The thesis entitled “Synthesis of Macrosphelides I and G; C1-C15 Fragment of Palmerolide A and Patulolides” is divided into three chapters.

Chapter I: Total Synthesis of Macrosphelides I and G

This chapter is dealt with the first total synthesis of macrosphelide I and total synthesis of macrosphelide G by a combination of asymmetric synthesis and chiron approach.

Macrosphelides A-L were isolated as inhibitors of the adhesion of HL-60 cells to a monolayer of LPS-activated human-umbilical-vein endothelial cells. Macrosphelides I (1) and G (2) were isolated along with A, C, E and H from a strain of Periconia byssoides separated from the gastrointestinal tract of the sea hare Aplysia kurodai. Numata et al\(^1\) described the absolute stereostructures of 1 and 2, based on the spectroscopic analyses and some chemical transformations. Macrolide 1 is a 16-membered tris-lactone with five asymmetric centres. The absolute configuration was determined as 3\(R\), 8\(R\), 9\(S\), 14\(R\) and 15\(S\). Due to their biological profiles and structural features, macrosphelides\(^2\) have become highly attractive target molecules as the next generation chemotherapeutical drugs against cancer.

**Figure 1**

![Macrosphelide I (1) and Macrosphelide G (2)]

**Total synthesis of macrosphelide I (1):**

Compound 1 on antithetic analysis (Scheme 1) revealed that bis-olefin 3 could be the late stage intermediate, which on RCM protocol would generate the macrolide ring structures. Ester 3, in turn could be realized by sequential esterification of 4 with 5 and 6. The segments 5 and 6 could be envisaged from (S)-lactic acid (7) and (S)-malic acid (8), respectively. Likewise, Thus, the segments 5 and 6 are common intermediates for the
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The synthesis of both 1 and 2. The main strategy would be to condense the fragments through Yamaguchi esterification reaction and C-C bond formation through RCM protocol to result in the macrocyclic ring system.

Scheme 1

The segments 4 and 5 were synthesized from (S)-lactic acid 7. Accordingly, the allylic alcohol 9 prepared from the known alcohol\(^3\) on Sharpless asymmetric epoxidation with (+)-DIPT, Ti(O\(^i\)Pr)\(_4\) and cumene hydroperoxide in dry CH\(_2\)Cl\(_2\) afforded epoxide 10.

Scheme 2

Reagents and conditions: a) (+)-DIPT, Ti(O\(^i\)Pr)\(_4\), cumene hydroperoxide, 4 Å MS, dry CH\(_2\)Cl\(_2\), -20 °C, 5 h; b) Ph\(_3\)P, CCl\(_4\), cat. NaHCO\(_3\), reflux, 3 h; c) Na, dry ether, 0 °C-rt, 12 h; d) TBDMSI, imidazole, CH\(_2\)Cl\(_2\), rt, 3 h; e) DDQ, aq. CH\(_2\)Cl\(_2\) (19:1), reflux, 3 h; f) O\(_3\), CH\(_2\)Cl\(_2\), dimethylsulphide, -78 °C, 15 min; g) Ph\(_3\)P=CHCOOEt, benzene, reflux, 2 h; h) PtO\(_2\), H\(_2\), ethyl acetate, rt, 3 h; i) LiOH, THF:MeOH:H\(_2\)O (3:1:1), rt, 4 h.
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Treatment of alcohol 10 with Ph₃P and NaHCO₃ in CCl₄ gave the chloride 11, which on further reaction with Na in dry ether furnished 12. Olefin 12 on silylation (TBDMSCl, imidazole) in CH₂Cl₂ afforded ether 13, which on reaction with DDQ in aq. CH₂Cl₂ underwent debenzylation to afford 5. Olefin 13 on ozonolysis in CH₂Cl₂ gave the corresponding aldehyde 14, which on Wittig reaction with (ethoxycarbonylmethylene) triphenyl phosphorane in benzene gave 14a. Ester 14a on catalytic hydrogenation (PtO₂ in EtOAc) under hydrogen atmosphere afforded the ester 15, which on subsequent hydrolysis (LiOH in THF:MeOH:H₂O-3:1:1) afforded acid 4. The fragments 4 and 5 encompassing four of the five stereocentres, were successfully prepared from (S)-lactic acid (7).

The known⁴ alcohol 16 [prepared from (S)-malic acid] on reaction with MPMBr and NaH in THF gave ether 17, which on acid (PTSA) catalysed acetonide deprotection in methanol afforded diol 18. Tosylation of 18 with p-TsCl and Et₃N in CH₂Cl₂ gave monotosylate 18a, which on further reaction with LAH in THF afforded 19.

Scheme 3

Reagents and conditions: a) MPMBr, NaH, THF, rt, 6 h; b) cat. PTSA, MeOH, rt, 5 h; c) TsCl, Et₃N, CH₂Cl₂, rt, 36 h; d) LAH, THF, 0 °C-rt, 3 h; e) acryloyl chloride, DIPEA, CH₂Cl₂, rt, 3 h; f) DDQ, aq. CH₂Cl₂, rt, 1 h; g) Dess Martin Periodinane, CH₂Cl₂, rt, 3 h; h) NaClO₂, NaH₂PO₄, 2-methyl-2-butene, r-BuOH:water (2:1), 0 °C-rt, 3 h

Esterification of 19 with acryloyl chloride and DIPEA in CH₂Cl₂ furnished acrylate ester 20. Compound 20 on oxidative deprotection with DDQ in aq. CH₂Cl₂ furnished alcohol 20a. Oxidation of 20a with Dess Martin periodinane⁵ gave the
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The corresponding aldehyde 21, which on subsequent oxidation with NaClO₂ and NaH₂PO₄, 2-methyl-2-butene in aq. t-butanol afforded 6.

Reaction of acid 4 under Yamaguchi⁶ reaction conditions using 2,4,6-trichlorobenzoyl chloride and Et₃N in THF, first gave the mixed anhydride, which in turn was condensed with the alcohol 5 in the presence of DMAP in toluene to afford the ester 22 (Scheme 4). Debenzylation of 22 on reaction with DDQ in aq. CH₂Cl₂ gave the hydroxy ester 23. Esterification of 23 with the mixed anhydride prepared from acid 6 under Yamaguchi conditions (2,4,6-trichlorobenzoyl chloride, Et₃N in THF) in the presence of DMAP in toluene afforded 24. Desilylation of tris-ester 24 with HF-pyridine complex in THF gave 3. Finally, ester 3 on treatment with Grubbs⁷ second generation catalyst in CH₂Cl₂ at reflux for 24 h furnished macrophelide I (1), whose spectral and optical rotation data were comparable with the data reported in the literature.¹ This report constitutes the first total synthesis of 1.

**Scheme 4**

![Scheme 4](image)

*Reagents and conditions:* a) 2,4,6-trichlorobenzoyl chloride, Et₃N, THF, then alcohol 5, DMAP, toluene, rt, 12 h; b) DDQ, aq. CH₂Cl₂ (19:1), reflux, 3 h; c) 2,4,6-trichlorobenzoyl chloride, Et₃N, THF, 6, DMAP, toluene, rt, 24 h; d) HF-Pyridine complex, rt, 6 h; e) Grubbs second generation catalyst, CH₂Cl₂, reflux, 24 h.

**Total synthesis of macrophelide G (2):**

From the retrosynthetic analysis of 2 (Scheme 5), bis-olefin 25 was envisaged as the late stage intermediates, which on RCM protocol would generate the macrolide ring structure. Ester 25 could be realized by sequential esterfication of 26 with 5 and 6, while 26 could be envisaged from the easily accessible S-propylene oxide (27). The main
strategy would be to condense the fragments through Yamaguchi esterification reaction and C-C bond formation through RCM protocol to result in the macrocyclic ring system.

**Scheme 5**

Kinetic resolution of 29 (Scheme 5) under Jacobsen reaction conditions\(^8\) \((S, S)-(+)\)-N,N'-Bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II) gave chiral epoxide 27 and diol 30. Treatment of S-propylene oxide (27) with 28 in the presence of n-BuLi and BF\(_3\).Et\(_2\)O in THF gave 31, which on reaction with MPM-Br (NaH in THF) afforded 32. Reaction of the ether 32 with cat. PTSA in THF afforded 33, which on reduction with LAH in THF afforded trans-olefin 34. Swern oxidation of allylic alcohol 34 gave the corresponding aldehyde, which on further oxidation with NaClO\(_2\), NaH\(_2\)PO\(_4\), 2-methyl-2-butene in aq. t-butanol afforded 26.

**Scheme 6**

For the synthesis of macrosphelide G (2), acid 26 was esterified with 5 through mixed anhydride prepared on reaction of 26 with 2,4,6-trichlorobenzoyl chloride (Et\(_3\)N, THF) in the presence of DMAP in toluene to afford the ester 35 (Scheme 7). Oxidative
deprotection of MPM group in ester 35 with DDQ in aq. CH$_2$Cl$_2$ afforded alcohol 36. Esterification of acid 6 under Yamaguchi conditions (2,4,6-trichlorobenzoyl chloride, Et$_3$N, THF, then DMAP in toluene) with alcohol 36 afforded 37. Exposure of tris-ester 37 to HF-pyridine complex in THF, resulted in the removal of TBS group and gave alcohol 25. Finally, cyclisation of 25 with Grubb’s catalyst II in CH$_2$Cl$_2$ afforded macrospelide G (2), whose spectral data was comparable with the reported data.

Scheme 7

\[ \begin{align*}
26 + 5 & \xrightarrow{a, b} 35 \quad (R = \text{MPM}) \\
& \xrightarrow{c, d} 36 \quad (R = \text{H}) \\
& \xrightarrow{e} 2 \\
& \xrightarrow{c, d} 37 \quad (R = \text{TBS}) \\
& \xrightarrow{e} 25 \quad (R = \text{H})
\end{align*} \]

Reagents and conditions: (a) 2,4,6-trichlorobenzoyl chloride, Et$_3$N, THF, DMAP, toluene, rt, 12 h; (b) DDQ, aq. CH$_2$Cl$_2$ (19:1), rt, 1 h; (c) 2,4,6-trichlorobenzoyl chloride, Et$_3$N, THF, 6, DMAP, toluene, rt, 24 h; (d) HF-Pyridine complex, rt, 6 h; (e) Grubbs catalyst II, CH$_2$Cl$_2$, reflux, 24 h.

Chapter II: Synthesis of C1-C15 Fragment of Palmerolide A

This chapter is dealt with the synthesis of C1-C15 fragment of palmerolide A by asymmetric synthesis:

The marine natural product, palmerolide A was isolated from the circumpolar tunicate Synoicum adareanum, which is commonly found in the shallow waters around Anvers Island on the Antarctic Peninsula by Baker and co-workers. It exhibits unusual selectivity against a number of cell lines in the 60 cell panel of the National Cancer Institute (NCI). Specifically, palmerolide A is found to exhibit potent activity against the melanoma cell line UACC-62 (LC$_{50}$ = 18 nM), only modest cytotoxicity against the colon cancer cell line HCC-2988 (LC$_{50}$ = 18 nM). Further studies revealed that palmerolide A (1) has been found to inhibit V-ATPase with an IC$_{50}$ of 2 nM. Palmerolide A is a 20-membered macrolide with a side chain containing an enamide, five stereogenic centers, 7 olefinic bonds and a carbamate moiety. The intriguing biological properties, impressive
molecular architecture and its relative scarcity of palmerolide A\textsuperscript{10} have attracted the chemical synthesis.

**Figure 2**

Palmerolide A 1

The retrosynthetic analysis of 1 revealed that it (Scheme 8) could be obtained from alcohol 2 and ester 3 by Stille coupling and subsequent Yamaguchi macrolactonisation. Ester 3, in turn, could be obtained from two building blocks 4 and 5, while aldehyde 4 could be obtained from 1,4-butane diol 6 by Sharpless epoxidation and 5 from 1,5-pentane diol in turn could be easily obtained by Sharpless epoxidation.

**Scheme 8**

The synthesis of 5, from 1,5-pentane diol is illustrated in Scheme 9. Accordingly, alcohol 7\textsuperscript{11} under Swern conditions\textsuperscript{12} gave the corresponding aldehyde, which on
subsequent Wittig olefination with (methoxycarbonylmethylene)triphenyl phosphorane in benzene at reflux furnished the α, β-unsaturated ester 8. Reduction of the ester 8 with DIBAL-H in CH₂Cl₂ at room temperature gave allylic alcohol 9. Sharpless epoxidation of 9 with (-)-DIPT, Ti(O’Pr)₄ and cumene hydroperoxide in dry CH₂Cl₂ afforded 10. Treatment of alcohol 10 with Ph₃P and NaHCO₃ in CCl₄ at reflux gave the chloride 11, which on base catalysed fragmentation with LDA¹³ in dry THF afforded 12. Protection of 12 with benzyl bromide and NaH in dry THF furnished 5.

Scheme 9

Reagents and conditions: a) (COCl)₂, DMSO, -78 °C, 2 h; b) Ph₃P=CHCOOCH₃, benzene, reflux, 2 h; c) DIBAL-H, CH₂Cl₂, 0 °C-rt, 4 h; d) (-)-DIPT, Ti(O’Pr)₄, cumene hydroperoxide, 4 Å MS, dry CH₂Cl₂, -20 °C, 5 h; e) Ph₃P, CCl₄, cat. NaHCO₃, reflux, 4 h; f) LDA, dry THF, -78 °C to -40 °C, 2 h; g) BnBr, NaH, dry THF, 5 h.

Thus, selective mono protection of 6 with MOMCl in the presence of DIPEA in CH₂Cl₂ at room temperature gave the ether 13 (Scheme 10), which on Swern oxidation gave the corresponding aldehyde. Wittig olefination of aldehyde with (methoxycarbonylmethylene)triphenyl phosphorane in benzene at reflux furnished ester 14. The ester 14 was subjected to reduction with DIBAL-H in CH₂Cl₂ at room temperature to give allylic alcohol 15. Sharpless epoxidation of 15 with (-)-DIPT, Ti(O’Pr)₄ and cumene hydroperoxide in dry CH₂Cl₂ afforded 16. Reaction of alcohol 16 with Ph₃P and NaHCO₃ in CCl₄ at reflux gave the chloride 17, which on further reaction with Na in dry ether afforded 18. Alcohol 18 on reaction with MPMBr and NaH in dry THF at room temperature furnished ether 19. Olefin 19 on dihydroxylation with OsO₄
and NMO in acetone/water at room temperature gave diol 20, which on oxidative cleavage with NaIO$_4$ and NaHCO$_3$ in CH$_2$Cl$_2$ afforded the aldehyde 4.

**Scheme 10**

\[ \text{HO-} \quad \overset{a}{\longrightarrow} \quad \text{MOMO-} \quad \overset{b,c,d}{\longrightarrow} \quad \text{MOMO-} \quad \overset{e,f}{\longrightarrow} \quad \text{R} \]

\[ 6 \quad 13 \quad 14 \quad 15 \]

\[ R = \text{CO}_2\text{Me} \quad R = \text{CH}_2\text{OH} \]

\[ 16 \quad 17 \quad 18 \quad 19 \quad 20 \]

\[ R = \text{OH} \quad R = \text{Cl} \quad R = \text{H} \quad R = \text{MPM} \]

**Reagents and conditions:** a) MOM-Cl, DIPEA, CH$_2$Cl$_2$, rt, 6 h; b) (COCl)$_2$, DMSO, -78 °C, 2 h; c) Ph$_3$P=CHCO$_2$CH$_3$, benzene, reflux, 2 h; d) DIBAL-H, CH$_2$Cl$_2$, 0 °C-rt, 4 h; e) (-)-DIPT, Ti(O$^i$Pr)$_4$, cumene hydroperoxide, 4 Å MS, dry CH$_2$Cl$_2$, -20 °C, 5 h; f) Ph$_3$P, CCl$_4$, cat. NaHCO$_3$, reflux, 4 h; g) Na in dry ether, rt, 12 h; h) MPMBr, NaH, dry THF, 6 h; i) OsO$_4$ (0.05 eq), NMO, acetone:water (4:1), rt, 24 h; j) NaIO$_4$, aq. NaHCO$_3$ soln, CH$_2$Cl$_2$, rt, 5 h.

The synthesis of 3 was initiated from aldehyde 4 and alkyne 5 as illustrated in Scheme 11. Accordingly, alkyne 5 on treatment with n-BuLi in dry THF at -78 °C and quenching acetylenic anion with aldehyde 4 furnished 21 and 22 as a separable diastereomeric mixture. In order to increase the diastereoselectivity in favor of the requisite stereocentre (syn to the existing one), we resorted to an oxidation-reduction protocol. Hence, hydroxy alkyne 22 was first oxidized under Swern reaction condition to the corresponding ketone 23. For the selective reduction, ketone 23 was treated with K-selectride$^{14}$ in dry THF at -78 °C to give 21 and 22 (9:1) as a diastereomeric mixture.

Reduction of 21 with Red-Al in dry ether at room temperature afforded 24, which on protection with BnBr and sodium hydride in dry THF at room temperature furnished 25. Treatment of 25 with PPTS in $t$-butanol at reflux gave alcohol 26, which on sequential oxidation under Swern reaction conditions, and treatment of the aldehyde with dimethyl(2-oxopropylphosphonate)$^{15}$, tosyl azide, K$_2$CO$_3$ (acetonitrile, methanol) at 0 °C afforded the alkyne compound 27. Desilylation of 27 with HF-pyridine complex in THF.
gave 28, which on oxidation under Swern conditions and subsequent Wittig olefination with (methoxycarbonylmethylene)triphenyl phosphorane in CH₂Cl₂ at room temperature furnished the ester 29.

**Scheme 11**

**Reagents and conditions:**
- a) n-BuLi, dry THF, -78 °C, 2 h;
- b) (COCl)₂, DMSO, -78 °C, 2 h;
- c) K-Selectride, dry THF, -78 °C, 4 h;
- d) Red-Al, dry ether, rt, 4 h;
- e) BnBr, NaH, dry THF, rt, 4 h;
- f) PPTS, t-butanol, reflux, 5 h;
- g) dimethyl(2-oxopropyl)phosphonate, tosyl azide, K₂CO₃, acetonitrile : methanol (2:1), 0 °C-rt, 8 h;
- h) HF-pyridine complex, dry THF, rt, 6 h;
- i) Ph₃P=CHCO₂CH₃, CH₂Cl₂, rt, 6 h.

By the time we have completed the synthesis of 29, in 2007, Nicolaou et al.¹⁶ reported the total synthesis of palmerolide A and revised its structure and absolute
stereochemistry. Accordingly, the configurations at C7, C10 and C11 are reported as 7S, 10S and 11S instead of the earlier 7R, 10R and 11R configuration.

**Figure 3**

Based on the above revised structure of palmerolide A 1a, synthesis of C1-C15 fragment was reconsidered with revised stereochemistry at C7, C10 and C11.

**Scheme 12**

Thus, retrosynthetic analysis revealed that the target compound 1a (Scheme 12) could be obtained from alcohol 2 and ester 30 by Stille coupling and subsequent Yamaguchi
macrolactonisation. Ester 30, in turn, could be obtained from two building blocks 31 and 32.

Sharpless epoxidation of allylic alcohol 9 with (+)-DIPT, Ti(O\text{OPr})₄ and cumene hydroperoxide in dry CH₂Cl₂ gave 33. Alcohol 33 on reaction with Ph₃P and NaHCO₃ in CCl₄ at reflux gave the chloride 34, which on treatment with LDA in dry THF for 2 h afforded 35. Etherification of alcohol 35 with benzyl bromide and sodium hydride in dry THF at room temperature furnished 31.

**Scheme 13**

\[
\begin{align*}
\text{TPSO} & \quad \text{CH₂OH} \quad \text{a, b} \quad \text{TPSO} \quad \text{H} \quad \text{R} \\
& \quad \text{OR} \quad \text{c, d} \quad \text{OR} \quad \text{R} = \text{H, } \text{31} \quad \text{R} = \text{Bn.}
\end{align*}
\]

*Reagents and conditions:* a) (+)-DIPT, Ti(O\text{OPr})₄, cumene hydroperoxide, 4 Å MS, dry CH₂Cl₂, -20 °C, 5 h; b) Ph₃P, CCl₄, cat. NaHCO₃, reflux, 4 h; c) LDA, dry THF, -78 °C to -40 °C, 2 h; d) BnBr, NaH, dry THF, 5 h.

Similarly, Sharpless epoxidation of allylic alcohol 15 (Scheme 14) with (+)-DIPT, Ti(O\text{OPr})₄ and cumene hydroperoxide in dry CH₂Cl₂ afforded 36. Reaction of alcohol 36 with Ph₃P and NaHCO₃ in CCl₄ at reflux gave the chloride 37, which on treatment with Na in dry ether afforded 38.

**Scheme 14**

\[
\begin{align*}
\text{MOMO} & \quad \text{OH} \quad \text{a, b} \quad \text{MOMO} \quad \text{H} \quad \text{OH} \\
& \quad \text{R} \quad \text{c, d} \quad \text{OR} \quad \text{R} = \text{H, } \text{38} \quad \text{R} = \text{H, } \text{39} \quad \text{R} = \text{MPM.}
\end{align*}
\]

\[
\begin{align*}
\text{MOMO} & \quad \text{OH} \quad \text{e} \quad \text{MOMO} \quad \text{OH} \quad \text{f} \quad \text{MOMO} \quad \text{CHO}
\end{align*}
\]
Abstract

Reagents and conditions: a) (+)-DIPT, Ti(OiPr)₄, cumene hydroperoxide, 4 Å MS, dry CH₂Cl₂, -20 °C, 5 h; b) Ph₃P, CCl₄, cat. NaHCO₃, reflux, 4 h; c) Na in dry ether, rt, 12 h; d) MPMBr, NaH, dry THF, 6 h; e) OSO₄(0.05 eq), NMO, acetone:water (4:1), rt, 24 h; f) NaIO₄, aq. NaHCO₃ soln, CH₂Cl₂, rt, 5 h.

Reaction of 38 with MPMBr and NaH in dry THF at room temperature gave ether 39. Dihydroxylation of 39 with OsO₄ and NMO in acetone/water at room temperature furnished diol 40. Diol 40 on treatment with NaIO₄ and NaHCO₃ solution in CH₂Cl₂ underwent oxidative cleavage to afford the aldehyde 32.

Alkyne 31 (Scheme 15) was treated with n-BuLi in dry THF at -78 °C and the resulting acetylenic anion was quenched with aldehyde 32 to furnish 41 and 42 as a diastereomeric mixture. To enhance the diastereoselectivity, alkyne 42 was first oxidized under Swern oxidation to the corresponding ketone 43 and subjected to reduction with K-Selectride in dry THF at -78 °C to afford 41 and 42 (9:1) as a separable diastereomeric mixture.

Scheme 15

Reagents and conditions: a) n-BuLi, dry THF, -78 °C, 2 h; b) (COCl)₂, DMSO, -78 °C, 2 h; c) K-Selectride, dry THF, -78 °C, 4 h.

To ascertain the stereochemistry of the newly created stereocenter in 41 and 42, they were converted to cyclic derivatives as described in schemes 16 and 17.

Acetylation of 41 on reaction with acetic anhydride and triethyl amine in CH₂Cl₂ furnished 44. Oxidative deprotection of MPM on reaction of 44 with DDQ in aq CH₂Cl₂ afforded the alcohol 45. Hydrolysis of hydroxy ester 45 with LiOH in THF, MeOH and
water gave the diol 46. Protection of diol 46 with 2,2-dimethoxy propane, PPTS in CH$_2$Cl$_2$ afforded the 47.

**Scheme 16**

Reagents and conditions: a) Ac$_2$O, Et$_3$N, CH$_2$Cl$_2$, 4 h; b) DDQ, aq. CH$_2$Cl$_2$ (19:1), 1 h; c) LiOH, THF:MeOH:H$_2$O (3:1:1), rt, 4 h; d) 2,2-dimethoxy propane, PPTS, CH$_2$Cl$_2$, rt, 5 h.

Similarly, acetylation of 42 on reaction with acetic anhydride and triethyl amine in CH$_2$Cl$_2$ furnished 48. Oxidative deprotection of MPM on reaction of 48 with DDQ in aq CH$_2$Cl$_2$ afforded the alcohol 49. Hydrolysis of hydroxy ester 49 with LiOH in THF, MeOH and water gave the diol 50. Protection of diol 50 with 2,2-dimethoxy propane, PPTS in CH$_2$Cl$_2$ afforded the 51.

**Scheme 17**
Abstract

Reagents and conditions: a) Ac₂O, Et₃N, CH₂Cl₂, 4 h; b) DDQ, aq. CH₂Cl₂ (19:1), 1 h; c) LiOH, THF:MeOH:H₂O (3:1:1), rt, 4 h; d) 2,2-dimethoxy propane, PPTS, CH₂Cl₂, rt, 5 h.

Compound 41 on reduction with Red-Al in dry ether at room temperature afforded 52, which on protection with BnBr and NaH in dry THF at room temperature furnished ether 53. MOM deprotection in 53 on treatment with PPTS in t-butanol at reflux furnished alcohol 54, which on oxidation under Swern conditions and which on Takai iodo olefiniation¹⁷ (CrCl₂/CHI₃/ THF) of the corresponding aldehyde 54a at 0 °C afforded the vinyl iodide 55.

Scheme 18

Reagents and conditions: a) Red-Al, dry ether, rt, 4 h ; b) BnBr, NaH, dry THF, rt, 4 h; c) PPTS, t-butanol, reflux, 5 h; d) (COCl)₂, DMSO, -78 °C, 2 h; e) CrCl₂, CHI₃, dry THF, 0 °C, 4 h; f) HF-pyridine complex, dry THF, rt, 6 h; g) Ph₃P=CHCO₂CH₃, CH₂Cl₂, rt, 6 h.

Desilylation of 55 with HF-pyridine complex in THF gave 56, which on oxidation under Swern conditions and subsequent Wittig olefination with (methoxycarbonylmethylene)triphenyl phosphorane in CH₂Cl₂ at room temperature furnished the ester 30.
Chapter III: Total synthesis of patulolide C and 11-epipatulolide C:

This chapter is dealt with the total synthesis of patulolide C and 11-epipatulolide C by asymmetric synthesis.

Patulolides C (1, 2) and A (3, 4), isolated from Penicillium urticae S11R59 have shown antifungal, antimicrobial, anti-inflammatory activity and were characterized by Yamada and his co-workers\textsuperscript{18}. Due to their biological profiles and structural features, patulolides\textsuperscript{19} have become highly attractive target molecules for the synthesis.

Figure 4

The retrosynthetic analysis of patulolides 1 and 2 indicates that the bis-olefins 5 and 6 respectively are the last stage intermediates, which on RCM would give the targets.

Scheme 18
Abstract

Olefins 5 and 6 could be envisaged from the epoxides 7 and 8 respectively, which in turn could be realized from the common intermediate, racemic epoxide 9. Compound 9 could be made from 10, which in turn would be obtained from the inexpensive 1, 8-octane diol 12. Thus, in the present strategy, the 4S hydroxy group could be installed through Sharpless epoxidation, while the 11-hydroxy group would be introduced by Jacobsen’s hydrolytic kinetic resolution.

1,8-Octane diol 12 (Scheme 19) on reaction with 2,3-dihyropyran in the presence of PTSA (cat.) in CH₂Cl₂ gave the THP-ether 13 (Scheme 17), which on oxidation under Swern conditions¹² gave the corresponding aldehyde 13a. Wittig olefination of 13a with (methoxycarbonylmethylene)triphenyl phosphorane in benzene at reflux furnished the ester 14. Reduction of the ester 14 with DIBAL-H in CH₂Cl₂ at room temperature gave allylic alcohol 15. Alcohol 15 on Sharpless asymmetric epoxidation ((+)-DIPT, Ti(O₂Pr)₄ and cumene hydroperoxide) in CH₂Cl₂ afforded 11. Treatment of alcohol 11 with Ph₃P and NaHCO₃ in CCl₄ at reflux gave the chloride 16, which on treatment with Na in dry ether afforded 17. Alcohol 17 on reaction with MOMCl and DIPEA in CH₂Cl₂ at room temperature furnished ether 18.

Scheme 19

Reagents and conditions: a) 2,3-dihydro-2H-pyran, cat. PTSA, CH₂Cl₂, 0 °C, 1 h; b) (COCl)₂, DMSO, -78 °C, 2 h; c) Ph₃P=CHCOOCH₃, benzene, reflux, 2 h; d) DIBAL-H, CH₂Cl₂, 0 °C-rt, 4 h; e) (+)-DIPT, Ti(O₂Pr)₄, cumene hydroperoxide, 4 Å MS, dry CH₂Cl₂, -20 °C, 5 h; f) Ph₃P, CCl₄, cat. NaHCO₃, reflux, 4 h; g) Na, dry ether, 0 °C-rt, 12 h; h) MOMCl, DIPEA, CH₂Cl₂, rt, 6 h; i) cat. PPTS, methanol, 5 h; j) Trimethylsulfonium iodide, DMSO, NaH, THF, 0 °C-rt, 4 h.

The depyranylation of THP ether in 18 (Scheme 20) with PPTS (cat.) in methanol at room temperature afforded the alcohol 10, which was oxidized to the corresponding aldehyde under Swern conditions and subsequently treated with trimethylsulfonium iodide,¹⁰ NaH and DMSO in THF to afford the corresponding epoxide 9. The racemic
epoxide 9 was subjected to hydrolytic kinetic resolution using Jacobsen reagent (S, S)-(+)-N,N'-bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediaminocobalt(II) to give diol 19 and chiral epoxide 7.

Reductive ring opening of 7 with LAH in THF at room temperature afforded 20, which on acryloylation with acryloyl chloride and DIPEA in CH₂Cl₂ at room temperature furnished acrylate ester 21. Deprotection of MOM group in 21 on treatment with PPTS in n-butanol at reflux temperature gave alcohol 5. Finally, treatment of 5 with Grubb’s catalyst II in CH₂Cl₂ at reflux temperature afforded patulolide C (1), whose spectral data was comparable with the reported data.

Similarly, epoxide 9 (Scheme 21) was subjected to Jacobsen’s hydrolytic kinetic resolution using (R,R)-(+)N,N'-bis(3,5-di-tert-butylsalicylidene)-1,2-cyclohexanediaminocobalt (II) to give diol 22 and chiral epoxide 8. Treatment of epoxide 8 with LAH in THF at room temperature afforded 23. Further reaction of 23 with acryloyl chloride and DIPEA in CH₂Cl₂ at room temperature gave the ester 24. Ether 24 on reaction with PPTS in n-butanol at reflux underwent MOM deprotection and furnished a lcohol 6, which on RCM with Grubb’s catalyst II afforded 11-epipatulolide C (2). Since the conversion of 1 and 2 on oxidation to give the respective enones 3 and 4 is reported in the literature, synthesis of 1 and 2 completes the formal synthesis of 3 and 4.
Abstract

Scheme 21

Reagents and conditions: a) (R, R) Jacobsen catalyst, H₂O, rt, 12 h; b) LAH, THF, 0 °C-rt, 2 h; c) acryloyl chloride, DIPEA, CH₂Cl₂, rt, 3 h; d) PPTS, n-butanol, reflux, 3 h; e) Grubbs catalyst II, CH₂Cl₂, reflux, 24 h.

References:

Abstract

Abstract
