan MAT INCOS 50 mass spectrometers. Merck silica gel 60 PF_{254} was used for PLC, Merck silica gel 60 and Merck silica gel 60H were employed for the flash column chromatography. Solvents were distilled before used. Dried, oxygen free THF (distilled from sodium / benzophenone) was used in all experiments. Lithium diisopropylamide (LDA) was prepared by the conventional method using *n*-butyllithium (purchased from Metallgesellschaft AG, molarity was determined by titration with 2,5-dimethoxybenzyl alcohol) and diisopropylamine in THF solution.

Preparation of Tetrahydro-4'-carbomethoxy-5'-alkyl-2'-furanone-3'-spiro-11-9,10-dihydro-9,10-ethanoanthracene, 5

Typical procedure

Tetrahydro-4'-carbomethoxy-5'-pentyl-2'-furanone-3'-spiro-11-9,10-dihydro-9,10-ethano-anthracene, **5*a*** : To a 500 ml round-bottomed flask equipped with a magnetic stirrer was fitted

with a three way stopcock with a septum cap and nitrogen inlet was added THF (100 ml) and dry diisopropylamine (9.1 ml, 64.5 mmol) *via* syringes. The mixture was cooled down to -78°C , *n*-butyllithium (1.02 N in hexane, 52.7 ml, 53.7 mmol) was added and the mixture left stirring at 0°C for 1 hr. A solution of dimethyl itaconate - anthracene adduct, **1**, (15.06 g, 44.8 mmol) in THF (100 ml) was introduced to the LDA solution at -78°C, then stirred at 0°C for 2 hr. Freshly distilled capronaldehyde (6.6 ml, 53.7 mmol) was added to the anion solution at -78°C after which the reaction mixture was left stirring at room temperature for 2 hr. The reaction mixture was quenched with saturated aqueous ammonium chloride solution at 0°C and the crude mixture was extracted several times with CH_2Cl_2. The dichloromethane solution was washed with H_2O, saturated NaCl solution, then dried over $MgSO_4$, filtered and evaporated to dryness.

The crude product was purified by flash column chromatography (silica gel) using EtOAc : acetone : hexane = 1 : 0.5 : 8.5 as eluent to give diastereomeric spiro-lactones, *tetrahydro-4'-carbomethoxy-5'-pentyl-2'-furanone-3'-spiro-11-9,10-dihydro-9,10-ethanoanthracene* **5*a*-*i*** - **5*a*-*iv***, in 24% (4.01 g), 46% (7.49 g), 3% (0.43 g) and 1% (0.15 g) respectively.

Compound **5*a*-*i*** : White crystals, m.p. 144 - 146°C (from hexane). IR ($CHCl_3$), ν_{max} 3028, 3014, 1781, 1737, 1172 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$), δ 0.90 (t, *J* 6.7 Hz, 3H), 1.20-1.70 (m, 8H), 1.44, 2.41, 4.34 (ABX system, *J* 13.0, 2.7, 2.6 Hz, 3H), 2.84 (d, *J* 5.5 Hz, 1H), 3.56 (s, 3H), 4.34 (s, 1H), 4.86 (ddd, 8.4, 5.5, 5.2 Hz, 1H), 7.05-7.35 (m, 8H). ^{13}C NMR (300 MHz, $CDCl_3$), δ 13.8, 22.3, 25.7, 31.3, 31.4, 36.9, 43.7, 48.8, 51.6, 52.6, 56.4, 76.8, 123.0, 123.8, 125.09, 125.1, 126.0, 126.01, 126.9, 127.1, 138.0, 139.2, 143.0, 143.5, 170.2, 176.3. Analysis C, 77.14 ; H, 7.11% $C_{26}H_{28}O_4$ requires C, 77.19 ; H, 6.98%. m/z (EIMS) 404 (M^+, 1%), 215 (5), 202 (4), 178 (87), 32 (57) and 28 (100).

Compound **5*a*-*ii*** : White crystals, m.p. 210 - 212°C (from CH_2Cl_2 / hexane). IR ($CHCl_3$), ν_{max} 3028, 3014, 1781, 1737, 1177 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$), δ 0.85 (t, *J* 6.8 Hz, 3H), 1.15-1.65 (m, 8H), 2.02, 2.11, 4.39 (ABX system, *J* 12.3, 3.1, 2.2 Hz, 3H), 2.24 (d, *J* 5.3 Hz, 1H), 3.85 (s, 3H), 4.32 (ddd, *J* 8.4, 5.3, 4.9 Hz, 1H), 4.64 (s, 1H), 7.00-7.55 (m, 8H). ^{13}C NMR (300 MHz, $CDCl_3$), δ 13.8, 22.2, 25.2, 30.8, 31.3, 40.5, 43.6, 46.7, 50.5, 51.5, 58.0, 76.3, 122.2, 123.9, 124.1, 125.75, 125.77, 126.0, 126.6, 127.3, 139.4, 140.7, 142.0, 143.3, 170.3, 176.9. Analysis C, 77.37 ; H, 6.98% $C_{26}H_{28}O_4$ requires C, 77.19 ; H, 6.98%. m/z (EIMS) 404 (M^+, 0.1%), 215 (3), 202 (3), 178 (100) and 32 (37).

Compound **5*a*-*iii*** : White crystals, m.p. 118 - 119°C (from hexane). IR ($CHCl_3$), ν_{max} 3028, 3015, 1770, 1733, 1171 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$), δ 0.93 (t, *J* 6.8 Hz, 3H), 1.28-1.75 (m, 8H), 2.12, 2.52, 4.39 (ABX system, *J* 12.5, 3.1, 2.4 Hz, 3H), 2.79 (d, *J* 10.4 Hz, 1H), 3.03 (s, 3H), 5.05 (ddd, 10.4, 9.3, 3.1 Hz, 1H), 4.53 (s, 1H), 7.08-7.36 (m, 8H). ^{13}C NMR (400 MHz, $CDCl_3$), δ 14.4 , 22.9, 25.8, 31.9, 34.7, 37.7, 44.3, 47.2, 51.6, 52.2, 56.6, 78.0, 123.6, 123.9, 125.1, 125.6, 126.3, 127.0, 127.07, 128.0, 138.4, 140.5, 143.8, 145.9, 169.1, 176.8. Analysis C, 77.34 ; H, 6.76% $C_{26}H_{28}O_4$ requires C, 77.19 ; H, 6.98%. m/z (EIMS) 404 (M^+, 2%), 215 (8), 202 (8), 178 (100), 32 (44) and 28 (94).

Compound **5*a-iv*** : White crystals, m.p. 83 - 85°C (from hexane). IR ($CHCl_3$), ν_{max} 3014, 3028, 1772, 1732, 1169 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$), δ 0.91 (t, *J* 6.5 Hz, 3H), 1.20-1.90 (m, 8H), 1.98, 2.58, 4.38 (ABX system, *J* 12.9, 3.2, 2.3 Hz, 3H), 2.93 (d, *J* 7.6 Hz, 1H), 3.24 (s, 3H), 4.41 (ddd, 7.7, 7.6, 4.9 Hz, 1H), 4.29 (s, 1H), 7.10-7.40 (m, 8H). ^{13}C NMR (300 MHz, $CDCl_3$), δ 13.9, 22.4, 24.9, 31.4, 34.9, 35.1, 43.8, 51.3, 51.9, 53.1, 56.7, 78.7, 122.6, 124.0, 125.6, 125.7, 126.2, 126.4, 126.8, 136.3, 139.4, 143.2, 143.5, 170.6, 177.0. Analysis C, 77.34 ; H, 6.96% $C_{26}H_{28}O_4$ requires C, 77.19 ; H, 6.98%. m/z (EIMS) 404 (M^+, 0.7%), 215 (3), 202 (3), 178 (100), 32 (4) and 28 (16).

Tetrahydro-4'-carbomethoxy-5'-undecyl-2'-furanone-3'-spiro-11-9,10-dihydro-9,10-ethano-anthracene, **5*b***

Compounds **5*b-i*** - **5*b-iv*** were obtained when laurinaldehyde was employed in the above *typical procedure.*

Compound **5*b-i*** (13% yield) : White crystals, m.p. 94 - 95°C (from hexane). IR ($CHCl_3$), ν_{max} 3029, 3013, 1780, 1738, 1172 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$), δ 0.89 (t, *J* 6.8 Hz, 3H), 1.20-1.70 (m, 20H), 1.44, 2.41, 4.35 (ABX system, *J* 13.1, 2.8, 2.7 Hz, 3H), 2.85 (d, *J* 5.5 Hz, 1H), 3.59 (s, 3H), 4.86 (ddd, 8.4, 5.5, 5.3 Hz, 1H), 4.33 (s, 1H), 7.05-7.35 (m, 8H). ^{13}C NMR (400 MHz, $CDCl_3$), δ 14.1, 22.6, 26.0, 29.27, 29.33, 29.4, 29.5, 31.4, 31.9, 37.0, 43.8, 48.9, 51.6, 52.6, 56.4, 76.8, 123.2, 123.9, 125.09, 125.11, 126.1, 126.9, 127.1, 138.0, 139.3, 143.0, 143.6, 170.3, 176.4. Analysis C, 78.85 ; H, 8.22% $C_{32}H_{40}O_4$ requires C, 78.64 ; H, 8.26%. m/z (EIMS) 488 (M^+, 0.2%), 215 (2), 203 (2) and 178 (100).

Compound **5*b-ii*** (45% yield) : White crystals, m.p. 159 - 160°C (from CH_2Cl_2 / hexane). IR ($CHCl_3$), ν_{max} 3018, 3028, 1782, 1737, 1172 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$), δ 0.87 (t, *J* 7.2 Hz, 3H), 1.15-1.70 (m, 20H), 1.98, 2.08, 4.39 (ABX system, *J* 12.4, 3.0, 2.3 Hz, 3H), 2.23 (d, *J* 5.2 Hz, 1H), 3.85 (s, 3H), 4.30 (ddd, *J* 8.4, 5.2, 5.1 Hz, 1H), 4.64 (s, 1H), 7.00-7.55 (m, 8H). ^{13}C NMR (400 MHz, $CDCl_3$), δ 14.0, 22.6, 25.6, 29.16, 29.2, 29.3, 29.46, 29.48, 30.9, 31.8, 40.6, 43.6, 46.7, 50.6, 51.6, 58.1, 76.4, 122.3, 123.9, 124.2, 125.8, 126.1, 126.6, 127.3, 139.4, 140.7, 142.0, 143.3, 170.3, 176.9. Analysis C, 78.50 ; H, 8.19% $C_{32}H_{40}O_4$ requires C, 78.64 ; H, 8.26%. m/z (EIMS) 488 (M^+, 0.3%), 215 (2), 203 (1) and 178 (100).

Compound **5*b-iii*** (7% yield) : White crystals, m.p. 78 - 79°C (from hexane). IR ($CHCl_3$), ν_{max} 3028, 3013, 1770, 1733, 1176 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$), δ 0.91 (t, *J* 7.0 Hz, 3H), 1.20-1.75 (m, 20H), 2.12, 2.51, 4.39 (ABX system, *J* 12.5, 3.0, 2.4 Hz, 3H), 2.78 (d, *J* 10.4 Hz, 1H), 3.03 (s, 3H), 5.04 (ddd, 10.4, 9.2, 3.0 Hz, 1H), 4.53 (s, 1H), 7.07-7.35 (m, 8H). ^{13}C NMR (400 MHz, $CDCl_3$), δ 14.2, 22.7, 25.8, 29.3, 29.4, 29.5, 29.6, 29.65, 29.66, 32.0, 34.3, 37.3, 43.9, 46.8, 51.2, 51.8, 56.2, 77.6, 123.2, 123.5, 124.7, 125.2, 126.0, 126.6, 126.7, 127.6, 138.0, 140.1, 143.4, 145.5, 168.7, 176.4. Analysis C, 78.82 ; H, 8.14% $C_{32}H_{40}O_4$ requires C, 78.64 ; H, 8.26%. m/z (EIMS) 488 (M^+, 0.4%), 215 (2), 203 (2) and 178 (100).

Compound **5*b-iv*** (5% yield) : White crystals, m.p. 71 - 73°C (from hexane). IR ($CHCl_3$), ν_{max} 3028, 3012, 1772, 1732, 1169 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$), δ 0.92 (t, *J* 7.0 Hz, 3H), 1.20-1.87 (m, 20H), 1.98, 2.58, 4.37 (ABX system, *J* 13.0, 3.2, 2.2 Hz, 3H), 2.92 (d, *J* 7.7 Hz 1H), 3.24 (s, 3H), 4.29 (s, 1H), 4.39 (ddd, 10.4, 7.7, 4.9 Hz, 1H), 7.11-7.37 (m, 8H). ^{13}C NMR (400 MHz, $CDCl_3$), δ 14.1, 22.7, 25.3, 29.3, 29.36, 29.40, 29.41, 29.6, 31.9, 35.0, 35.2, 43.9, 51.4, 52.0, 53.2, 56.8, 78.7, 122.6, 124.1, 125.7, 125.8, 126.3, 126.5, 126.9, 139.4, 139.5, 143.3, 143.6, 170.7, 177.0. Analysis C, 78.77 ; H, 8.31% $C_{32}H_{40}O_4$ requires C, 78.64 ; H, 8.26%. m/z (EIMS) 488 (M^+, 0.3%), 215 (4), 203 (2) and 178 (100).

Tetrahydro-4'-carbomethoxy-5'-tridecyl-2'-furanone-3'-spiro-11-9,10-dihydro-9,10-ethanoanthracene, **5*c***. Four diastereoisomers, **5*c-i*** - **5*c-iv*** were obtained when tetradecanal was employed in the reaction mentioned above.

Compound **5*c-i*** (15% yield) : White Crystals, m.p. 67 - 69°C (from hexane). IR ($CHCl_3$), ν_{max} 3030, 3013, 1780, 1739, 1172 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$), δ 0.92 (t, *J* 7.0 Hz, 3H), 1.20-1.75 (m, 24H), 1.48, 2.45, 4.38 (ABX system, *J* 13.1, 2.8, 2.6 Hz, 3H), 2.88 (d, *J* 5.5 Hz, 1H), 3.62 (s, 3H), 4.36 (s, 1H), 4.89 (ddd, 8.7, 5.5, 4.5 Hz, 1H), 7.10-7.40 (m, 8H). ^{13}C NMR (400 MHz, $CDCl_3$), δ 14.5, 23.1, 26.5, 29.76, 29.77, 29.8, 29.9, 30.0, 30.07, 30.1, 31.9, 32.3, 37.4, 44.2, 49.4, 52.1, 53.1, 56.9, 77.3, 123.7, 124.4, 125.6, 126.5, 127.4, 127.6, 138.5, 139.7, 143.5, 144.1, 170.7, 176.8. Analysis C, 79.26 ; H, 8.43% $C_{34}H_{44}O_4$ requires C, 79.02 ; H, 8.59%. m/z (EIMS) 516 (M^+, 0.6%), 215 (2), 202 (1) and 178 (100).

Compound **5*c-ii*** (45% yield) : White Crystals, m.p. 165 - 166°C (from CH_2Cl_2 / hexane). IR ($CHCl_3$), ν_{max} 3030, 3013, 1782, 1736, 1174 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$), δ 0.90 (t, *J* 6.9 Hz, 3H), 1.20-1.70 (m, 24H), 2.01, 2.11, 4.42 (ABX system, *J* 12.4, 3.2, 2.1 Hz, 3H), 2.26 (d, *J* 5.1 Hz, 1H), 3.85 (s, 3H), 4.34 (ddd, 8.4, 5.1, 4.7 Hz, 1H), 4.67 (s, 1H), 7.00-7.55 (m, 8H). ^{13}C NMR (300 MHz, $CDCl_3$), δ 14.1, 22.6, 25.7, 29.2, 29.26, 29.28, 29.4, 29.5, 29.57, 29.6, 31.0, 31.9, 40.7, 43.7, 46.8, 50.6, 51.6, 58.2, 76.4, 122.3, 123.9, 124.3, 125.86, 125.88, 126.1, 126.7, 127.4, 139.5, 140.8, 142.1, 143.3, 170.3, 176.9. Analysis C, 79.17 ; H, 8.81% $C_{34}H_{44}O_4$ requires C, 79.02 ; H, 8.59%. m/z (EIMS) 516 (M^+, 5%), 215 (5), 202 (1) and 178 (100).

Compound **5*c-iii*** (3% yield) : White Crystals, m.p. 84 - 85°C (from hexane). IR ($CHCl_3$), ν_{max} 3029, 3013, 1770, 1733, 1177 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$), δ 0.88 (t, *J* 6.7 Hz, 3H), 1.20-1.70 (m, 24H), 2.09, 2.48, 4.35 (ABX system, *J* 12.5, 3.1, 2.3 Hz, 3H), 2.74 (d, *J* 10.4 Hz, 1H), 2.99 (s, 3H), 4.49 (s, 1H), 5.01 (ddd, 10.4, 9.1, 3.1 Hz, 1H), 7.00-7.30 (m, 8H). ^{13}C NMR (300 MHz, $CDCl_3$), δ 14.1, 22.7, 25.7, 29.3, 29.32, 29.4, 29.5, 29.6, 29.61, 29.64, 31.9, 34.3, 37.2, 43.9, 46.7, 51.2, 51.8, 56.1, 77.6, 123.1, 123.4, 124.7, 125.1, 125.9, 126.5, 126.6, 127.5, 137.9, 140.0, 143.3, 145.4, 168.6, 176.3. Analysis C, 79.28 ; H, 8.64% $C_{34}H_{44}O_4$ requires C, 79.02 ; H, 8.59%. m/z (EIMS) 516 (M^+, 0.4%), 215 (2), 202 (1) and 178 (100).

Compound **5*c-iv*** (2% yield) : White Crystals, m.p. 86 - 87°C (from hexane). IR ($CHCl_3$), ν_{max} 3029, 3013, 1772, 1733, 1170 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$), δ 0.88 (t, *J* 6.8 Hz, 3H), 1.20-1.80 (m, 24H), 1.95, 2.55, 4.35 (ABX system, *J* 13.0, 3.2, 2.2 Hz, 3H), 2.89 (d, *J* 7.8 Hz, 1H), 3.21 (s, 3H), 4.25 (s, 1H), 4.35 (ddd, 11.1, 7.8, 4.8 Hz, 1H), 7.05-7.40 (m, 8H). ^{13}C NMR (300 MHz, $CDCl_3$), δ 14.1, 22.7, 25.3, 29.2, 29.3, 29.4, 29.5, 29.6, 29.62, 29.7, 31.9, 35.0, 35.1, 43.8, 51.3, 51.9, 53.1, 56.8, 78.7, 122.6, 124.0, 125.8, 126.3, 126.4, 126.8, 139.3, 139.5, 143.3, 143.6, 170.7, 177.0. Analysis C, 79.29 ; H, 8.33% $C_{34}H_{44}O_4$ requires C, 79.02 ; H, 8.59%. m/z (EIMS) 516 (M^+, 1%), 215 (1), 202 (1) and 178 (100).

Base induced isomerization reaction of Tetrahydro-4'-carbomethoxy-5'-tridecyl-2'-furanone-3'-spiro-11-9,10-dihydro-9,10-ethanoanthracene, 5

Typical procedure

To a solution of the spiro-lactone, **5*a-i*** (139.5 mg, 0.35 mmol) in THF (10 ml) and MeOH (2 ml) was added at 0°C sodium methoxide solution (1.38 N in anhydrous MeOH, 0.13 ml, 0.17 mmol) and the mixture was left stirring at room temperature for 2 days. The reaction mixture was quenched with saturated NH_4Cl solution and extracted several times with CH_2Cl_2. The combined organic layer was washed with H_2O, saturated NaCl solution, then dried over $MgSO_4$, filtered and evaporated to dryness in vacuo. TLC analysis (silica gel, using EtOAc : acetone : hexane = 1 : 0.5 : 8.5 as eluent) indicated that the isomerization reaction was almost complete. Crystallization of the crude residue with hexane gave the thermodynamically more stable *trans-* isomer, **5*a-iii*** (117 mg, 84% yield). Similar treatment of **5*a-ii*** provided **5*a-iv*** .

Isomerization of **5*b-i*** and **5*b-ii*** furnished **5*b-iii*** and **5*b-iv*** respectively, and, under the same reaction conditions, **5*c-i*** and **5*c-ii*** gave **5*c-iii*** and **5*c-iv*,** in 85 - 90% yields.

Flash vacuum pyrolysis of tetrahydro-4'-carbomethoxy-5'-alkyl-2'-furanone-3'-spiro-11-9,10-dihydro-9,10-ethanoanthracene, 5

Flash vacuum pyrolysis of **5** (*trans-* isomers) by the method previously described[2] induced the retro Diels-Alder reaction to provide the corresponding α-methylene γ-butyrolactone in almost quantitative yields.

Methyl tetrahydro-4-methylene-5-oxo-2-pentyl-3-furancarboxylate (Methylenolactocin methyl ester), **6*a***,[7d] was obtained as colourless oil. IR (film), ν_{max} 1770, 1742 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$), δ 0.90 (t, *J* 7.0 Hz, 3H), 1.20-1.55 (m, 6H), 1.70 (m, 2H), 3.60 (ddd, *J* 7.0, 3.0, 3.0 Hz, 1H), 3.80 (s, 3H), 4.82 (ddd, *J* 7.0, 6.0, 6.0 Hz, 1H), 5.94 (d *J* 2.5 Hz, 1H), 6.42 (d, *J* 2.5 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$), δ 14.0, 22.5, 24.5, 31.4, 35.7, 49.8, 53.0, 79.1, 125.3, 133.1, 168.4, 169.8. Analysis C, 63.2 ; H, 8.3% $C_{12}H_{18}O_4$ requires C, 63.7 ; H, 8.0%. m/z (HREIMS) 226.12024 (M^+), $C_{12}H_{18}O_4$ requires 226.12051.

Methyl tetrahydro-4-methylene-5-oxo-2-undecyl-3-furancarboxylate, **6b** : was obtained as white crystals, m.p. 38°C (from hexane). IR (KBr-pellet), ν_{max} 1760, 1663, 1261, 1206 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$), δ 0.89 (t, *J* 7.1 Hz, 3H), 1.20-1.60 (m, 18H), 1.60-1.80 (m, 2H), 3.59 (ddd, *J* 5.7, 3.0, 2.7 Hz 1H), 3.81 (s, 3H), 4.81 (ddd, *J* 7.2, 7.2, 5.7 Hz, 1H), 5.93 (d, *J* 2.7 Hz, 1H), 6.42 (d, *J* 3.0 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$), δ 14.5, 23.1, 25.2, 29.6, 29.7, 29.8, 29.9, 30.0, 32.3, 36.1, 50.2, 53.3, 79.4, 125.5, 133.5, 168.7, 170.1. Analysis C, 69.44 ; H, 9.61% $C_{18}H_{30}O_4$ requires C, 69.63 ; H, 9.75%. m/z (LC/(+)ESI-MS) 643.3 ($2M+Na^+$, 81%), 333.1 ($M+Na^+$, 100) and 311.2 (M^++1, 23).

Methyl tetrahydro-4-methylene-5-oxo-2-tridecyl-3-furancarboxylate (Protolichesterinic acid methyl ester), **6c** : White crystals, m.p. 44 - 45°C (from hexane). IR (KBr-pellet), ν_{max} 1760, 1662, 1263, 1206 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$), δ 0.90 (t, *J* 7.0 Hz, 3H), 1.20-1.60 (m, 22H), 1.60-1.80 (m, 2H), 3.60 (ddd, *J* 5.7, 3.0, 2.7 Hz, 1H), 3.82 (s, 3H), 4.81 (ddd, *J* 7.2, 7.2, 5.7 Hz, 1H), 5.93 (d, *J* 2.7 Hz, 1H), 6.42 (d, *J* 3.0 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$), δ 14.5, 23.1, 25.2, 29.6, 29.7, 29.8, 29.9, 29.99, 30.03, 30.1, 32.3, 36.2, 50.2, 53.3, 79.4, 125.5, 133.5, 168.7, 170.1. Analysis C, 71.10 ; H, 10.17% $C_{20}H_{34}O_4$ requires C, 70.95 ; H, 10.13%. m/z (LC/(+)ESI-MS) 699.3 ($2M+Na^+$, 88%), 333.1 ($M+Na^+$, 100) and 339.2 (M^++1, 59).

Hydrolysis of Methyl tetrahydro-4-methylene-5-oxo-2-alkyl-3-furancarboxylate, 6

Typical procedure

Tetrahydro-4-methylene-5-oxo-2-pentyl-3-furancarboxylic acid [(±)-Methylenolactocin], **3a**[7] : Acid catalyzed hydrolysis of **6a**, performed according to the known method[7d] using 6M HCl in 2-butanone, provided methylenolactocin, **3a**, as white crystalline, m.p. 82 - 83°C [from EtOAc / hexane; lit.[7d] m.p. 82 - 83°C (EtOAc / hexane)] whose spectroscopic data are identical in all respects to those reported.[7c,d] IR ($CHCl_3$), ν_{max} 3126, 1744, 1718, 1660, 1254, 1412, 1220 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$), δ 0.91 (t, *J* 6.9 Hz, 3H), 1.28-1.60 (m, 6H), 1.67-1.85 (m, 2H), 3.65 (ddd, *J* 5.6, 3.0, 2.7 Hz, 1H), 4.83 (ddd, *J* 7.2, 7.2, 5.6 Hz), 6.04 (d, *J* 2.7 Hz, 1H), 6.48 (d, *J* 3.0 Hz, 1H), 8.66 (broad peak, 1H). ^{13}C NMR (400 MHz, $CDCl_3$), δ 14.3, 22.8, 24.8, 31.7, 36.1, 49.9, 79.4, 126.4, 132.8, 168.8, 174.7. Analysis C, 61.94 ; H, 7.70% $C_{11}H_{16}O_4$ requires C, 62.23 ; H, 7.60%. m/z (LC/(+)ESI-MS) 446.8 ($2M+Na^+$, 28%) and 234.9 ($M+Na^+$, 100).

Tetrahydro-4-methylene-5-oxo-2-undecyl-3-furancarboxylic acid, **3b**,[8c] was obtained (77% isolated yield) as white crystals, m.p. 86 - 88°C. IR (KBr-pellet), ν_{max} 3103, 1745, 1718, 1662, 1257, 1222 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$), δ 0.90 (t, *J* 7.1 Hz, 3H), 1.20-1.68 (m, 18H), 1.68-1.85 (m, 2H), 3.65 (ddd, *J* 5.5, 2.9, 2.5 Hz, 1H), 4.83 (ddd, *J* 6.9, 6.9, 5.5 Hz, 1H), 6.05 (d, *J* 2.5 Hz, 1H), 6.49 (d, *J* 2.9 Hz, 1H), 6.90 (broad peak, 1H). ^{13}C NMR (400 MHz, $CDCl_3$), δ 14.5, 23.1, 25.2, 29.6, 29.7, 29.8, 29.9, 30.0, 32.3, 36.1, 49.9, 79.3, 126.3, 132.8, 168.7,

174.7. Analysis C, 68.42 ; H, 9.45% $C_{17}H_{28}O_4$ requires C, 68.87 ; H, 9.53%. m/z (LC/(+)ESI-MS) 319 ($M+Na^+$, 100%).

Tetrahydro-4-methylene-5-oxo-2-tridecyl-3-furancarboxylic acid [(±)-Protolichesterinic Acid], **3c**,[8] was obtained as white crystalline solid, m.p. 101 - 103°C [from EtOAc / hexane; lit.[8a] m.p. 103 - 105°C (EtOAc / hexane)]. IR (KBr-pellet), ν_{max} 3097, 1746, 1718, 1662, 1256, 1219 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$), δ 0.89 (t, *J* 6.4 Hz, 3H), 1.20-1.65 (m, 22H), 1.65-1.85 (m, 2H), 3.65 (ddd, *J* 5.4, 2.9, 2.4 Hz, 1H), 4.83 (ddd, *J* 6.8, 6.8, 5.4 Hz, 1H), 6.04 (d, *J* 2.4 Hz, 1H), 6.49 (d, *J* 2.9 Hz, 1H), 7.15 (broad peak, 1H). ^{13}C NMR (300 MHz, $CDCl_3$), δ 14.1, 22.7, 24.7, 29.2, 29.3, 29.4, 29.5, 29.57, 29.61, 29.7, 31.9, 35.7, 49.5, 78.9, 125.9, 132.4, 168.3, 174.3. Analysis C, 70.27 ; H, 10.04% $C_{19}H_{32}O_4$ requires C, 70.32 ; H, 9.95%. m/z (LC/(+)ESI-MS) 347 ($M+Na^+$, 100%) and 325.2 (M^++1, 3).

Reaction of the ester enolate 4 with lithium alkoxide of glycolaldehyde monomer. Formation of 2'7'-dioxabicyclo[3.3.0]octan-3',6'-dione-4'spiro-11-9,10-dihydro-9,10-ethanoanthracene 11*a* and 12*a*

To a 100 ml round-bottomed flask equipped with a magnetic stirring bar and a three way stopcock with a septum cap and nitrogen inlet was added freshly distilled THF (20 ml) and dry diisopropylamine (1 ml, 7.27 mmol) *via* syringes. The mixture was cooled down to -78°C, *n*-butyllithium (1.02 N in hexane, 6 ml, 6.06 mmol) was added and the mixture left stirring at 0°C for 1hr. A solution of dimethyl itaconate - anthracene adduct, **1** (1.02 g, 3.03 mmol) in THF (20 ml) was introduced to the LDA solution at -78°C, then stirred at 0°C for 2 hr. Anhydrous $ZnCl_2$ solution (0.41 g, 3.44 mmol) in THF (10 ml) and a solution of glycolaldehyde dimer (0.18 g, 1.52 mmol) in THF (20 ml) were successively added to the anion solution at -78°C. The reaction mixture was left stirring at room temperature for 2 hr. and then quenched with saturated NH_4Cl solution and 10% HCl. The crude mixture was extracted several times with CH_2Cl_2, the dichloromethane solution was washed with H_2O, saturated NaCl solution, then dried over $MgSO_4$, filtered and evaporated in vacuo.

The crude product was purified by flash column chromatography (silica gel) using acetone : EtOAc : hexane = 1.5 : 1 : 7.5 as eluent to give compounds **11*a***, **12*a***, **13*a*** and **14*a*** in 19%, 13%, 12% and 15% yields respectively.

Compound **11*a*** : White crystals, m.p. 270°C (from acetone / hexane). IR (KBr-pellet), ν_{max} 3071, 3042, 1778, 1203, 1165, 760 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$), δ 1.95, 2.24, 4.42 (ABX system, *J* 12.5, 2.8, 2.5 Hz, 3H), 2.50 (d, *J* 4.7 Hz, 1H), 4.24 (dd, *J* 11.4, 3.4 Hz, 1H), 4.54 (d, *J* 11.4 Hz, 1H), 4.94 (dd, *J* 4.7, 3.4 Hz, 1H), 5.11 (s, 1H), 7.10-7.80 (m, 8H). ^{13}C NMR (300 MHz, $CDCl_3$), δ 42.4, 43.6, 44.2, 49.5, 51.2, 69.5, 75.4, 122.7, 123.2, 126.0, 126.1, 126.3, 126.4, 126.6, 127.3, 139.3, 140.8, 142.2, 143.0, 171.2, 175.0. Analysis C, 75.46 ; H, 4.99% $C_{21}H_{16}O_4$ requires C, 75.88 ; H, 4.86%. m/z (LC/(+)ESI-MS) 687.6 ($2M+Na^+$, 49%) and 355.3 ($M+Na^+$, 100).

Compound **12*a*** : Colourless crystals, m.p. 214 - 215°C. IR (KBr-pellet), ν_{max} 3071, 3042, 1778, 1203, 1165, 760 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$), δ 2.00, 2.99, 4.49 (ABX system, *J* 13.3, 2.9, 2.5, Hz, 3H), 2.84 (d, *J* 5.6 Hz, 1H), 4.19 (s, 1H), 4.40 (dd, *J* 11.5, 4.0 Hz, 1H), 4.59 (d, *J* 11.5 Hz, 1H), 5.49 (dd, *J* 5.6, 4.0 Hz, 1H), 7.10-7.80 (m, 8H). ^{13}C NMR (300 MHz, $CDCl_3$), δ 30.7, 43.6, 47.4, 51.7, 52.1, 70.3, 75.8, 123.3, 124.5, 125.1, 125.2, 126.1, 127.3, 127.6, 137.2, 138.7, 143.2, 143.7, 171.2, 175.0. Analysis C, 75.56 ; H, 4.76% $C_{21}H_{16}O_4$ requires C, 75.88 ; H, 4.86%. m/z (LC/(+)ESI-MS) 687.5 ($2M+Na^+$, 19%) and 355.2 ($M+Na^+$, 100).

4-Methylene-2,7-dioxabicyclo[3.3.0]octan-3,6-dione, 2*a*

Flash vacuum pyrolysis of either **11*a*** or **12*a*** provided the methylene bislactone **2*a*** in 72% yield.

Compound **2*a*** : White crystals, m.p. 86 - 87°C (from CH_2Cl_2 / hexane). IR (KBr-pellet), ν_{max} 3102, 3036, 1753, 1662, 1216, 1198 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$), δ 4.00 (ddd, *J* 7.2, 2.2, 2.0 Hz, 1H), 4.65 (d, *J* 3.3 Hz, 2H), 5.34 (ddd, *J* 7.2, 3.3, 3.3 Hz, 1H), 6.22 (d, *J* 2.0 Hz, 1H), 6.52 (d, *J* 2.2 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$), δ 44.3, 72.5, 75.7, 127.6, 129.5, 167.2, 172.5. Analysis C, 54.61 ; H, 4.09% $C_7H_6O_4$ requires C, 54.54 ; H, 3.93%. m/z (LC/(+) ESI-MS) 176.7 ($M+Na^+$, 26%), 102.3 (100) and 74.8 (9).

Synthesis of 2-benzyloxyalkanal

Typical procedure

2-Benzyloxybutanal, **9*b*** : The sodium salt of 2-hydroxybutanoic acid (5.0 g, 39.68 mmol) was subjected to benzylation using NaH (60% in white oil, 1.74 g, 43.65 mmol) and benzylbromide (9.8 ml, 81.34 mmol) in DMF (150 ml) at room temperature. Conventional work-up provided benzyl 2-benzyloxybutanoate (7.57 g, 67%).

Benzyl 2-benzyloxybutanoate (7.57 g, 26.65 mmol) was reduced with LAH (3.54 g, 93.29 mmol) in THF (140 ml) at -10°C to yield the corresponding alcohol, 2-benzyloxybutanol (4.69 g, 98%).

2-Benzyloxybutanol (4.69 g, 26.05 mmol) was converted to the desired product, 2-benzyloxybutanal, **9*b***, in 90% yield by Swern oxidation using oxalyl chloride (2.5 ml, 28.68 mmol), DMSO (2.0 ml, 28.68 mmol) in CH_2Cl_2 (200 ml) and the crude product was purified by bulb to bulb distillation under reduced pressure.

2-Benzyloxybutanal, **9*b*** : Colourless liquid. IR (neat), ν_{max} 3032, 2937, 1732, 1496, 1455, 1378, 1089 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$), δ 1.01 (t, *J* 7.4 Hz, 3H), 1.65-1.85 (m, 2H), 3.74 (ddd, *J* 5.4, 4.4, 2.1Hz, 1H), 4.64 (AB system, *J* 11.8 Hz, 2H), 7.32-7.47 (m, 5H), 9.68 (d, *J* 2.1 Hz, 1H). m/z (EIMS) 178 (M^+), $C_{11}H_{14}O_2$ requires 178.

2-Benzyloxyhexanal, **9*c*** : Colourless liquid (70% overall yield from 2-hydroxyhexanoic acid). IR (neat), ν_{max} 2950, 1730, 1500, 1455, 1380, 1100 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$), δ 0.85 (t, *J* 7.2 Hz, 3H), 1.20-1.45 (m, 4 H), 1.59-1.67 (m, 2H), 3.70 (dt, *J* 6.5, 2.1 Hz, 1H), 4.55 (AB system, *J* 11.7 Hz, 2H), 7.20-7.35 (m, 5H), 9.60 (d, *J* 2.1 Hz, 1H). m/z (EIMS) 206 (M^+), $C_{13}H_{18}O_2$ requires 206.

2-Benzyloxyoctanal, **9*d*** : Colourless liquid (71% overall yield from 2-hydroxyoctanoic acid). IR (neat), ν_{max} 2930, 2859, 1714, 1455, 1379, 1166 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$), δ 0.87 (t, *J* 6.1 Hz, 3H), 1.20-1.50 (m, 8H), 1.60-1.72 (m, 2H), 3.73 (dt, *J* 6.4, 2.1 Hz, 1H), 4.58 (AB system, *J* 11.7 Hz, 2H), 7.25-7.37 (m, 5H), 9.62 (d, *J* 2.1 Hz, 1H). m/z (EIMS) 234 (M^+), $C_{15}H_{22}O_2$ requires 234.

Reaction of the ester enolate 4 with 2-benzyloxyalkanal, 9

Typical procedure

Reaction of the ester enolate **4** *with 2-benzyloxybutanal,* **9*b*** ; *Formation of 8'-Ethyl-2'7'-dioxabicyclo [3.3.0] octan-3',6'-dione-4'-spiro-11-9,10-dihydro-9,10-ethanoanthracene* **11*b***, **11*c***, *and* **12*c*** ; To a solution of LDA (1.1 eq., 41.91 mmol) in THF (150 ml) at -78°C was added a solution of dimethyl itaconate - anthracene adduct, **1** (12.80 g, 38.10 mmol) in THF (50 ml) and the mixture was left stirring at 0°C for 1 hr. 2-Benzyloxybutanal, **9*b*** (7.12 g, 40.0 mmol) was added at -78°C and stirred at -78°C for 0.5 hr. and at room temperature for 3 hr. The mixture was quenched with saturated aqueous ammonium chloride solution and the crude product was extracted into dichloromethane, the combined dichloromethane extract was washed with water, dried over $MgSO_4$ and evaporated to dryness to give the crude product.

The crude product was dissolved in ethyl acetate (200 ml) and 5% palladium on charcoal (catalytic amount) and three drops of conc. HCl were added. The mixture was subjected hydrogenolysis at room temperature. The reaction mixture was filtered through celite and the filtrate washed with saturated aqueous $NaHCO_3$ solution, water, dried over $MgSO_4$ and evaporated to dryness. The residue was column chromatographed (silica gel, using hexane : dichloromethane = 4 : 6 as eluent) to give recovered starting material **1** (2.67 g, 79% conversion), **11*b*** (0.12 g, 1%), **11*c*** (3.82 g, 33%) and **12*c*** (3.92 g, 34%).

Compound **11*b*** : White crystals, m.p. 270 - 272°C (from CH_2Cl_2 / hexane). IR ($CHCl_3$), ν_{max} 3028, 2960, 1777, 1460 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$), δ 1.06 (t, *J* 7.5 Hz, 3H), 1.77-2.03 (m, 2H), 1.91, 2.19, 4.41 (ABX system, *J* 12.5, 2.8, 2.5 Hz, 3H), 2.48 (d, *J* 4.5 Hz, 1H),

4.19 (dt, *J* 7.2, 3.2 Hz, 1H), 4.75 (dd, *J* 4.5, 3.2 Hz, 1H), 5.11 (s, 1H), 7.12-7.82 (m, 8H). ^{13}C NMR (400 MHz, $CDCl_3$), δ 9.5, 22.0, 42.3, 43.6, 44.5, 49.4, 53.1, 76.2, 81.5, 122.7, 123.2, 126.0, 126.1, 126.2, 126.4, 126.6, 127.3, 139.4, 141.0, 142.2, 143.0, 171.0, 175.2. Analysis C, 76.52 ; H, 5.57% $C_{23}H_{20}O_4$ requires C, 76.64 ; H, 5.60%. m/z (LC/(+)ESI-MS) 383.3 ($M+Na^+$, 71%), 361.4 (M^++1, 40) and 179.1 (100).

Compound **11*c*** : White crystals, m.p. 272 - 274°C (from CH_2Cl_2 / hexane). IR ($CHCl_3$), ν_{max} 3024, 3012, 2998, 1791, 1459, 1359, 1157 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$), δ 0.96 (t, *J* 7.5 Hz, 3H), 1.43-1.57 (m, 2H), 1.89, 2.18, 4.38 (ABX system, *J* 12.5, 2.8, 2.5 Hz, 3H), 2.46 (d, *J* 4.7 Hz, 1H), 4.60 (d, *J* 4.7 Hz, 1H), 4.48 (t, *J* 7.2 Hz, 1H), 5.06 (s, 1H), 7.09-7.8 (m, 8H). ^{13}C NMR (400 MHz, $CDCl_3$), δ 9.8, 25.6, 43.1, 44.3, 49.8, 51.4, 79.2, 83.6, 123.9, 124.4, 127.1, 127.3, 127.4, 127.5, 127.9, 128.5, 140.6, 142.1, 143.6, 144.2, 172.5, 176.5. Analysis C, 76.71 ; H, 5.44% $C_{23}H_{20}O_4$ requires C, 76.64 ; H, 5.60%. m/z (LC/(+)ESI-MS) 360.7 (M^++1, 100%), 178.9 (57) and 85.4 (11).

Compound **12*c*** : White crystals, m.p. 198 - 199°C (from CH_2Cl_2 / hexane). IR ($CHCl_3$), ν_{max} 3028, 2942, 1773, 1459, 1359, 1172, 1147, 1034, 765 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$), δ 1.06 (t, *J* 7.4 Hz, 3H), 1.59-1.77 (m, 2H), 2.25, 3.18, 4.51 (ABX system, *J* 13.3, 2.9, 2.3 Hz, 3H), 2.86 (d, *J* 5.6 Hz, 1H), 4.21 (s, 1H), 4.57 (dd, *J* 7.5, 6.6 Hz, 1H), 5.17 (d, *J* 5.6 Hz, 1H), 7.15-7.45 (m, 8H). ^{13}C NMR (400 MHz, $CDCl_3$), δ 9.5, 26.2, 31.1, 43.9, 47.7, 51.7, 52.4, 79.3, 83.8, 123.6, 124.8, 125.5, 126.4, 126.5, 127.6, 128.0, 137.7, 139.1, 143.6, 144.1, 173.2, 175.7. Analysis C, 76.48 ; H, 5.44% $C_{23}H_{20}O_4$ requires C, 76.64 ; H, 5.60%. m/z (LC/(+)ESI-MS) 360.7 (M^++1, 9.4%), 190.9 (6) and 178.9 (100).

8'-Butyl-2'7'-dioxabicyclo[3.3.0]octan-3',6'-dione-4'-spiro-11-9,10-dihydro-9,10-ethano-anthracene **11*d*, 11*e*** *and* **12*e*** ; According to the *Typical procedure* described above, compounds **11*d*, 11*e*** and **12*e*** were obtained from the reaction of the enolate **4** and 2-benzyloxyhexanal, **9*c***.

Compound **11*d*** (2% yield) : White plates, m.p. 177 - 178°C (from CH_2Cl_2 / hexane). IR ($CHCl_3$), ν_{max} 3028, 2961, 1779, 1460, 1215, 742 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$), δ 0.9 (t, *J* 7.2 Hz, 3H), 1.23-1.92 (m, 6H), 1.85, 2.12, 4.36 (ABX system, *J* 12.5, 2.9, 2.4 Hz, 3H), 2.4 (d, *J* 4.5 Hz, 1H), 4.18 (ddd, *J* 6.5, 4.4, 3.4 Hz, 1H), 4.64 (dd, *J* 4.5, 3.4 Hz, 1H), 5.07 (s, 1H), 7.05-7.78 (m, 8H). ^{13}C NMR (300 MHz, $CDCl_3$), δ 13.7, 22.3, 27.2, 28.2, 42.1, 43.5, 44.3, 49.3, 52.9, 76.4, 80.1, 122.6, 123.1, 125.8, 126.0, 126.1, 126.3, 126.5, 127.2, 139.3, 140.8, 142.1, 143.0, 170.9, 175.2. Analysis C, 76.99 ; H, 6.33% $C_{25}H_{24}O_4$ requires for C, 77.29 ; H, 6.23%. m/z (EIMS) 388 (M^+, 1%) and 178 (100).

Compound **11*e*** (34% yield) : White plates, m.p. 255°C (decomposed, from CH_2Cl_2 / hexane). IR ($CHCl_3$), ν_{max} 3029, 2961, 1777, 1460, 1355, 1210 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$), δ 0.87 (t, *J* 7.1 Hz, 3H), 1.2-1.5 (m, 6H), 1.95, 2.17, 4.38 (ABX system, *J* 12.5, 2.8, 2.4 Hz, 3H), 2.46 (d, *J* 4.5 Hz, 1H), 4.53 (t, *J* 7.3 Hz, 1H), 4.58 (d, *J* 4.5 Hz, 1H), 5.05 (s, 1H),

7.08-7.8 (m, 8H). ^{13}C NMR (300 MHz, $CDCl_3$), δ 13.6, 22.0, 26.7, 31.4, 42.3, 43.5, 44.2, 49.1, 50.9, 78.5, 81.4, 122.6, 123.1, 125.8, 126.0, 126.1, 126.3, 126.6, 127.2, 139.3, 140.8, 142.2, 142.9, 171.0, 174.9. Analysis C, 77.60 ; H, 6.37% $C_{25}H_{24}O_4$ requires C, 77.29 ; H, 6.23%. m/z (EIMS) 388 (M^+, 13%), 178 (100) and 91 (41).

Compound **12*e*** (29% yield) : White plates, m.p. 184 - 185°C (from CH_2Cl_2 / hexane). IR ($CHCl_3$), ν_{max} 3020, 2922, 1773, 1460, 1350, 1220, 738, 780, 671 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$), δ 0.89 (t, *J* 7.2 Hz, 3H), 1.22-1.65 (m, 6H), 1.96, 2.96, 4.44 (ABX system, *J* 13.3, 3.0, 2.5 Hz, 3H), 2.80 (d, *J* 5.6 Hz, 1H), 4.16 (s, 1H), 4.56 (dt, *J* 7.9, 6.1 Hz, 1H), 5.11 (d, *J* 5.6 Hz, 1H), 7.07-7.4 (m, 8H). ^{13}C NMR (300 MHz, $CDCl_3$), δ 13.6, 21.9, 26.6, 30.6, 32.0, 43.4, 47.0, 51.2, 51.8, 79.1, 82.1, 123.1, 124.2, 125.0, 125.04, 125.8, 125.9, 127.0, 127.4, 137.2, 138.5, 143.1, 143.6, 172.6, 175.1. Analysis C, 77.22 ; H, 6.18% $C_{25}H_{24}O_4$ requires C, 77.29 ; H, 6.23%. m/z (LC/(+)ESI-MS) 389.2 (M^++1, 2%), 193.1 (5) and 179.1 (100).

8'-Octyl-2'7'-dioxabicyclo[3.3.0]octan-3',6'-dione-4'-spiro-11-9,10-dihydro-9,10-ethano-anthracene **11*f*, 11*g*** *and* **12*g*** ; Compounds **11*f*, 11*g*** and **12*g*** were obtained from the reaction of the enolate **4** and 2-benzyloxyoctanal, **9*d***.

Compound **11*f*** (6% yield) : White plates, m.p. 169 - 171°C (from CH_2Cl_2 / hexane). IR ($CHCl_3$), ν_{max} 3029, 2930, 1778, 1459, 1326 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$), δ 0.87 (t, *J* 6.7 Hz, 3H), 1.16-1.51 (m, 8H), 1.65-1.98 (m, 2H), 1.85, 2.12, 4.36 (ABX system, *J* 12.5, 3.0, 2.6 Hz, 3H), 2.41 (d, *J* 4.5 Hz, 1H), 4.19 (ddd, *J* 8.0, 6.4, 3.2 Hz, 3H), 4.65 (dd, *J* 4.5, 3.2 Hz, 1H), 5.06 (s, 1H), 7.06-7.77 (m, 8H). ^{13}C NMR (300 MHz, $CDCl_3$), δ 13.9, 22.4, 25.1, 28.5, 28.8, 31.4, 42.1, 43.5, 44.3, 49.3, 52.9, 76.4, 80.1, 122.6, 123.1, 125.8, 126.0, 126.1, 126.3, 126.5, 127.2, 139.3, 140.8, 142.1, 142.9, 170.9, 175.1. Analysis C, 77.93 ; H, 7.0% $C_{27}H_{28}O_4$ requires C, 77.85 ; H, 6.78%. m/z (LC/(+)ESI-MS) 416.2 (M^++1, 0.5%) and 179.1 (100).

Compound **11*g*** (52% yield) : White plates, m.p. 205 - 206°C (from CH_2Cl_2 / hexane). IR ($CHCl_3$), ν_{max} 3029, 2931, 1777, 1459, 1358 cm^{-1}. ^1H NMR (300MHz, $CDCl_3$), δ 0.86 (t, *J* 7.0 Hz, 3H), 1.1-1.5 (m, 10H), 1.86, 2.12, 4.36 (ABX system, *J* 12.5, 2.8, 2.5 Hz, 3H), 2.44 (d, *J* 4.6 Hz, 1H), 4.49 (t, *J* 7.1 Hz, 1H), 4.54 (d, *J* 4.6 Hz, 1H), 5.04 (s, 1H), 7.0-7.8 (m, 8H). ^{13}C NMR (300 MHz, $CDCl_3$), δ 13.8, 22.3, 24.6, 28.4, 31.3, 31.5, 42.1, 43.4, 44.1, 49.0, 50.5, 78.5, 81.3, 122.6, 123.1, 125.7, 125.9, 126.0, 126.2, 126.5, 127.1, 139.3, 140.7, 142.2, 142.9, 171.0, 174.9. Analysis C, 77.54 ; H, 6.63% $C_{27}H_{28}O_4$ requires C, 77.85 ; H, 6.78%. m/z (LC/(+)ESI-MS) 417.3 (M^++1, 4%), 221.4 (4) and 179.1 (100).

Compound **12*g*** (16% yield) : White plates, m.p. 196 - 197°C (from CH_2Cl_2 / hexane). IR ($CHCl_3$), ν_{max} 3028, 2932, 2861, 1773, 1459, 1359 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$), δ 0.86 (t, *J* 6.9 Hz, 3H), 1.1-1.7 (m, 10H), 1.93, 2.93, 4.42 (ABX system, *J* 13.3, 2.9, 2.5 Hz, 3H), 2.78 (d, *J* 5.6 Hz, 1H), 4.11 (s, 1H), 4.56 (dt, *J* 7.9, 6.2 Hz, 1H), 5.08 (d, *J* 5.6 Hz, 1H), 7.05-7.38 (m, 8H). ^{13}C NMR (300 MHz, $CDCl_3$), δ 13.9, 22.3, 24.6, 28.6, 30.6, 31.4, 32.5, 43.5,

47.1, 51.3, 52.0, 79.1, 82.2, 123.1, 124.4, 125.0, 125.9, 126.0, 127.1, 127.5, 137.2, 138.6, 143.1, 143.7, 172.6, 175.1. Analysis C, 77.98 ; H, 7.03% $C_{27}H_{28}O_4$ requires C, 77.85 ; H, 6.78%. m/z (LC/(+)ESI-MS) 417.1 (M^++1, 32%), 239.2 (33) and 179.2 (100).

Pyrolysis of 8'-Alkyl-2'7'-dioxabicyclo[3.3.0]octan-3',6'-dione-4'-spiro-11-9,10-dihydro-9,10-ethanoanthracene (11*b*, 11*c*, 12*c*, 11*d*, 11*e*, 12*e*, 11*f*, 11*g* and 12*g*)

8-Ethyl-4-methylene-2,7-dioxabicyclo[3.3.0]octan-3,6-dione [(±)-Xylobovide], **2*b*** *from* **11*b*** : The adduct **11*b*** (22 mg, 0.061 mmol) was subjected to pyrolysis according to the procedure described above to provide *(±)*-xylobovide, **2*b*** (6 mg, 95% yield), whose spectroscopic data were identical to those reported.[6] Colourless crystals, m.p. 106 - 107°C [from CH_2Cl_2 / hexane; lit.[6] m.p. 106°C]. IR ($CHCl_3$), ν_{max} 3029, 2974, 1777, 1226 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$), δ 1.08 (t, *J* 7.4 Hz, 3H), 1.94 (m, 2H), 4.01 (dt, *J* 6.7, 1.9 Hz, 1H), 4.58 (dt, *J* 7.1, 4.8 Hz, 1H), 5.16 (dd, *J* 6.7, 4.8 Hz, 1H), 6.15 (d, *J* 1.9 Hz, 1H), 6.46 (d, *J* 2.0 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$), δ 10.2, 22.7, 46.8, 77.7, 84.9, 128.5, 131.0, 168.8, 173.4. m/z (LC/(+)ESI-MS) 182.7 (M^++1, 13%), 164.7 (100), 154.8 (44) and 136.9 (24).

Pyrolysis of compounds **11*c*** *and / or* **12*c*** *furnished 8-ethyl-4-methylene-2,7-dioxabicyclo [3.3.0]octan-3,6-dione [(±)-epi-Xylobovide],* **2*c*** : Colourless crystals, m.p. 107 - 108°C (from CH_2Cl_2 / hexane, 93% and 99%yield from **11*c*** and **12*c*** respectively). IR ($CHCl_3$), ν_{max} 3029, 1778, 1667, 1360, 1298, 962, 918 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$), δ 1.04 (t, *J* 7.4 Hz, 3H), 1.76 (m, 2H), 3.98 (dt, *J* 7.3, 2.2 Hz, 1H), 4.61 (dt, *J* 7.0, 1.2 Hz, 1H), 4.90 (dd, *J* 7.3, 1.2 Hz, 1H), 6.15 (d, *J* 2.0 Hz, 1H), 6.44 (d, *J* 2.2 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$), δ 9.1, 27.0, 45.0, 79.7, 86.3, 127.6, 129.9, 167.6, 172.5. Analysis C, 59.40 ; H, 5.71% $C_9H_{10}O_4$ requires for C, 59.32 ; H, 5.54%. m/z (LC/(+)ESI-MS) 182.2 (M^++1, 7%), 164.8 (54), 154.9 (29), 136.9 (100).

8-Butyl-4-methylene-2,7-dioxabicyclo[3.3.0]octan-3,6-dione [(±)-Canadensolide], **2*d***,[4] *from* **11*d*** : The adduct **11*d*** (0.21 g, 0.54 mmol) was subjected to pyrolysis according to the procedure described above to provide canadensolide, **2*d*** (57 mg, 98% yield) : Colourless crystals, m.p. 96 - 97°C [from CH_2Cl_2 / hexane; lit.[4c] m.p. 92.5 - 93.5°C (ether)]. IR ($CHCl_3$), ν_{max} 3030, 2962, 1776, 1229 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$), δ 0.92 (t, *J* 7.1 Hz, 3H), 1.33-1.54 (m, 4H), 1.79-1.94 (m, 2H), 3.99 (dt, *J* 6.7, 1.9 Hz, 1H), 4.58 (ddd, *J* 6.7, 4.8, 1.0 Hz, 1H), 5.09 (dd, *J* 6.7, 4.8 Hz, 1H), 6.09 (d, *J* 2.0 Hz, 1H), 6.40 (d, *J* 2.2 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$), δ 14.2, 22.7, 27.8, 28.9, 46.5, 77.5, 83.1, 127.7, 130.2, 167.8, 172.4. Analysis C, 62.63 ; H, 6.68 % $C_{11}H_{14}O_4$ requires C, 62.83 ; H, 6.72%. m/z (EIMS) 212 (M^++2, 2%), 96 (94), 68 (67) and 29 (100).

Pyrolysis of **11e** *and / or* **12e** *furnished 8-butyl-4-methylene-2,7-dioxabicyclo[3.3.0]octan-3,6-dione [(±)-epi-Canadensolide],* **2e**,[4c] : Colourless crystals, m.p. 49 - 50°C [from CH_2Cl_2 / hexane; lit.[4c] m.p. 47.5 - 48.5°C (ether)], 93% and 94% yield from **11e** and **12e** respectively). IR ($CHCl_3$), ν_{max} 3036, 2961, 2865, 1777, 1467, 1359, 1220 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$), δ 0.93 (t, *J* 6.9 Hz), 1.32-1.52 (m, 4H), 1.68-1.8 (m, 2H), 4.02 (dt, *J* 7.2, 2.2 Hz, 1H), 4.68 (dt, *J* 7.1, 1.1 Hz, 1H), 4.93 (dd, *J* 7.2, 1.1 Hz, 1H), 6.17 (d, *J* 2.0 Hz, 1H), 6.46 (d, *J* 2.3 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$), δ 13.6, 22.0, 26.3, 33.1, 44.5, 79.5, 84.8, 127.1, 129.4, 167.1, 172.1. Analysis C, 62.59 ; H, 7.01% $C_{11}H_{14}O_4$ requires C, 62.83 ; H, 6.72%. m/z (EIMS) 211 (M^++1, 0.3%), 96 (24), 68 (18) and 28 (100).

8-Octyl-4-methylene-2,7-dioxabicyclo[3.3.0]octan-3,6-dione [(±)-Sporothriolide], **2f**,[5] *from* **11f** : The adduct **11f** (0.30 g, 7.09 mmol) was subjected to pyrolysis according to the procedure described above to provide sporothriolide, **2f** (0.09 g, 98% yield) : Colourless crystals, m.p. 96 - 98°C [from CH_2Cl_2 / hexane; lit.[5] m.p. 101°C (CH_2Cl_2 / ether)]. IR ($CHCl_3$), ν_{max} 3029, 2930, 1778, 1266, 1218 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$), δ 0.86 (t, *J* 6.9 Hz), 1.2-1.55 (m, 8H), 1.75-1.92 (m, 2H), 3.98 (dt, *J* 6.7, 2.0 Hz, 1H), 4.63 (ddd, *J* 4.7, 4.5, 1.9 Hz, 1H), 5.12 (dd, *J* 6.7, 4.7 Hz, 1H), 6.09 (d, *J* 1.8 Hz, 1H), 6.40 (d, *J* 1.9 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$), δ 14.0, 22.4, 25.3, 28.8, 28.9, 31.5, 46.1, 77.1, 82.7, 127.2, 129.8, 167.4, 172.0. Analysis C, 65.77 ; H, 7.48% $C_{13}H_{18}O_4$ requires C, 65.51 ; H, 7.62%. m/z (LC/(+)ESI-MS) 239.2 (M^++1, 7%), 221.1 (100), 211.2 (61) and 203.2 (24).

Pyrolysis of compounds **11g** *and / or* **12g** *furnished 8-butyl-4-methylene-2,7-dioxabicyclo [3.3.0]octan-3,6-dione [(±)-epi-Sporothriolide],* **2g** : Colourless crystals, m.p. 65 - 67°C (from CH_2Cl_2 / hexane, 92% and 99%yield from **11g** and **12g** respectively). IR ($CHCl_3$), ν_{max} 3029, 2931, 2860, 1778 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$), δ 0.88 (t, *J* 6.9 Hz), 1.2-1.5 (m, 8H), 1.66-1.76 (m, 2H), 3.99 (dt, *J* 7.5, 2.2 Hz, 1H), 4.68 (dt, *J* 7.0, 1.4 Hz, 1H), 4.95 (dd, *J* 7.5, 1.4 Hz, 1H), 6.17 (d, *J* 2.2 Hz, 1H), 6.47 (d, *J* 2.2 Hz, 1H). ^{13}C NMR (400 MHz, $CDCl_3$), δ 13.9, 22.4, 24.3, 28.6, 31.4, 33.5, 44.5, 79.5, 84.8, 127.3, 129.4, 167.1, 172.0. Analysis C, 65.62 ; H, 7.93% $C_{13}H_{18}O_4$ requires C, 65.51 ; H, 7.62%. m/z (LC/(+)ESI-MS) 239.1 (M^++1, 10%), 221.1 (50), 211.2 (10) and 203.1 (100).

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