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An Improved and Novel Approach To Macrolactonisation using Di-tert-butyl dicarbonate$^{\Psi}$

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Abstract: A new, facile, mild and simple method for the synthesis of macrolides was achieved from ω- hydroxy acids using di-tert-butyl dicarbonate (Boc_2O), a cheap and commercially available reagent. A wide range of substrates were tested and give good yield of lactones. The effect of various simple bases on the yield of the macrolactonisation reaction was also studied. © 1999 Published by Elsevier Science Ltd. All rights reserved.
Keywords: Macrolides; Lactones; Olefins; Isomerisation; Lactonisation.

Introduction

Over the years, a large number of macrolides possessing diverse biological activity such as antibiotic, anticancer, antifungal and antitumor have been isolated and are important therapeutic agents in clinical medicine and have commercial importance in the fragrance industry.[1-2] The discovery of numerous complex macrolides[3-6] has presently generated a surge of interest in new solutions to the problem of macrocyclic lactone synthesis. As a result, a wide variety of approaches,[1-6] such as Corey-Nicolaou double activation method,[7-9] Gerlach-Thalmann method,[10-12] Schmidt method,[13-15] Masamune method,[16-18] Mukaiyama method,[19-22] Venkatraman-Wagle method,[23,24] Yamaguchi method,[25] Roush-pivolic anhydride method,[26,27] Mitsunobu method,[28,29] Keck method,[30] Vorbruggen-Krolikiewicz method,[31] Hanessian-organotin method,[32,33] Raphael imidazole method[34] and Enzyme mediated method[35-37] have been developed. Yet macrolide construction continues to be a significant challenge in synthetic methodology. Recently, Yamamoto *et al*[38] developed a high yielding method for macrolide construction using $Sc(OTf)_3$ in CH_3CN. But this method failed to produce even trace amounts of the target lactone in the total synthesis of tuckolide.[39]

In principle, macrolactones can be generated by cyclization of open long chain precursors of ω-hydroxy acids. Polymerization due to intermolecular rather than intramolecular interaction is often a serious problem, although subject to experimental control. In general, maintenance of low substrate concentration in the cyclisation flask (high dilution conditions) is a trivial, well established requirement for successful avoidance of dimerisation.[1] The enthalpic and entropic factors associated with cyclisations that give rise to medium sized rings are relatively quite unfavourable.[40,41] The discovery of an efficient, new and mild synthetic methodology for the construction of complex macrolides certainly simplifies the problem to a considerable extent.

During the course of the synthesis of azamacrolides,[42-44] a new class of defensive compounds, we have discovered that Boc_2O can be used as an efficient reagent for the activation of carboxylic acids in the synthesis of macrolides. Boc_2O is widely used in the literature for the introduction of Boc-protecting groups in amino acids, peptides and proteins.[45,46] This is an efficient t-butoxy carbonylating agent for alcohols, thiols, amines and various carbon nucleophiles.[47,48] It is widely used in the synthesis of isocyanates,[49] symmetrical and

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unsymmetrical ureas,[50,51] symmetrical and unsymmetrical anhydrides,[52,53] esters,[54] and substituted hydrazines.[55] Recent work from our laboratory has also demonstrated the utility of Boc_2O in cyclodehydration of N-acylamino acids[36] into oxazoles and benzoxazinones and as a condensing reagent for the synthesis of dipeptides.[37]

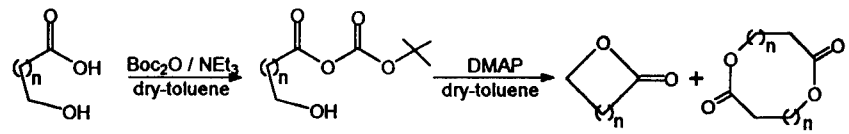
The macrolactonisation is generally involved in the final stages during the synthesis of macrolides. Therefore, the reagents and the reaction conditions employed should be mild and efficient, so as not to affect other sensitive functionalities that would be present in the molecule. The widely used approach[1,2] for the synthesis of these lactones is by the ring closure of the corresponding ω-hydroxy acids which involves the activation of the carboxylic acid followed by nucleophilic displacement of the leaving group by the hydroxy moiety in an intramolecular fashion.

Some of the preliminary results of this macrolactonisation method[58] and its application to the synthesis of biologically active macrolides such as, (-) A26771B (antibiotic macrolide),[59] R-(+)-Ricinoleic acid lactone and (±)-12-OH stearic acid lactone[60] have been communicated recently. In this paper, we present the full details of our work as well as the base effect on the macrolactonisation reaction and improved reaction conditions.

Results and Discussion

Our macrolactonisation method mainly involves two steps, the activation of the carboxylic acid by converting it into its mixed anhydride and macrolactonisation of the resultant mixed anhydride under high dilution conditions (scheme-1). As depicted in scheme-1, the acid alcohol **1** is treated with an equivalent amount of Boc_2O and Et_3N in a small volume of dry toluene at rt to get mixed anhydride **2** (not isolated). The pre-activated substrate **2** is diluted

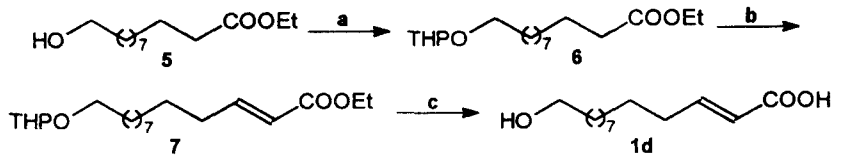
Scheme-1



with a large volume of toluene and is slowly added via a dropping funnel to a cyclization flask containing the solution of 8-10 equiv. of DMAP (a well known acyl transfer agent) in hot toluene to afford macrolides **3** and diolides **4** in varying yields depending upon the ring size. Though the actual reaction process occurs in a much more complicated way and its precise mechanistic details are not yet clear.[61] Among various solvents (CH_3CN, benzene, toluene, CH_2Cl_2 and dioxane) screened for macrolactonisation, good yields of lactones and clean reaction were observed in toluene.

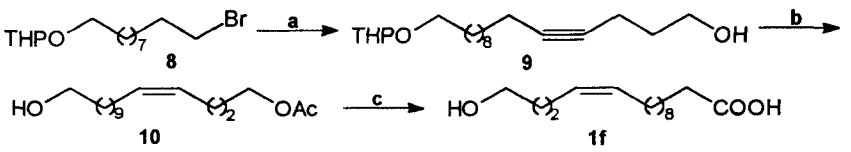
For the present macrolactonisation study, various simple, unfunctionalized *seco* acids **1** (Table-1) were prepared according to the literature procedure.[38] The non commercially available *seco* acids **1d** & **1f** were prepared according to schemes 2 & 3 by standard procedure. The readily available hydroxy ester **5** was protected as its pyranyl ether **6**. Compound **6** was treated with Dibal-H at -78°C followed by Wittig reaction with Ph_3P=CH-COOEt under reflux conditions (one-pot) to afford ester **7**. Compound **7** was then treated with methanolic HCl, followed by ester hydrolysis using LiOH to furnish pure hydroxy acid **1d** in 80% yield. The *seco* acid **1f** was prepared from the bromo derivative[62] **8** in four steps. Compound **8** was treated with tetrahydrofurfuryl chloride in the presence of $LiNH_2$ in Liq-NH_3 to afford acetylene derivative **9**. Compound **9** was subjected to partial hydrogenation over Lindlar catalyst, followed by acetylation using Ac_2O-pyridine and acidic work-up to give *cis* olefin **10**. The acetyl derivative **10** was oxidized to the aldehyde and further oxidation with alkaline Ag_2O in ethanol furnished pure hydroxy acid **1f** in 70% yield (2-steps). As lactone formation becomes relatively slow in going from medium to large ring sizes, slow addition of ω-hydroxy acid to the medium is required for maintenance of high dilution.

Scheme-2



Reagents: a) DHP / PTSA, CH_2Cl_2, 92%; b) Dibal-H, -78C, toluene, 1h; then Ph_3P=CH-COOEt, reflux, 91%; c) (i) CH_3OH / H+, (ii) LiOH, THF-H_2O (1:1), 90%.

Scheme-3



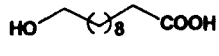
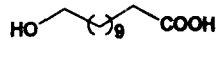
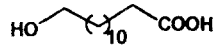
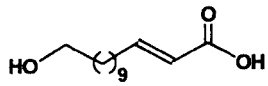
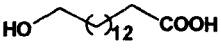
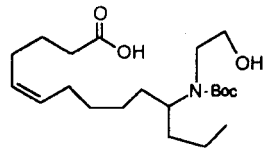
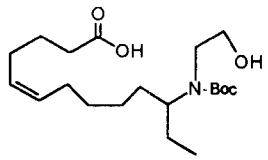
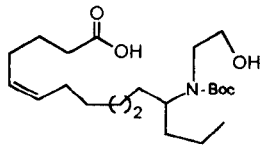
Reagents: a) Tetrahydrofurfuryl Chloride, $LiNH_2$, liq-NH_3; b) (i) Pd (5%) in $CaCO_3$ (Lindlar catalyst), CH_3OH, Cat-quinoline; (ii) Ac_2O / Pyridine; c) (i) CH_3OH / H+, (ii) PCC / CH_2Cl_2, r.t; (iii) Ag_2O, Ethanol, r.t, 70% (2-steps).

Initially for the standardisation of experimental conditions, the *seco* acid **1b** (table-1) was subjected to macrolactonization using 1.5 eq. of Boc_2O and Et_3N in dry toluene in the presence of 6 eq. of DMAP to afford 40% of macrolide **3b** and 38% of diolide **4b**. The yield of this macrolide and diolide are not consistent under these conditions. After many trials using different ratios of reagents (Boc_2O, Et_3N and DMAP), the best and most consistent result was obtained using 4 eq. each of Boc_2O and Et_3N, 8-10 eq. of DMAP under high dilution conditions in dry toluene. Employing the above conditions, a series of simple ω-hydroxy acids **1** (**a, b, c, d, e** and **f**) were subjected to macrolactonisation to give varying yields of macrolides **3** and diolide **4** (table-1). From this, it is observed that when the ring size was gradually increased from 12-membered to 16-membered, the formation of the macrolides **3** also increased from 39% to 71% yield and the diolide **4** formation was gradually decreased from 33% to 11% yield. From table-1, the hydroxy acids **1d** and **1f** show no isomerisation of double bond under these conditions. From these observations, it is evident that this method gives good yields for higher membered lactones and average yields for medium membered lactones.

In order to demonstrate the versatility of this macrolactonisation approach, it was further applied to the synthesis of biologically active azamacrolides.[42-44] The hydroxy acids **1g, 1h** and **1i,** key intermediates in the synthesis of azamacrolides [epilachnene (**11**), norepilachnene (**12**) and homoepilachnene (**13**)], were subjected to these macrolactonization conditions to give good yields of macrolides **3g, 3h** and **3i** without diolide formation (table-1). The resultant macrolides **3g, 3h** and **3i** when further treated with TFA according to the literature procedure[42-44] gave azamacrolides **11, 12** and **13** as shown in scheme 4. All the isolated macrolides were characterised by ^{1}HNMR, MS, HRMS or microanalysis and are well in agreement with those of reported values.[42-44] *The successful synthesis of these azamacrolides* **11, 12** *and* **13** *demonstrate the utility of the present* macrolactonisation strategy.

An investigation was undertaken in order to study the effect of bases and activating agents on the yield of the macrolactonisation reaction. For the present study, the tetradecanhydroxy acid **1e** was subjected to our macrolactonisation conditions using various base combinations such as, pyridine / DMAP, Et_3N / DMAP, 2,6-lutidine / DMAP, $(i\text{-}Pr)_2NEt$ / DMAP, $(i\text{-}Pr)_2NEt$ / pyrrolidinopyridine (4-PP) and the isolated yield of macrolide **3e** and diolide **4e** are shown in table-2. In the case of Boc_2O-pyridine / DMAP conditions (table-2, entry-1), the macrolide yield was very low (34%) and the overall yield of lactone **3e** plus diolide **4e** was not high (53%). The yields of macrolide **3e** and diolide **4e** were not significantly altered by using various bases as shown in table-2 (entry 2-4) except entry-1. Using Boc_2O-diisopropylethyl amine / pyrrolidinopyridine combination, the macrolide **3e** was isolated in 87% yield along with trace amount of the diolide **4e**. From these observations,

Table - 1: Lactonisation of ω- hydroxy acids

Entry No.	Hydroxy acid (1) Φ	Ring Size	Macrolide (3) Yield * (%)	Diolide (4) Yield* (%)
a		12	39	33
b		13	44	27
c		14	65	24
d		14	70	13
e		16	71	12
f		16	70	11
g		15	53	–
h		15	55	–
i		16	54	–

Φ - Lactonisation was carried out using Boc_2O - Et_3N / DMAP Condition
* - Isolated yield

it is concluded that the optimum yield of macrolide **3e** was obtained using Boc_2O-$(i\text{-}Pr)_2NEt$ / 4-PP combinations. The results in table-2 revealed that bases do not have any special role in the present macrolactonisation approach.

In order to demonstrate the generality of an improved reagent combination of Boc_2O-$(i\text{-}Pr)_2NEt$ / 4-PP for the present macrolactonisation study, it was further applied to various known hydroxy acids **1a** and **1b** and gave good yields of lactones as shown in scheme 5. These improved reagent conditions give a better ratio of macrolide **3** to diolide **4** compared to the condition initially developed by us (table-1).[58]

Scheme-4

3g n = 1 ; R = ethyl
3h n = 1 ; R = methyl
3i n = 2 ; R = ethyl

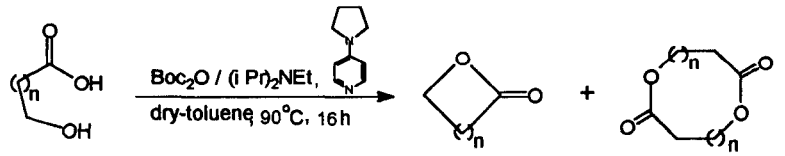
11 n = 1 ; R = ethyl
12 n = 1 ; R = methyl
13 n = 2 ; R = ethyl

Table - 2: Effect of Bases and activating agents on Macrolactonisation

Entry No.	Hydroxy Acid	Reaction condition	Ring size	Macrolide (3e)*	Diolide (4e)*
1	1e	Boc_2O - Pyridine / DMAP#	16	34	19
2	"	Boc_2O - Et_3N / DMAP#	"	71	20
3	"	Boc_2O - 2,6 - Lutidine / DMAP#	"	74	13
4	"	Boc_2O - $(i\text{-}Pr)_2NEt$ / DMAP#	"	76	16
5	"	Boc_2O -$(i\text{-}Pr)_2NEt$ / 4-PP $	"	87	Trace

* isolated yields ; # 4-Dimethylaminopyridine ; $ 4-Pyrrolidinopyridine.

Scheme-5



1a ; n = 9
1b ; n = 10

3a (45%)
3b (67%)

4a (27%)
4b (27%)

Conclusion

In conclusion, the present procedure for the synthesis of macrolides is expected to be an useful and important addition to the present methodologies. The main advantages of this new method are mild reaction conditions, commercially and readily available low cost reagents, stability of the reagent, tolerance to the olefinic double bond, no isomerisation during the reaction, simple and easy work-up of the reaction mixture and good yields. Another advantage of the present method is that the byproducts, t-butanol and CO_2 do not require any tedious purification / separation from the reaction mixture compared to the existing well known methods which

tend to give by-products. The application of this method to the synthesis of biologically active azamacrolides proves its efficiency. Further application of the described method for the synthesis of other complex macrolides is under progress.

Experimental

General: Melting points were recorded on Buchi 535 melting point apparatus and are uncorrected. All solvents and reagents were purified and dried according to procedures given in Vogel' s Text Book of Practical Organic Chemistry. All reactions were carried out under nitrogen atmosphere with dry, freshly distilled solvents under anhydrous conditions unless otherwise noted. Yields refer to chromatographically and spectroscopically homogeneous materials isolated unless otherwise stated. All the reactions were monitored by Analytical Thin Layer Chromatography (TLC) performed on E-Merck 0.25mm silica gel plates. Visualization was accomplished with UV light (256 nm), iodine and by dipping in 2% phosphomolybdic acid in 15% aq.H_2SO_4 or 2.75% p-anisaldehyde in 3% H_2SO_4 and 1% AcOH in EtOH followed by heating. IR spectra were recorded on a Perkin-Elmer 683 spectromer. Optical rotations were measured with a JASCO DIP 370 digital polarimeter. ^{1}H NMR spectra were recorded on varian FT-200 MHz in $CDCl_3$, unless otherwise stated. Chemical shifts are expressed in (ppm) downfield from TMS as an internal standard. Mass spectra were recorded on a CEC-21-110B, Finnigan Mat 1210 Spectrometer at 20 eV using a direct inlet system and HRMS were recorded on a VG AUTOSPEC M at 70 eV using a direct inlet system. Elemental analysis was carried out on a Perkin-Elmer analyser 240C.

Ethyl 11-tetrahydro-2H-2-pyranyloxy undecanoate (6):

To a solution of compound **5** (9.0 g, 39.13 mmol) in CH_2Cl_2 (100 ml) was added DHP (5.36 ml, 58.69 mmol) and cat. PTSA at 0°C and stirred at room temperature for 5h. Then the reaction mixture was neutralized with Et_3N, concentrated under vacuum and passed over a small pad of silica gel (60-120 mesh) using 5% ethyl acetate in petroleum ether as an eluent to afford compound **6** (11.3g, 92%) as a colourless liquid. IR ($CHCl_3$): 2985,1715 cm^{-1}; ^{1}H NMR ($CDCl_3$): 4.51 (bs, 1H), 4.10 (q , 2H , J = 6.2 Hz), 3.72-3.30 (m, 4H), 2.24 (t, 2H, J = 5.8 Hz), 1.70-1.20 (m, 22H), 1.05 (t, 3H, J = 6.4 Hz).

E thyl 13-tetrahydro-2H-2-pyranyloxy-(E)-2-tridecenoate (7):

To a stirred solution of compound **6** (11.2 g, 35.67 mmol) in dry toluene (75 ml) was added DIBAL-H (2 M solution in toluene) (17.83 ml, 35.67 mmol) at -78°C under N_2 atm. and the stirring was continued for 2 h. Methanol (2.0 ml) was carefully added to the reaction mixture to quench excess DIBAL-H and slowly brought to room temperature. Then ethoxycarbonylmethylenetriphenylphosphorane (18.5 g, 53.50 mmol) was added to the reaction mixture and refluxed for 6h. The solvent was concentrated under vacuum and the residue was purified through silica gel column chromatography (60-120 mesh) using hexane-ethyl acetate (9:1) as an eluent to give compound **7** (11.0 g, 90.7%) as a colourless oil. IR ($CHCl_3$): 2985, 1690 cm^{-1}; ^{1}H NMR ($CDCl_3$): 6.95-6.88 (m, 1H), 5.80 (d, 1H, J = 15.4 Hz), 4.50 (1H, bs), 4.05 (q, 2H, J = 5.8 Hz), 3.70-3.35 (m, 4H), 2.30-2.21 (m, 2H), 1.80-1.20 (m, 22H), 0.95 (t, 3H, J = 6.8 Hz); Analysis calcd. for $C_{20}H_{36}O_4$: C, 70.55%, H, 10.66%; Found: C, 70.41%, H, 10.52%.

13-Hydroxy-(E)-3-tridecenoic acid (1d):

To a stirred solution of compound **7** (10.0 g, 29.41 mmol) in methanol was added 1M HCl (10 ml) and stirred at rt for 2h. Then the reaction mixture was concentrated under vacuum, diluted with water and extracted with ethyl acetate (50 ml). The organic layer was washed with satd.$NaHCO_3$, water, brine, dried over Na_2SO_4 and concentrated to afford crude hydroxy ester which was used in the next reaction without purification.

To the above crude mixture in THF-H_2O (1:1) (40 ml) was added LiOH (1.41 g, 58.83 mmol) and stirred at rt for 8h. Then the reaction mixture was concentrated under vacuum, diluted with water and extracted

with ethyl acetate (50 ml). The organic layer was washed with 2% citric acid solution, water, brine, dried over Na_2SO_4 and concentrated to afford hydroxy acid **1f** (6.05 g, 90%) as a semi solid. IR (CCl_4): 3400, 2965, 1710, 1645 cm^{-1}; ^1H NMR ($CDCl_3$): 6.95 (m, 1H), 5.80 (d, 1H, J = 16.0 Hz), 3.65 (t, 2H, J = 6.0 Hz), 2.30-2.20 (m, 2H), 1.70-1.45 (m, 4H), 1.40-1.20 (m, 12H); Analysis calcd. for $C_{13}H_{24}O_3$: C, 68.37%, H, 10.60%; Found: C, 68.23%, H, 10.46%.

15-Tetrahydro-2H-2-pyranyloxy-4-pentadecyn-1-ol (9):[63,64]

To a freshly prepared suspension of $LiNH_2$ [prepared from Li (1.45 g, 207.6 mmol) and cat. ferric nitrate] in liq. NH_3 (300 ml) was added tetrahydrofurfurylchloride (10.0 g, 83.02 mmol) over a period of 15 min. at -20°C and the reaction mixture was stirred at room temperature for 1 h. Then HMPA (2 ml) was added and the reaction mixture was cooled to -20°C. Bromo compound[62] **8** (34.65 g, 107.93 mmol) in THF (100 ml) was added slowly over a period of 15 min. and the stirring was continued at room temperature for 6h. The ammonia was allowed to evaporate completely, quenched with satd. NH_4Cl solution and extracted with ethyl acetate (2x100 ml). The combined organic extracts were washed with water, brine, subsequently dried (Na_2SO_4) and concentrated under reduced pressure. The organic residue was purified through silica gel column chromatography (60-120 mesh) using hexane-ethyl acetate (9:1) as an eluent to furnish compound **9** (27.0 g, 77%) as a yellow oil. IR (Neat): 3450 (br, OH), 2975, 2200 (W) cm^{-1}; ^1H NMR ($CDCl_3$): 4.51 (bs, 1H), 3.85-3.70 (m, 2H), 3.65-3.25 (m, 4H), 2.30-2.15 (m, 4H), 1.85-1.30 (m, 24H); Analysis calcd. for $C_{20}H_{36}O_3$: C, 74.03%, H, 11.18%; Found: C, 73.86%, H, 11.03%.

15-Hydroxy-(Z)-4-pentadecenyl acetate (10):

To a solution of compound **9** (10.0 g, 30.86 mmol) in dry methanol was added Lindlar catalyst [Pd (5%) in $CaCO_3$ - Pb] (3.0 g; For 1 mmol compound, 0.01 mmol catalyst used) and cat. quinoline and stirred at room temperature for 5 h. Then the reaction mixture was filtered over celite and concentrated under vacuum and used for the next reaction without purification.

To the above crude reaction mixture (9.1g, 27.91 mmol) in CH_2Cl_2 (50 ml), Ac_2O (2.95 ml, 31.29 mmol), pyridine (4.22 ml, 52.20 mmol) and cat. DMAP were added and stirred at room temperature for 2 h. Then the reaction mixture was concentrated under vacuum, stirred with 10% HCl solution at room temperature for 2 h. The reaction mixture was extracted with ethyl acetate (2x75 ml), washed with satd. $NaHCO_3$, water, brine, dried over Na_2SO_4 and concentrated under reduced pressure. The organic residue was purified through silica gel column chromatography (60-120 mesh) using hexane-ethyl acetate (9:1) as an eluent to furnish compound **10** (7.0 g, 88%) as a colourless oil. IR (Neat): 3460 (br, OH), 2985, 1710 cm^{-1}; ^1H NMR ($CDCl_3$): 5.35-5.26 (m, 2H), 4.00 (t, 2H, J = 4.4 Hz), 3.60 (t, 2H, J = 4.8 Hz), 2.10-2.00 (m, 7H), 1.65-1.45 (m, 4H), 1.40-1.20 (m, 14H); Analysis calcd. for $C_{17}H_{32}O_3$: C, 71.79%, H, 11.34%; Found: C, 71.68%, H, 11.23%.

15-Hydroxy-(Z)-11-pentadecenoic acid (1f):

To a solution of compound **10** (6.0 g, 21.13 mmol) in CH_2Cl_2 was added PCC (6.83 g, 31.7 mmol) and celite (4.0 g) and stirred at room temperature for 3h. Then the reaction mixture was filtered over celite and concentrated under vacuum to afford crude aldehyde (4.9 g, 82%) as a colourless oil which was used as such in the next reaction.

To a stirred suspension of alkaline Ag_2O (5.55 g, 23.94 mmol) in ethanol (40 ml), crude aldehyde (4.5 g, 15.96 mmol) in ethanol (10 ml) was added and stirred at room temperature for 8 h. The reaction mixture was filtered through a celite and concentrated under reduced pressure. The residue was diluted with water, neutralized with dil. HCl and extracted with ethyl acetate (2x50 ml). The combined organic extracts were washed with water, brine, dried over Na_2SO_4 and concentrated. The residue was purified by silica gel column chromatography (60-120 mesh) using hexane-acetone (8:2) as an eluent to afford acid alcohol **1f** (3.1g, 76%) as a semi solid. IR (CCl_4): 3470 (br, OH), 2980, 1610 cm^{-1}; ^1H NMR ($CDCl_3$): 5.40-5.30 (m, 2H), 3.65 (t, 2H, J =

5.8 Hz), 2.30 (t, 2H, J = 7.0 Hz), 2.15-2.02 (m, 4H), 1.70-1.60 (m, 4H), 1.45-1.20 (m, 14H); Analysis calcd. for $C_{15}H_{28}O_3$: C, 70.25%, H, 11.01%; Found: C, 70.11%, H, 10.87%.

General procedure for macrolactonisation:

To a stirred solution of *seco* acid **1** (0.40 mmol) in dry toluene (3.0 ml), Et_3N (1.6 mmol) and Boc_2O (1.6 mmol) were added sequentially under N_2 atm and stirred at room temperature for 2 h. Then the resultant mixed anhydride was dissolved in toluene (for 1.0 mmol of substrate, 540 ml of dry toluene used; 0.002M) and was added dropwise, via-additional funnel to a stirred, preheated solution (90-95°C) of DMAP (3.2 mmol) in dry toluene (for 1.0 mmol of DMAP, 20 ml of dry toluene used; 0.05M) over a period of 5 h and the stirring was continued for 12-14 h at the same temperature. Then the reaction mixture was concentrated under reduced pressure, diluted with ether (100 ml), washed with 5% citricacid solution (2x75 ml), water, brine, dried over Na_2SO_4 and concentrated under vacuum. The crude product was purified through a silica gel column chromatography (finer than 200 mesh) using 2% ethyl acetate in petroleum ether as an eluent to furnish pure macrolide **3** and diolide **4** as shown in the table-1. **Note:** 1) The macrolactonisation reaction was performed in all the substrates **1 (a-i)** using 0.40 mmol scale. 2) In silica gel column chromatography, all the macrolides **3** are eluted first (less polar), followed by diolides **4** (more polar, eluted second).

2-Oxacyclododecan-1-one (3a)[38]: Light yellow oil; perfumes like odour; IR ($CHCl_3$): 2930, 2860, 1735, 1460 cm^{-1}; ^1H NMR ($CDCl_3$): 4.20 (t, 2H, J = 4.4 Hz), 2.35 (m, 2H), 1.80-1.60 (m, 4H), 1.45-1.20 (m, 12H); EIMS (20 eV) : m/z 185 (MH^+, 2%), 184 (M^+, 2%), 166 (M^+- H_2O, 2%), 124 (20%), 112 (40%), 98 (100%); Analysis calcd. for $C_{11}H_{20}O_2$: C, 71.68%, H, 10.95%; Found: C, 71.49%, H, 11.11%.

2,14-Dioxacyclotetracosane-1,13-dione (4a)[38]: White crystalline solid; M.P. 70-71°C (lit.[7] M.P. 73-74°C); ^1H NMR ($CDCl_3$): 4.12 (t, 4H, J = 4.9 Hz), 2.32 (t, 4H, J = 5.77 Hz), 1.80-1.60 (m, 8H), 1.50-1.20 (m, 24H); EIMS (20 eV): m/z 368 (M^+, 2%), 350 (M^+- H_2O, 30%), 227 (15%), 185 (40%), 149 (80%), 98 (100%); Analysis calcd. for $C_{22}H_{40}O_4$: C, 71.7%, H, 10.94%; Found: C, 72.09%, H, 11.21%.

2-Oxacyclotridecan-1-one (3b)[38]: Light yellow oil; perfume like odour; GC purity: 99.02% (column: Se-30 (g), flow rate: 20 ml / min); IR ($CHCl_3$): 2932, 2861, 1733, 1335 cm^{-1}; ^1H NMR ($CDCl_3$): 4.05 (t, 2H, J = 4.4 Hz), 2.25 (m, 2H), 1.65-1.45 (m, 4H), 1.40-1.20 (m, 14H); EIMS (20 eV): m/z 198 (M^+, 10%), 180 (M^+- H_2O, 30%), 167 (10%), 152 (30%), 138 (80%), 111 (100%); HRMS Calcd. for $C_{12}H_{22}O_2$: 198.1619; Found: 198.1618.

2,15-Dioxacyclohexacosane-1,14-dione (4b)[38]: White solid; M.P. 99-99.5°C (lit.[7] M.P. 103-104°C); IR ($CHCl_3$): 2930, 2885, 1730 cm^{-1}; ^1H NMR ($CDCl_3$): 4.05 (t, 4H, J = 4.4 Hz), 2.25 (t, 4H, J = 4.8 Hz), 1.65-1.45 (m, 8H), 1.45-1.20 (m, 28H); EIMS (20 eV): m/z 396 (M^+, 2%), 377 (MH^+- H_2O, 50%), 276 (15%), 241 (20%), 199 (40%), 149 (30%), 98 (100%); Analysis Calcd. for $C_{24}H_{44}O_4$: C, 72.68%, H, 11.18%; Found: C, 72.57%, H, 11.04%.

2-Oxacyclotetradecan-1-one (3c)[38]: Light yellow oil; perfume like odour; IR ($CHCl_3$): 2930, 2860, 1735, 1465 cm^{-1}; ^1H NMR ($CDCl_3$): 4.15 (t, 2H, J = 5.2 Hz), 2.35 (m, 2H), 1.75-1.55 (m, 5H), 1.50-1.20 (m, 16H); EIMS (20 eV): m/z 212 (M^+, 5%), 194 (M^+- H_2O, 10%), 152 (30%), 124 (25%), 110 (50%), 96 (30%), 82 (100%); HRMS Calcd. for $C_{13}H_{24}O_2$: 212.1776; Found: 212.1770.

2,16-Dioxacyclooctacosane-1,15-dione (4c)[38]: White crystalline solid; M.P. 79-80°C (lit.[7] MP 81-82°C); IR ($CHCl_3$): 2930, 2855, 1730, 1465 cm^{-1}; ^1H NMR ($CDCl_3$): 4.10 (t, 4H, J = 5.2 Hz), 2.30 (t, 4H, J = 6.4 Hz), 1.75-1.55 (m, 8H), 1.45-1.20 (m, 32H); EIMS (20 eV): m/z (M^+, 2%), 406 (M^+- H_2O, 20%), 213 (20%), 192

(10%), 149 (10%), 98 (50%), 55 (100%); Analysis calcd. for $C_{26}H_{48}O_4$: C, 73.54%, H, 11.39%; Found: C, 73.45%, H, 11.21%.

(E)-14-Oxa-2-cyclotetradecene-1-one (3d): Viscous yellow oil; HPLC purity : 90.32% (colour: silica; system: 2% isopropanol in n-heptane, UV: 225 nm, Flow rate: 0.6 ml / min.); IR ($CHCl_3$): 2940, 2870, 1720, 1450 cm^{-1}; ^1H NMR ($CDCl_3$): 6.95 (m, 1H), 5.75 (d, 1H, J = 16.5 Hz), 4.20 (t, 2H, J = 5.5 Hz), 2.25-2.15 (m, 2H), 1.73-1.50 (m, 4H), 1.45-1.15 (m, 12H); EIMS (20 eV): m/z 210 (M^+, 5%), 150 (10%), 124 (20%), 109 (30%), 95 (60%), 81 (100%); HRMS Calcd. for $C_{13}H_{22}O_2$: 210.1619; Found: 210.1615.

(2E,16E)-14,28-Dioxa-2,16-cyclooctacosadiene-1,15-dione (4d): Semi solid; IR ($CHCl_3$): 2935, 2875, 1715, 1445 cm^{-1}; ^1H NMR ($CDCl_3$): 6.90 (m, 2H), 5.70 (d, 2H, J = 16.6 Hz), 4.20 (t, 4H, J = 5.8 Hz), 2.28-2.18 (m, 4H), 1.70-1.60 (m, 8H), 1.50-1.20 (m, 24H); EIMS (20 eV): m/z 420 (M^+, 15%), 394 (10%), 210 (25%), 192 (20%), 164 (30%), 149 (40%), 95 (60%), 85 (100%); HRMS Calcd. for $C_{26}H_{44}O_4$: 420.3240; Found: 420.3261.

2-Oxacyclohexadecan-1-one (3e)[38]: Light yellow oil; perfume like odour; GC purity: 96.21% (Column: Se-30 (g), Flow rate: 20 ml/min); IR (Neat): 2930, 2855, 1730, 1465 cm^{-1}; ^1H NMR ($CDCl_3$): 4.10 (t, 2H, J = 5.5 Hz), 2.30 (t, 2H, J = 6.0 Hz), 1.75-1.50 (m, 4H), 1.50-1.20 (m, 20H); EIMS (20 eV): m/z 240 (M^+, 15%), 222 (M^+-H_2O, 25%), 192 (35%), 180 (15%), 152 (10%), 110 (40%), 96 (80%), 83 (90%), 69 (100%); HRMS Calcd. for $C_{15}H_{28}O_2$: 240.2089 ; Found: 240.2085.

2,18-Dioxacyclodotriacontane-1,17-dione (4e)[38]: White solid; M.P. 88-89°C (lit.[7] M.P. 90-91°C); IR ($CHCl_3$): 2930, 2855, 1725, 1465 cm^{-1}; ^1H NMR ($CDCl_3$): 4.05 (t, 4H, J = 6.0 Hz), 2.25 (t, 4H, J = 6.6 Hz), 1.70-1.50 (m, 8H), 1.40-1.20 (m, 40H); EIMS (20 eV): m/z 480 (M^+, 5%), 462 (M^+- H_2O, 50%), 241 (35%), 223 (30%), 149 (100%), 98 (60%), 57 (90%); HRMS Calcd. for $C_{30}H_{56}O_4$: 480.4179; Found: 480.4172.

(6Z)-2-Oxa-6-cyclohexadecen-1-one (3f): Odourless gummy oil; IR (Neat): 2935, 2860, 1730, 1665 cm^{-1}; ^1H NMR ($CDCl_3$): 5.40-5.20 (m, 2H), 4.10 (t, 2H, J = 4.8 Hz), 2.30 (t, 2H, J = 5.6 Hz), 2.20-1.95 (m, 4H), 1.80-1.55 (m, 4H), 1.45-1.25 (m, 12H); EIMS (20 eV): m/z 238 (M^+, 20%), 109 (20%), 96 (40%), 82 (70%), 68 (100%), 55 (20%); HRMS Calcd. for $C_{15}H_{26}O_2$: 238.1933; Found: 238.1942.

(6Z, 22Z)-2,18-dioxa-6,22-cyclodotriacontadiene-1,17-dione (4f): Semi solid; IR ($CHCl_3$): 2930, 2855, 1725, 1660 cm^{-1}; ^1H NMR ($CDCl_3$): 5.40-5.15 (m, 4H), 4.05 (t, 4H, J = 5.8 Hz), 2.30 (t, 4H, J = 7.1 Hz), 2.20-1.90 (m, 8H), 1.75-1.50 (m, 8H), 1.45-1.20 (m, 24H); EIMS (20 eV): m/z 476 (M^+, 2%), 436 (5%), 238 (30%), 220 (35%), 149 (20%), 110 (30%), 95 (60%), 81 (85%), 55 (100%); Analysis calcd for $C_{30}H_{52}O_4$: C, 75.63%; H, 10.92%; Found: C, 75.47%; H, 10.76%.

Z-11-Propyl-12-aza-[N-(tert-butoxycarbonyl)-amino]-cyclopentadec-5-enyl-15-olide (3g)[42-44]: IR($CHCl_3$): 1740, 1670 cm^{-1}; ^1H NMR ($CDCl_3$): 5.30 (m, 2H), 4.20 (m, 2H), 3.80 (m, 1H), 3.25 (m, 2H), 2.33 (t, 2H, J = 6.0 Hz), 2.10 (m, 4H), 1.60-1.15 (m, 21H), 0.90 (t, 3H, J = 6.6 Hz); EIMS : 267 (M^+- Boc); Analysis calcd for $C_{21}H_{37}NO_4$: C, 68.61%, H, 10.15%, N, 3.81%; Found: C, 68.42%, H, 10.19%, N, 3.58%.

Z-11-Ethyl-12-aza-[N-(tert-butoxycarbonyl)-amino]-cyclopentadec-5-ene-15-olide (3h)[42-44]: IR(neat): 1750,1680 cm^{-1}; ^1H NMR ($CDCl_3$): 5.20 (m, 2H), 4.10 (m, 2H), 3.82 (m, 1H), 3.15 (m, 2H), 2.25 (t, 2H, J = 5.8 Hz), 2.10 (m, 4H), 1.60-1.10 (m, 19H), 0.91 (t, 3H, J = 6.2 Hz); EIMS: 253 (M^+- Boc); Analysis calcd for $C_{20}H_{35}NO_4$: C, 67.94%, H, 9.99%, N, 3.97%; Found: C, 67.68%, H, 10.16%, N, 3.72%.

Z-12-propyl-13-aza-[N-(tert-butoxycarbonyl)-amino]-cyclohexadec-5-ene-16-olide (3i)[42-44]: IR(neat): 1740, 1680 cm^{-1}; ^1H NMR ($CDCl_3$): 5.30 (m, 2H), 4.15 (m, 2H), 3.82 (m, 1H), 3.25 (m, 2H), 2.30 (t, 2H, J =

6.2 Hz), 2.10 (m, 4H), 1.60-1.15 (m, 23H), 0.90 (t, 3H, J = 6.4 Hz); EIMS: 281 (M^+- Boc); **Analysis calcd for** $C_{22}H_{39}NO_4$: C, 69.24%, H, 10.31%, N, 3.67%; Found: C, 69.02%, H, 10.36%, N, 3.41%.

General Procedure for Boc- deprotection:[42-44]

Trifluoroacetic acid (2 ml) was added to the lactone **3g** (0.045 g, 0.123 mmol), **3h** (0.040g, 0.114 mmol) and **3i** (0.045g, 0.118 mmol) at 0°C and stirred for 30 min. Then ice-cold water (10 ml) was added to the reaction mixture, neutralized with solid $NaHCO_3$, extracted with ethyl acetate (2x30 ml) and concentrated under reduced pressure. The crude product was purified by flash chromatography (silica gel 60-120 mesh) using hexane-acetone (7:3) as eluent to afford epilachnene **11** (0.025 g, 76%), norepilachnene **12** (0.023g, 80%) and homoepilachnene **13** (0.026g, 78%) as a thick syrups.

Z-11-Propyl-12-azacyclopentadec-5-enyl-15-olide (11): IR (CCl_4): 3450, 1740 cm^{-1}; ^1H NMR ($CDCl_3$): 5.32 (m, 2H), 4.32 (m, 1H), 4.00 (m, 1H), 3.02 (m, 1H), 2.80 (m, 1H), 2.46-2.24 (m, 3H), 2.20-1.98 (m, 4H), 1.76 (m, 2H), 1.52-1.20 (m, 10H), 0.90 (t, 3H, J = 6.4 Hz); EIMS : 267 (M^+), 224 (M^+- propyl, 100%); HRMS Calcd. for $C_{16}H_{29}O_2N$: 267.2198; Found: 267.2196.

Z-11-Ethyl-12-azacyclopentadec-5-ene-15-olide (12): IR (CCl_4): 3500, 2935, 1735 cm^{-1}; ^1H NMR ($CDCl_3$): 5.30 (m, 2H), 4.32 (m, 1H), 3.97 (m, 1H), 3.00 (m, 1H), 2.78 (m, 1H), 2.45-2.28 (m, 3H), 2.22-2.00 (m, 4H), 1.76 (m, 2H), 1.50-1.20 (m, 8H), 0.88 (t, 3H, J = 6.2 Hz); EIMS: 253 (M^+), 224 (M^+- ethyl, 100%); HRMS Calcd. for $C_{15}H_{27}O_2N$: 253.2041; Found: 253.2053.

Z-12-Propyl-13-azacyclohexadec-5-ene-16-olide (13): IR (CCl_4): 3450, 2985, 1740 cm^{-1}; ^1H NMR ($CDCl_3$): 5.30 (m, 2H), 4.25 (m, 1H), 4.05 (m, 1H), 2.78 (m, 2H), 2.48 (bs, 1H), 2.30 (t, 2H, J = 7.2 Hz), 2.12-1.88 (m, 4H), 1.76 (m, 4H), 1.50-1.20 (m, 10H), 0.86 (t, 3H, J = 6.4 Hz); EIMS: 281 (M^+), 238 (M^+- propyl, 100%); HRMS Calcd. for $C_{17}H_{31}O_2N$: 281.2354; Found: 281.2358.

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