Concise strategy for the synthesis of eleven-membered and ansa-bridged thirteen-membered lactone macrolides by ring-closing metathesis reaction

Krishna C. Majumdar, Buddhadeb Chattopadhyay, and Inul Ansary

Abstract: The eleven-membered macrolides and thirteen-membered ansa-bridged macrolides have been synthesized successfully by ring-closing metathesis reaction in the absence of the additive $Ti(OiPr)_4$, which is essential for the metathesis reaction of the ester precursors.

Key words: ring-closing metathesis, Grubbs catalyst, macrolide, eleven- and thirteen-membered lactone.

Résumé : On a réalisé la synthèse de macrolides à onze chaînons et de macrolides à pont ansa à treize chaînons par le biais d'une réaction de fermeture de cycle impliquant une métathèse, en l'absence du catalyseur $Ti(OiPr)_4$ qui est essentiel aux réactions de métathèse dans lesquelles les précurseurs sont des esters.

Mots-clés : fermeture de cycle impliquant une métathèse, catalyseur de Grubbs, macrolide, lactones à 11 et 13 chaînons.

[Traduit par la Rédaction]

Introduction

Recently, Singh et al. have reported[1] the isolation of two natural products, aspercyclides (Fig. 1, **a** and **b**), from the fungal metabolites and claimed that these natural products (**a** and **b**) possess several important biological activities.[2] The natural products aspercyclides consist of an eleven-membered lactone moiety that is flanked by differently substituted diaryl ether lactone. Subsequently, Furstner and Muller[3] achieved the total synthesis of "aspercyclide C" (Fig. 1, **a**) to explore its biological activity.

Moreover, numerous natural products possess a macrolactone subunit and exhibit important biological and cytotoxic activities.[4] *Pondaplin* D,[5] an ansa-bridged thirteen-membered macrolide isolated from *Annoa glabra* is known to be cytotoxic against six different human tumor cell lines (Fig. 2).[5] This thirteen-membered ansa-bridged macrolide framework confers strong rigidity to the whole structure. Therefore, all these factors made its synthesis a challenging purpose.

With the discovery of useful as well as air-stable catalysts, ring-closing metathesis (RCM) is now a practical and beneficial method of choice for the synthesis of cyclic compounds from highly functionalized molecules.[6] This protocol has been tremendously applied for the synthesis of macrolactones of different ring sizes.[7] The synthesis of ansa-bridged macrolides by ring-closing metathesis has been developed only in few cases.[3,8] This has prompted us to undertake a study of the synthesis of new lactone macrolides[9] for possible evaluation as biologically active compounds or any other useful compounds by the application of the ring-closing metathesis reaction of less studied ester precursors. Additional interest is derived from our interest in the synthesis of heterocycles by transition metal-mediated[10] heterocyclization.

Received 21 July 2008. Accepted 27 October 2008. Published on the NRC Research Press Web site at canjchem.nrc.ca on 28 January 2009.

K.C. Majumdar,[1] B. Chattopadhyay, and I. Ansary. Department of Chemistry, University of Kalyani, Kalyani 741235, W.B. India.

[1]Corresponding author (e-mail: kcm_ku@yahoo.co.in).

Results and discussion

The preparation of starting materials **6a**–**6f** is depicted on Scheme 1. Commercially available 2-hydroxy ethyl benzoate **1a** was conveniently allylated in dry acetone in the presence of anhyd. K_2CO_3 with allyl bromide for 15 h in refluxing condition to give *O*-allylated compound **2a**. Compound **2a** under saponification condition yielded the corresponding acid **3a**, which was finally converted to acid chloride **4a** by treatment with $SOCl_2$ in the presence of a catalytic amount of DMF. 2-Hydroxyl-1-allyl naphthalene **5a** was prepared according to the earlier reported procedure.[10a] The starting material **6a** was obtained by coupling of two partners **5a** and **4a** in dry DCM–Et_3N solvent in the presence of a catalytic amount of DMAP at 0 °C –RT for 12 h. Similarly, other starting materials **6b, 6c**, and **6d**–**6f** were prepared.

Attempts to carry out the metathesis reaction of the substrate **6a** with Grubbs first-generation catalyst in dichloromethane at RT proved unsuccessful. The entire starting material remained unchanged in the reaction mixture. When the reaction was conducted in refluxing condition for two days, only the decomposition of the catalyst was observed, leaving the starting material unchanged. However, when the substrate **6a** was refluxed with 5 mol% Grubbs second-generation catalyst in dry dichloromethane solution under nitrogen atmosphere for two days, the eleven-membered macrolide **7a** was obtained in 62% yield (Scheme 2). We have obtained only the *E*-olefin as evidenced by the *J* values (17.6 Hz) for the

Fig. 1. Naturally occurring aspercyclides, eleven-membered macrolides.

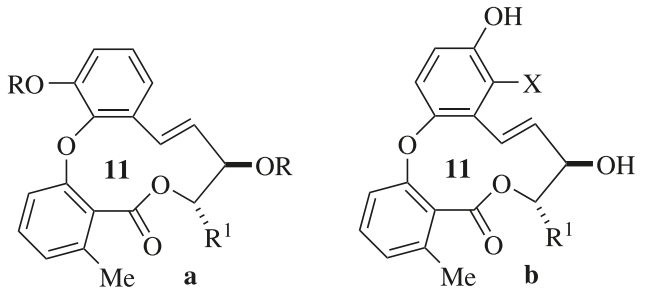
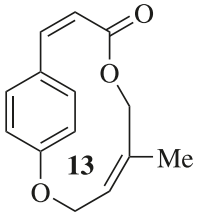


Fig. 2. Pondaplin, ansa-bridged thirteen-membered macrolide.



olefinic protons. To test the generality of this macrolization, the substrates **6b** and **6c** were treated under similar reaction conditions as above to afford the macrolides **7b** and **7c** in 59% and 63% yields, respectively.

We then extended the reaction to the synthesis of the thirteen-membered macrolides. Initially, we attempted the reaction of **6d** using Grubbs first-generation catalyst in dry dichloromethane solution under nitrogen atmosphere for 2–3 day without any success. No cyclized product was obtained even at the refluxing conditions. We then tried to carry out the same reaction by changing the solvent DCM with benzene, toluene, or xylene, but no macrolization was observed. Finally, we have succeeded in obtaining the thirteen-membered macrolide **7d** in 63% yield from **6d** by treatment with Grubbs second-generation catalyst in refluxing dichloromethane solution under nitrogen atmosphere for 4 days.

Here, the preparations of both the eleven- and thirteen-membered macrolides were achieved under high dilution.[11] The macrolides **7e** and **7f** were also prepared accordingly.

We have also attempted to extend the reaction by changing the allyl part of the compound **4** by crotyl and propargyl moieties. Unfortunately, we failed to obtain any cyclized product. The reaction conditions are summarized in Table 1.

Recently, Furstner[12] reported that the substrates possessing carboxylate moiety in one of the diene partners of the metathesis precursors cannot undergo the metathesis reaction with the Grubbs catalyst in the absence of additive $Ti(OiPr)_4$ in the reaction mixture. The reaction does not proceed because of the fact that the ruthenium carbene complex coordinates on to the ester by chelation with the ester carbonyl moiety and the olefin (Fig. 3).

When the reaction is conducted in the presence of $Ti(OiPr)_4$ along with the Grubbs catalyst, $Ti(OiPr)_4$ probably acts because of factors such as (*i*) $Ti(OiPr)_4$ is weakly Lewis acidic additive and consequently avoids the formation of unreactive chelate complex by coordination with the ester carbonyl moiety, (*ii*) $Ti(OiPr)_4$ may abstract one of the basic PCy_3 ligands from the Grubbs catalyst and thereby enhancing the catalytic activity of the Grubbs catalyst.

Conclusion

In conclusion, we have successfully synthesized the eleven-membered macrolides that are present in many natural-product core moieties such as aspercyclide C and thirteen-membered ansa-bridged macrolides that are the core structure of the natural product "pondaplin" by the implementation of ring-closing metathesis reaction without $Ti(OiPr)_4$ additive.[12] We believe that the methodology is simple and straightforward and will be useful to the synthetic community.

Experimental

General remarks

Melting points were determined in open capillaries and are uncorrected. IR spectra were run for KBr discs (and neat for liquid samples), and NMR spectra were determined for solutions in $CDCl_3$ with TMS as internal standard. Silica gel (60–120 mesh) was used for chromatographic separation. Silica gel-G was used for TLC. Petroleum ether refers to the fraction between 60 and 80 °C.

General methods for the preparation of compounds 6a–6f

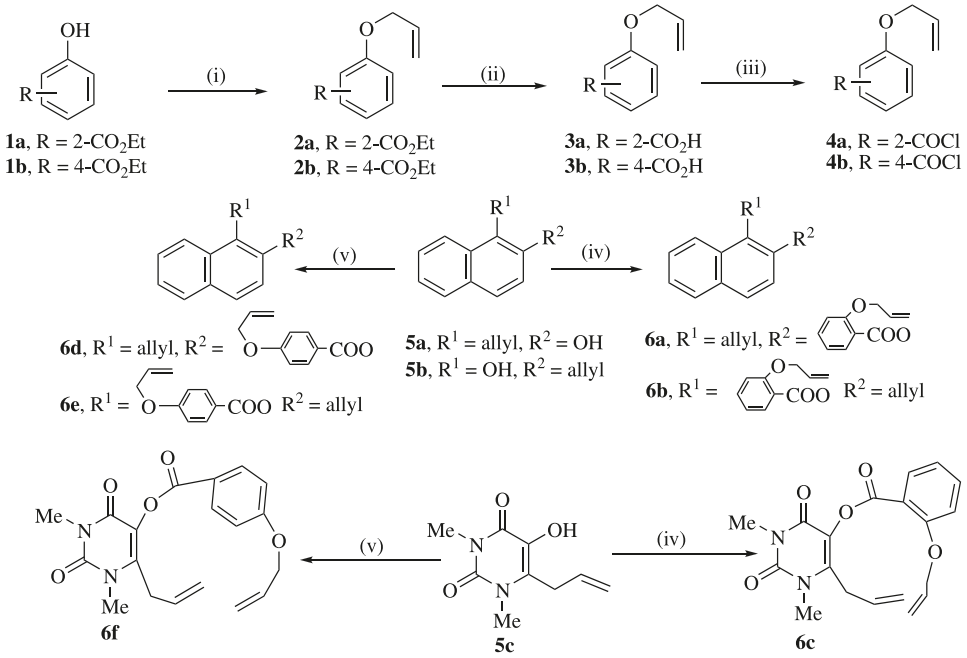
A mixture of 2-hydroxy ethyl benzoate **1a** (4.0 g, 24.07 mmol), allyl bromide (3.49 g, 28.88 mmol), anhyd. potassium carbonate (13.30 g, 96.28 mmol), and catalytic amount of sodium iodide in dry acetone (100 mL) was refluxed for 15 h. The reaction mixture was cooled, filtered, and acetone was evaporated to give the corresponding *O*-allylated compound **2a** (4.9 g). Compound **2a** (4.9 g) was hydrolyzed with potassium hydroxide (3.3 g, 59.41 mmol) in ethanolic solution (50 mL) for 4 h at refluxing condition. Excess ethanol was removed by distillation, and the reaction mixture was cooled and was made acidic by adding 6 N HCl to give the corresponding acid **3a** (4.0 g, 95%).

The acid **3a** (0.425 g, 2.38 mmol) was then refluxed with $SOCl_2$ (1.5 mL) in the presence of DMF (catalytic amount) for 1 h, and excess $SOCl_2$ was removed under reduced pressure to give the acid chloride (0.47 g, 100%) **4a**. Finally, the acid chloride **4a** (0.47 g, 2.39 mmol) in dry dichloromethane (15 mL) was added dropwise to a mixture of 1-allyl-2-naphthol **5a** (440 mg, 2.39 mmol), triethylamine (2 mL), and a catalytic amount of DMAP in dry dichloromethane solution (30 mL) at ice-cold temperature. The reaction mixture was stirred at RT for 12 h to afford the esterified compound **6a** (0.69 g, 82%). Similarly, other starting materials **6b–6f** were prepared. Compounds **6a–6f** were recrystallized from dichloromethane–petroleum ether (60–80 °C).

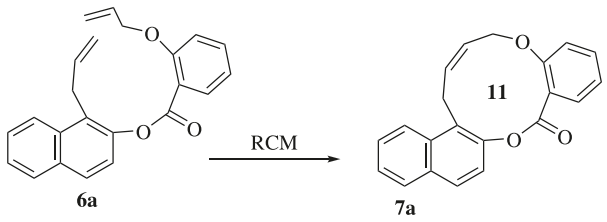
Compound 6a

Yield: 82%; colourless solid; mp 53–54 °C (dichloromethane–petroleum ether). IR (KBr, cm^{-1}): 1744, 2853, 2923. ^1H NMR ($CDCl_3$, 400 MHz) δ_H: 3.85 (d, 2H, J = 5.9 Hz, CH_2), 4.68 (d, 2H, J = 5.0 Hz, OCH_2), 4.99–5.03 (m, 2H, $=CH_2$), 5.25 (dd, 1H, J = 10.6 Hz, J = 1.4 Hz, $=CH_aH_b$), 5.49 (dd, 1H, J = 17.2 Hz, J = 1.4 Hz, $=CH_aH_b$), 5.96–6.08 (m, 2H, =CH), 7.04 (d, 1H, J = 8.2 Hz, ArH), 7.08 (d, 1H, J = 7.7 Hz, ArH), 7.34 (d, 1H, J = 8.8 Hz, ArH), 7.45

Scheme 1. Reagents and conditions: (i) Acetone, K_2CO_3, allyl bromide, reflux, 15 h. (ii) EtOH, KOH, reflux, 4 h. 6 N HCl. (iii) $SOCl_2$, DMF, reflux, 1 h. (iv) dry DCM, **4a**, Et_3N, DMAP, 0 °C –RT, stirring, 12 h. (v) dry DCM, **4b**, Et_3N, DMAP, 0 °C–RT, stirring, 12 h.



Scheme 2.



(d, 1H, *J* = 6.9 Hz, ArH), 7.48–7.55 (m, 2H, ArH), 7.79 (d, 1H, *J* = 8.8 Hz, ArH), 7.86 (d, 1H, *J* = 7.9 Hz, ArH), 8.03 (d, 1H, *J* = 8.0 Hz, ArH), 8.06 (d, 1H, *J* = 1.6 Hz, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C: 30.2, 69.4, 113.6, 115.9, 117.7, 119.5, 120.5, 122.0, 124.3, 125.2, 126.2, 126.3, 128.0, 128.6, 132.1, 132.3, 132.5, 132.8, 134.1, 135.8, 146.7, 158.7, 164.9. HRMS: Calcd. for $C_{23}H_{20}O_3$: 367.1318 (M + Na). Found: 367.1310 (M + Na).

Compound 6b

Yield: 88%; colourless solid; mp 56–57 °C (dichloromethane–petroleum ether). IR (KBr, cm^{-1}): 1744, 2868, 2921. ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 3.51 (d, 2H, *J* = 6.4 Hz, CH_2), 4.71 (d, 2H, *J* = 5.0 Hz, OCH_2), 5.11–5.16 (m, 2H, $=CH_2$), 5.39 (dd, 1H, *J* = 10.6 Hz, *J* = 1.1 Hz, $=CH_aH_b$), 5.58 (dd, 1H, *J* = 17.2 Hz, *J* = 1.1 Hz, $=CH_aH_b$), 5.99–6.19 (m, 2H, =CH), 7.05 (d, 2H, *J* = 7.9 Hz, ArH), 7.41–7.55 (m, 3H, ArH), 7.78 (d, 1H, *J* = 8.4 Hz, ArH), 7.89 (dd, 1H, *J* = 8.8 Hz, *J* = 1.7 Hz, ArH), 7.93 (dd, 1H, *J* = 7.6 Hz, *J* = 1.7 Hz, ArH), 8.13 (d, 2H, *J* = 8.8 Hz, ArH). MS *m*/*z*: 344 (M$^+$). Anal. calcd. for $C_{23}H_{20}O_3$: C, 80.21; H, 5.85. Found: C, 80.43; H, 6.01.

Compound 6c

Yield: 79%; colourless solid; mp 94–95 °C (dichloromethane–petroleum ether). IR (KBr, cm^{-1}): 1664, 1706, 1753, 2853, 2923. ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 3.39 (s, 3H, $-NCH_3$), 3.40 (d, 3H, *J* = 6.3 Hz, $-CH_2$), 3.44 (s, 3H, $-NCH_3$), 4.62 (d, 2H, *J* = 5.0 Hz, OCH_2), 5.18–5.23 (m, 2H, $=CH_2$), 5.25 (dd, 1H, *J* = 10.6 Hz, *J* = 1.3 Hz, $=CH_aH_b$), 5.44 (dd, 1H, *J* = 17.9 Hz, *J* = 1.3 Hz, $=CH_aH_b$), 5.79–5.86 (m, 1H, =CH), 5.98–6.08 (m, 1H, =CH), 6.97–7.04 (m, 2H, ArH), 7.50 (dd, 1H, *J* = 8.6 Hz, *J* = 1.5 Hz, ArH), 8.00 (dd, 1H, *J* = 7.7 Hz, *J* = 1.4 Hz, ArH). MS *m*/*z*: 356 (M$^+$). Anal. calcd. for $C_{19}H_{20}N_2O_5$: C, 64.04; H, 5.66; N, 7.86. Found: C, 63.91; H, 5.88; N, 8.03.

Compound 6d

Yield: 84%; colourless solid; mp 84–85 °C (dichloromethane–petroleum ether). IR (KBr, cm^{-1}): 1730, 2849, 2917. ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 3.80 (d, 2H, *J* = 5.9 Hz, CH_2), 4.63 (d, 2H, *J* = 5.2 Hz, OCH_2), 4.96–5.01 (m, 2H, $=CH_2$), 5.34 (dd, 1H, *J* = 10.5 Hz, *J* = 1.1 Hz, $=CH_aH_b$), 5.44 (dd, 1H, *J* = 16.3 Hz, *J* = 1.1 Hz, $=CH_aH_b$), 5.93–6.12 (m, 2H, =CH), 7.01 (d, 2H, *J* = 8.8 Hz, ArH), 7.31 (d, 1H, *J* = 8.8 Hz, ArH), 7.45–7.59 (m, 3H, ArH), 7.79 (d, 1H, *J* = 8.8 Hz, ArH), 7.86 (d, 1H, *J* = 7.9 Hz, ArH), 8.02 (d, 1H, *J* = 8.4 Hz, ArH), 8.19 (d, 1H, *J* = 8.8 Hz, ArH). MS *m*/*z*: 344 (M$^+$). Anal. calcd. for $C_{23}H_{20}O_3$: C, 80.21; H, 5.85. Found: C, 79.99; H, 5.63.

Compound 6e

Yield: 86%; colourless solid; mp 72–73 °C (dichloromethane–petroleum ether). IR (KBr, cm^{-1}): 1732, 2858, 2919. ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: 3.46 (d, 2H, *J* = 6.4 Hz, CH_2), 4.65 (d, 2H, *J* = 5.0 Hz, OCH_2), 5.04–5.09 (m, 2H, $=CH_2$), 5.34 (dd, 1H, *J* = 10.6 Hz, *J* = 1.1 Hz, $=CH_aH_b$), 5.44 (dd, 1H, *J* = 17.2 Hz, *J* = 1.1 Hz, $=CH_aH_b$), 5.91–5.99 (m, 2H, =CH), 7.05 (d, 2H, *J* = 8.8 Hz, ArH), 7.40 (d, 1H, *J* = 8.3 Hz, ArH), 7.42–7.46 (m, 2H, ArH), 7.73 (d, 1H, *J* = 8.5 Hz, ArH), 7.77 (t, 1H, *J* = 5.7 Hz, ArH), 7.84 (dd, 1H,

Table 1. Summarized results of the macrolization by ring-closing metathesis reaction.

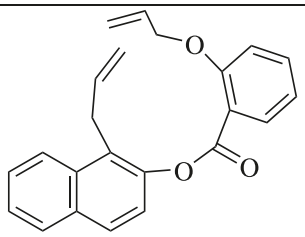
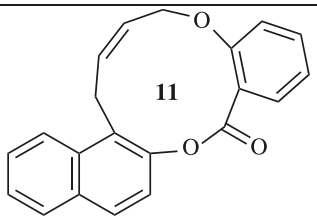
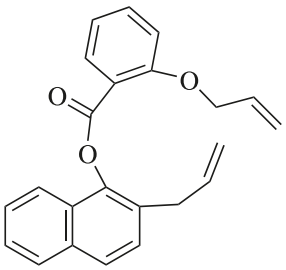
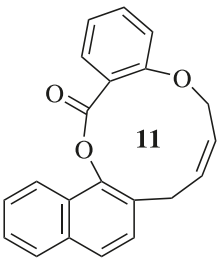
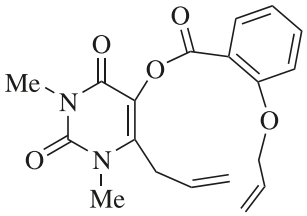
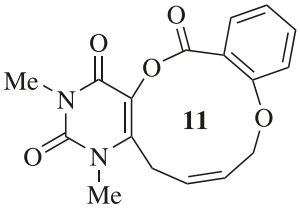
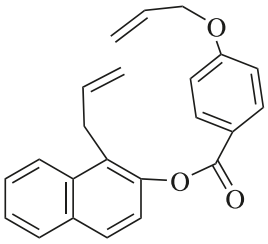
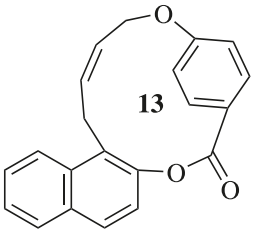
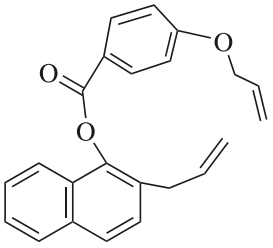
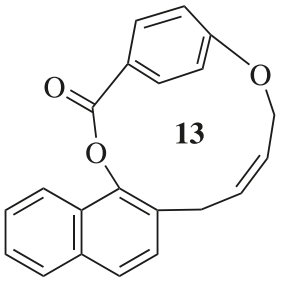
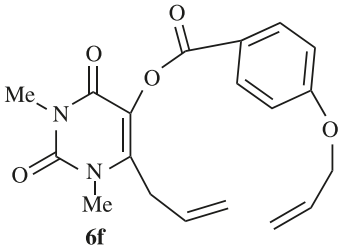
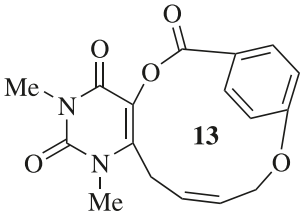
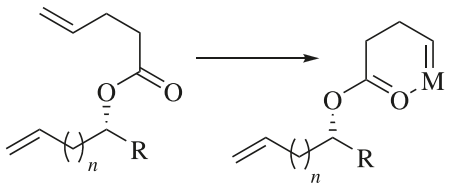
Entry	Substrates	Conditions	Products	Yield (%)
1	 **6a**	Cat: 5 mol%; DCM, reflux, 2 day	 **7a**	62
2	 **6b**	Cat: 5 mol%; DCM, reflux, 2 day	 **7b**	59
3	 **6c**	Cat: 5 mol%; DCM, reflux, 2 day	 **7c**	64
4	 **6d**	Cat: 10 mol%; DCM, reflux, 4 day	 **7d**	63
5	 **6e**	Cat: 10 mol%; DCM, reflux, 4 day		57
6	 **6f**	Cat: 10 mol%; DCM, reflux, 4 day	 **7f**	59

Fig. 3. Unreactive chelate complex of Ru with esterified double bond.



J = 7.7 Hz, J = 1.3 Hz, ArH), 8.27 (d, 2H, J = 8.8 Hz, ArH). MS *m/z*: 344 (M^+). Anal. calcd. for $C_{23}H_{20}O_3$: C, 80.21; H, 5.85. Found: C, 80.29; H, 6.11.

Compound 6f

Yield: 85%; colourless solid; mp 109–110 °C (dichloromethane–petroleum ether). IR (KBr, cm^{-1}): 1663, 1704, 1741, 2851, 2918. ^1H NMR ($CDCl_3$, 400 MHz) δ_H: 3.39 (s, 3H, $-NCH_3$), 3.40 (d, 2H, J = 6.3 Hz, $-CH_2$), 3.43 (s, 3H, $-NCH_3$), 4.59 (d, 2H, J = 5.0 Hz, $-OCH_2$), 5.08–5.16 (m, 2H, $=CH_2$), 5.19 (dd, 1H, J = 10.6 Hz, J = 1.3 Hz, $=CH_aH_b$), 5.39 (dd, 1H, J = 17.9 Hz, J = 1.3 Hz, $=CH_aH_b$), 5.77–5.81 (m, 1H, =CH), 5.98–6.04 (m, 1H, =CH), 6.99 (d, 2H, J = 8.1 Hz, ArH), 7.41 (dd, 1H, J = 7.7 Hz, J = 1.9 Hz, ArH), 7.99 (dd, 1H, J = 8.2 Hz, J = 1.9 Hz, ArH). MS *m/z*: 356 (M^+). Anal. calcd. for $C_{19}H_{20}N_2O_5$: C, 64.04; H, 5.66; N, 7.86. Found: C, 64.23; H, 5.83; N, 7.68.

General methods for the synthesis of macrolides 7a–7f

To a solution of the substrate **6a** (30 mg, 0.16 mmol) in dry degassed dichloromethane (40 mL) under nitrogen atmosphere was added Grubbs second-generation catalyst (5 mol%, 17 mg) and the reaction was stirred at rt for 1 h. The mixture was then refluxed for 2 days. The solvent was distilled off and the residue was purified by flash column chromatography on silica gel using 10% ethyl acetate-petroleum ether to afford the compound **7a**. Accordingly compounds **7b-7f** were synthesized. Compounds **7a-7f** were recrystallized from dichloromethane-petroleum ether (60–80 °C).

Compound 7a

Yield: 62%; colourless solid; mp 104–105 °C (dichloromethane–petroleum ether). IR (KBr, cm^{-1}): 1740, 2851, 2957. ^1H NMR ($CDCl_3$, 400 MHz) δ_H: 4.04 (d, 2H, J = 5.0 Hz, CH_2), 4.59 (d, 2H, J = 5.0 Hz, OCH_2), 5.96 (dt, 1H, J = 17.6 Hz, J = 5.0 Hz, =CH), 6.09 (dt, 1H, J = 17.6 Hz, J = 5.0 Hz, =CH), 6.94 (d, 1H, J = 6.8 Hz, ArH), 7.02 (dt, 1H, J = 6.0 Hz, J = 3.1 Hz, ArH), 7.30 (d, 1H, J = 7.1 Hz, ArH), 7.45–7.55 (m, 3H, ArH), 7.76 (d, 1H, J = 7.1 Hz, ArH), 7.84 (dd, 1H, J = 7.1 Hz, J = 1.4 Hz, ArH), 7.89 (d, 1H, J = 6.6 Hz, ArH), 8.07 (d, 1H, J = 7.3 Hz, ArH). ^{13}C NMR ($CDCl_3$, 100 MHz) δ_C: 29.1, 70.1, 112.9, 120.4, 120.7, 121.9, 124.2, 125.2, 125.3, 125.9, 126.4, 128.0, 128.7, 131.8, 132.1, 132.8, 133.6, 133.9, 146.5, 157.6, 166.9. HRMS: Calcd. for $C_{21}H_{16}O_3$: 339.0997 (M + Na). Found: 339.0990 (M + Na).

Compound 7b

Yield: 59%; colourless solid; mp 96–97 °C (dichloromethane–petroleum ether). IR (KBr, cm^{-1}): 1742, 2850, 2921. ^1H NMR ($CDCl_3$, 400 MHz) δ_H: 3.49 (d, 2H, J = 5.0 Hz, CH_2), 4.63 (d, 2H, J = 5.0 Hz, OCH_2), 5.85 (dt, 1H, J = 17.6 Hz, J = 5.0 Hz, =CH), 6.06 (dt, 1H, J = 17.6 Hz, J = 5.0 Hz, =CH), 6.98 (dd, 1H, J = 7.9 Hz, J = 1.7 Hz, ArH), 7.40 (d, 1H, J = 6.9 Hz, ArH), 7.44 (m, 2H, ArH), 7.49 (dt, 1H, J = 7.1 Hz, J = 3.0 Hz, ArH), 7.53 (d, 1H, J = 8.1 Hz, ArH), 7.63 (dd, 1H, J = 6.7 Hz, J = 1.0 Hz, ArH), 7.72 (dt, 1H, J = 7.7 Hz, J = 3.0 Hz, ArH), 7.80 (t, 1H, J = 7.0 Hz, ArH), 8.04 (dt, 1H, J = 7.4 Hz, J = 2.3 Hz, ArH). MS *m/z*: 316 (M^+). Anal. calcd. for $C_{21}H_{16}O_3$: C, 79.73; H, 5.10. Found: C, 79.61; H, 5.23.

Compound 7c

Yield: 64%; colourless solid; mp 149–150 °C (dichloromethane–petroleum ether). IR (KBr, cm^{-1}): 1649, 1701, 1739, 2849, 2920. ^1H NMR ($CDCl_3$, 400 MHz) δ_H: 3.37 (s, 6H, -NCH_3), 3.41 (d, 2H, J = 5.4 Hz, CH_2), 5.09 (d, 2H, J = 5.4 Hz, OCH_2), 5.77 (dt, 1H, J = 17.6 Hz, J = 5.0 Hz, =CH), 5.92 (dt, 1H, J = 17.6 Hz, J = 5.0 Hz, =CH), 6.90–7.04 (m, 2H, ArH), 7.47 (dd, 1H, J = 8.5 Hz, J = 1.7 Hz, ArH), 7.99 (dd, 1H, J = 7.5 Hz, J = 1.7 Hz, ArH). MS *m/z*: 328 (M^+). Anal. calcd. for $C_{17}H_{16}N_2O_5$: C, 62.19; H, 4.91; N, 8.53. Found: C, 62.33; H, 5.09; N, 8.66.

Compound 7d

Yield: 63%; colourless solid; mp 120–121 °C (dichloromethane–petroleum ether. IR (KBr, cm^{-1}): 1730, 2850, 2920. ^1H NMR ($CDCl_3$, 400 MHz) δ_H: 3.79 (d, 2H, J = 5.0 Hz, CH_2), 4.61 (d, 2H, J = 5.0 Hz, OCH_2), 5.88 (dt, 1H, J = 17.6, J = 5.0 Hz, =CH), 6.03 (dt, 1H, J = 17.6 Hz, J = 5.0 Hz, =CH), 7.08 (d, 1H, J = 7.5 Hz, ArH), 7.29–7.33 (m, 2H, ArH), 7.49 (dt, 2H, J = 7.9 Hz, J = 3.0 Hz, ArH), 7.69 (dd, 1H, J = 6.9 Hz, J = 1.1 Hz, ArH), 7.79 (t, 1H, J = 8.0 Hz, ArH), 7.81 (dd, 1H, J = 6.8 Hz, J = 1.2 Hz, ArH), 8.01 (d, 1H, J = 8.8 Hz, ArH), 8.11 (d, 1H, J = 7.9 Hz, ArH). MS *m/z*: 316 (M^+). Anal. calcd. for $C_{21}H_{16}O_3$: C, 79.73; H, 5.10. Found: C, 79.86; H, 4.89.

Compound 7e

Yield: 57%; colourless solid; mp 113–114 °C (dichloromethane–petroleum ether). IR (KBr, cm^{-1}): 1731, 2851, 2921. ^1H NMR ($CDCl_3$, 400 MHz) δ_H: 3.47 (dd, 2H, J = 5.7 Hz, J = 1.0 Hz, CH_2), 4.62 (dd, 2H, J = 7.3 Hz, J = 1.0 Hz, OCH_2), 6.00 (dt, 1H, J = 17.6 Hz, J = 5.0 Hz, =CH), 6.09 (dt, 1H, J = 17.6 Hz, J = 5.0 Hz, =CH), 7.00 (d, 1H, J = 6.8 Hz, ArH) 7.08 (d, 1H, J = 7.3 Hz, ArH), 7.38–7.43 (m, 3H, ArH), 7.51 (dd, 2H, J = 8.8 Hz, J = 1.7 Hz, ArH), 7.85 (dt, 1H, J = 7.1 Hz, J = 3.0 Hz, ArH), 8.14 (d, 2H, J = 8.0 Hz, ArH). MS *m/z*: 316 (M^+). Anal. calcd. for $C_{21}H_{16}O_3$: C, 79.73; H, 5.10. Found: C, 79.69; H, 5.33.

Compound 7f

Yield: 59%; colourless solid; mp 157–158 °C (dichloromethane–petroleum ether). IR (KBr, cm^{-1}): 1650, 1705, 1734, 2851, 2921. ^1H NMR ($CDCl_3$, 400 MHz) δ_H: 3.36 (d, 2H, J = 5.6 Hz, CH_2), 3.38 (s, 3H, $-NCH_3$), 3.45 (s, 3H, $-NCH_3$), 5.17 (d, 2H, J = 5.6 Hz, OCH_2), 5.80 (dt, 1H, J = 17.6 Hz, J = 5.0 Hz, =CH), 6.03 (dt, 1H, J = 17.6 Hz, J = 5.0 Hz, =CH), 6.95 (d, 2H, J = 7.7 Hz, J = 1.7 Hz, ArH), 8.09 (dd, 2H, J = 8.9 Hz, J = 3.0 Hz, ArH). MS *m/z*: 328 (M^+). Anal. calcd. for $C_{17}H_{16}N_2O_5$: C, 62.19; H, 4.91; N, 8.53. Found: C, 61.97; H, 5.11; N, 8.69.

Acknowledgements

We thank the DST (New Delhi) and the CSIR (New Delhi) for financial assistance. Two of us (BC and IA) are grateful to the CSIR (New Delhi) and UGC (New Delhi) for a senior and a junior research fellowships, respectively.

References

(1) Singh, S. B.; Jayasuriya, H.; Zink, D. L.; Polishook, J. D.; Dombrowski, A. W.; Zweerink, H. *Tetrahedron Lett.* **2004**, *45*, 7605. doi:10.1016/j.tetlet.2004.08.116.

(2) (a) Kinet, J.-P. *Annu. Rev. Immunol.* **1999**, *17*, 931 doi:10.1146/annurev.immunol.17.1.931. PMID:10358778.; (b) Jardieu, P. *Curr. Opin. Immunol.* **1995**, *7*, 779 doi:10.1016/0952-7915(95)80047-6. PMID:8679119.; (c) For the structure of the human high-affinity IgE receptor, see: Garman, S. C.; Kinet, J.-P.; Jardetzky, T. S. *Annu. Rev. Immunol.* **1999**, *17*, 973 doi:10.1146/annurev.immunol.17.1.973. PMID:10358779.; (d) For peptidic antagonists of the high-affinity IgE receptor, see: Nakamura, G. R.; Reynolds, M. E.; Chen, Y. M.; Starovasnik, M. A.; Lowman, H. B. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99*, 1303; and refs. cited therein. doi:10.1073/pnas.022635599. PMID:11830661.

(3) Furstner, A.; Muller, C. *Chem. Commun.* **2005**, 5583. doi:10.1039/b512877c. PMID:16358071.

(4) (a) Norcross, R. D.; Paterson, I. *Chem. Rev.* **1995**, *95*, 2041 doi:10.1021/cr00038a012.; (b) Ishibashi, M.; Kobayashi, J. *Heterocycles*, **1997**, *44*, 543.

(5) Liu, X.-X.; Pilarinou, E.; McLaughlin, J. L. *Tetrahedron Lett.* **1999**, *40*, 399. doi:10.1016/S0040-4039(98)02401-0.

(6) (a) Trnka, T. M.; Grubbs, R. H. *Acc. Chem. Res.* **2001**, *34*, 18 doi:10.1021/ar000114f.; (b) Furstner, A. *Angew. Chem. Int. Ed.* **2000**, *39*, 3012 doi:10.1002/1521-3773(20000901)39:17<3012::AID-ANIE3012>3.0.CO;2-G.; (c) Grubbs, R. H.; Chang, S. *Tetrahedron,* **1998**, *54*, 4413 doi:10.1016/S0040-4020(97)10427-6.; (d) Armstrong, S. K. *J. Chem. Soc. Perkin Trans.* **1998**, *1*, 371 doi:10.1039/a703881j.; (e) Schuster, M.; Blechert, S. *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2036 doi:10.1002/anie.199720361.; (f) Bressy, C.; Piva, O. *Synlett,* **2003**, 87.

(7) (a) Fürstner, A.; Langemann, K. *J. Org. Chem.* **1996**, *61*, 3942 doi:10.1021/jo960733v. PMID:11667264.; (b) Goldring, W. P. D.; Hodder, A. S.; Weiler, L. *Tetrahedron Lett.* **1998**, *39*, 4955 doi:10.1016/S0040-4039(98)00966-6.; (c) Fürstner, A.; Thiel, O. R.; Ackermann, L. *Org. Lett.* **2001**, *3*, 449 doi:10.1021/ol0069554. PMID:11428036.; (d) Fürstner, A.; Dierkes, T.; Thiel, O. R.; Blanda, G. *Chem. Eur. J.* **2001**, *7*, 5286. doi:10.1002/1521-3765(20011217)7:24<5286::AID-CHEM5286>3.0.CO;2-G.

(8) (a) Boger, D. L.; Hong, J.-Y. *J. Am. Chem. Soc.* **2001**, *123*, 8515 doi:10.1021/ja011271s. PMID:11525659.; (b) Fürstner, A.; Gastner, T.; Weintritt, H. *J. Org. Chem.* **1999**, *64*, 2361 doi:10.1021/jo982088t.; (c) Martin, S. F. J.; Humphrey, M.; Ali, A.; Hillier, M. C. *J. Am. Chem. Soc.* **1999**, *121*, 866 doi:10.1021/ja9829259.; (d) Nicolaou, K. C.; Vassilikogiannakis, G.; Montagnon, T. *Angew. Chem. Int. Ed.* **2002**, *41*, 3276 doi:10.1002/1521-3773(20020902)41:17<3276::AID-ANIE3276>3.0.CO;2-P.; (e) Bach, T.; Lemarchand, A. *Synlett*, **2002**, 1302. doi:10.1055/s-2002-32958.

(9) (a) For eleven- and thirteen-membered rings by RCM strategy, see: Bressy, C.; Piva, O. *Synlett,* **2003**, 87; (b) Ramana, C. V.; Mondal, M. A.; Puranik, V. G.; Gurjar, M. K. *Tetrahedron Lett.* **2007**, *48*, 7524 doi:10.1016/j.tetlet.2007.08.050.; (c) For other examples of macrolization reactions via RCM using various catalysts, see: Miller, S. J.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 5855 doi:10.1021/ja00126a027.; (d) Miller, S. J.; Blackwell, H. E.; Grubbs, R. H. *J. Am. Chem. Soc.* **1996**, *118*, 9606 doi:10.1021/ja961626l.; (e) Clark, T. D.; Ghadiri, M. R. *J. Am. Chem. Soc.* **1995**, *117*, 12364 doi:10.1021/ja00154a051.; (f) Konig, B.; Horn, C. *Synlett*, **1996**, 1013. doi:10.1055/s-1996-5643.

(10) (a) Majumdar, K. C.; Chattopadhyay, B.; Sinha, B. *Tetrahedron Lett.* **2008**, *49*, 1319 doi:10.1016/j.tetlet.2007.12.096.; (b) Majumdar, K. C.; Chattopadhyay, B.; Nath, S. *Tetrahedron Lett.* **2008**, *49*, 1609 doi:10.1016/j.tetlet.2008.01.035.; (c) Majumdar, K. C.; Chattopadhyay, B. *Synlett,* **2008**, 979 doi:10.1055/s-2008-1072510.; (d) Majumdar, K. C.; Chattopadhyay, B.; Ray, K. *Tetrahedron Lett.* **2007**, *48*, 7633 doi:10.1016/j.tetlet.2007.08.121.; (e) Majumdar, K. C.; Chattopadhyay, B.; Taher, A. *Synthesis,* **2007**, 3647 doi:10.1055/s-2007-990846.; (f) Majumdar, K. C.; Pal, A. K.; Taher, A.; Debnath, P. *Synthesis*, **2007**, 1707. doi:10.1055/s-2007-966052.; (g) Majumdar, K. C.; Muhuri, S.; Rahaman, H.; Islam, R.; Roy, B. *Chem. Lett.* **2006**, *35*, 1430 doi:10.1246/cl.2006.1430.; (h) Majumdar, K. C.; Rahaman, H.; Islam, R.; Roy, B. *Tetrahedron Lett.* **2006**, *47*, 2111 doi:10.1016/j.tetlet.2006.01.132.; (i) Majumdar, K. C.; Islam, R.; Rahaman, H.; Roy, B. *Org. Biomol. Chem.* **2006**, *4*, 2393 doi:10.1039/b603125k. PMID:16763684.; (j) Majumdar, K. C.; Rahaman, H.; Roy, B. *Synlett*, **2006**, 0466 doi:10.1055/s-2006-926238.; (k) Majumdar, K. C.; Rahaman, H.; Roy, B. *Lett. Org. Chem.* **2006**, *3*, 526 doi:10.2174/157017806778341816.; (l) Majumdar, K. C.; Maji, P. K.; Rahaman, H.; Roy, B. *Lett. Org. Chem.* **2006**, *3*, 845 doi:10.2174/157017806779117094.; (m) Majumdar, K. C.; Rahaman, H.; Roy, B. *Curr. Org. Chem.* **2007**, 1339. doi:10.2174/138527207782023166.

(11) Illuminati, G.; Mandolini, L. *Acc. Chem. Res.* **1981**, *14*, 95. doi:10.1021/ar00064a001.

(12) (a) Furstner, A. *J. Am. Che. Soc.* **1997**, *119*, 9130 doi:10.1021/ja9719945.; (b) Furstner, A.; Langemann, K. *Synthesis*, **1997**, 792 doi:10.1055/s-1997-4472.; (c) Furstner, A. *Angew. Chem. Int. Ed.* **2000**, *39*, 3012. doi:10.1002/1521-3773(20000901)39:17<3012::AID-ANIE3012>3.0.CO;2-G.