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A Novel Synthesis of α-Methylene-γ-butyrolactones

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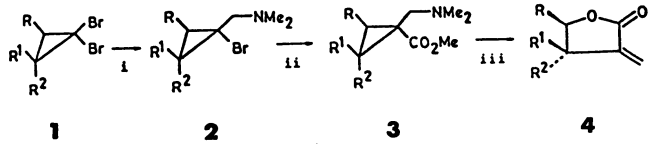
A new method is reported for constructing α-methylene-γ-butyrolactone moiety under neutral, anhydrous conditions. Olefin–dibromocarbene adducts were transformed into methyl 1-(dimethylaminomethyl)cyclopropanecarboxylates (**3**). Treatment of **3** with trimethylsilyl iodide followed by thermolytic distillation of the crude products gave α-methylene-γ-butyrolactones with high regio- and stereoselectivity.

Many compounds of natural or synthetic origin having α-methylene-γ-butyrolactone moiety possess a variety of biological activity.[1] Efforts for synthesizing the structural unit have been made extensively,[2,3] but a highly selective method seems still awaited. We found a novel method for constructing the structure under neutral, anhydrous conditions. The process involves ring reorganization of methyl 1-(dimethylaminomethyl)cyclopropanecarboxylates (**3**) with concomitant elimination of the amino group,[4] and is characterized by its high stereo- and regioselectivity. The transformation is accomplished by treatment of **3** with trimethylsilyl iodide[5] followed by thermolytic distillation.[6]



1 **2** **3** **4**

	R	R^1	R^2
a	Ph	H	H
b	n-C_6H_{13}	H	H
c	$-(CH_2)_4-$		H
d	n-C_6H_{13}	n-C_6H_{13}	H
e	n-C_6H_{13}	H	n-C_6H_{13}

i) BuLi, $CH_2{=}N^+Me_2I^-$; ii) BuLi (or *t*-BuLi), $(MeO)_2C{=}O$; iii) Me_3SiI, distillation.

Scheme 1.

The amino esters **3** were prepared as shown in Scheme 1. *gem*-Dibromocyclopropanes **1** underwent bromine–lithium exchange reaction on treatment with butyllithium at −95 °C.[7] The resulting carbenoids then reacted with *N,N*-dimethylmethaniminium iodide[8] to give amino bromides **2**. The configuration of the dimethylaminomethyl group was inferred to be *cis* or *endo* relative to the substituents R and R^1 of **2a**—**d** on the analogy of our previous observation.[9] Successively, **2** were converted into cyclopropyllithium by the action of butyllithium (for **2a**) or *t*-butyllithium (for **2b**—**e**) at −78 °C. The bromine–lithium exchange was particularly facilitated by the dimethylamino group which coordinates lithium cation.[10] The cyclopropyllithium reacted with dimethyl carbonate to give **3**.

The amino esters **3** were treated with 3 mol of trimethylsilyl iodide in benzene (for **3a**, **3b**) or 1,2-dichloroethane (for **3c**—**e**) at 50—95 °C for several hours. After the starting esters were consumed (TLC), all the volatile materials were evaporated *in vacuo*. At first, we dissolved the residue in high boiling solvents and heated as high as 200 °C, but no trace of the desired product was formed.[11] The transformation into the lactones **4** was effectively executed by the thermolytic distillation of the residue under reduced pressure with bath temperature of 170 °C or above by use of Kugelrohl, thermally unstable product being immediately removed from the hot reaction pot. The results are summarized in Table 1.

The transformation of **3a** afforded a plant growth inhibitory α-methylene-γ-lactone (**4a**)[1i] as the sole product. Thus, the bond between the substituted carbons of cyclopropane ring is preferentially cleaved. The same preference was observed in the reaction of **3b** which gave **4b** as the major product (71%) accompanied by the regioisomer (29%).[12] The carbon-carbon bond cleavage and carbon-oxygen bond formation proceeded with retention of configuration as observed in the reaction of **3c**—**e**. Only the *cis* product **4c** was produced from **3c**, and **4d** (*cis-trans* 94 : 6) from **3d** which was derived from **1d** (*cis-trans* 84 : 16). The reaction of *trans* isomer **3e** gave only the *trans* lactone **4e**.

Of special interest in the transformation is the intermediary species leading to **4**. Treatment of **3c** with trimethylsilyl iodide followed by evaporation as above gave an oil which exhibited a singlet peak at δ 3.69 (^{1}H-NMR in $CDCl_3$) without reasonably intense

Table 1. Synthesis of α-methylene-γ-butyrolactones[a]

	Starting dibromide **1** R	R^1	R^2	Yield[b] of **2**/%	Yield[b] of **3**/%	Yield[b] of **4**/%
a	Ph	H	H	59	73	62
b	n-C_6H_{13}	H	H	71[c]	60[c]	58[d]
c	$-(CH_2)_4-$		H	61	61	64
d[e]	n-C_6H_{13}	n-C_6H_{13}	H	49[e]	51[e]	67[f]
e	n-C_6H_{13}	H	n-C_6H_{13}	51	48	73

a) See the Experimental part for each transformations. b) Isolated yields. c) Contained 12% of the stereoisomer. d) Contained 29% of the regioisomer. e) Derived from 7-tetradecene (*cis*: *trans* 84 : 16). f) Contaminated by **4e** (6%).

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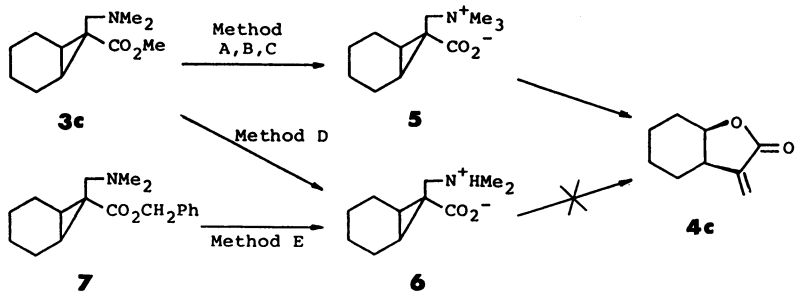
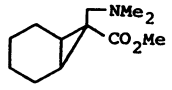
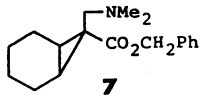
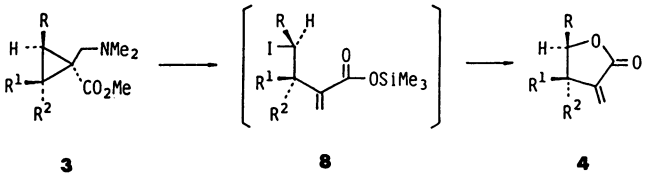


Scheme 2.

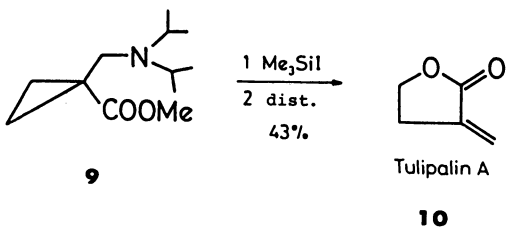
Table 2. Synthesis of the lactone **4c** by means of various methods[a)]

Starting amino ester	Method	Yield[b)] of **4c**/%
 **3c**	A 1) MeI 2) Me_3SiI (2 equiv) 3) dist.	49
	B 1) MeI 2) aq KOH 3) dist.	43
	C 1) aq KOH 2) MeI 3) dist.	34
	D 1) KOH (1.2 equiv) 2) HCl (1.2 equiv) 3) dist.	—
 **7**	E 1) Pd/C, H_2 2) dist.	—
	F 1) Me_3SiI 2) dist.	61
	G 1) Pd/C, H_2 2) MeI 3) dist.	51

a) For the detail procedures, see the Experimental parts. b) Isolated yields.



Scheme 3.



Scheme 4.

peaks due to trimethylsilyl groups. The IR spectrum (neat) revealed the presence of carboxylate (1620, 1400 cm^{-1}) and/or carboxylic acid (3650—2200, 1710 cm^{-1}) functional group(s). Thus, the most likely intermediate seems to be **5** which is derived from trimethylsilyl iodide mediated ester hydrolysis and quaternization. The initial phase of the reaction would be *N*-trimethylsilyl ammonium formation followed by trimethylsilyl-methyl exchange.[13)] Indeed, when **5** was produced alternatively by quaternization with methyl iodide and hydrolysis with a base, subsequent thermolysis gave **4c** albeit in somewhat lower yields (Table 2, method A—C). Another possible intermediate **6** could clearly be eliminated as following two procedures failed to give **4c** (Scheme 2): D, (1) hydrolysis of **3c** with aq KOH, (2) neutralization with HCl, (3) distillation; E, (1) hydrogenolysis of benzyl ester **7**, (2) distillation. Of course, the benzyl ester **7** was transformed into **4c** by the standard procedure or by hydrogenolysis followed by quaternization and distillation (Table 2, method F, G). According to recent studies on the trimethylsilyl iodide mediated ring opening of cyclopropanecarboxylates,[14)] the stereoselectivity can be explained by the intermediacy of **8** (Scheme 3).

Thus the α-methylene-γ-butyrolactone synthesis described herein has a remarkable feature involving anhydrous, neutral conditions in sharp contrast to the related system which employs aqueous strong acidic conditions.[15)] Furthermore, the method has wide applicability as the starting *gem*-dibromocyclopropanes are readily available from olefins and dibromocarbene.

Finally, the sequence was successfully applied to the synthesis of tulipalin A (**10**), a cytotoxic lactone isolated from tulip bulbs[16)] and also from Adder's Tongue (*Erythronium americanum*),[17)] starting from amino ester **9** (Scheme 4). In this reaction diisopropylamino group is especially pertinent as the dimethylamino derivatives gave only trace amount of **10**. The bulky amino leaving group seems essential for the isolation of the remarkably unstable product.[17)]

Experimental

Bulb-to-bulb distillation was carried out by use of Kugelrohr (Büchi) and boiling points were determined by measuring the bath temperature. All mp and bp are not corrected. ^1H-NMR spectra (tetramethylsilane as an internal standard) were obtained on a Varian EM-390 spectrometer, chemical shift being given in ppm units, IR spectra of neat liquid film samples (unless otherwise noted) on a Shimadzu IR-27G spectrometer, MS on a Hitachi RMU-6L spectrometer, and exact mass on a Hitachi M 80 spectrometer. Preparative TLC plates were prepared with Merck Kiesel-gel PF_{254}. Column chromatography was carried out with silica gel

(Wakogel C-100) at atmospheric pressure.

*Transformation of 7,7-Dibromonorcarane (**1c**) into the Lactone **4c** (A Typical Procedure).* *7*-exo-*Bromo-7*-endo-*(dimethylaminomethyl)norcarane (**2c**)*: At −95 °C a hexane solution of butyllithium (1.7 M†, 3.4 ml, 5.8 mmol) was added under an argon atmosphere to **1c**[18] (1.32 g, 5.2 mmol) dissolved in THF (30 ml). After 10 min stirring *N,N*-dimethylmethaniminium iodide (1.40 g, 7.5 mmol) was added portionwise at −95 °C. The heterogeneous reaction mixture was stirred for 15 h and warmed gradually to r.t. Workup followed by column chromatography (hexane–ether 10 : 1 to 1 : 100) gave **2c** (0.73 g, 61% yield). Bp 70—80 °C (bath temp)/0.3 Torr;†† ^{1}H-NMR (CCl_4): δ=0.9—2.0 (m, 10H), 2.27 (s, 6H), 2.63 (s, 2H); IR: 2950, 2870, 2835, 2780, 1450, 1025 cm^{-1}; MS: *m/e* (rel intensity) 233 (M^++2, 1), 232 (M^++1, 0.7), 231 (M^+, 1), 152(21), 91(19), 79(31), 68(21), 59(81), 58(43), 46(100), 44(86). Found: *m/e* 231.0641. Calcd for $C_{10}H_{18}BrN$: M^+, 231.0622.

7-exo-*Methoxycarbonyl-7*-endo-*(dimethylaminomethyl)norcarane (**3c**)*: A pentane solution of *t*-butyllithium (2.3 M, 1.5 ml, 3.4 mmol) was added to a THF (25 ml) solution of **2c** (0.71 g, 3.1 mmol) at −78 °C under an argon atmosphere. After stirring for 1 h, dimethyl carbonate (0.54 g, 6.0 mmol) was added at −78 °C. The whole was stirred for 15 h and warmed to r.t. Workup and column chromatography (hexane–ether 5 : 1 to 1 : 100) gave **3c** (0.39 g, 61% yield). Bp 85—100 °C (bath temp)/0.5 Torr; ^{1}H-NMR (CCl_4): δ=1.1—2.0 (m, 10H) 2.17 (s, 6H), 2.67 (s, 2H), 3.57 (s, 3H); IR: 2950, 2870, 2830, 2780, 1720, 1238, 1186, 1164, 1145 cm^{-1}; MS: *m/e* (rel intensity) 211 (M^+, 1), 168(3), 107(5), 99(4), 90(4), 79(9), 67(4), 59(87), 45(100). Found: C, 68.13; H, 10.25; N, 6.39%. Calcd for $C_{12}H_{21}NO_2$: C, 68.21; H, 10.02; N, 6.63%.

cis-*Hexahydro-3-methylene-2(3H)-benzofuranone (**4c**)*: Trimethylsilyl iodide (0.52 g, 2.6 mmol) was added to **3c** (170 mg, 0.81 mmol) in 1,2-dichloroethane (7 ml) under an argon atmosphere, and the reaction mixture was stirred at reflux temperature for 14 h. Concentration and distillation of the residue (Kugelrohr) gave the crude product collected at 160—210 °C (bath temp) at 0.05 Torr. Purification by preparative TLC (hexane–ether 1 : 1) gave **4c** (R_f 0.4, 78 mg, 64% yield) identical in all respects with the reported data.[19] Bp 105—110 °C (bath temp)/0.5 Torr; ^{1}H-NMR (CCl_4): δ=1.1—2.2 (m, 8H), 2.8—3.2 (m, 1H), 4.46 (dq, *J*=5.1, 6.2 Hz, 1H), 5.43 (d, *J*=2.6 Hz, 1H), 6.08 (d, *J*=2.6 Hz, 1H); IR: 2950, 2860, 1765, 1665, 1255, 1123, 1100, 1010, 889 cm^{-1}; MS: *m/e* 152 (M^+).

This procedure applies to the transformation of **1a**, **1b**, **1d**, and **1e** into **4a**, **4b**, **4d**, and **4e** respectively. Physical properties are summarized below.

r-*1-Bromo-1-(dimethylaminomethyl)*-t-*2-phenylcyclopropane (**2a**) from **1a***:[18] Bp 105—115 °C (bath temp)/0.2 Torr; ^{1}H-NMR (CCl_4): δ=1.4—1.7 (m, 2H), 1.88 (d, *J*=13.8 Hz, 1H), 2.12 (s, 6H), 2.56 (d, *J*=13.8 Hz, 1H), 2.75 (t, *J*=8.5 Hz, 1H), 7.20 (s, 5H); IR: 2950, 2830, 2780, 1602, 1500, 1452, 1036, 774, 701 cm^{-1}; MS: *m/e* (rel intensity) 255 (M^++2, 3), 254 (M^++1, 1), 253 (M^+, 3), 175(10), 135(12), 134(100), 129(27), 128(18), 115(15), 91(13), 77(10), 70(15), 59(13), 58(100). Found: *m/e* 253.0472. Calcd for $C_{12}H_{16}BrN$: M^+, 253.0466.

1-(Dimethylaminomethyl)-r-*1-methoxycarbonyl*-t-*2-phenylcyclopropane (**3a**)*: Bp 105—115 °C (bath temp)/2 Torr; ^{1}H-NMR (CCl_4): δ=1.42 (dd, *J*=3.0, 4.7 Hz, 1H), 1.44 (d, *J*=8.4 Hz, 1H), 1.86 (dd, *J*=3.0, 5.8 Hz, 1H), 1.92 (s, 6H), 2.46 (dd, *J*=4.7, 5.8 Hz, 1H), 2.66 (d, *J*=8.4 Hz, 1H), 3.44 (s, 3H), 6.6—6.9 (m, 5H); IR: 2970, 2840, 2780, 1718, 1605, 1502, 1460, 1437, 1243, 1176, 765, 700 cm^{-1}; MS: *m/e* (rel intensity) 234 (M^++1, 2), 233 (M^+, 4), 219(2), 142(72), 134(19), 129(26), 115(8), 91(9), 58(100). Found: C, 71.84; H, 8.25; N, 6.06%. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00%.

*5-Phenyl-4,5-dihydro-3-methylene-2(3H)-furanone (**4a**)*:[2x,20] Mp 48—49.5 °C; ^{1}H-NMR (CCl_4): δ=2.88 (ddt, *J*=6.6, 17.0, 2.9 Hz, 1H), 3.40 (ddt, *J*=8.0, 17.0, 2.5 Hz, 1H), 5.50 (dd, *J*=6.6, 8.0 Hz, 1H), 5.66 (dd, *J*=2.5, 2.9 Hz, 1H), 6.28 (dd, *J*=2.5, 2.9 Hz, 1H), 7.34 (s, 5H); IR: 1760, 1665, 1500, 1265, 1120, 1015 cm^{-1}; MS: *m/e* 174 (M^+).

r-*1-Bromo-1-(dimethylaminomethyl)*-t-*2-hexylcyclopropane (**2b**)*: The dibromocyclopropane **1b**[18] was converted into a stereoisomeric mixture of **2b** and **2b′**, *r*-1-bromo-1-(dimethylaminomethyl)-*c*-2-hexylcyclopropane. The ratio of **2b** to **2b′** (88 : 12) was estimated by the examination of the ^{1}H-NMR spectrum of a mixture of **3b** and **3b′**. The mixture of **2b** and **2b′** showed bp 72—80 °C (bath temp)/0.5 Torr; ^{1}H-NMR (CCl_4): δ=0.5—1.6 (m, 15H), 2.04 (m, 1H), 2.26 (s, 6H), 2.32 (d, *J*=13.5 Hz, 1H), 2.79 (d, *J*=13.5 Hz, 1H); IR: 2950, 2870, 2825, 2780, 1460, 1250, 1190, 1128, 1038 cm^{-1}; MS: *m/e* (rel intensity) 263 (M^++2, 2), 262 (M^++1, 1), 261 (M^+, 2), 182(18), 142(5), 96(6), 85(9), 70(8), 67(11), 58(100), 55(20), 46(55), 45(46), 44(46), 43(44). Found: *m/e* 261.1068. Calcd for $C_{12}H_{24}BrN$: M^+, 261.1092.

1-(Dimethylaminomethyl)-r-*1-methoxycarbonyl*-t-*2-hexylcyclopropane (**3b**)*: The mixture of **2b** and **2b′** was transformed into an 88 : 12 mixture of **3b** and the stereoisomer **3b′**, 1-(dimethylaminomethyl)-*r*-1-methoxycarbonyl-*c*-2-hexylcyclopropane, having ^{1}H-NMR (CCl_4): δ=0.5—1.6 (m, 16H), 2.08 (d, *J*=13.1 Hz, 1H), 2.13 (s, 6H), 2.98 (d, *J*=13.1 Hz, 1H), 3.57 (s, CO_2Me, 2.64H), 3.61 (s, CO_2Me, 0.36H); IR: 2935, 2860, 2820, 2770, 1725, 1245, 1185, 1152, 1133, 1025 cm^{-1}; MS: *m/e* (rel intensity) 241 (M^+, 3), 198(2), 170(2), 157(2), 142(13), 98(4), 58(100), 46(34), 45(78), 44(21). Found: C, 69.45; H, 11.52; N, 5.55%. Calcd for $C_{14}H_{27}NO_2$: C, 69.66; H, 11.28; N, 5.80%. Bp 72—80 °C (bath temp)/0.5 Torr.

*5-Hexyl-4,5-dihydro-3-methylene-2(3H)-furanone (**4b**)*:[2g,20] The 88 : 12 mixture of **3b** and **3b′** gave the lactones **4b** and **4b′**, 4-hexyl-4,5-dihydro-3-methylene-2(3*H*)-furanone, as a 71 : 29 regioisomeric mixture,[12] ^{1}H-NMR (CCl_4): δ=0.7—1.9 (m, 13H), 1.1—1.8 (m, 10H), 2.41 (ddt, *J*=6.0, 17.0, 3.0 Hz, HC<u>H</u> of **4b**, 0.71H), 2.9—3.1 (m+ddt (δ=3.00, *J*=7.5, 17.0, 2.6 Hz, <u>H</u>CH of **4b**), 1H), 3.93 (dd, *J*=5.7, 9.0 Hz, HC<u>H</u> of **4b′**, 0.29H), 4.35—4.55 (m+dd(δ=4.42, *J*=8.3, 9.0 Hz, <u>H</u>CH of **4b′**), 1H), 5.55 (d, *J*=2.8 Hz, 0.29H), 5.58 (dd, *J*=2.6, 3.0 Hz, 0.71H), 6.18 (dd, *J*=2.6, 3.0 Hz, 0.71H), 6.23 (d, *J*=2.8 Hz, 0.29H); IR: 1760, 1662 cm^{-1}; MS: *m/e* (rel intensity) 182 (M^+, 1), 140(10), 97(100), 41(42); bp 102—108 °C (bath temp)/0.5 Torr. Found: *m/e* 181.1274. Calcd for $C_{11}H_{17}O_2$: M^+−1, 181.1226.

When stereochemically pure **3b** was subjected to the reaction conditions, the product ratio was improved a little (**4b**: **4b′** 82 : 18).

r-*1-Bromo*-c-*2*,c-*3-dihexyl-1-(dimethylaminomethyl)cyclopropane (**2d**)*: The reported procedure[21] was applied to the transformation of 7-tetradecene (*cis* : *trans* 84 : 16)[22] into the dibromocyclopropane **1d** together with the *trans* isomer **1e** (85% tield), bp 120—125 °C/0.11 Torr; ^{1}H-NMR (CCl_4): δ=0.7—1.6 (m, 28H); IR: 1464, 1455, 715 cm^{-1}. Found: *m/e* 366.0516. Calcd for $C_{15}H_{28}Br_2$: M^+, 366.0558.

The stereoisomer **2d** showed ^{1}H-NMR (CCl_4): δ=0.7—1.7 (m, 28H), 2.26 (s, 6H), 2.48 (s, 2H); IR: 1466, 1034 cm^{-1}; MS: *m/e* (rel intensity) 347 (M^++2, trace), 345 (M^+, trace), 267(8), 266(10), 69(16), 58(100), 55(26), 46(22), 45(66), 43(29), 41(29); bp 165—167 °C (bath temp)/0.12 Torr. Found: C, 62.68; H, 10.70; N, 3.96%. Calcd for $C_{18}H_{36}BrN$: C, 62.41; H, 10.48; N, 4.04%.

† 1 M=1 mol dm^{-3}; †† 1 Torr=133.322 Pa.

t-*2*,t-*3-Dihexyl-1-(dimethylaminomethyl)*-r-*1-(methoxycarbonyl)-cyclopropane (3d)*: Bp 142 °C (bath temp)/0.07 Torr; ^{1}H-NMR (CCl_4): δ=0.7—1.7 (m, 28H), 2.23 (s, 6H), 2.64 (s, 2H), 3.58 (s, 3H); IR: 1721, 1476, 1259, 1197 cm^{-1}; MS: *m/e* (rel intensity) 325 (M^+, trace), 310 (trace), 240(14), 58(93), 46(76), 45(100), 44(23), 43(17), 41(19). Found: C, 73.58; H, 12.23; N, 4.07%. Calcd for $C_{20}H_{39}NO_2$: C, 73.79; H, 12.08; N, 4.03%.

cis-*4,5-Dihexyl-4,5-dihydro-3-methylene-2(3H)-furanone (4d)*: A 94 : 6 stereoisomeric mixture of **4d** and its *trans* isomer **4e** was synthesized from the amino esters (**3d** and **3e**) which were derived from 7-tetradecene (*cis* : *trans* 84 : 16). The mixture of **4d** and **4e** showed bp 141—142 °C (bath temp)/0.18 Torr; ^{1}H-NMR (CCl_4): δ=0.7—1.6 (m, 26H), 2.80 (m, 1H), 4.30 (dt, J=5.1, 6.3 Hz, 1H), 5.30 (d, J=2.3 Hz, 1H), IR: 1764, 1660, 1464, 1264, 1111 cm^{-1}; MS: *m/e* (rel intensity) 266 (M^+, 2), 152(56), 96(72), 95(72), 82(100), 55(64), 54(92). Found: C, 76.46; H, 11.49%. Calcd for $C_{17}H_{30}O_2$: C, 76.64; H, 11.35%.

r-*1-Bromo*-c-*2*,t-*3-dihexyl-1-(dimethylaminomethyl)cyclopropane (2e)*: *trans*-1,1-Dibromo-2,3-dihexylcyclopropane (**1e**) was prepared from *trans*-7-tetradecene[22] according to the reported procedure[21] (75% yield, 97% yield based on the consumed olefin). ^{1}H-NMR (CCl_4) of **1e**: δ=0.7—1.7 (m, 28H); IR: 1466, 733, 722 cm^{-1}; bp 105—115 °C/0.08 Torr. Found: C, 49.02; H, 7.70%. Calcd for $C_{15}H_{28}Br_2$: C, 48.93; H, 7.67%.

The amino bromide **2e** showed bp 162—163 °C (bath temp)/0.11 Torr; ^{1}H-NMR (CCl_4): δ=0.7—1.8 (m, 28H), 2.23 (s, 6H), 2.28 (d, J=12.8 Hz, 1H), 2.85 (d, J=12.8 Hz, 1H); IR: 1464, 1454, 1033 cm^{-1}; MS: *m/e* (rel intensity) 266 (M^+—Br, 5), 81(5), 79(4), 69(5), 67(5), 58(100), 46(13), 45(43). Found: *m/e* 266.2854. Calcd for $C_{18}H_{36}N$: M^+—Br, 266.2846.

c-*2*,t-*3-Dihexyl-1-(dimethylaminomethyl)*-r-*1-(methoxycarboxyl)-cyclopropane (3e)*: Bp 165 °C (bath temp)/0.11 Torr; ^{1}H-NMR (CCl_4): δ=0.7—1.7 (m, 28H), 2.16 (s, 6H), 2.30 (d, J=13.2 Hz, 1H), 2.75 (d, J=13.2 Hz, 1H), 3.65 (s, 3H); IR: 1724, 1461, 1190, 1158 cm^{-1}; MS: *m/e* (rel intensity) 325 (M^+, trace), 310(1), 382(1), 240(12), 226(4), 58(100), 46(45), 45(55). Found: C, 73.56; H, 12.28; N, 4.17%. Calcd for $C_{20}H_{39}NO_2$: C, 73.79; H, 12.08; N, 4.30%.

trans-*4,5-Dihexyl-4,5-dihydro-3-methylene-2(3H)-furanone (4e)*: Bp 140—142 °C (bath temp)/0.18 Torr; ^{1}H-NMR (CCl_4): δ=0.7—1.8 (m, 26H), 2.53 (m, 1H), 4.04 (dt, J=3.6, 5.3 Hz, 1H), 5.45 (d, J=2.6 Hz, 1H), 6.13 (d, J=2.6 Hz, 1H); IR: 1763, 1658, 1465, 1265, 1116 cm^{-1}; MS: *m/e* (rel intensity) 266 (M^+, 1), 181(16), 152(39), 95(45), 82(52), 67(41), 55(57), 43(91), 41(100). Found: C, 76.83; H, 11.23%. Calcd for $C_{17}H_{30}O_2$: C, 76.64; H, 11.35%.

Preparation of the Lactone 4c from the Amino Ester 3c or 7.

Method A: Treatment of **3c** (98 mg, 0.47 mmol) with methyl iodide (1 ml) at reflux temperature for 14 h was followed by concentration. The resulting residue was allowed to react with trimethylsilyl iodide (186 mg, 0.93 mmol) in 1,2-dichloroethane at 50 °C for 15 h. Evaporation of all the volatile materials and the subsequent thermolysis gave **4c** (35 mg, 45% yield).

Method B: The ester **3c** (105 mg, 0.50 mmol) in methyl iodide (2 ml) was stirred for 2 h at reflux temperature, and the excess reagent was then removed. The residue was treated with a methanol–water (1 : 1) solution of potassium hydroxide (0.24 M, 0.59 mmol) at 80 °C (bath temp) for 15 h. Concentration of the reaction mixture *in vacuo* followed by distillation gave **4c** (33 mg, 43% yield).

Method C: Treatment of **3c** (90 mg, 0.43 mmol) with a methanol–water (1 : 1) solution of potassium hydroxide (0.23 M, 0.51 mmol) followed by concentration gave a solid. Methyl iodide (2 ml) was added to the residue and the whole was stirred at reflux temperature for 2.5 h. Removal of excess methyl iodide and the thermolytic distillation gave **4c** (22 mg, 34% yield).

Method D: Hydrolysis of **3c** (90 mg, 0.43 mmol) with a methanol–water (1 : 1) solution of potassium hydroxide (0.24 M, 0.51 mmol) was followed by neutralization with hydrochloric acid (1.0 M, 0.51 mmol). Concentration of the reaction mixture *in vacuo* and the subsequent distillation failed to give the desired lactone **4c**.

Method E: Benzyl alcohol (0.23 g, 2.1 mmol) was treated with sodium hydride (1.8 mmol) in benzene (4 ml) at 80 °C for 30 min, and **3c** (192 mg, 0.91 mmol) in benzene (1 ml) was then added at r.t. After stirring for 3 h at 80 °C, workup and distillation gave 7-*exo*-benzyloxycarbonyl-7-*endo*-(dimethylaminomethyl)norcarane (**7**) (108 mg, 42% yield); bp 162—163 °C (bath temp)/0.11 Torr; ^{1}H-NMR (CCl_4): δ=1.0—2.1 (m, 10H), 2.16 (s, 6H), 2.71 (s, 2H), 4.98 (s, 2H), 7.26 (br s, 5H); IR: 1710, 1244, 1172, 695 cm^{-1}; MS: *m/e* (rel intensity) 287 (M^+, trace), 196(15), 91(95), 65(29), 58(100), 46(74), 45(94), 44(42). Found: C, 74.97; H, 8.80; N, 4.78%. Calcd for $C_{18}H_{25}NO_2$: C, 75.22; H, 8.77; N, 4.87%.

An ethanol (1 ml) solution of **7** (115 mg, 0.42 mmol) was treated with Pd on carbon (5%, 12 mg) under a hydrogen atmosphere for 20 h. Filtration followed by concentration and the thermolysis failed to give **4c**.

Method F: Treatment of **7** (72 mg, 0.25 mmol) with trimethylsilyl iodide (51 mg, 0.51 mmol) in refluxing 1,2-dichloroethane (2 ml) for 15 h was followed by concentration. Thermolysis of the residue gave **4c** (23 mg, 60% yield).

Method G: An ethanol (1 ml) solution of **7** (94 mg, 0.33 mmol) was stirred with Pd on carbon (5%, 10 mg) under a hydrogen atmosphere for 15 h. Filtration and concentration gave a solid, which was treated with methyl iodide (3 ml) at reflux temperature for 1.5 h. Removal of the excess reagent followed by the thermolysis gave **4c** (25 mg, 51% yield).

Synthesis of Tulipalin A (10). Methyl 2-(bromomethyl)acrylate was prepared from dimethyl bis(hydroxymethyl)-malonate according to reported methods[23] (32% overall yield). ^{1}H-NMR (CCl_4): δ=3.78 (s, 3H), 4.12 (s, 2H), 5.91 (s, 1H), 6.27 (s, 1H); IR: 1716, 1628, 1440, 1321, 1300, 1210, 1187, 1162, 1110 cm^{-1}; MS: *m/e* (rel intensity) 180 (M^++2, 17), 178 (M^+, 18), 149(21), 147(21), 121(21), 119(21), 99(100), 69(21), 59(50), 45(16), 41(24). Found: C, 33.65; H, 4.07%. Calcd for $C_5H_7BrO_2$: C, 33.56; H, 3.91%. Bp 85—90 °C/32 Torr.

A reported procedure[23b] was applied to the transformation of methyl 2-(bromomethyl)acrylate into methyl 2-(diisopropylaminomethyl)acrylate (91% yield). Bp 70—78 °C/1 Torr; ^{1}H-NMR (CCl_4): δ=0.98 (d, J=6.6 Hz, 12H), 2.99 (septet, J=6.6 Hz, 2H), 3.21 (t, J=1.8 Hz, 2H), 5.8—5.9 (m, 1H), 6.0—6.1 (m, 1H); IR: 2980, 1717, 1630, 1436, 1366, 1287, 1250, 1172, 1125 cm^{-1}; MS: *m/e* (rel intensity) 199 (M^+, 11), 185(100), 142(43), 110(100), 69(54), 41(47). Found: C, 66.37; H, 10.90; N, 6.95%. Calcd for $C_{11}H_{21}NO_2$: C, 66.29; H, 10.62; N, 7.03%.

Thus prepared amino ester (1.1 g, 5.58 mmol) was treated with an ether (10 ml) solution of diazomethane (large excess) for 15 h at 25 °C and the reaction mixture was concentrated. A benzene (50 ml) solution of the residue was placed in a Pyrex tube and irradiated with a 200 W high-pressure mercury lamp externally for 7 h at 25 °C under a nitrogen atmosphere. Purification of the concentrated residue by column chromatography (hexane–ether 5 : 1) gave methyl 1-(diisopropylaminomethyl)cyclopropanecarboxylate (**9**) (0.42 g, 35% yield). Bp 118 °C (bath temp)/1 Torr; ^{1}H-NMR (CCl_4): δ=0.5—0.8 (m, 2H), 0.8—1.1 (m+d (δ=0.95, J=6.3 Hz), 14H), 2.78 (s, 2H), 2.96 (septet, J=6.3 Hz, 2H), 3.57 (s, 3H); IR: 2990, 1720,

1436, 1348, 1241, 1180, 1134 cm^{-1}; MS: *m/e* (rel intensity) 213 (M^+, 9), 198(100), 124(46), 114(42), 113(26), 86(20), 83(27), 81(35), 44(36), 43(25), 41(27). Found: C, 67.78; H, 10.79; N, 6.61%. Calcd for $C_{12}H_{23}NO_2$: C, 67.56; H, 10.87; N, 6.57%.

A 1,2-dichloroethane (6 ml) solution of **9** (107 mg, 0.51 mmol) was treated with trimethylsilyl iodide (402 mg, 2.01 mmol) at reflux temperature for 15 h under an argon atmosphere. Thermolysis of the concentrated residue yielded the crude product. Purification by preparative TLC (hexane–ether 1 : 1) gave **10** (21 mg, 43% yield, R_f 0.3) identical in all respects with the reported data.[24] Bp 92—95 °C (bath temp)/11 Torr; ^{1}H-NMR (CCl_4): δ=2.97 (tt, J=2.9, 7.4 Hz, 2H), 4.63 (t, J=7.4 Hz, 2H), 5.64 (t, J=2.9 Hz, 1H), 6.24 (t, J=2.9 Hz, 1H); IR ($CHCl_3$): 1759, 1667, 1107, 1021, 940 cm^{-1}; MS: *m/e* 98 (M^+).

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