CHAPTER II

Stereoselective synthesis of (-)-Salicylihalamides A & B
PRESENT WORK

The use of plant and marine extracts in the search for biologically active natural products continues to be a powerful method for the identification of lead compounds for many chemistry programs in drug discovery. Natural products have served as good starting points in developing druglike candidates. One of the initial steps in the development of therapeutic agents is the identification of lead compounds that bind to a receptor or enzyme target of interest. Many analogues of these lead compounds are then prepared and studied in structure activity relationships (SARS) to define the key recognition elements for maximal activity. Compounds originating from natural sources still play a major role in drug therapy. In fact, almost half the drugs on the market are descendants of natural products.

In continuation of our efforts towards the synthesis of biologically active anti-tumor agents, we initiated a programme on the total synthesis of novel, highly potent cytotoxic macrolide (-)-salicylihalamide. Salicylihalamides A & B were isolated from an unidentified species of the marine sponge *Haliclona*. These compounds incorporates salicylic acid, a 12 membered macrolactone ring and highly unsaturated N-acyl enamine side chain.

(-)-Salicylihalamide A shows a striking pattern of differential cytotoxicity profile in the NCI 60 cell line screen. The mean GI₅₀ concentration was approximately 15 nM with a range of differential sensitivity ≤ 10⁷. The melanoma cell lines showed the highest average sensitivity (GI₅₀ 7 nM, TGI 60 nM). More importantly, the mean graph profiles of (-)-salicylihalamide A shows no significant correlation to those of any other antitumor compounds contained in the NCI data base suggesting a new mechanism of action.

The novel structure and potent biological activity of (-)-salicylihalamide A has prompted intense synthetic interest culminating in syntheses by various organic chemists. The major challenge in contemporary organic chemistry lies in the development of efficient and concise routes to complex natural products. Such targets would provide an important venue for the design and functional arrays that form the substituted framework of the molecule of interest. The emphasis on reducing the length
of routes to natural products places a significant burden on the chemist to be as innovative as possible with respect to formulation of the synthetic plan. Towards this end, the efficiency of bond constructions and functional group interconversions must be maximized, starting materials, reagents and chemical reactions must be judiciously selected.

The approach to (-)-salicylihalamide utilizes the advantage of stereoselective iodolactonization, Yamaguchi protocol epoxide opening, Sharpless asymmetric epoxidation, NaCNBH$_3$ mediated regioselective reduction, Diels-Alder reaction, Mitsunobu esterification and the ring closing metathesis protocols. All these approaches are of such a kind that by maneuvering the reactions/reagents other diastereomers could easily be prepared which would serve as a better option for new analogues.

(-)-Salicylihalamide A and B differ only by the orientation at C17 position, where (-)-salicylihalamide A is an E isomer and (-)-salicylihalamide B is an Z isomer. We envisaged that the enamide side chain could be prepared at a later stage and started for the main macrolactone core. Thus the retrosynthetic analysis of both (-)-salicylihalamides A & B revealed two main parts 1) a macrolactone core (shown in Scheme 1) and 2) an enamide 4. Macrolactone core intum could be generated using two synthons, a) derivative of salicylic acid 3 and b) a chiral aliphatic chain 2 which can be synthesized from chiral epoxy ester 5 obtained from $R$-(+)-Pulegone 6.
Formal Total Synthesis of (-)-Salicylihalamides A & B

Scheme 1
Formal Total Synthesis of (-)-Salicylihalamides A & B

Synthesis of the chiral aliphatic fragment 3 started with the commercially available chiral \( R(+)-Pulegone \) 6. Passing of dry HCl gas through \( (R)(+)-Pulegone \) at low temperature and then, simple addition of dilute NaOH at room temperature yielded \( R(+)-citrone!lic acid \) 7 with the double bond exclusively isopropylene position were obtained (Scheme 2). Acid 7 was characterized by its PMR spectrum, which showed resonance at 5.05 ppm as a triplet \((J = 5.6 \text{ Hz})\) for olefinic proton.

\[
\text{\begin{center}
\begin{tikzpicture}
\node[draw,shape=circle,fill=white,minimum size=0.5cm] (a) at (0,0) {6};
\node[draw,shape=circle,fill=white,minimum size=0.5cm] (b) at (1,0) {7};
\node[draw,shape=circle,fill=white,minimum size=0.5cm] (c) at (2,0) {8};
\node[draw,shape=circle,fill=white,minimum size=0.5cm] (d) at (3,0) {9};
\node[draw,shape=circle,fill=white,minimum size=0.5cm] (e) at (4,0) {10};
\draw[->] (a) -- (b) node[midway,above] {\text{Dry HCl gas 94\%}};
\draw[->] (b) -- (c) node[midway,above] {\text{5\% NaOH 25\°C, 4 h}};
\draw[->] (c) -- (d) node[midway,above] {\text{BnOH/ DCM, DCC, DMAP, 0 \°C 97\%}};
\draw[->] (d) -- (e) node[midway,above] {\text{O}_3/ DCM, -78 \°C, DMS, 91\%}};
\end{tikzpicture}
\end{center}
\]

Scheme 2

Acid 7 was protected as its benzyl ester 8 by using benzyl alcohol and DCC in the presence of DMAP in DCM. Compound 8 in its PMR spectrum showed two benzylic protons resonating at 5.10 ppm as a singlet. Ester 8 was subjected to ozonolysis by passing \( O_3 \) gas at \(-78 \text{ °C}\) in the presence of 2 equivalents of DMS to afford aldehyde derivative 9 (Scheme 3). The aldehyde 9 was converted to acid 10 in 97% yield on treatment with \( \text{NaClO}_2 \) and \( \text{NaH}_2\text{PO}_4 \) in DMSO. In the PMR spectrum of compound 10 showed a multiplet at 2.40-2.28 ppm corresponding to methylene protons attached to acid group. Compound 10 was also characterized by its IR spectrum, which showed an absorption bands at 1700 and 3446 cm\(^{-1}\) corresponding to \(-\text{COOH}\) stretching.

\[
\text{\begin{center}
\begin{tikzpicture}
\node[draw,shape=circle,fill=white,minimum size=0.5cm] (a) at (0,0) {7};
\node[draw,shape=circle,fill=white,minimum size=0.5cm] (b) at (1,0) {8};
\node[draw,shape=circle,fill=white,minimum size=0.5cm] (c) at (2,0) {9};
\node[draw,shape=circle,fill=white,minimum size=0.5cm] (d) at (3,0) {10};
\node[draw,shape=circle,fill=white,minimum size=0.5cm] (e) at (4,0) {COOH};
\node[draw,shape=circle,fill=white,minimum size=0.5cm] (f) at (5,0) {COOH};
\draw[->] (a) -- (b) node[midway,above] {\text{BnOH/ DCM, DCC, DMAP, 0 \°C 97\%}};
\draw[->] (b) -- (c) node[midway,above] {\text{O}_3/ DCM, -78 \°C, DMS, 91\%}};
\draw[->] (c) -- (d) node[midway,above] {\text{NaClO}_2 / \text{NaH}_2\text{PO}_4 \text{ DMSO, 97\%}};
\draw[->] (d) -- (e) node[midway,above] {\text{CHO}};
\draw[->] (e) -- (f) node[midway,above] {\text{COOH}};
\end{tikzpicture}
\end{center}
\]

Scheme 3
The resulting acid 10 was subjected for oxidative decarboxylation\(^7\) with lead tetra acetate, copper diacetate and pyridine in refluxing benzene to afford alkene 11 in 72% yield, which in its PMR spectrum showed two multiplets at 5.80-5.67 ppm and 5.03-4.88 ppm corresponding to the olefinic protons. This was also confirmed by its IR spectrum analysis, which showed an \(-\text{C}=\text{C}-\) stretching band at 1620 cm\(^{-1}\) and an absorption at 1730 cm\(^{-1}\) for ester functionality. Hydrolysis of the ester functionality in compound 11 was treated with LiOH.H\(_2\)O in THF, MeOH and water to produce acid derivative 13. PMR spectrum of compound 13 showed a characteristic signal resonating as a broad singlet for \(-\text{COOH}\) proton at 11.6 ppm, which showed an IR absorption band at 3470 cm\(^{-1}\) corresponding to \(-\text{COOH}\) stretching and at 1580 cm\(^{-1}\) for \(-\text{C}=\text{C}-\) stretching. Acid 13 was subjected to stereoselective iodolactonization\(^8\) by using iodine, potassium iodide and NaHCO\(_3\) in THF to produce iodolactone derivative 14 quantitatively. In the PMR spectrum of compound 14, the methylene protons attached to iodine atom resonated at 3.48-3.28 ppm as a multiplet and at 3.12 ppm as a triplet \((J = 9.52\) Hz). Compound 14 was also characterized by its IR spectrum, which showed the absence of corresponding acid moiety and an absorption band at 1779 cm\(^{-1}\) corresponding to cyclic carbonyl stretching and this was also confirmed by its ESIMS data, which showed \((\text{M}^+ + \text{H})\) peak at \(m/z\) 241.

The iodolactone 14 on treatment with K\(_2\)CO\(_3\) in MeOH resulted in the formation of chiral epoxy ester 5 with good yield. The PMR spectrum of compound 5, the newly generated ester methoxy protons were resonated as a singlet at 3.67 ppm and the
Formal Total Synthesis of (-)-Salicylihalamides A & B

corresponding epoxy protons resonated at 2.82-2.64 ppm and 2.58-2.47 ppm as multiplets. The presence of ester moiety and epoxy group was further confirmed by its IR spectrum, which showed absorption bands at 1738 cm\(^{-1}\) and at 1258 & 1196 cm\(^{-1}\) respectively. Compound 5 was also characterized by its ESIMS data, which showed (M\(^+\)+H) peak at \(m/z\) 145. Epoxy ester 5 was subjected to Yamaguchi protocol epoxide opening with THP protected propargyl alcohol to afford secondary alcoholic derivative 15. Epoxide Methyl (3S)-3-[(2S) oxiran-2-yl] butanoate 5 was opened\(^9\) by alkynyl borane reagent prepared \textit{insitu} at \(-78\) °C in anhydrous THF by the reaction of lithium acetylide (from THP protected propargyl alcohol 12 and n-BuLi) with BF\(_3\),OEt\(_2\) (Scheme 5) to yield a β-hydroxy acetylene derivative 15 in 87% yield. The PMR spectrum of compound 15 revealed two methylene protons adjacent to the triple bond at 4.25-4.07 ppm showed as multiplet. IR absorption showed characteristic band at 3457 cm\(^{-1}\) for hydroxyl functionality and stretching band at 1735 cm\(^{-1}\) corresponding to ester group.

\[
\begin{align*}
\begin{array}{c}
\text{O} \\
\text{THP}
\end{array} & \xrightarrow{n-BuLi} \\
\text{THF, -78 °C} & \xrightarrow{\text{BF}_3\text{,OEt}_2} \\
\begin{array}{c}
\text{O} \\
\text{THP}
\end{array} & \xrightarrow{\text{THF, -78 °C}} \\
12 & \rightarrow \\
\begin{array}{c}
\text{O} \\
\text{THP}
\end{array} & \rightarrow \\
5 & \rightarrow
\end{align*}
\]

Scheme 5

Ester group in compound 15 was reduced with LAH in anhydrous THF to obtain diol 16 in 95% yield. PMR spectrum of 16 showed the absence of resonance due to ester functionality while the IR spectrum disclosed the absorption band at 3490 and 3400 cm\(^{-1}\) indicating the presence of dihydroxyl functionality. The primary hydroxyl group of compound 16 was selectively mono protected as its silyl ether 17 with
TBDPSCI and TEA with catalytic amount of DMAP in dry DCM at room temperature to afford 17 in 97% yield. Resonance at 7.67-7.60, 7.42-7.31 ppm in PMR spectrum indicated the presence of ten diphenyllic protons along with the characteristic –C(CH₃)₃– protons of OTBDPS. IR spectrum of compound 17 showed the characteristic band at 3455 cm⁻¹ indicated the presence of free secondary hydroxyl functionality. The free secondary hydroxyl group of compound 17 was protected as its methoxy methyl ether in presence of N, N diisopropylethylamine (Hunig’s base) and MOM-Cl in dry DCM at 0 °C to afford 18 in 96% yield. Presence of MOM moiety in the compound was confirmed by its PMR spectrum, which revealed the characteristic –OCH₃O- protons resonated at 4.65 and 4.54 ppm as doublets with coupling constant $J = 6.7$ Hz along with the two-propargylic protons that resonated at 4.22-4.07 ppm as a multiplet and three –OCH₃ protons at 3.32 ppm as a singlet. Compound 18 was also characterized by its IR and mass analysis.

The compound 18 was treated with catalytic amount of pyridinium para-toluuenesulphonate (PPTS) in ethanol at 60 °C to afford propargylic derivative 19. PMR spectrum of 19 showed the absence of resonance due to THP functionality while the IR spectrum disclosed the absorption band at 3455 cm⁻¹ indicating the presence of –OH functionality. The propargylic alcohol compound 19 was hydrogenated to a trans-allylic...
alcohol\(^{11}\) in 93% yield by refluxing with 3 equivalents of lithium aluminium hydride in dry THF. Compound 20 in its PMR spectrum showed the chemical shifts for olefinic protons that resonated at 5.69-5.63 ppm as a multiplet and allylic hydroxyl protons resonated at 4.04 ppm as a broad doublet \((J = 3.8 \text{ Hz})\). IR studies indicated the \(-\text{C}=\text{C}-\) stretching at 1427 cm\(^{-1}\). Sharpless asymmetric epoxidation\(^{12}\) of 20 using 0.20 equivalents of diisopropyl L(+) tartrate, 0.20 equivalents of titanium isopropoxide and 2.2 equivalents of tert-butylhydroperoxide (4.6 M solution in toluene) in dry dichloromethane at \(-20^\circ \text{C}\) with 4 Å molecular sieves afforded the epoxy alcohol 21 in 89% isolated yield and 87% de, determined by \(^1\text{H}\) NMR studies of the crude product (Scheme 7). The structure was also confirmed by its PMR study which showed the absence of olefinic protons and the presence of two oxirane protons at 3.02-2.96 and 2.90-2.87 ppm as multiplets and methylene protons adjacent to hydroxyl group with an upfield shift at 3.77-3.57 ppm as a multiplet (versus 4.04-3.98 ppm for allyl alcohol). \(^{13}\text{C}\) NMR spectrum revealed the absence of peaks at 131.3 and 129.27 ppm corresponding to olefinic carbons. Compound 21 was also characterized by its Mass and IR spectrum analysis.

The epoxy alcohol 21 was converted to the corresponding 1,3-diol 22 by treating with 2 equivalents of sodium bis(methoxyethoxy)aluminiumhydride (Red-Al) in dry
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THF at room temperature. The compound 22 was characterized by its PMR spectrum, which showed resonance at 4.12-3.96 ppm as a multiplet for OCH\textsubscript{2} proton and at 3.80 ppm as a triplet for \(-\text{CH}_2\text{OH}\) with \(J\) value of 5.6 Hz, while the IR spectrum revealed the presence of absorption bands for free hydroxyl functionalities at 3460 and 3413 cm\(^{-1}\). The diol compound 22 was protected as its \textit{para-}methoxybenzyledene acetal 23 with PMB acetal in DCM using catalytic amount of camphor sulphonic acid (CSA) at 0 °C. The PMR spectrum of compound 23 revealed the presence of PMB group, which was resonated at 5.43 ppm as singlet for \(-\text{OCHO}\) and three \(-\text{OCH}_3\) protons at 3.80 ppm as a singlet. Disappearance of hydroxyl absorption bands at 3460 cm\(^{-1}\) and 3413 cm\(^{-1}\) in IR spectrum confirmed the complete formation of PMB compound.

Deprotection of silyl ether derivative in 23 with tetrabutylammonium fluoride (TBAF) in THF at room temperature furnished the primary alcohol 24. The product was characterized by PMR study, which showed the disappearance of resonance for aromatic protons and there is no chemical shift at 1.03 ppm as singlet for tert-butyl protons from TBDPS moiety. The presence of primary free alcohol was confirmed by its IR spectroscopy that showed the absorption band at 3403 cm\(^{-1}\). The compound 24 was also confirmed by mass spectrometry, which in its ESIMS displayed \((M^+ + H)\) peak at \(m/z\) 355.

\[
\begin{align*}
\text{OTBDPS} & \xrightarrow{\text{TBAF} / \text{THF}} \text{OH} \\
\text{DMSO:DCM (2:6:3)} & \xrightarrow{\text{SO}_2\text{py} / \text{TEA}} \text{MP} \\
\text{NaCNBH}_3 / \text{TMSCl} & \xrightarrow{\text{CH}_3\text{CN, 4 Å MS}} \text{MPMO}
\end{align*}
\]

Scheme 8
The primary hydroxyl group of compound 24 was oxidized to its aldehyde 25 in 93% yield by using SO$_2$-py complex in dichloromethane and dimethyl sulphoxide solvent system. PMR spectrum of compound 25 showed a singlet at 9.75 ppm for formyl proton and a multiplet at 2.72-2.10 ppm for –CHO, -CH(CH$_3$)- protons. The other protons resonated at their respective chemical shifts. IR spectrum showed the absorption band at 1713 cm$^{-1}$ characteristic for carbonyl functionality.

The resulting aldehyde 25 was subjected for one carbon Wittig olefination to afford alkene 26 in 81% yield using methyltriphenylphosphoniumiodide with 'BuOK and 18-crown 6 at −78 °C. The compound 26 in its PMR spectrum revealed the presence of three olefinic protons that resonated at 5.84-5.64 ppm and 5.05-4.94 ppm as a multiplets. IR spectrum showed the absorption band at 1613 cm$^{-1}$ indicated the -C=C- stretching. The compound 26 in its mass spectrometry (ESIMS) showed (M$^+$+H) peak at m/z 355. The acetal functionality in compound 26 was reduced regioselectively$^{13}$ with NaCNBH$_3$ and TMSCl in acetonitrile to afford the required chiral aliphatic alcohol 2. Resonance at 4.42 ppm as singlet in PMR spectrum indicated the protons for the two para methoxy benzylic protons along with the characteristic -CH(OMOM)- proton at 4.01-3.83 ppm as multiplet. The compound 2 was also characterized by $^{13}$C NMR spectroscopy. The presence of secondary free alcohol was confirmed by its IR spectroscopy that showed the absorption band at 3448 cm$^{-1}$. The compound 2 was also confirmed by mass spectrometry that in its ESIMS displayed (M$^+$+H) peak at m/z 353. High resolution mass spectroscopy was also characterized for the compound 2, which in its HRMS (ESIMS) showed (M$^+$+Na) peak at 375.2145.

The second key fragment was prepared through a Diels-Alder reaction. Accordingly, preparation of dienophile started with the commercially available homopropargyl alcohol 27, which was protected as its para methoxy benzylic ether using sodium hydride, catalytic amount of tetrabutylammoniumiodide and p-methoxybenzylbromide in anhydrous THF at 0 °C to afford product 28 in 95% yield. The PMR spectrum of compound 28 revealed the presence of four aromatic protons at 7.22 and 6.82 ppm as doublets with coupling constant $J$ value of 6.4 Hz and two benzylic protons that resonated at 4.44 ppm as a singlet.
Compound 28 was added to a freshly prepared ethyl magnesium bromide solution in THF at 0 °C to generate the intermediate derivative acetylide ion and that was quenched with ethylchloroformate to afford the compound 29. The product 29 was characterized by PMR spectroscopy, which showed the resonance at 7.22 ppm and 6.82 ppm as doublets (J = 8.4 Hz) for four aromatic protons, at 4.43 ppm (singlet) for two benzylic protons and characteristic quartet and triplet for ethyl peaks at 4.20 and 1.32 ppm. The other protons resonated at their respective chemical shifts. IR spectrum showed the absorption band at 1709 cm⁻¹ characteristic for carbonyl functionality.

The diene was prepared starting from anisole 30 which on Birch reduction using Lithium in liquid ammonia and ethanol as the proton source afforded 1-methoxy-1,4-cyclohexadiene 31. The product was characterized by PMR study that showed chemical shifts for four allylic protons at 2.88-2.60 ppm as multiplet. Upfield shift of –OMe protons at 3.54 ppm (versus 3.80 ppm in anisole), disappearance of resonance for aromatic protons and appearance of resonance for olefinic protons at their respective chemical shifts revealed the presence of the product. IR spectrum showed absorption band at 1653 cm⁻¹ for olefinic functionality.
With the presence of dienophile in hand, the reaction was set for Diels-Alder reaction. Thus 1-methoxy-1, 4-cyclohexadiene on treating with dienophile 29 in presence of catalytic amount of dichloromaleic anhydride (promotes in conversion of 1,4-diene to 1,3-diene) at 180 °C for 3 h in a sealed tube afforded the derivatized salicylic ester 32 in 92% yield. The compound 32 was characterized by its PMR and $^{13}$C NMR spectroscopy, which in its PMR spectrum revealed the characteristic peaks at 3.82 and 3.78 ppm as singlets corresponding to two methoxy groups. IR spectrum showed the characteristic absorption band at 1726 cm$^{-1}$ for carbonyl functionality. The compound 32 was also confirmed by its mass spectrometry, FABMS showing (M$^{+}$+H) peak at m/z 345.

\[ \text{Scheme 11} \]

The compound 32 on p-methoxy benzyl group deprotection using DDQ in dichloromethane furnished alcohol 33 in 94% yield, which was characterized by $^1$H NMR showing downfield shift of $^\text{CH}_2\text{OH}$ protons from 3.60 ppm to 3.79 ppm and the absence of p-methoxy benzyl moiety. IR spectrum showed hydroxyl absorption band at 3431 cm$^{-1}$. Oxidation of compound 33 with PCC, Swern conditions and iodoxybenzoic acid always resulted in mixture of products 34 and 34a.
Finally, the free alcohol 33 was oxidized to aldehyde by using Dess-Martin periodinane\textsuperscript{16} in dichloromethane to afford 34 in 95% yield. PMR spectrum of compound 34 showed a singlet at 9.66 ppm for formyl proton and a doublet at 3.65 ppm with $J$ value of 2.4 Hz for $\text{CH}_2\text{CHO}$ protons. IR spectrum showed two carbonyl stretching bands at 1725 cm\textsuperscript{-1} and 1706 cm\textsuperscript{-1} for ester and aldehyde functionalities respectively. The aldehyde 34 was homologated by one carbon Wittig olefination\textsuperscript{17} using methyltriphenylphosphoniumiodide with 'BuOK and 18-crown-6 at −78 °C to afford the product 35 in 50% yield, which was also characterized by its PMR and IR spectroscopic analysis.

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {\textbf{Scheme 12}};
\node (b) at (-2.5,1.5) {32};
\node (c) at (-2.5,0) {33};
\node (d) at (2,1.5) {34};
\node (e) at (2,0) {35};
\node (f) at (5.5,0) {3};
\node (g) at (0,2) {DDQ (DCM : H$_2$O) (19:1) 0 °C to r.t., 94%};
\node (h) at (5,2) {Dess-Martin Periodinane DCM, 0 °C to r.t 95%};
\node (i) at (2,1) {OMPM \textsuperscript{192}};
\node (j) at (-2,1) {OMPM \textsuperscript{192}};
\node (k) at (2,-0.5) {OMPM \textsuperscript{192}};
\node (l) at (-2,-0.5) {OMPM \textsuperscript{192}};
\node (m) at (0,-2) {OMPM \textsuperscript{192}};
\node (n) at (5.5,-2) {OMPM \textsuperscript{192}};
\node (o) at (2,0.5) {\textsuperscript{13}C NMR spectroscopy that showed resonance at 172.3 ppm for \text{COOH}, which in its PMR spectrum displayed the absence of protons corresponding to the ethyl group. The compound 3 was also characterized by its El mass spectrometry with (M$^+$) peak at m/z 192.}.
\end{tikzpicture}
\end{center}
Having both the acid 3 and secondary alcohol 2 in hand, the rest was to couple both by employing Mitsunobu esterification reaction conditions. Accordingly, the mixture of acid 3 and diethyl azodicarboxylate was added to the pre-stirred solution of alcohol 2 and TPP in benzene at room temperature to afford the required ester 36 in 91% yield with the appropriate stereogenic center. PMR spectrum of compound 36 showed the characteristic chemical shift of alcohol attached proton, which was resonated at 5.52-5.27 ppm as a multiplet. While the remaining protons resonated at their respective chemical shifts. $^{13}$C NMR spectrum of compound 36 showed the signal at 167.6 ppm corresponding to the ester carbon. IR spectrum showed the absorption band for ester carbonyl functionality at 1720 cm$^{-1}$. Mass spectrum (ESIMS) of compound 36 showed (M$^+$+Na) peak at m/z 549. The compound 36 was also characterized using high resolution mass spectroscopy technique, which in its HRMS (ESIMS) showed (M$^+$+Na) peak at 549.2846.

![Scheme 13](image)

The compound 36 was subjected to olefin metathesis reaction using benzylidene-bis(tricyclohexyl phosphine) dichlororuthenium (Cy$_3$P)Cl$_2$Ru=CHPh, first generation Grubbs catalyst for macrolactone formation in dichloromethane to afford the desired product trans macrolactone 37 in 75% yield along with the undesired cis
macrolactone as a minor isomer (10% yield). *Trans* macrolactone was evidenced by its PMR study in which one of the olefinic protons showed a doublet of doublet having $J$ value of 16.2 and 6.8 Hz. The compound 37 was also characterized by $^{13}$C NMR, which revealed the presence of two olefinic carbons at 130.3 and 128.3 ppm. The compound 37 was also characterized by high resolution mass spectrometric analysis, which in its HRMS (ESIMS) displayed (M$^+$+Na) peak at 521.2508.

**General mechanism for Ring Closing Metathesis**

The compound 37 on treating with 2,3 dichloro 5,6 dicyano *para*- benzoquinone (DDQ) in DCM afforded the alcohol 38. The compound 38 in its PMR spectrum showed chemical shifts for the MOM moiety that resonated at 4.56 and 4.45 ppm as doublets with $J$ value of 6.8 Hz for $-\text{OCH}_2\text{O}$- (methylene protons from MOM) and 3.29 ppm for $-\text{OMe}$ group (from MOM) and at 3.79 ppm as a singlet for OMe group on phenyl ring, at 5.49-5.40 ppm and 5.20-5.12 ppm for olefinic protons and the remaining protons resonated at their respective chemical shifts.
The compound 38 was also characterized by IR spectrum analysis, which showed the absorption band at 3470 cm\(^{-1}\) for free hydroxyl functionality. Mass spectrum (ESIMS) of compound 38 showed (M\(^{+}\)+H) peak at \(m/z\) 379. High resolution mass spectroscopy also characterized the compound 38, which in its HRMS (ESIMS) showed the characteristic (M\(^{+}\)+Na) peak at 401.1943. The compound 38 was already converted to the final target by further few steps as reported by Furstner et al.\(^{20}\) Thus the present strategy completes the formal total synthesis of (-)-salicylihalamides A & B and it has been accomplished by involving high yielding steps.
EXPERIMENTAL
EXPERIMENTAL SECTION

3,7-dimethyl-6-octenoic acid (7)

Dry HCl gas was passed through (R)-(+) Pulegone (32.5 mL, 200 mmol) at low temperature for 2 h and then without isolating the intermediate pulegonehydrochloride, after allowing to room temperature the reaction mixture was quenched by simple addition of 5% dilute NaOH. After 2 h, the resulting salt was again treated with 5N HCl (till pH = 4) to release the compound. Then extracted with EtOAc (2 x 100 mL) and washed the extracts with water (100 mL) and brine (100 mL). Finally organic extracts were concentrated and passed through flash column chromatography to afford the R-(+)-citronellic acid 7 (31.3 g, in 92% yield) as a colourless oil. Rf = 0.4 (silica gel, 30% EtOAc in petroleum ether).

$^{[\alpha]}_D{^{25}}$ : +17.6 (c 2.0, CHCl$_3$)

$^1$$H$ NMR (300 MHz, CDCl$_3$) : δ 9.68 (br s, 1H, -COOH), 5.10-5.00 (m, 1H, olefinic-H), 2.35 (dd, 1H, $J = 14.7$, 5.66 Hz, Allylic-H), 2.13 (dd, 1H, $J = 14.7$, 5.66 Hz, Allylic-H), 2.07-1.90 (m, 3H, -CH$_2$COOH, -CHCH$_3$), 1.67 (s, 3H, -CH$_3$), 1.59 (s, 3H, -CH$_3$), 1.45-1.17 (m, 2H, -CH$_2$CH(CH$_3$)-), 0.99 (d, 3H, $J = 6.80$ Hz, -CH(CH$_3$)-).

IR (Neat) : 3453, 2830, 1710, 1246, 1017

Benzyl 3,7-dimethyl-(3R)-6-octenoate (8)
To a solution of acid (22 mL, 120 mmol) and alcohol (13.64 mL, 132 mmol) in dry CH₂Cl₂ (200 mL) at 0 °C, DCC (27.23 g, 132 mmol) was added. After stirring for 5 min, DMAP (2.47 g, 12 mmol) was added. After stirring for 2 h, the reaction mixture was filtered through celite and diluted with DCM (50 mL), washed with saturated aqueous NH₄Cl solution (120 mL), brine (120 mL), dried over anhydrous Na₂SO₄ and concentrated in vacuo. Column chromatography gave pure ester compound 8 (30.06 g, 96%) as a colorless oil. Rᵣ = 0.6 (silica gel, 10% EtOAc in petroleum ether).

$^1$H NMR (300 MHz, CDCl₃) : δ 7.41-7.24 (m, 5H, Aromatic-Ø), 5.12-4.99 (m, 3H, -COOCH₂Ph- and one olefinic-Ø), 2.36 (dd, 1H, $J$ = 14.12, 5.94 Hz, Allylic-Ø), 2.16 (dd, 1H, $J$ = 14.12, 5.94 Hz, Allylic-Ø), 2.09-1.86 (m, 3H, -CH₂COOBn, -CH(CH₃)-), 1.68 (s, 3H, -CH₃), 1.60 (s, 3H, -CH₃), 1.44-1.12 (m, 2H, -CH₂CH(CH₃)-), 0.96 (d, 3H, $J$ = 6.69 Hz, -CH(CH₃)-).

IR (Neat) : 3066, 3030, 2902, 2856, 1641, 1495, 1454, 1361, 1100 cm⁻¹

MASS (EI-MS) : m/z 261 (M⁺).

**Benzyl 5-formyl-3-methyl-(3R)-pentanoate (9)**

Ozone gas enriched O₂ was bubbled through a solution of compound (26.1 g, 100 mmol) in 200 mL of DCM at -78 °C until a blue colour appeared in the solution. The excess ozone was removed with an argon punge and DMS (6.4 mL, 100 mmol) was added. The cooling bath was removed and the temperature was allowed to room temperature. After 2 h, additional DMS (6.4 mL, 100 mmol) was added and the reaction mixture stirred at room temperature for 2 h. The solvent was removed under vacuum and the crude was subjected to column chromatography to afford compound 9 as a viscous liquid (21.76 g, 93% yield). Rᵣ = 0.5 (silica gel, 25% EtOAc in petroleum ether).
Formal Total Synthesis of (-)-Salicylihalamides A & B

$^1$H NMR (200 MHz, CDCl$_3$) : δ 9.77 (s, 1H, -CHO), 7.34-7.23 (m, 5H, Aromatic-H), 5.08 (s, 2H, -COOCH$_2$Ph), 2.46-2.22 (m, 4H, -CH$_2$CHO, -CH$_2$COOBn), 1.78-1.32 (m, 3H, -CH$_2$CH$_2$CHO, -CHCH$_3$), 0.97 (d, 3H, J = 6.69 Hz, -CH(CH$_3$)-).

IR (Neat) : 3033, 2860, 1726, 1685, 1258, 1013, 911 cm$^{-1}$

MASS (EIMS) : m/z 234 (M$^+$.)

(4R)-6-(benzyloxy)-4-methyl-6-oxohexanoic acid (10)

\[
\text{HOOC} \begin{array}{c} \text{COOBn} \\ \end{array}
\]

An aqueous solution of NaClO$_2$ (80%, 14.85 g, 165 mmol) and NaH$_2$PO$_4$.2H$_2$O (3.43 g, 22 mmol) were added dropwise to a solution of aldehyde 9 (25.74 g, 110 mmol) in DMSO (110 mL) and 2-methyl-2-butene (15 mL) over 1 h period. The resultant mixture was stirred at room temperature for 1 h and then an additional 1 equivalent of NaClO$_2$/NaH$_2$PO$_4$.2H$_2$O was added. After stirring an additional 6 h at the same temperature, the 5% aqueous solution of NaHCO$_3$ was added. Then it was extracted with ether (2 x 125 mL), washed with brine (2 x 50 mL), dried over Na$_2$SO$_4$ and concentrated in vacuo, thus giving the acid 10 (26.95 g, 98%) as a gummy liquid, which was used directly in the next step. $R_f$ = 0.3 (silica gel, 50% EtOAc in petroleum ether).

$^1$H NMR (200 MHz, CDCl$_3$) : δ 10.06 (br s, 1H, -COOH), 7.36-7.24 (m, 5H, Aromatic-H), 5.09 (s, 2H, -COOCH$_2$Ph), 2.40-2.28 (m, 3H, -CH$_2$COOH and one of -CH$_2$COOBn), 2.24-2.14 (m, 1H, one of -CH$_2$COOBn), 2.08-1.96 (m, 1H, -CH(CH$_3$)-), 1.78-1.44 (m, 2H, -CH$_2$CH(CH$_3$)-), 0.96 (d, 3H, J = 6.80 Hz, -CH(CH$_3$)-).

$^{13}$C NMR (50 MHz CDCl$_3$) : δ 138.8, 128.2, 127.4, 72.9, 66.9, 49.8, 46.8, 32.8.

IR (Neat) : 3032, 2860, 1603, 1495, 1258, 1101, 912 cm$^{-1}$
Formal Total Synthesis of (-)-Salicylamides A & B

**MASS (ESIMS)**

!: m/z 251 (M⁺+H).

**Benzyl-(3S)-3-methyl-4-pentenoate (11)**

\[
\text{COOBn}
\]

A mixture of acid 10 (25 g, 100 mmol), pyridine (1.0 mL, 13 mmol), cupric acetate (500 mg, 2.5 mmol) and benzene (200 mL) were stirred at room temperature until the mixture became a homogeneous green solution. LTA (22.16 g, 50 mmol) was added and the reaction mixture was stirred for 2 h in the dark under nitrogen atmosphere. The reaction mixture was then heated to 80 °C, at which point vigorous gas evolution occurred. After 1 h, the reaction mixture was cooled and filtered through a small mat of alumina to remove inorganic residues. A small amount of hot methanol was used to aid the transfer. After the alumina was washed with 2 x 50 mL of ether, the organic filtrates were combined, washed with water (60 mL), IN HCl (50 mL) and saturated NaHCO₃ solution (50 mL), then dried over Na₂SO₄ and concentrated. Column chromatography of the crude product afforded 11 as a colorless liquid (15.7 g, 77%). \( R_f = 0.7 \) (silica gel, 10% EtOAc in petroleum ether).

\(^1\)H NMR (400 MHz, CDCl₃) : \( \delta 7.36-7.25 \) (m, 5H, Aromatic-H), 5.80-5.67 (m, 1H, olefinic-H), 5.09 (s, 2H, -COOCH₂Ph), 5.03-4.88 (m, 2H, olefinic-H), 2.75-2.62 (m, 1H, -CH(CH₃)), 2.44-2.23 (m, 2H, -CH₂COOBn), 1.05 (d, 3H, \( J = 6.80 \) Hz, -CH(CH₃)-).

IR (Neat) : 1730, 1620 cm⁻¹

**MASS (EIMS)** : ! m/z 204 (M⁺).

**COOH**

**Benzyl-(3S)-3-methyl-4-pentenoicacid (13)**

\[
\text{COOH}
\]

Saponification of 11 (22.44 g, 110 mmol) was carried out in THF: MeOH: H₂O (3:1:1, 110 mL) at 0 °C using LiOH: H₂O (8.8 g, 220 mmol). After 1 h, the reaction
Formal Total Synthesis of (-)-Salicylihalamides A & B

mixture was acidified by adding 1N HCl till pH = 2. Then it was diluted with EtOAc (50 mL), washed with brine (2 x 50 mL), dried over Na₂SO₄ and concentrated in vacuo. Column chromatography (SiO₂, 10-40% EtOAc in petroleum ether eluant) gave pure acid moiety 13 (12.16 g, 97%) as a clear oil. R₇ = 0.5 (silica gel, 50% EtOAc in petroleum ether)

\[
\begin{align*}
\text{Rf} & = 0.5 \ (\text{silica gel, 50% EtOAc in petroleum ether}) \\
^1\text{H NMR} \ (200 \text{ MHz, CDCl}_3) & : \delta \ 11.50 \ (\text{br s, 1H, -COOH}), \ 5.90-5.66 \ (m, \ 1H, \ \text{olefinic-H}), \ 5.18-4.90 \ (m, \ 2H, \ \text{olefinic-H}), \ 2.80-2.60 \ (m, \ 1H, \ -\text{CHCH}_3), \ 2.42-2.20 \ (m, \ 2H, \ -\text{CH}_2\text{COOH}), \ 1.12 \ (d, \ 3H, J = 6.7 \text{ Hz, } -\text{CH(CH}_3)_2^-). \\
\text{IR (Neat)} & : 3470, 1684, 1580 \text{ cm}^{-1} \\
\text{MASS (EIMS)} & : m/z 110 (M^+) \\
\end{align*}
\]

\((4R,5S)-5-(\text{iodomethyl})-4-\text{methyl tetrahydro-2-furanone (14)}\)

To a stirred solution of acid 13 (11.4 g, 100 mmol) in THF (50 mL), added 0.5 M NaHCO₃ solution (25.2 g in 600 mL H₂O) followed by a solution of I₂ (25.4 g, 100 mmol) in water at 0 °C and allowed to stir at room temperature for over night in dark. The reaction mixture was extracted with ethyl acetate (2 x 60 mL), washed with saturated Na₂S₂O₃ solution (100 mL) and brine (60 mL) successively. The organic layer was dried over anhydrous Na₂SO₄, concentrated in vacuo and the crude obtained was purified by column chromatography to afford 14 in 95% yield (22.8 g, liquid). R₇ = 0.6 (silica gel, 20% EtOAc in petroleum ether).

\[
\begin{align*}
^1\text{H NMR} \ (200 \text{ MHz, CDCl}_3) & : \delta \ 4.72-4.54 \ (m, \ 1H, \ -\text{CHOCO-}), \ 3.48-3.28 \ (m, \ 1H, \ \text{one of } -\text{CH}_2\text{I}), \ 3.12 \ (t, \ 1H, J = 9.52 \text{ Hz, one of } -\text{CH}_2\text{I}), \ 2.88-2.62 \ (m, \ 2H, \ -\text{CH}_2\text{COO-}), \ 2.50-2.12 \ (m, \ 1H, \ -\text{CH(CH}_3)_2^-), \ 1.08 \ (d, \ 3H, J = 6.6 \text{ Hz, } -\text{CH(CH}_3)_2^-). \\
\end{align*}
\]

55
**Formal Total Synthesis of (-)-Salicylihalamides A & B**

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<td>MASS (EIMS)</td>
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**Methyl (3S)-3-[(2S) oxiran-2-yl] butanoate (5)**

A 250 mL round-bottomed flask equipped with a magnetic stirring bar, dry nitrogen inlet, reflux condenser and septum was flushed with nitrogen and charged with iodolactone 14 (14.88 g, 62 mmol) and finely powdered K\(_2\)CO\(_3\) (17.13 g, 124 mmol) in 120 mL of methanol. The reaction mixture was refluxed for 1 h, completion of the reaction was monitored by TLC. The resulting solution was brought to room temperature, concentrated under reduced pressure and partitioned between (60 mL) water and (60 mL) ether. The organic layer was washed with brine (30 mL) and water (30 mL), dried over Na\(_2\)SO\(_4\) and evaporated under reduced pressure to give the crude product. The residue was subjected to column chromatography (SiO\(_2\), 8-10% EtOAc in petroleum ether eluant) to provide the pure epoxy ester 5 (8.57 g, 96% yield) as a clear oil. \(R_t = 0.7\) (silica gel, 20% EtOAc in petroleum ether)

\([\alpha]_D^{25}\) : +3.8 (c 2.0, CH\(_2\)Cl\(_2\))

**\(^1\)H NMR (200 MHz, CDCl\(_3\))**

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<td>1.07 (d)</td>
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**\(^13\)C NMR (75 MHz, CDCl\(_3\))**

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**IR (Neat)**

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**MASS (ESIMS)**

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<td>167</td>
<td>M(^{+})+Na</td>
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</table>
Formal Total Synthesis of (−)-Salicylihalamides A & B

Methyl (35,4R)-4-hydroxy-3-methyl-8-(tetrahydro-2H-2-pyranyloxy)-6-octynoate (15)

Under nitrogen atmosphere, a solution of n-butyl lithium in hexane (45 mL, 72 mmol, 1.6 M solution in hexane) was added to a solution of THP ether of propargy? alcohol (7.45 g, 54 mmol) in THF (45 mL) at −78 °C and the mixture was stirred for 15 min. Then, BF3·OEt2 (5.65 mL, 45 mmol) was added to the solution and the stirring was continued for 15 min at the same temperature. Finally a solution of epoxy ester 5 (6.48 g, 45 mmol) in dry THF (40 mL) was added, after stirring the reaction mixture for 3 h at −78 °C, the reaction was quenched by adding saturated aqueous NH4Cl solution (30 mL). Then the reaction mixture was extracted with ethyl acetate (2 x 50 mL) and dried over anhydrous Na2SO4. Evaporation of the solvents resulted in crude alcohol, which was purified by column chromatography (SiO2, 30–33% EtOAc in petroleum ether eluant) to afford the pure alcohol 15 (11.12 g, 87% yield) as colorless liquid. Rf = 0.5 (silica gel, 40% EtOAc in petroleum ether)

[α]D^25 : +2.3 (c 2.0, CHCl3)

1H NMR (200 MHz, CDCl3) : δ 4.82–4.76 (m, 1H, -OCHO- of THP ring), 4.23–4.07 (m, 2H, -CH2OTHP), 3.91–3.67 (m, 2H, -OCH2 of THP ring), 3.66 (s, 3H, -COOCH3), 3.60–3.40 (m, 1H, -CH(OH)-), 2.80–2.08 (m, 5H, -CH2CH(OH), -CH(CH3)- and -CH2COOCH3), 1.90–1.30 (m, 6H, 3 x CH2 of THP ring), 0.96 (d, J = 6.8 Hz, -CH(CH3)-).

13C NMR (75 MHz, CDCl3) : δ 175.44, 96.58, 85.3, 80.05, 72.0, 61.8, 53.95, 51.11, 37.82, 36.57, 34.4, 30.01, 25.03, 25.0, 18.8

IR (Neat) : ν 3457, 2945, 2873, 1735, 1438, 1352, 1263, 1174, 1117, 1078, 1021 cm⁻¹

MASS (ESIMS) : m/z 285 (M⁺+H), 307 (M⁺+Na), 201
Formal Total Synthesis of (−)-Salicylihalamides A & B

HRMS (EIMS) : Calcd for C_{15}H_{24}O_{5} (M^+): 284.1702, Found: 284.1700.

(3S,4R)-3-methyl-8-(tetrahydro-2H-2-pyran-oxo)-6-octyn-1,4-diol (16)

To the suspension of LAH (1.273 g, 33.5 mmol) in dry THF (30 mL) under nitrogen atmosphere at 0 °C was added compound 15 (9.514 g, 33.5 mmol) in dry THF (70 mL) and stirred at room temperature for 4 h. The reaction mixture was cooled to 0 °C, diluted with wet ether and quenched the excess of LAH with saturated Na_{2}SO_{4} solution (15 mL). When the effervescence subsided, the reaction mixture was filtered through a pad of celite and washed with chloroform (30 mL) and hot ethyl acetate (30 mL). The filtrate was evaporated under vacuum and the residue was purified by column chromatography to furnish compound 16 as a viscous liquid (8.32 g, in 97% yield). R_f = 0.4 (silica gel, 60% EtOAc in petroleum ether).

[a]_D^{25} : -6.5 (c 2.0, CHCl_3)

\(^1\)H NMR (200 MHz, CDCl\_3) : δ 4.80–4.74 (m, 1H, \(-OCHO- of THP ring\)), 4.23–4.16 (br d, 2H, J = 6.04 Hz, \(-CH_2OTH\)), 4.17–4.04 (m, 2H, \(-OCH_2- in THP ring\)), 3.80 (t, 2H, J = 9.05 Hz, \(-CH_2CH_2OH\)), 3.67 (br s, 1H, \(-OH\)), 3.58–3.43 (m, 2H, \(-CHOH and one of THP ring\)), 2.38 (br d, 2H, J = 7.55 Hz, \(-CH_2CH\equivCH\)), 2.18 (br s, 1H, \(-OH\)), 1.88–1.68 (m, 8H, 3 x CH_2's in THP ring, \(-CH_2CH_2OH and -CHCH_2\)), 0.94 (d, 3H, J = 6.79 Hz, \(-CH(CH_3)\)).

IR (Neat) : 3400, 2939, 2874, 1447, 1350, 1264, 1117, 1021 cm\(^{-1}\)

MASS (ESIMS) : m/z 257 (M^+H), 279 (M^+Na), 173
Formal Total Synthesis of (-)-Salicylihalamides A & B

(3S,4R)-1-[[1-(tert-butyl)-1,1-diphenylsilyl]oxy]-3-methyl-8-(tetrahydro-2H-2-pyran-2-yl)-6-octyn-4-ol (17)

Diol 16 (8.32 g, 32.5 mmol) was dissolved in dry CH$_2$Cl$_2$ (80 mL) under nitrogen atmosphere, Et$_3$N (6.78 mL, 48.75 mmol) and TBDPSCI (9.16 mL, 35.75 mmol) were added sequentially at 0 °C. Next, a catalytic amount of DMAP (0.397 g, 3.25 mmol) was added to the reaction mixture. After being stirred for 0.5 h at room temperature the reaction mixture was quenched with saturated aqueous NH$_4$Cl solution (20 mL) and extracted with DCM (2 x 40 mL). The organic extracts were dried over Na$_2$SO$_4$ and concentrated in vacuo. Purification by column chromatography gave pure compound 17 (15.25 g, 96% yield in 2 steps) as clear oil. $R_f = 0.7$ (silica gel, 30% EtOAc in petroleum ether)

$[\alpha]_D^{25}: -5.52$ (c 2.0, CHCl$_3$)

$^1$H NMR (200 MHz, CDCl$_3$)

$^13$C NMR (75 MHz, CDCl$_3$)

IR (Neat)

MASS (ESIMS): $m/z$ 496 (M$^+$+H), 513, 517 (M$^+$+Na), 411
Formal Total Synthesis of (−)-Salicylihalamides A & B

HRMS (ESIMS) : Calcd for C_{36}H_{44}O_{7}Si (M^+ + H): 495.2931, Found: 495.2927.

tert-butyl-{{(3S,4/?)-4-(methoxymethoxy)-3-methyl-8-(tetrahydro-2H-2-
pyran-2-yloxy)-6-octynyloxy} diphenyl silane (18)

\[
\begin{align*}
\text{THPO} & \quad \text{OMOM} \\
\text{OMOM} & \quad \text{OTBDPS}
\end{align*}
\]

To a cold (0 °C) solution of alcohol 17 (12.63 g, 25.55 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (150 mL) were added N\textsubscript{2} N\textsubscript{2} diisopropyl ethyl amine (44.4 mL, 255.5 mmol, 10 eq) chloro methyl methyl ether (MOM-Cl) (9.64 mL, 127.7 mmol, 5 eq) and tetra butyl ammonium iodide (0.943 mg, 2.55 mmol, 0.1 eq) the reaction mixture was immediately allowed to warm to room temperature and protected from light. After 6 h, saturated aqueous NaHCO\textsubscript{3} solution (25 mL) was added along with Et\textsubscript{2}O. The organic layer was washed with brine (40 mL) and the aqueous layer was extracted with Et\textsubscript{2}O (2 x 40 mL) and combined extracts were dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated in vacuo. Purification by column chromatography (SiO\textsubscript{2}, 10–12% EtOAc in petroleum ether eluant) gave pure compound 18 (12.92 g, 94%). \(R_f = 0.8\) (silica gel, 15% EtOAc in petroleum ether).

\([\alpha]_{D}^{25}\) : −5.75 (c 2.0, CHCl\textsubscript{3})

\(^{1}\text{H NMR (200 MHz, CDCl}\textsubscript{3})\) : δ 7.70-7.61 (m, 4H, Aromatic-H), 7.41-7.30 (m, 6H, Aromatic-H), 4.77-4.73 (m, 1H, -OCHO in THP), 4.65 (d, 1H, J = 6.7 Hz, one proton in -OCH\textsubscript{2}O-), 4.54 (d, 1H, J = 7.4 Hz, one proton in -OCH\textsubscript{2}O-), 4.22-4.07 (m, 2H, -OCH\textsubscript{2}CH=CH), 3.82-3.42 (m, 5H, -OCH\textsubscript{2} of THP ring, -CH\textsubscript{2}OTBDPS, -CHOMOM), 3.32 (s, 3H, -CH\textsubscript{2}OCH\textsubscript{3}), 2.53-2.31 (m, 2H, -CH\textsubscript{2}CH=CH), 2.14-2.00 (m, 1H, -CH\textsubscript{2}CH\textsubscript{3}), 1.88-1.32 (m, 8H, 3 x CH\textsubscript{2}'s of THP ring, -CH\textsubscript{2}CH\textsubscript{2}OTBDPS), 1.05 (d,
Formal Total Synthesis of (-)-Salicylihalamides A & B

\[ \text{9H, } J = 8.17 \, \text{Hz, -SiC(CH}_3\text{)}_3-, 0.85 \, \text{(d, 3H, } J = 6.7 \, \text{Hz, -CH(CH}_3\text{)})-]. \]

\[^{13}\text{C NMR (75 MHz, CDCl}_3\text{)} : \delta 135.52, 133.99, 129.48, 127.55, 96.69, 96.22, 83.42, 79.66, 61.92, 55.56, 54.53, 35.63, 32.50, 30.26, 26.83, 25.35, 22.28, 19.11, 15.88, 13.92. \]

\[ \text{IR (Neat)} : 2932, 2858, 2236, 1715, 1466, 1427, 1387, 1259, 1110, 1023, 900 \text{ cm}^{-1}. \]

\[ \text{MASS (ESIMS)} : m/z 539 (M^+\text{+H}), 562 (M^+\text{+Na}), 557, 456. \]

\[ (5R,6S)-8-\{[1-(\text{tert-butyl}-1,1\text{-diphenylsilyl})\text{oxy}]\text{-5-(methoxymethoxy)-6-methyl-2-octyn-1-ol (19)} \]

\[
\begin{align*}
\text{HO} & \quad \text{OTBDPS} \\
\text{OMOM} & \quad \text{OMOM}
\end{align*}
\]

The residual compound 18 (13.20 g, 24.51 mmol) was dissolved in EtOH (60 mL) and stirred along with catalytic amount of pyridinium p-toluenesulphonate (PPTS) (0.307 g, 1.23 mmol) at 60 °C for 1 h. The mixture was quenched by addition of saturated aqueous NaHCO\textsubscript{3} solution (10 mL). Ethanol was evaporated under reduced pressure and the aqueous phase was extracted with ethyl acetate (2 x 30 mL). The organic extracts were washed by brine (1 x 30 mL) and dried over anhydrous Na\textsubscript{2}SO\textsubscript{4}. After evaporating the solvent, the product was purified by column chromatography to afford pure alcohol 19 (10.23 g, 94% yield) as a colorless liquid. \( R_f = 0.7 \) (silica gel, 30% EtOAc in petroleum ether)

\[^{[\alpha]}_D^{25} = -2.74 \quad (c \, 2.0, \text{CHCl}_3) \]

\[^1\text{H NMR (200 MHz, CDCl}_3\text{)} : \delta 7.67-7.59 \text{ (m, 4H, Aromatic-H)}, 7.41-7.30 \text{ (m, 6H, Aromatic-H)}, 4.67 \text{ (d, 1H, } J = 6.8 \, \text{Hz, one of } -\text{OCH}_2\text{OH-}), 4.55 \text{ (d, 1H, } J = 6.8 \, \text{Hz, one of } -\text{OCH}_2\text{OH-}), 4.13 \text{ (s, 2H, } -\text{CH}_2\text{(OH) of propargyl}), 3.78-3.62 \text{ (m, 2H, } -\text{CH}_2\text{OTBDPS}), 3.59-3.48 \text{ (m, 1H, } -\text{CH(OH)-}), 3.32 \text{ (s, 3H, } -\text{OCH}_3\text{), 2.49-2.36} \]

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Formal Total Synthesis of (-)-Salicylihalamides A & B

\[ (E,5R,6S)-8-\{1-(\text{tert-butyl})-1,1\text{-diphenylsilyl}\text{oxy}\}-5\text{-}(\text{methoxymethoxy})-6\text{-methyl-2-octene-1\,ol} \]  

To the suspension of LAH (0.610 g, 16 mmol) in dry THF (16 mL) under nitrogen atmosphere at 0 °C was added compound 19 (7.26 g, 16 mmol) in dry THF (32 mL) and stirred at room temperature for 3 h. The reaction mixture was cooled to 0 °C, diluted with wet ether and quenched the excess of LAH with saturated Na₂SO₄ solution (10 mL). When the effervescence subsided, the reaction mixture was filtered through a pad of celite and washed with chloroform (30 mL) and hot ethyl acetate (30 mL). The filtrate was washed with brine (2 x 40 mL), dried over Na₂SO₄, evaporated under vacuum and the residue was purified by column chromatography to furnish compound 4 (6.78 g, 93% yield) as a viscous liquid. \( R_f = 0.5 \) (silica gel, 30% EtOAc in petroleum ether) \( \left[\alpha\right]_{D}^{25} \approx -7.75 \) (\( c \) 2.0, CHCl₃)
Formal Total Synthesis of (-)-Salicylihalamides A & B

$^1$H NMR (200 MHz, CDCl$_3$)

$^1$H NMR (200 MHz, CDCl$_3$) : $\delta$ 7.67-7.60 (m, 4H, Aromatic-H), 7.43-7.31 (m, 6H, Aromatic-H), 5.69-5.63 (m, 2H, olefinic-H), 4.61-4.52 (m, 2H, -CH$_2$O-), 4.04 (br d, 2H, $J = 3.8$ Hz, -CH$_2$(OH) of allylic), 3.80-3.58 (m, 2H, -CH$_2$(OTBDPS)-), 3.48-3.38 (m, 1H, -CH(OMOM)-), 3.31 (s, 3H, -OCH$_3$), 2.33-2.14 (m, 2H, -CH$_2$CH(OMOM)-), 2.00-1.82 (m, 1H, -CH(CH$_3$)-), 1.81-1.66 (m, 1H, one of -CH$_2$CH$_2$OTBDPS), 1.42 (br s, 1H, -OH) 1.38-1.23 (m, 1H, one of -CH$_2$CH$_2$OTBDPS), 1.04 (s, 9H, -Si(C$_3$H$_3$)$_3$), 0.84 (d, 3H, $J = 7.5$ Hz, -CH(CH$_3$)-).

$^{13}$C NMR (75 MHz, CDCl$_3$)

$^{13}$C NMR (75 MHz, CDCl$_3$) : $\delta$ 135.48, 133.84, 131.29, 129.50, 129.27, 127.56, 95.75, 80.98, 63.44, 61.86, 55.53, 35.26, 34.16, 32.04, 26.80, 19.14, 14.29

IR (Neat)

IR (Neat) : 3435, 2931, 2859, 1723, 1589, 1471, 1427, 1387, 1259, 1108, 1036 cm$^{-1}$

MASS (ESIMS)

MASS (ESIMS) : m/z 458 (M$^+$+H), 480 (M$^+$+Na), 475, 425, 169

HRMS (ESIMS)

HRMS (ESIMS) : Calcd for C$_{27}$H$_{40}$O$_4$Si (M$^+$+H): 457.2774, Found: 457.2769.

{(2S,3R)-3-[(2R,3S)-5-{[1-(tert-butyl)-1,1-diphenylsilyl]oxy}-2-(methoxymethoxy)-3-methyl pentyl] oxiran-2-yl]methanol (21)

To a suspension of activated powdered 4 A$^\circ$ molecular sieves (1.06 g, 20 wt%) in CH$_2$Cl$_2$ (35 mL), Ti(O$^\prime$Pr)$_4$ (0.626 mL, 2.106 mmol) and (+)-DIPT (0.487 mL, 2.316 mmol) were added sequentially at -24 °C. After being stirred for 20 min, TBHP (6.27 mL, 26.33 mmol, 4.2 M solution in toluene) was added and stirring continued for
another 30 min at the same temperature. To the above solution, compound 20 (4.8 g, 10.53 mmol) in CH₂Cl₂ (15 mL) was added and stirred for 3 h at -24 °C. The reaction mixture was quenched with water (60 mL), warmed to room temperature and stirred for 1 h. After re-cooling to 0 °C, an aqueous solution of NaOH (30% (w/v), 16 mL), saturated with NaCl, was added to it and stirred at 0 °C for 10 min. CH₂Cl₂ was removed under reduced pressure, the compound was extracted with ether (2 x 40 mL), and washed with brine (40 mL), dried over Na₂SO₄, filtered and concentrated in vacuo.

Purification by column chromatography afforded pure compound 21 (4.42 g, 89% yield) as colorless oil. R<sub>f</sub> = 0.5 (silica gel, 50% EtOAc in petroleum ether)

[α]<sub>D</sub><sup>25</sup>: -24.65 (c 2.0, CHCl₃)

H NMR (200 MHz, CDCl₃): δ 7.63 (d, 4H, J = 6.2 Hz, Aromatic-H), 7.42-7.31 (m, 6H, Aromatic-H), 4.60 (s, 2H, -OCH₂O-), 3.80 (dd, 1H, J = 12.4, 2.3 Hz, -CH(OMOM)-), 3.77-3.57 (m, 4H, -CH₂(OH) and -CH₂OTBDPS), 3.31 (s, 3H, -OCH₃), 2.99 (t, 1H, J = 6.2 Hz, -CH₂CH(O)-), 2.88 (q, 1H, J = 3.1 Hz, -CH(O)CH₂-), 2.04-1.91 (m, 1H, -CH(CH₃)-), 1.86-1.74 (m, 2H, -CH₂CH(OMOM)-), 1.73-1.64 (m, 1H, one of -CH₂CH₂OTBDPS), 1.60-1.50 (m, 1H, one of -CH₂CH₂OTBDPS), 1.04 (s, 9H, SiC(CH₃)₃), 0.83 (d, 3H, J = 7.1 Hz, -CH(CH₃)-).

C NMR (75 MHz, CDCl₃): δ 135.5, 133.8, 129.54, 127.6, 96.1, 79.2, 62.02, 61.7, 59.04, 55.57, 53.94, 34.38, 33.28, 32.59, 26.80, 19.12, 14.96

IR (Neat): 3438, 2933, 2888, 1467, 1386, 1105, 1038 cm⁻¹

MASS (ESIMS): m/z 473 (M⁺+H), 495 (M⁺+Na)

(3R,5R,6S)-8-[(1-tert-butyl)-1,1-diphenylsilyl]oxy]-5-(methoxymethoxy)-6-methyloctane-1,3-diol (22)

To a stirred solution of epoxy alcohol 21 (2.5 g, 5.3 mmol) in dry THF (15 mL) under nitrogen atmosphere was added sodium bis(2-methoxyethoxy)aluminiumhydride (Red-Al) (4.42 mL, 15.9 mmol, 70% (w/w)) by drop wise at 0°C and stirred at room temperature for 2 h. Then the reaction mixture was cooled to 0°C, diluted with wet ether and quenched the excess of Red-Al with saturated NH₄Cl (30 mL) solution. When the effervescence subsided, the reaction mixture was filtered through a pad of celite and washed with chloroform (20 mL) and hot ethyl acetate (20 mL). The filtrate was washed with brine (2 x 30 mL), dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by column chromatography to furnish the compound 22 (2.33 g, 93% yield) as a viscous liquid. $R_f = 0.4$ (silica gel, 60% EtOAc in petroleum ether)

$[\alpha]_D^{25} : -28.75$ (c 2.0, CHCl₃)

$^1$H NMR (200 MHz, CDCl₃) : δ 7.65-7.59 (m, 4H, Aromatic-H), 7.41-7.30 (m, 6H, Aromatic-H), 4.59 (ABq, 2H, J = 6.6 Hz, -OCH₂O-), 4.12-3.96 (m, 1H, -CH₂CH(OH)CH₂-), 3.80 (t, 2H, J = 5.6 Hz, -CH₂OTBDPS), 3.76-3.58 (m, 3H, -CH₂(OH) and -CH(OMOM)-), 3.40 (s, 3H, -OCH₃), 2.00-1.83 (m, 1H, -CH(CH₃)-), 1.55 (m, 4H, -CH₂CH₂OH and -CH₂CH(OMOM)-), 1.54-1.46 (m, 2H, -CH₂CH₂OTBDPS), 1.04 (s, 9H, -Si(C(CH₃)₃)-), 0.83 (d, 3H, J = 6.9 Hz, -CH(CH₃)-).

$^{13}$C NMR (75 MHz, CDCl₃) : δ 135.45, 133.82, 129.48, 127.53, 96.8, 79.35, 68.18, 62.04, 61.67, 55.78, 38.44, 38.1, 34.4, 32.97, 26.76, 19.1, 15.24
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IR (Neat) : 3413, 2933, 2859, 1467, 1427, 1385, 1149, 1037 cm$^{-1}$

MASS (ESIMS) : m/z 475 (M$^+$+H), 497 (M$^+$+Na)

HRMS (ESIMS) : Calcd for C$_{27}$H$_{43}$O$_5$Si (M$^+$+H): 475.2880, Found: 475.2877.

tert-butyl({(3S,4R)-4-(methoxymethoxy)-5-[(4R)-2-(4-methoxyphenyl)-1,3-dioxan-4-yl]-3-methyl pentyloxyl}oxy)diphenyl silane (23)

![Chemical Structure](image)

To a solution of 1,3-diol compound 22 (1.327 g, 2.8 mmol) in dry CH$_2$Cl$_2$ (10 mL), p-methoxybenzaldehyde dimethyl acetal (0.573 mL, 3.36 mmol) and CSA (7 mg, 0.028 mmol) were added sequentially at 0 °C. After being stirred for 1 h at the same temperature, the reaction mixture was quenched with saturated aqueous NaHCO$_3$ solution (15 mL), extracted with EtOAc (2 x 20 mL), washed with brine (25 mL), dried over Na$_2$SO$_4$ and concentrated in vacuo. Purification by column chromatography gave the compound 23 (1.57 g, 95%) as colorless oil. $R_f$ = 0.7 (silica gel, 20% EtOAc in petroleum ether)

$[\alpha]_D^{25}$ : $-18.75$ (c 2.0, CHCl$_3$)

$^1$H NMR (200 MHz, CDCl$_3$) : 6 7.72-7.59 (m, 4H, Aromatic-H), 7.48-7.30 (m, 8H, Aromatic-H), 6.85 (d, 2H, $J = 9.1$ Hz, Aromatic-H), 5.43 (s, 1H, -OCHO-), 4.64 (ABq, 2H, $J = 6.8$ Hz, -OCH$_2$O-), 4.25 (dd, 1H, $J = 11.3, 3.8$ Hz, -CH(OMOM)-), 4.06-3.88 (m, 2H, -CH$_2$OPMB), 3.80 (s, 3H, -OCH$_3$ phenolic), 3.78-3.60 (m, 3H, -CHOPMB and -CH$_2$OTBDPS), 3.34 (s, 3H, -OCH$_3$), 2.05-1.74 (m, 3H, -CH(CH$_3$)$_2$), -CH$_2$CH(OMOM)-), 1.73-1.22 (m, 4H, -CH$_2$CH$_2$OTBDPS, -
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CH$_2$CH(OMP)-, 1.03 (s, 9H, -SiC(CH$_3$)$_3$-),
0.83 (d, 3H, $J = 7.6$ Hz, -CH(CH$_3$)$_3$-).

$^{13}$C NMR (75 MHz, CDCl$_3$) :
δ 160.04, 135.56, 129.54, 127.62, 127.16,
113.55, 100.77, 96.2, 73.69, 67.1, 62.31, 55.27,
37.29, 34.24, 32.4, 31.88, 26.88, 19.2, 15.23

IR (Neat) :
2955, 2857, 1614, 1518, 1427, 1249, 1104, 1037,
917 cm$^{-1}$

MASS (LSIMS) :
m/z 593 (M$^+$+H), 615 (M$^+$+Na)

HRMS (LSIMS) :
Calcd for C$_{35}$H$_{48}$O$_6$Si (M$^+$+Na): 615.3118, Found:
615.3113.

(3S,4R)-4-methoxymethoxy-5-[(4S)-2-(4-methoxyphenyl)-1,3-dioxan-4-yl]-3-
methyl-pentan-1-ol (24)

To a solution of compound 23 (1.534 g, 2.6 mmol) in dry THF (10 mL) and
TBAF (3.9 mL, 3.9 mmol, 1 M solution in THF) was added at 0 °C. Reaction mixture
was warmed to room temperature and stirred for 1 h. The reaction was quenched with
saturated aqueous NH$_4$Cl solution (20 mL), extracted with EtOAc (2 x 30 mL), washed
with brine (25 mL), dried over Na$_2$SO$_4$ and concentrated in vacuo. Purification by
column chromatography afforded compound 24 (0.883 g, 96%) as a clear oil. $R_f = 0.4$
(silica gel, 50% EtOAc in petroleum ether)

$[\alpha]_D^{25}$ :
-32.75 (c 2.0, CHCl$_3$)

$^1$H NMR (200 MHz, CDCl$_3$) :
δ 7.33 (d, 2H, $J = 8.5$ Hz, Aromatic-H), 6.83 (d,
2H, $J = 8.5$ Hz, Aromatic-H), 5.39 (s, 1H, -
OCHO-), 4.67 (ABq, 2H, $J = 6.9$ Hz, -OCH$_2$O-),
4.23 (dd, 1H, $J = 10.8$, 3.9 Hz, -CH(OMP)-),
4.01-3.81 (m, 3H, -CH$_2$OH and one of -

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CH<sub>2</sub>OPMB), 3.78 (s, 3H, -OCH<sub>3</sub> phenolic), 3.73-3.64 (m, 1H, -CH(OMOM)-), 3.62-3.53 (m, 1H, -CHOPMB), 3.38 (s, 3H, -OCH<sub>3</sub>), 2.02-1.88 (m, 1H, -CH<sub>2</sub>CH(O-MOM)-), 1.86-1.68 (m, 2H, -CH<sub>2</sub>CH(OMOM)-), 1.67-1.58 (m, 2H, -CH<sub>2</sub>CH<sub>2</sub>OH), 1.47 (br d, 1H, J = 12.4 Hz, one of -CH<sub>2</sub>CH(OMPM)-), 1.41-1.28 (m, 1H, one of -CH<sub>2</sub>CH(OMPM)-), 0.91 (d, 3H, J = 7.7 Hz, -CH(CH<sub>3</sub>)).

<sup>13</sup>C NMR (75 MHz, CDCl<sub>3</sub>)

δ 159.65, 131.20, 127.15, 113.42, 100.64, 96.46, 77.9, 73.42, 66.9, 61.43, 55.7, 55.14, 36.8, 34.64, 33.86, 31.7, 16.43

IR (Neat)

3403, 2932, 1715, 1605, 1514, 1462, 1380, 1252, 1150, 1099, 1035 cm<sup>-1</sup>

MASS (ESIMS)

m/z 355 (M<sup>+</sup>+H), 377 (M<sup>+</sup>+Na)

HRMS (ESIMS)

Calcd for C<sub>19</sub>H<sub>30</sub>O<sub>6</sub>: (M<sup>+</sup>+H): 355.2121, Found: 355.2119.

7,9-di(benzyloxy)-4-methyl-(4S,5R,7R)-1-nonen-5-ol (25)

To a solution of 24 (0.531 g, 1.5 mmol) in dry CH<sub>2</sub>Cl<sub>2</sub>:DMSO (3:2.6, 9 mL) at 0 °C, Et<sub>3</sub>N (1.04 mL, 7.5 mmol) was added followed by portionwise addition of SO<sub>3</sub>-pyridine complex (1.19 g, 7.5 mmol) with stirring under N<sub>2</sub> atmosphere. After stirring for half an hour at 0 °C the reaction mixture was quenched with saturated aqueous ammonium chloride solution (10 mL) and extracted with EtOAc (2 x 30 mL). The combined organic extracts were washed with brine (2 x 20 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and
concentrated in vacuo, thus giving aldehyde (510 mg, 97%), which was used directly in the next step. \( R_f = 0.6 \) (silica gel, 40% EtOAc in petroleum ether)

\[ \alpha \] D25 : -22.75 (c 2.0, CHCl3)

\(^1\)H NMR (200 MHz, CDCl3) : \( \delta \) 9.75 (s, 1H, -CHO), 7.37 (d, 2H, \( J = 8.2 \) Hz, Aromatic-H), 6.86 (d, 2H, \( J = 8.2 \) Hz, Aromatic-H), 5.43 (s, 1H, -OCHO-), 4.67 (ABq, 2H, \( J = 6.96 \) Hz, -OCH2O-), 4.26 (dd, 1H, \( J = 11.2, 4.5 \) Hz, -CH2CH(OMPM)-), 4.09-3.83 (m, 2H, CH2OMPM-), 3.80 (s, 3H, phenolic-OCH3), 3.37 (s, 3H, -CH2OCH3), 2.72-2.10 (m, 3H, -CH2CHO, -CHCH3), 2.06-1.40 (m, 4H, -CH2CH(OMPM)-, -CH2CH(OMOM)-), 0.95 (d, 3H, \( J = 6.7 \) Hz, -CH(CH3)-).

\(^13\)C NMR (75 MHz, CDCl3) : \( \delta \) 202.30, 159.71, 131.19, 127.1, 113.47, 100.72, 96.44, 78.38, 76.9, 73.32, 66.9, 55.76, 55.18, 47.24, 46.18, 37.04, 31.70, 31.45, 15.7

IR (Neat) : 3403, 2926, 2854, 1713, 1606, 1513, 1461, 1380, 1256, 1150, 1099, 1034 cm⁻¹

MAAS (ESIMS) : m/z 353 (M⁺+H), 375 (M⁺+Na)

(4S)-4-[(2R,3S)-2-(methoxymethoxy)-3-methyl-5-hexenyl]-2-(4-methoxyphenyl)-1,3-dioxan (26)

To a mixture of methyltriphenylphosphonium iodide (3.15 g, 7.8 mmol) and \(^1\)BuOK (0.582 g, 5.2 mmol) in dry THF (15 mL) at -78 °C was added 18 crown 6 (~5 mg) and the solution was stirred for 1 h. Then aldehyde 25 (0.457 g, 1.3 mmol) in dry THF (6 mL) was added to this solution and stirring was continued until the starting
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Material had been consumed. The reaction mixture was quenched by addition of water (6 mL) and the solvent was evaporated. The residue was taken in ethyl acetate (25 mL) and the organic layer was washed with water (1 x 15 mL) followed by brine (1 x 15 mL) and dried over anhydrous Na₂SO₄. The solvent was evaporated under reduced pressure. Purification by column chromatography afforded the pure product 26 (0.396 g, 87% yield in 2 steps) as a viscous liquid. Rᵣ = 0.7 (silica gel, 30% EtOAc in petroleum ether)

[α]₀²⁵ : -15.25 (c 2.0, CHCl₃)

¹H NMR (200 MHz, CDCl₃)

: δ 7.34 (d, 2H, J = 8.3 Hz, Aromatic-H), 6.83 (dd, 2H, J = 9.1, 2.3 Hz, Aromatic-H), 5.84-5.64 (m, 1H, olefinic-H), 5.40 (s, 1H, -OCHO-), 5.05-4.94 (m, 2H, olefinic-H), 4.64 (q, 2H, J = 6.8 Hz, -OCH₂O-), 4.24 (dd, 1H, J = 11.3, 4.5 Hz, -CH(OMPM)-), 4.03-3.84 (m, 3H, -CH₂OPMB and -CH(OMOM)), 3.79 (s, 3H, -OCH₃ phenolic), 3.37 (s, 3H, -OCH₃), 2.40-2.20 (m, 1H, one of allylic -CH₂), 2.00-1.70 (m, 3H, -CH₂CH(OMOM)- and one of allylic -CH₂), 1.69-1.52 (m, 2H, -CH(CH₃)- and one of -CH₂CH(OMOM)-), 1.51-1.40 (m, 1H, one of -CH₂CH(OMOM)-), 0.88 (d, 3H, J = 6.7 Hz, -CH(CH₃)-).

¹³C NMR (75 MHz, CDCl₃)

: δ 160.03, 137.72, 131.90, 127.19, 115.61, 113.42, 100.67, 96.66, 77.63, 73.62, 66.93, 55.61, 55.18, 37.63, 36.65, 36.18, 31.76, 14.70.

IR (Neat)

: 2925, 2852, 1713, 1613, 1516, 1461, 1370, 1249, 1215, 1100, 1036 cm⁻¹

MASS (ESIMS)

: m/z 351 (M⁺+H), 373 (M⁺+Na)

HRMS (ESIMS)

To a solution of 26 (0.336 g, 0.96 mmol) in dry CH₃CN (20 mL), activated and powdered molecular sieves (4 Å, 124 mg) were added at room temperature. After being stirred for 5 min, the reaction mixture was cooled to 0 °C and NaCNBH₃ (0.362 g, 5.78 mmol) and TMS-Cl (0.74 mL, 5.78 mmol) were added sequentially. The resulting solution was stirred for 15 min before quenching with saturated aqueous NH₄Cl (1 x 25 mL) solution and extracted with EtOAc (2 x 30 mL), washed with brine, dried over Na₂SO₄, filtered and concentrated in vacuo. Purification by column chromatography provided compound 2 (0.267 g, 79% yield) as a clear oil. Rf = 0.4 (silica gel, 30% EtOAc in petroleum ether).

[a]₀²⁵: +21.12 (c 2.3, CHCl₃)

^1^H NMR (300 MHz, CDC1₃): δ 7.20 (br d, 2H, J = 8.3 Hz, Aromatic-H), 6.82 (d, 2H, J = 8.3 Hz, Aromatic-H), 5.82-5.64 (m, 1H, olefinic-H), 5.04-4.93 (m, 2H, olefinic-H), 4.64 (s, 2H, -OCH₂O-), 4.42 (s, 2H, -OCH₃PMP), 4.01-3.83 (m, 1H, -CH(OMOM)-), 3.79 (s, 3H, -OCH₃ phenolic), 3.75-3.50 (m, 3H, -CH₂OPMB and -CH₂CH(OH)-), 3.38 (s, 3H, -OCH₃), 2.37-2.18 (m, 1H, one of allylic -CH₂), 2.12-1.95 (m, 1H, one of allylic -CH₂), 1.94-1.34 (m, 5H, -CH(CH₃)-, -CH₂CH(OH)-, -CH₃ phenolic), 0.87 (d, 3H, J = 6.8 Hz, -CH(CH₃)-).

^1^C NMR (75 MHz, CDC1₃): δ 159.08, 137.53, 130.14, 129.18, 115.77, 113.68, 97.12, 79.15, 72.26, 68.25, 66.84, 64.82, 55.79, 55.19, 38.59, 36.85, 36.40, 14.89.
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IR (Neat) : 3448, 2925, 2854, 1740, 1612, 1513, 1461, 1375, 1248, 1150, 1095 cm\(^{-1}\)

MASS (ESIMS) : \textit{m/z} 375 (M\(^+\)+Na)

HRMS (ESIMS) : Calcd for C\(_{20}\)H\(_{32}\)O\(_3\) (M\(^+\)+Na): 375.2147, Found: 375.2145.

1-[(3-butylnyloxy) methyl]-4-methoxybenzene (28)

\[\text{\textendash}O\text{OPM}\]

To a stirred suspension of NaH (9.6 g, 400 mmol, 60% W/V dispersion in mineral oil) in dry THF (300 mL) was added dropwise a solution of 3-butyn-1-ol (14 g, 200 mmol) at 0 °C. After stirring for 30 minutes at 0 °C, TBAI (1 g) and para methoxybenzyl bromide (47.5 mL, 220 mmol) were added subsequently and stirred overnight at room temperature. The reaction mixture was quenched with small ice-pieces and extracted with ethyl acetate (2 x 150 mL). The combined organic layers were washed with water (150 mL), brine (150 mL) and dried over anhydrous Na\(_2\)SO\(_4\). Solvent was removed \textit{in vacuo} and the residue was purified by silica gel column chromatography to afford 28 (36.10 g, 95% yield) as a colorless liquid. \(R_f = 0.5\) (SiO\(_2\), 20% EtOAc in hexane).

\(^1\)H NMR (200 MHz, CDCl\(_3\)) : \(\delta\) 7.22 (d, 2H, \(J = 6.4\) Hz, Aromatic - H), 6.82 (d, 2H, \(J = 6.4\) Hz, Aromatic - H), 4.44 (s, 2H, -OCH\(_2\)Ph), 3.79 (s, 3H, -OCH\(_3\)), 3.53 (t, 2H, \(J = 6.8\) Hz, -CH\(_2\)CH\(_2\)OMPM), 2.43 (t, 2H, \(J = 6.8\) Hz, -CH\(_2\)CH\(_2\)OMPM), 1.88 (t, 1H, \(J = 6.8\) Hz, acetylene - H).

IR (Neat) : 2974, 2937, 2236, 1513, 1461, 1250, 1034 cm\(^{-1}\).

MASS (EIMS) : \textit{m/z} 190 (M\(^+\)).

Ethyl 5-[(4-methoxybenzyl) oxy]-2-pentynoate (29)

\[\text{EtO}_{2}\text{C}\text{\textendash}O\text{OPM}\]

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To a freshly prepared ethylmagnesium bromide solution [from ethyl bromide (9.3 mL, 124 mmol) and magnesium (3.0 g, 125 mmol) in dry THF (100 mL)] under nitrogen atmosphere at 0 °C was added alkyne 28 (10.0 g, 62.5 mmol) and allowed to stir at room temperature for 1 h. To this reaction mixture at 0 °C, freshly distilled ethyl chloroformate (12 mL, 125 mmol) was added slowly. After the addition was complete, the mixture was further stirred overnight at room temperature. The reaction mixture was quenched with saturated aqueous NH₄Cl solution (25 mL) and extracted with ethyl acetate. The organic extract was washed with water (2 x 50 mL), brine (1 x 50 mL), dried over anhydrous Na₂SO₄, filtered and concentrated under vacuum. Purification of the crude by column chromatography afforded the ester 29 (14.24 g, 87% yield) as a colorless syrupy liquid. Rf = 0.7 (silica gel, 15% EtOAc in petroleum ether).

\(^1\)H NMR (200 MHz, CDCl₃) : δ 7.22 (d, 2H, J = 8.4 Hz, Aromatic – H), 6.82 (d, 2H, J = 8.4 Hz, Aromatic – H), 4.43 (s, 2H, -OCH₂Ph), 4.20 (q, 2H, J = 6.80 Hz, -COOCH₂CH₃), 3.78 (s, 3H, -OCH₃), 3.58 (t, 2H, J = 6.80 Hz, -CH₂CH₂OMPM), 2.60 (t, 2H, J = 6.80 Hz, -CH₂CH₂OMPM), 1.32 (t, 3H, J = 6.80 Hz, -COOCH₂CH₃).

IR (Neat) : 2937, 2866, 2241, 1709, 1513, 1365, 1252, 1096, 822 cm⁻¹

MASS (EIMS) : m/z 262 (M⁺).

1-Methoxyhexa-1,4-diene (31)

A solution of anisole 30 (17.5 mL, 140 mmol) in anhydrous ether (50 mL) and liq. NH₃ (500 mL) was treated by slow addition of lithium (4.5 g, 5 eq). After stirring for 15 min. absolute ethanol (30 mL) was added over 30 min. The color of the mixture...
is changed from blue to colorless. Excess ammonia was allowed to evaporate and extraction of the residue by ether afforded the product. Distillation of the product at 150 °C afforded 31 pure 1-methoxycyclohexa-1, 4-diene (12.9 g, 84 % yield).

\[ \text{HNMR (200 MHz, CDCl}_3 \text{)} : \delta 5.64-5.60 \text{ (m, 2H, } -\text{CH}_2\text{CH=CHCH}_2\text{-}), \ 4.60-4.50 \text{ (m, 1H, } -\text{CH=CH}(\text{OCH}_3)\text{-}), \ 3.54 \text{ (s, 3H, } -\text{OCH}_3\text{), 2.85-2.60 \text{ (m, 4H, 2 x } -\text{CH}_2\text{-)}.} \]

IR (Neat) : 3033, 2830, 1690, 1653, 1442, 1386, 1217, 1166, 1025, 956 cm\(^{-1}\)

**Ethyl 2-methoxy-6-{2-[(4-methoxybenzyl)oxy]ethyl}benzoate (32)**

A neat solution of 1-methoxycyclohexa-1,4-diene 31 (4.75 g, 43.1 mmol) and ester 29 (5.6 g, 21.5 mmol) along with a catalytic amount of dichloromaleic anhydride (DCMA) (5 mg) was heated at 180 °C for 3 h in a sealed tube. The reaction mixture was cooled to room temperature diluted with ethylacetate (25 mL) and washed with 20% NaHCO\(_3\) solution (30 mL) followed by brine (1 x 25 mL). The organic layer was dried over anhydrous Na\(_2\)SO\(_4\), filtered and evaporated to give the crude oil which was purified by column chromatography to afford 32 (6.80 g, 92%) as a pale yellow liquid.

\[ \text{H NMR (200 MHz, CDCl}_3 \text{)} : \delta 7.30-7.12 \text{ (m, 3H, 2 from phenyl, one subs.aryl -H), 6.91-6.72 \text{ (m, 4H, 2 from phenyl, two subs. aryl-H), 4.40 \text{ (s, 2H, } -\text{OCH}_2\text{Ph}), 4.32 \text{ (q, 2H, } J = 14.1, 6.8 \text{ Hz, } -\text{COOCH}_2\text{CH}_3\text{), 3.82 \text{ (s, 3H, } -\text{OCH}_3\text{), 3.78 \text{ (s, 3H, } -\text{OCH}_3\text{), 3.59 \text{ (t, 2H, } J = 7.4 \text{ Hz, } -\text{CH}_2\text{OMPM), 2.83 \text{ (t, 2H, } J = 6.8 \text{ Hz, } -\text{CH}_2\text{OMPM), 1.33 \text{ (t, 3H, } J = 6.8 \text{ Hz, } -\text{COOCH}_2\text{CH}_3\text{).}} \]
Formal Total Synthesis of (-)-Salicylihalamides A & B

$^{13}$C NMR (50 MHz, CDCl$_3$) : δ 167.9, 158.9, 156.1, 136.9, 129.9, 129.0, 124, 121.9, 113.45, 108.9, 72.24, 70.1, 60.94, 55.5, 55.03, 33.61, 14.06.

IR (Neat) : 2938, 2862, 1726, 1585, 1471, 1364, 1265, 1091, 1033, 757 cm$^{-1}$

MASS (FABMS) : m/z 345 (M$^+$+H).

Ethyl 2-(2-hydroxyethyl)-6-methoxybenzoate (33)

To a solution of compound 32 (3.44 g, 10 mmol) in CH$_2$Cl$_2$ (47 mL) and water (~3 mL) was added DDQ (2.73 g, 12 mmol). After stirring for 1.5 h at room temperature, the yellow slurry was poured into saturated NaHCO$_3$ (25 mL) and water (30 mL) and an extraction was performed with EtOAc (3 x 30 mL). The combined organic layers were dried over Na$_2$SO$_4$ and concentrated in vacuo. The residue was purified by flash column chromatography (SiO$_2$, 50% EtOAc in petroleum ether eluant) to give colorless alcohol 33 (2.10 g, 94% yield) as a clear oil. $R_f$ = 0.6 (silica gel, 40% EtOAc in petroleum ether).

$^1$H NMR (300 MHz, CDCl$_3$) : δ 7.27 (t, 1H, $J = 7.9$ Hz, Aromatic H), 6.84 (d, 1H, $J = 7.6$ Hz, Aromatic H), 6.77 (d, 1H, $J = 7.6$ Hz, Aromatic H), 4.38 (q, 2H, $J = 14.3$, 7.2 Hz, -COOCH$_2$CH$_3$), 3.83 (s, 3H, -OCH$_3$), 3.79 (t, 2H, -CH$_2$CH$_2$OH, $J = 6.4$ Hz), 2.79 (t, 2H, $J = 6.4$ Hz, -CH$_2$CH$_2$OH), 1.90 (br s, 1H, -OH), 1.39 (t, 3H, $J = 7.2$ Hz, -COOCH$_2$CH$_3$).

IR (Neat) : 3431, 2942, 2842, 1724, 1584, 1472, 1268, 1072, 979 cm$^{-1}$.

MASS (EIMS) : m/z 224 (M$^+$).
Formal Total Synthesis of (-)-Salicylihalamides A & B

Ethyl 2-formylmethyl-6-methoxybenzoate (34)

![Chemical structure of 34]

Dess Martin Periodinane (3.73 g, 8.8 mmol) was added to a solution of alcohol 33 (1.79 g, 8 mmol) in dry CH₂Cl₂ (40 mL) at 0 °C under nitrogen atmosphere. The turbid solution was allowed to warm to room temperature and stirred for 1 h. The reaction was diluted with ethyl acetate (40 mL) and quenched with saturated aqueous NaHCO₃ (30 mL), and saturated aqueous Na₂S₂O₃ (20 mL). The mixture was vigorously stirred until a clear solution resulted. The aqueous layer was extracted with ethyl acetate (2 x 30 mL). The combined organic extracts were washed with brine (1 x 30 mL), dried over anhydrous Na₂SO₄ and concentrated to give the crude aldehyde. Purification by column chromatography afforded the pure aldehyde 34 (1.68 g, 95%) as a colorless oil. Rᵢ = 0.7 (silica gel, 30% EtOAc in petroleum ether).

¹H NMR (200 MHz, CDCl₃) : δ 9.66 (s, 1H, -CHO), 7.38 (t, 1H, J = 8.6 Hz, Aromatic-H), 6.96-6.78 (m, 2H, Aromatic-H), 4.38 (q, 2H, J = 14.2, 7.1 Hz, -OCH₂CH₃), 3.83 (s, 3H, -OCH₃), 3.64 (d, 2H, -CH₂CHO, J = 2.4 Hz), 1.38 (t, 3H, J = 7.3 Hz, -OCH₂CH₃).

¹³C NMR (75 MHz, CDCl₃) : δ 198.2, 166.7, 157, 130.1, 122.3, 110.5, 61.3, 55.9, 48.1, 14.1

IR (Neat) : 2979, 2841, 2728, 1725, 1586, 1472, 1269, 1075, 763 cm⁻¹

Ethyl 2-allyl-6-methoxybenzoate (35)

![Chemical structure of 35]
To a mixture of methyltriphenylphosphonium iodide (7.63 g, 18.9 mmol) and tBuOK (1.41 g, 12.6 mmol) in dry THF (20 mL) at -78 °C was added 18-crown-6 (~5 mg) and the solution was stirred for half an hour. Aldehyde 34 (1.40 g, 6.30 mmol) in dry THF (10 mL) was added to this solution and stirring was continued until the starting material had been consumed. The reaction mixture was quenched by addition of water (10 mL) and the solvent was evaporated. The residue was taken in ethyl acetate (30 mL) and the organic layer was washed with water (1 x 30 mL) followed by brine (1 x 30 mL) and dried over anhydrous Na₂SO₄. The solvent was evaporated under reduced pressure. Purification by flash chromatography afforded the pure product 35 (0.693 g, 50% yield). Rₚ = 0.7 (silica gel, 25% EtOAc in petroleum ether).

¹H NMR (200 MHz, CDCl₃) : δ 7.30-7.18 (m, 1H, Aromatic-H), 6.82-6.72 (m, 2H, Aromatic-H), 6.02-5.76 (m, 1H, -CH=CH₂), 5.10-4.96 (m, 2H, -CH=CH₂), 4.34 (q, 2H, J = 14.1, 7.3 Hz, -OCH₂CH₃), 3.82 (s, 3H, -OCH₃), 3.34 (d, 2H, J = 6.8 Hz, -CH₂CH=CH₂), 1.38 (t, 3H, J = 7.3 Hz, -OCH₂CH₃).

IR (Neat) : 2923, 2853, 1711, 1596, 1514, 1463, 1256, 1170, 1032 cm⁻¹

2-allyl-6-methoxybenzoic acid (3)

To a solution of ester 35 (1.0 g, 4.5 mmol) in MeOH:Water (3:1; 10 mL) was added LiOH·H₂O (1.6 g, 36 mmol) and the mixture was heated to 70 °C for 48 h. The solvent was evaporated and the residue in water was washed with ether (2 x 15 mL). The aqueous solution was acidified by 2N HCl (20 mL) and extracted with ethyl acetate (2 x 15 mL). The organic layer was washed with brine (25 mL), dried over Na₂SO₄ and concentrated to get the crude acid. The product was purified over silica gel column...
chromatography to afford colorless solid 3 (0.74 g, 85% yield). R_f = 0.3 (silica gel, 40% EtOAc in petroleum ether).

M.P : 105-107 °C.

^1^H NMR (200 MHz, CDCl3) : δ 7.30 (t, 1H, J = 8.1 Hz, Aromatic-H), 6.83 (t, 2H, J = 8.1 Hz, Aromatic-H), 6.06-5.80 (m, 1H, -CH=CH2), 5.17-5.00 (m, 2H, -CH=CH2), 3.90 (s, 3H, -OCH3), 3.50 (d, 2H, J = 6.2 Hz, Aryl-CH2-), 1.25 (s, 1H, Acid-OH).

^13^C NMR (75 MHz, CDCl3) : δ 172.3, 157.1, 139.6, 136.4, 131.3, 122.4, 122.2, 116.3, 108.9, 56.2, 37.8.

IR (KBr) : 3011, 2910, 1700, 1588, 1470, 1290, 1267, 1125, 1074, 913 cm⁻¹

MASS (EIMS) : m/z 192 (M⁺)

Anal. Calcd. for C_{11}H_{12}O_{3} : C 68.74, H 6.29; Found C 68.52, H 6.18.

(1S,3R,4S)-1-{2-[(4-methylbenzyl)oxy]ethyl}-3-methoxymethoxy-4-methyl-6-heptenyl 2-allyl-6-methoxy benzoate (36)

To a well-stirred solution of alcohol 2 (0.169 g, 0.48 mmol) and triphenylphosphine (0.629 g, 2.4 mmol) in anhydrous benzene (4 mL) at room temperature was added pre-stirred solution of acid 3 (0.092 g, 0.48 mmol) and Diethyl azodicarboxylate (DEAD) (0.437 mL, 2.4 mmol) in benzene (4 mL). The mixture was stirred for 14 h. Solvent was evaporated and the residue was washed with dry ether (20 mL) and filtered through a sintered funnel. The filtrates were dried over anhydrous Na₂SO₄ and evaporation of the solvent followed by column chromatography of the
crude residue afforded pure ester 36 (0.230 g, 91% yield) as a pale pink colored viscous liquid. $R_t = 0.7$ (silica gel, 20% EtOAc in petroleum ether)

$\lbrack \alpha \rbrack_25^{25} : -9.44$ (c 1.60, CHCl$_3$)

$^1$H NMR (300 MHz, CDCl$_3$) : δ 7.36-7.22 (m, 3H, Aromatic-H), 6.92-6.73 (m, 4H, Aromatic-H), 6.05-5.65 (m, 2H, olefinic-H), 5.52-5.27 (m, 1H, -CH(OCO)-), 5.13-4.94 (m, 4H, olefinic-H), 4.64 (s, 2H, -OCH$_2$O-), 4.45 (s, 2H, -OCH$_2$PMP), 3.81 (s, 3H, -OCH$_3$ phenolic), 3.78 (s, 3H, -OCH$_3$ phenolic), 3.70-3.52 (m, 3H, -CH(OMOM) and -CH$_2$OPMB), 3.42-3.30 (m, 5H, -OCH$_3$ and ArCH$_2$-CH=CH$_2$), 2.40-2.14 (m, 1H, one of allylic -CH$_2$), 2.12-1.73 (m, 6H, -(CHCH$_3$)$_2$), -(CH$_2$CH(OMOM)), -(CH$_2$CH$_2$OPMB, one of allylic -CH$_2$), 0.88 (d, 3H, $J = 6.5$ Hz, -CH(CH$_3$)$_2$).

$^{13}$C NMR (75 MHz, CDCl$_3$) : δ 167.6, 159.2, 156.3, 138.2, 137.6, 136.3, 130.5, 130.2, 129.3, 124.2, 121.7, 116.3, 115.7, 113.9, 108.8, 96.2, 78.1, 72.9, 70.7, 66.5, 55.8, 55.5, 37.9, 37.3, 36.2, 35.8, 35.3, 34.5, 13.8

IR (Neat) : 2930, 1720, 1585, 1512, 1466, 1375, 1253, 1096, 1036, 915, 759 cm$^{-1}$

MAAS (ESIMS) : $m/z$ 549 (M$^+$+Na)

HRMS (ESIMS) : Calcd for $C_{31}H_{42}O_7$ (M$^+$+Na) 549.2828, Found 549.2846.
Formal Total Synthesis of (-)-Salicylihalamides A & B

(3S,5R,6S)-14-Methoxy-3-{2-[(4-methoxybenzyl)oxy]ethyl}-5-(methoxymethoxy)-6-methyl-3,4,5,6,7,10-hexahydro-1H-2-benzoxacyclododecin-1-one (37)

To a solution of the Grubb’s catalyst (Cy₃P)₂Cl₂Ru=CHPh (0.035 g, 0.04 mmol) in dry CH₂Cl₂ (40 mL) was added a solution of compound 36 (0.210 g, 0.4 mmol) in CH₂Cl₂ (4 mL). The reaction mixture was stirred for 3 h at ambient temperature and poured into water (20 mL). The organic phase was washed with brine (1 x 20 mL), dried over anhydrous Na₂SO₄, filtered and concentrated. Column chromatography of the crude residue afforded pure product 37 (0.169 g, 85% yield (9:1 E : Z isomer) as a light brown colored viscous liquid. Rf=0.4 (silica gel, 30% EtOAc in petroleum ether)

[α]D²⁵ : -27.53 (c 1.30, CHCl₃)

¹H NMR (500 MHz, CDCl₃) : δ 7.32-7.21 (m, 3H, Aromatic-H), 6.87 (d, 2H, J = 8.6 Hz, Aromatic-H), 6.78 (dd, 2H, J = 8.3, 3.8 Hz, aromatic-H), 5.52-5.40 (m, 1H, olefinic-H), 5.34-5.25 (m, 1H, -CH(OCO)-), 5.15 (dd, 1H, J = 16.2, 6.8 Hz, olefinic-H), 4.56 (d, 1H, J = 6.8 Hz, one of -OCH₂O-), 4.50 (d, 1H, J = 11.2 Hz, one of -OCH₂PMP), 4.44 (d, 1H, J = 6.8 Hz, one of -OCH₂O-), 4.41 (d, 1H, J = 11.2 Hz, one of -OCH₂PMP), 4.32 (q, 1H, J = 6.8 Hz, -CH(OMOM)⁻), 3.80 (s, 3H, -OCH₃ phenolic), 3.76-3.68 (m, 4H, -OCH₃ phenolic and one of ArCH₂-CH=CH₂), 3.67-3.58 (m, 2H, -CH₂OPMB), 3.29 (s, 3H, -OCH₃), 3.17 (dd, 1H, J = 14.6, 2.6 Hz, one of ArCH₂-CH=CH₂), 2.07-1.79 (m, 4H, -CH₂-CH=CH- and -CH₂CH₂OPMB
Formal Total Synthesis of (-)-Salicylihalamides A & B

\[ \delta \] 167.7, 159.1, 157.2, 139.55, 133.48, 130.57, 130.3, 129.35, 128.3, 123.64, 122.87, 113.74, 109.77, 95.8, 79.7, 73.87, 72.79, 66.26, 55.79, 55.35, 55.24, 38.38, 37.42, 37.35, 35.7, 34.53, 14.1.

IR (Neat) : 2924, 2853, 1726, 1513, 1464, 1253, 1096 cm\(^{-1}\)

HRMS (ESIMS) : Calcd for C\(_{29}\)H\(_{38}\)O\(_7\) (M\(^{+}\)+Na) 521.2515, Found 521.2508.

(3S,5R,6S)-3-(2-hydroxyethyl)-14-methoxy-5-(methoxymethoxy)-6-methyl-3,4,5,6,7,10-hexahydro-1H-2-benzoxacyclododecin-1-one (38)

To a solution of benzolactone 37 (0.165 g, 0.33 mmol) in CH\(_2\)Cl\(_2\) (10 mL) and water (~0.5 mL) was added DDQ (0.091 g, 0.40 mmol). After stirring for 1.5 h at room temperature, the yellow slurry was poured into saturated NaHCO\(_3\) (15 mL) and water (30 mL) and an extraction was performed with EtOAc (3 x 20 mL). The combined organic layers were dried over Na\(_2\)SO\(_4\) and concentrated in vacuo. The residue was purified by flash column chromatography to give colorless alcohol 38 (0.117 g, 94% yield) as a clear oil. \(R_f = 0.6\) (silica gel, 70% EtOAc in petroleum ether). lit.\(^{66}\) \([\alpha]_D^{25} = -34.5\) (c 1.0, CHCl\(_3\))

\([\alpha]_D^{25}\) : -31.3 (c 0.5, CHCl\(_3\))
Formal Total Synthesis of (-)-Salicylihalamides A & B

[α]D25 : -52.6 (c 5.5 in MeOH)

1H NMR (500 MHz, CDCl3)

δ 7.29-7.23 (m, 1H, Aromatic-H), 6.81 (t, 2H, J = 8.6 Hz, Aromatic-H), 5.49-5.40 (m, 1H, olefinic-H), 5.35-5.27 (m, 1H, -CH(OCO)-), 5.20-5.12 (m, 1H, olefinic-H), 4.56 (d, 1H, J = 6.8 Hz, one of -OCH₂O-), 4.45 (d, 1H, J = 6.8 Hz, one of -OCH₂O-), 3.91-3.82 (m, 1H, -CH(OMOM)-), 3.79 (s, 3H, -OCH₃ phenolic), 3.72 (q, 2H, J = 10.3 Hz, -CH₂OH), 3.63 (dd, 1H, J = 11.9, 2.6 Hz, one of ArCH₂CH=CH₂), 3.29 (s, 3H, -OCH₂OCH₃), 3.18 (dd, 1H, J = 11.9, 2.6 Hz, one of ArCH₂CH=CH₂), 2.91 (br s, 1H, -OH), 2.03–1.52 (m, 7H, -CH(CH₃)₂, -CH₂CH(OMOM)-, -CH₂CH₂OH), 0.96 (d, 3H, J = 6.8 Hz, -CH(CH₃)-).

13C NMR (75 MHz, CDCl₃)

δ 168.2, 156.1, 139.0, 131.1, 129.9, 128.2, 124.2, 122.9, 109.1, 96.7, 79.3, 72.7, 59.1, 55.5, 55.4, 38.8, 37.6, 35.7, 33.9, 13.3.

IR (Neat)

3470, 2927, 1721, 1583, 1466, 1274, 1117, 1074, 1037, 973, 839 cm⁻¹

MAAS (ESIMS)

m/z 379 (M⁺+H)

HRMS (ESIMS)

Calcd for C₂₁H₃₀O₆ (M⁺+Na) 401.1940, Found 401.1943.
REFERENCES
Formal Total Synthesis of (-)-Salicylihalamides A & B

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SPECTRA
$^1$H NMR SPECTRUM OF COMPOUND 5
$^{13}$C NMR SPECTRUM OF COMPOUND 5
Sample: JSY-EPOXY ESIMS [NEAT]
Collection time: Wed Jan 04 12:06:56 2006 (GMT+05:30)
Bench: Thermo Nicolet Nexus 670 Spectrometer
Resolution: 4cm⁻¹

IR SPECTRUM OF COMPOUND 5
Detector: DTGS KBr
Beamsplitter: KBr
Source: IR
Analyst Name:
H NMR SPECTRUM OF COMPOUND 16
H NMR SPECTRUM OF COMPOUND 17
Sample: JSY-OTBDPS [NEAT]
Collection time: Wed Jan 04 12:10:10 2006 (GMT+05:30)
Bench: Thermo Nicolet Nexus 670 Spectrometer
Resolution: 4cm⁻¹

IR SPECTRUM OF COMPOUND 17
Detector: DTGS KBr
Beamsplitter: KBr
Source: IR
Analyst Name:
'H NMR SPECTRUM OF COMPOUND 21
$^1$H NMR SPECTRUM OF COMPOUND 21
Sample: EPOXY [NEAT]
Collection time: Fri Nov 25 11:58:24 2005 (GMT+05:30)
Bench: Thermo Nicolet Nexus 670 Spectrometer
Resolution: 4cm-1

Detector: DTGS KBr
Beamsplitter: KBr
Source: IR
Analyst Name:
Sample: JSY-OH [NEAT]
Collection time: Tue Nov 29 12:01:30 2005 (GMT+05:30)
Bench: Thermo Nicolet Nexus 670 Spectrometer
Resolution: 4cm-1

IR SPECTRUM OF COMPOUND 24
Detector: DTGS KBr
Beamsplitter: KBr
Source: IR
Analyst Name:
H NMR SPECTRUM OF COMPOUND 25
H NMR SPECTRUM OF COMPOUND 26
$^{13}$C NMR SPECTRUM OF COMPOUND 2
$^{13}$C NMR SPECTRUM OF COMPOUND 32
$^1$H NMR SPECTRUM OF COMPOUND 33
$^1$H NMR SPECTRUM OF COMPOUND 34
$^{13}$C NMR SPECTRUM OF COMPOUND 34
$^1$H NMR SPECTRUM OF COMPOUND 3
SHAC.LRP     SH-Acid

Scan 4    RT= 0:16  No.ions= 378  Base=100.0%F  TIC=474741

EIMS SPECTRUM OF COMPOUND 3
1H NMR SPECTRUM OF COMPOUND 36
Sample: JSY-DIENE [NEAT]
Collection time: Tue Dec 06 12:12:16 2005 (GMT+05:30)
Bench: Thermo Nicolet Nexus 670 Spectrometer
Resolution: 4cm-1

**IR SPECTRUM OF COMPOUND 36**

Detector: DTGS KBr
Beamsplitter: KBr
Source: IR

Analyst Name:
HRMS SPECTRUM OF COMPOUND 36
$^1$H NMR SPECTRUM OF COMPOUND 37
$^1$H NMR SPECTRUM OF COMPOUND 37
H NMR SPECTRUM OF COMPOUND 38
$^{13}$C NMR SPECTRUM OF COMPOUND 38
Sample: JSY-DDQ [NEAT]
Collection time: Tue Dec 06 12:33:04 2005 (GMT+05:30)
Bench: Thermo Nicolet Nexus 670 Spectrometer
Resolution: 4cm⁻¹

IR SPECTRUM OF COMPOUND 38
Detector: DTGS KBr
Beamsplitter: KBr
Source: IR
Analyst Name: