CHAPTER-2

Asymmetric Total Synthesis of Naturally Occurring 10-Membered Lactones

Section A:– Enantioselective Total Synthesis of Decarestrictine J

Section B:– First Asymmetric Total Synthesis of Aspinolide A
2.1 Section A

ENANTIOSELECTIVE TOTAL SYNTHESIS OF DECARESTRICTINE J

2.1.1. Introduction

Decanolides have attracted special attention over the last years\textsuperscript{1,2,3} and an important class of compounds is the decarestrictine family. The decarestrictines are secondary metabolites that were isolated from various Penicillium strains and identified as bioactive compounds by chemical screening.\textsuperscript{4,5,6} Among them, several members of the decarestrictine family of natural products have been shown to inhibit the biosynthesis of cholesterol.\textsuperscript{4,6}

It is worthy of note that maintenance of cholesterol blood level is of considerable interest for the control of coronary diseases, which are responsible for about 40\% of morbidity in developed countries. Efficient drugs are now in the market and most of these compounds, known as statines or mevinic acids, are more or less related to a family of lactonic compounds derived from the lead compounds pravastatin 1 and mevinolin 2 (Figure 1).\textsuperscript{7} The structural difference between decarestrictines and these well-known cholesterol inhibitors suggests another mode of action to be operative. In addition, decarestrictines exhibit no other effects such as antibacterial or antifungal activities. Taking together their strong and selective biological profile, decarestrictines are attractive compounds for developing a new class of cholesterol-lowering drugs.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure1.png}
\caption{Commercial drugs used for lowering cholesterol level in the blood.}
\end{figure}
The absolute stereochemistry of decarestrictine J itself has not been reported. However, because it coexisted with decarestrictine B, whose absolute configuration had been determined by an X-ray analysis, Yamada and co-workers\textsuperscript{8} suggested (7R, 9R)-stereochemistry for natural (-)-decarestrictine J.

![Chemical structures of decarestrictine J, B, G, and C](image)

**Figure 2:** Examples of 10-membered lactones

### 2.1.2. Review of Literature: Decarestrictine J

Only one total synthesis of the proposed structure of (-)-decarestrictine J (3a) was reported by Yamada *et al.* when we completed our total synthesis. In the literature report Sharpless asymmetric epoxidation and samarium(II) iodide-promoted Reformatsky reaction were employed as the key steps.\textsuperscript{8}

**Yamada *et al.* (1995)\textsuperscript{8}**

Yamada and co-workers synthesized (-)-decarestrictine J (3a) by utilizing the readily available starting material (R)-propylene oxide and tetrahydropyranyl propargyl ether 4. Thus as shown in scheme 1, the base-promoted ring opening of propylene oxide with 4 afforded 5. Compound 5 was transformed to trans-allylic alcohol 8 by selective triple bond reduction with LAH. The (–)-epoxy alcohol 9, which was obtained by the Sharpless asymmetric epoxidation of trans-allylic alcohol 8, was converted to bromoacetoxy aldehyde 18 through a nine-step sequence. The samarium (II) iodide-promoted intramolecular Reformatsky reaction of 18 and subsequent oxidation afforded keto lactone 19 which, on treatment with trimethylsilyl bromide, provided (–)-decarestrictine J (3a).
Scheme 1: Reagents and conditions: (a) LiNH₂, liq. NH₃, (R)-propylene oxide, 60%; (b) BnBr, NaH, TBAI; (c) TsOH, MeOH; (d) LAH, THF, 88%; (e) (+)-DET, Ti(OiPr)₄, TBHP, MS-4Å; (f) Dess-Martin periodinane; (g) (EtO)₂P(O)CH₂COOEt, NaH, THF; (h) DIBAL, CH₂Cl₂, 70%; (i) TBSCI, Et₃N, DMAP, CH₂Cl₂; (j) MOMCl, DIPEA, CH₂Cl₂; (k) H₂/Pd-C, EtOH; (l) BrCH₂C(O)Br, Me₂NPh, Et₂O; (m) HF, CH₃CN; (n) PCC, CH₂Cl₂; (o) SmI₂, THF, 79%; (p) TMSBr, CH₂Cl₂.
2.1.3 PRESENT WORK

Objective

As a part of our research programme aimed at developing enantioselective synthesis of biologically active natural products based on hydrolytic kinetic resolution (HKR), we considered devising a simple and concise route to decarestrictine J. Herein we describe our successful endeavours towards the total synthesis of 3a employing HKR, Yamaguchi esterification and ring-closing metathesis (RCM) as the key steps.

The HKR method involves the readily accessible cobalt based chiral salen complex as catalyst and water to resolve a racemic epoxide into an enantiomerically enriched epoxide and diol, which serve as useful precursor in the synthesis of various compounds of biological importance.

Our retrosynthetic analysis for the synthesis of decarestrictine J 3a is based on convergent approach as outlined in Scheme 2. We envisioned that the ring-closing could be affected by ring-closing metathesis of diene 21. Diene 21 could be prepared by intermolecular Yamaguchi esterification of the alcohol 22 and acid 23. Alcohol 22 could be obtained from rac-propylene epoxide 26 via iterative HKR, while acid fragment 23 could be prepared from 1,3-propane diol (25).

\[ \text{Scheme 2: Retrosynthetic analysis of decarestrictine J} \]
2.1.4. Results and Discussion

Synthesis of alcohol fragment 22

As shown in Scheme 3, synthesis of alcohol fragment 22 started with a Jacobsen’s hydrolytic kinetic resolution of rac-epoxide 26 using (R,R)-salen-Co-(OAc) catalyst to give epoxide (R)-26 as a single isomer which was easily isolated from diol 27 by distillation.\textsuperscript{10b}

\[ \text{Scheme 3: Synthesis of fragment 22} \]

Epoxide (R)-26 was treated with vinylmagnesium bromide in the presence of cuprous iodide to give homoallylic alcohol 28 in 89\% yield.\textsuperscript{9e} The IR spectrum of 28 gave broad hydroxyl absorption at 3400 cm\textsuperscript{-1}. The \textsuperscript{1}H NMR spectrum of 28 gave olefin peaks at 5.85-5.77 (multiplet, one proton), 5.12 (doublet, one proton), 5.09 (doublet, one proton). We then further proceeded to explore the stereoselective outcome of the epoxidation reaction with hydroxyl group protection. Towards this end, the hydroxyl group of homoallylic alcohol 28 was first protected as the TBDMS ether, followed by...
epoxidation with \textit{m}-CPBA to afford epoxide 30. The epoxide thus obtained was found to be a mixture of two diastereomers (\textit{anti:syn}/3:1). The $^1$H NMR spectrum of 30 showed epoxide peaks at $\delta$ 3.13-3.01 (multiplet, one proton), 2.81-2.69 (multiplet, one proton), 2.52-2.43 (multiplet, one proton) in $^1$H NMR spectrum. In order to improve the diastereoselectivity, we attempted at the hydrolytic kinetic resolution method (HKR) as depicted in Scheme 3. Thus, the HKR was performed on epoxide 30 with (S,S)-salen-Co-(OAc) complex (0.5 mol %) and water (0.55 eq) in THF (0.55 eq) to afford the diastereomerically pure epoxide 24 in 70% yield (>95% ee) and diol 31 in 22% yield. As the HKR method provided the desired epoxide 24 along with unwanted diol 31, we thought it would be appropriate to convert diol 31 into the required epoxide 24 via internal nucleophilic substitution of a secondary mesylate.\textsuperscript{14} Accordingly chemoselective pivalation of diol 31 with pivaloyl chloride followed by mesylation of the secondary hydroxyl and treatment of the crude mesylate with K$_2$CO$_3$ in methanol led to deprotection of the pivalate ester. Concomitant ring closure via intramolecular S$_2$N$_2$ displacement of the mesylate furnished the epoxide 24 in 61% overall yield. Epoxide 24 on reaction with dimethylsulfonium methyldide\textsuperscript{15} afforded one-carbon homologated allylic alcohol 32 in 70% yield. The IR spectrum of 32 gave broad hydroxyl absorption at 3430 cm$^{-1}$. The $^1$H NMR spectrum of 32 gave olefin peaks at $\delta$ 5.83-5.67 (multiplet, one proton) and 5.18-5.01 (multiplet, two protons). Alcohol 32 was protected as its MEM ether using MEMCl, DIPEA in anhydrous CH$_2$Cl$_2$ at ambient temperature followed by TBDMS removal to furnish the alcohol fragment 22 in 75% yield from both the steps. The IR spectra of 22 showed hydroxyl absorption at 3462 cm$^{-1}$. The $^1$H NMR spectra of 22 showed multiplet resonating at $\delta$ 4.81-4.73 (OCH$_2$O), $\delta$ 3.39 (OCH$_3$), and a multiplet at 3.62-3.53 (OCH$_2$CH$_2$O) corresponding with MEM group (Scheme 3). It may be noted that the alcohol fragment 22 could be synthesized in eight steps employing iterative HKR method, while our previous method involving Sharpless asymmetric dihydroxylation required three additional steps to prepare the same alcohol fragment.\textsuperscript{9h}

\textbf{Synthesis of acid fragment 23}

As shown in Scheme 4, synthesis of acid fragment 23 started from 1,3-propanediol 25. Selective monoprotection of hydroxy group with \textit{p}-methoxybenzyl bromide (PMBBr) in the presence of NaH afforded compound 33 in 89% yield. The $^1$H NMR
spectrum gave benzylic protons at $\delta$ 4.47 (singlet, two protons) and aromatic protons at $\delta$ 7.29-7.24 (multiplet) and 6.92-6.88 (multiplet). The IR spectrum gave hydroxyl absorption at 3410 cm$^{-1}$. The compound 33 was subjected to Swern oxidation$^{16}$ followed by reaction of the resulting aldehyde with allylmagnesium bromide to furnish the homoallylic alcohol 34 in 80% yield. The appearance of terminal olefin at $\delta$ 5.96-5.75 and 5.18-5.07 in $^1$H NMR and broad hydroxyl absorption band at 3386 cm$^{-1}$ in IR spectrum confirmed the product.

![Scheme 4: Synthesis of fragment 23]

Protection of the hydroxy group of 34 as its TBDMS ether followed by removal of the PMB group$^{17}$ by DDQ resulted in the primary alcohol 36 with 94% yield. The IR spectra of 36 showed hydroxyl absorption at 3460 cm$^{-1}$. In the $^1$H NMR spectra, the peaks owing to PMB group disappeared. The alcohol 36 was oxidised to the aldehyde using 2-iodoxybenzoic acid (IBX) followed by subsequent oxidation using NaClO$_2$ to give the required acid fragment 23 in 80% yield. The IR spectra of 23 showed hydroxyl absorption at 3310 cm$^{-1}$ and acid carbonyl at 1714 cm$^{-1}$. The $^1$H NMR and $^{13}$C NMR spectra of 23 were compatible with the assigned structure.

**Coupling of Acid fragment 23 and Alcohol fragment 22 and completion of the Synthesis of Decarestrictine J**

With substantial amount of both the fragments in hand the coupling of alcohol 22 and acid 23 was achieved by using the intermolecular Yamaguchi esterification
protocol to afford the diene ester 21 in 89% yield. The IR spectra of 21 showed ester carbonyl at 1735 cm$^{-1}$. In $^{13}$C NMR, peak owing to carbonyl carbon was present at $\delta$ 171.4. Ring-closing metathesis of 21 under various conditions using Grubbs’ 1st and 2nd generation catalysts failed to provide the required ten-membered lactone 37. In order to circumvent the problem, we thought it appropriate to first remove the TBDMS group and then use the ring-closing metathesis for macrocyclization.

Scheme 5: Coupling of acid fragment 23 and alcohol fragment 22

Thus the TBDMS group of diene 21 was removed to give the alcohol 38 which on ring-closing metathesis by using Grubbs 1st generation catalyst furnished the cyclized product 39 as a mixture of E/Z isomers in 82% yield. The IR spectrum of 39 showed carbonyl group of lactone at 1720 cm$^{-1}$. The appearance of internal olefin at $\delta$ 5.73-5.54 in $^1$H NMR confirmed the product. Compound 38 was subjected to hydrogenation using 10% Pd/C to give 40 in 90% yield. In the $^1$H NMR spectrum of 40 peak owing to olefin was absent. Compound 40 was oxidized using Dess-Martin
periodinane (DMP) to afford keto compound 41 in 80% yield. The IR spectra of 41 showed the absence of hydroxyl absorption at 3459 cm\(^{-1}\). In \(^{13}\)C NMR, peak owing to carbonyl carbon was present at \(\delta\) 202.3. Finally, removal of the MEM group using TiCl\(_4\) afforded the target compound 3a in 78% yield. \([\alpha]_{D}^{25} = -152.4\ (c\ 0.1,\ MeOH)\) \([\text{lit}^{8}\ [\alpha]_{D}^{23} = -154.0\ (c\ 0.1,\ MeOH)]\). The physical and spectroscopic data of 3a were in full agreement with the literature data.\(^{8}\)

### 2.1.5. Conclusion

In conclusion, a convergent and efficient total synthesis of decarestrictine J, with high enantioselectivities has been accomplished in which stereocentres were generated by means of iterative Jacobsen’s hydrolytic kinetic resolution and cyclization was achieved by ring closing metathesis. This approach could be used for the synthesis of other members of decarestrictine family for structure–activity relationship. Currently work is in progress in this direction.

### 2.1.6. Experimental Section

**General information:**

All reactions were carried out under argon or nitrogen in oven-dried glassware using standard gas-light syringes, cannulas and septa. Solvents and reagents were purified and dried by standard methods prior to use. Optical rotations were measured at room temperature. IR spectra were recorded on an FT-IR instrument. \(^1\)H NMR spectra were recorded on 200 MHz, 300 MHz and 500 MHz and are reported in parts per million (\(\delta\)) downfield relative to CDCl\(_3\) as internal standard and \(^{13}\)C NMR spectra were recorded at 50 MHz, 75 MHz and 125 MHz and assigned in parts per million (\(\delta\)) relative to CDCl\(_3\). Column chromatography was performed on silica gel (100-200 and 230-400 mesh) using a mixture of petroleum ether and ethyl acetate as the eluent. Enantiomeric excess was determined using chiral HPLC.

\((R)\)-Propylene oxide \((R-26)\).
The racemic propylene oxide 26 was resolved to chiral epoxide \( R-26 \) in high enantiomeric excess (>99% ee) by the HKR method following a literature procedure.\(^{10b}\)

\([\alpha]_D^{25} \): +11.5 (neat), lit.\(^{10b}\) [\( \alpha \)]\(_D^{25} \): −11.6 (neat) (for (S)-propylene oxide)

\((R)\)-Pent-4-en-2-ol (28)

A round bottomed flask was charged with copper (I) iodide (1.64 g, 8.6 mmol), gently heated under vacuum, and slowly cooled with a flow of argon, and dry THF (20 mL) was added. This suspension was cooled to −20 °C and vigorously stirred, and vinylmagnesium bromide (1M in THF, 172 mL, 172.4 mmol) was injected to it. A solution of propylene oxide \((R)\)-90 (5 g, 86.09 mmol) in THF (10 mL) was added slowly to the above reagent, and the mixture was stirred at −20 °C for 12 h. The reaction mixture was quenched with a saturated aqueous solution of \( \text{NH}_4\text{Cl} \). The organic layer was washed with brine, dried (\( \text{Na}_2\text{SO}_4 \)) and concentrated to afford the crude homoallylic alcohol which on distillation provided alcohol 28 (6.6 g, 89%) as a colorless liquid (bp 115 °C)

Yield: 6.6 g, 89%

B.P.: 115 °C, lit.\(^9\) 115 °C

Mol. Formula: \( \text{C}_5\text{H}_{10}\text{O} \)

\([\alpha]_D^{25} \): −10.86 (c 3.2 in \( \text{Et}_2\text{O} \)).

IR (\( \text{CHCl}_3, \text{cm}^{-1} \)): \( \nu_{\max} \) 3400, 3078, 2931, 2975, 1562, 1457, 1432, 1243, 1071, 914.

\(^1\text{H NMR} \) (500 MHz, \( \text{CDCl}_3 \)): \( \delta \) 5.85-5.77 (m, 1H), 5.12 (d, \( J = 6.6 \) Hz, 1H), 5.09 (d, \( J = 2.4 \) Hz, 1H), 3.86-3.80 (m, 1H), 2.38-2.22 (m, 2H), 1.82 (s, 1H), 1.18 (d, \( J = 6.1 \), 3H).

\(^{13}\text{C NMR} \) (50 MHz, \( \text{CDCl}_3 \)): \( \delta \) 134.6, 116.6, 66.5, 43.2, 22.1.

LC–MS: \( m/z =109 \) [M + Na]⁺.
**Chapter 2: Section A**

**tert-Butyldimethyl(((2R)-1-(oxiran-2-yl)propan-2-yl)oxy)silane (30)**

To a stirred solution of alcohol 28 (3.0 g, 34.83 mmol) in CH₂Cl₂ (25 mL), imidazole (3.57, 52.24 mmol) was added. To this solution tert-butyldichlorodimethylsilane (5.77 g, 38.31 mmol) was added at 0 °C and reaction was stirred at room temperature for 4 h. The reaction mixture was quenched with a saturated aqueous solution of NH₄Cl and extracted with CH₂Cl₂ (3 X 50 mL). The extract was washed with brine, dried (Na₂SO₄) and concentrated. Silica gel column chromatography of the crude product using pet ether/EtOAc (49:1) as eluent provided 29.

**Yield:** 6.56 g, 94%.

To a stirred solution of olefin 29 (6 g, 30.0 mmol) in CH₂Cl₂ (50 mL) at 0 °C was added m-CPBA (50%) (12.42 g, 36.0 mmol). The reaction mixture was stirred at room temperature for 2 h and quenched by saturated NaHCO₃ solution, extracted with CH₂Cl₂, washed with sat. NaHCO₃ and brine, dried (Na₂SO₄), concentrated and purified by silica gel column chromatography using pet ether/EtOAc (9:1) as eluent to yield the epoxide 30 as a colorless liquid in diastereomeric mixture (3:1).

**Yield:** 5.83 g, 90%.

**Mol. Formula:** C₁₁H₂₄O₂Si

**tert-Butyldimethyl(((R)-1-((S)-oxiran-2-yl)propan-2-yl)oxy)silane (24)**

A solution of epoxide 30 (5 g, 23.1 mmol) and (R,R)-Salen-Co(III)-OAc (0.076 g, 0.11 mmol) in THF (0.23 mL) was stirred at 0 °C for 5 min, and then distilled water (230 µL, 12.6 mmol) was added. After stirring for 14 h, it was concentrated and purified by silica gel column chromatography using pet ether/EtOAc (9:1) to afford 24 (3.5g, 70%) as a yellow color liquid. Continued chromatography with pet ether/EtOAc (3:2) provided the diol 31 as a brown color liquid as a single diastereomer.
Yield: 3.5g, 70%

Mol. Formula: C_{11}H_{24}O_2Si

[α]_D^{25}: −11.4 (c 0.67, CHCl_3).

IR (CHCl_3, cm⁻¹): ν_max 3018, 2958, 2930, 1858, 1472, 1463, 1377, 1256, 1216, 1101, 1005, 938, 878, 760.

¹H NMR (500 MHz, CDCl_3): δ 3.96-3.83 (m, 1H), 3.13-3.01 (m, 1H), 2.81-2.69 (m, 1H), 2.52-2.43 (m, 1H), 1.95-1.76 (m, 1H), 1.69-1.60 (m, 1H), 1.18 (d, J = 6.53 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 6H).

¹³C NMR (50 MHz, CDCl_3): δ 70.5, 50.1, 47.8, 47.0, 25.6, 19.6, 17.9, −4.4, −4.7.

LC–MS: m/z =239 [M + Na]^+.

Conversion of 31 into 24.

Yield: 1.19g, 22%

Mol. Formula: C_{11}H_{26}O_3Si

[α]_D^{25}: +32.6 (c 1.04, CHCl_3).

IR (CHCl_3, cm⁻¹): ν_max 3430, 3018, 2957, 2931, 2859, 1652, 1471, 1379, 1256, 1212, 1101, 1036, 971, 869, 758.

¹H NMR (200 MHz, CDCl_3): δ 4.5-4.41 (m, 1H), 3.99-3.96 (m, 1H), 3.56-3.47 (m, 2H), 1.73-1.54 (m, 4H), 1.08 (d, J = 6.57 Hz, 3H), 0.82-0.81 (m, 9H), 0.00-0.01 (m, 6H).

¹³C NMR (50 MHz, CDCl_3): δ 72.4, 70.5, 70.4, 47.0, 25.8, 17.9, −4.4, −4.7.

LC–MS: m/z =257 [M + Na]^+.

Conversion of 31 into 24.
Diol 31 (1 g, 4.25 mmol) was dissolved under argon in dry CH₂Cl₂ (10 mL) and treated with pivaloyl chloride (0.56 g, 4.7 mmol), Et₃N (0.51 g, 5.1 mmol) and catalytic amount of DMAP. The mixture was stirred at room temperature for 2 h, then worked up (extraction with CH₂Cl₂). Removal of volatiles under reduced pressure gave an oily crude mono pivalate. The crude compound was then dissolved under argon in dry CH₂Cl₂ (15 mL) and treated with MsCl (0.49 g, 4.25 mmol), Et₃N (0.516 g, 5.1 mmol) and catalytic amount of DMAP. The reaction mixture was stirred at room temperature for 1 h and then quenched with water. The water layer was extracted with CH₂Cl₂ (3 x 25 mL). The combined organic layer was washed with brine, dried (Na₂SO₄) and concentrated to give a crude product which was dissolved in MeOH (10 mL) and treated with K₂CO₃ (0.585 g, 4.25 mmol). The reaction mixture was then stirred overnight at room temperature and filtered through Celite. Removal of volatile under reduced pressure and column chromatography on silica gel using pet ether/EtOAc (9:1) as eluent gave the epoxide 24 as a yellow color liquid.

**Yield:** 0.565 g, overall yield 61%

[α]_D^{25}: −11.4 (c 0.67, CHCl₃).

**Mol. Formula:** C₁₂H₂₆O₂Si

(3S, 5R)-5-((tert-Butyldimethylsilyl)oxy)hex-1-en-3-ol (32)

To a suspension of trimethylsulfonium iodide (5.76 g, 28.2 mmol) in dry THF (10 mL) at −20 °C was added n-BuLi (14.3 mL, 2.1 M solution in hexane, 30.0 mmol) dropwise over 20 min and stirred for 30 min. Then the epoxide 24 (1 g, 4.6 mmol) in dry THF (10 mL) was added to the above reaction mixture and stirred for 2 h. After consumption of the starting material the reaction mixture was quenched with H₂O (15 mL) and extracted with EtOAc (4 × 15 mL). The combined extracts were washed with brine, dried over Na₂SO₄ and concentrated. The column chromatography of crude product using pet ether/ethyl acetate (85:15) gave 32.

**Yield:** 0.74 g, 70%

**Mol. Formula:** C₁₂H₂₆O₂Si
[α]D\textsuperscript{25} \textasciitilde -29.18 (c 1.04, CHCl₃).

**IR** (CHCl₃, cm\textsuperscript{-1}): \( \nu_{\text{max}} \) 3430, 3018, 2957, 2859, 1652, 1471, 1379, 1256, 1212, 1101, 1036, 971, 869, 758.

\(^1\text{H NMR}\) (200 MHz, CDCl₃): \( \delta \) 5.83-5.67 (m, 1H), 5.18-5.01 (m, 2H), 4.54-4.41 (m, 1H), 4.27-4.18 (m, 1H), 1.74-1.59 (m, 2H), 1.08 (d, \( J = 6.44 \) Hz, 3H), 0.82 (s, 9H), \(-0.01\) (s, 6H).

\(^{13}\text{C NMR}\) (50 MHz, CDCl₃): \( \delta \) 140.8, 114.2, 71.3, 70.6, 40.1, 25.8, 18.9, \(-4.6\), \(-4.7\).

**LC–MS**: \( m/z =253 \ [M + Na]^+ \).

\((2R, 4S)-4-(2\text{-Methoxyethoxy})\text{methoxy})\text{hex-5-en-2-ol (22)}.

A mixture of compound 32 (0.5 g, 2.17 mmol), diisopropylethylamine (0.84 g, 1.13 mL, 6.5 mmol), MEM-Cl (0.32 g, 0.30 mL, 2.60 mmol) in CH₂Cl₂ (20 mL) was stirred at room temperature for 8 h. The reaction mixture was quenched with water and extracted with CH₂Cl₂, washed with water, brine, dried (Na₂SO₄) and evaporated to afford crude product, which was used as such for the next step without purification.

To a solution of olefin (0.69 g, 2.17 mmol) in THF (10 mL) was added TBAF (3.25 mL, 3.25 mmol, 1.0 M solution in THF) at room temperature. The reaction mixture was stirred for 6 h and then diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried (Na₂SO₄) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (7:3) as eluent gave alcohol 22 as a colorless liquid.

**Yield**: 0.33 g, 75%

**Mol. Formula**: C\(_{10}\)H\(_{20}\)O\(_4\)

[α]D\textsuperscript{25} \textasciitilde -95.88 (c 1.22, CHCl₃).

**IR** (CHCl₃, cm\textsuperscript{-1}): \( \nu_{\text{max}} \) 3462, 3016, 2968, 2893, 2448, 1645, 1456, 1422, 1367, 1241, 1216, 1133, 1098, 993.
\[ ^{1}H\text{ NMR}\ (200\text{ MHz, CDCl}_{3})\text{: }\delta \text{ }5.79\text{-}5.61\text{ }\text{(m, 1H)}, \text{ }5.27\text{-}5.14\text{ }\text{(m, 2H)}, \text{ }4.81\text{-}4.73\text{ }\text{(m, 2H)}, \text{ }4.11\text{-}4.01\text{ }\text{(m, 1H)}, \text{ }3.73\text{-}3.68\text{ }\text{(m, 1H)}, \text{ }3.62\text{-}3.53\text{ }\text{(m, 4H)}, \text{ }3.39\text{ }\text{(s, 3H)}. \text{ }2.36\text{ }\text{(brs, 1H)}, \text{ }1.64\text{-}1.55\text{ }\text{(m, 2H)}, \text{ }1.17\text{ }\text{(d, }J=6.2\text{ Hz, 3H)}.\]

\[ \text{LC–MS: } m/z =227\ [M+Na]^+.\]

3-(4-Methoxybenzyloxy)propan-1-ol (33):

To a solution of 1,3-propanediol 25 (5.0 g, 65.71 mmol) in dry DMF (200 mL) was added sodium hydride (60%, 2.90 g, 72.28 mmol) at 0 °C. The reaction mixture was then stirred at room temperature for 30 min after which it was again cooled to 0 °C. To this was added slowly \textit{p}-methoxybenzyl chloride (11.32 g, 10.75 mL, 72.28 mmol) and \textit{tetr}a \textit{n}-butylammonium iodide (2.6 g, 6.57 mmol) with further stirring for 4 h at the same temperature. The reaction mixture was quenched with addition of cold water at 0 °C. The two phases were separated and the aqueous phase was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with water (3 x 100 mL), brine, dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated. The residual oil was purified by silica gel column chromatography using petroleum ether/EtOAc (6:4) as eluent to furnish the mono-PMB protected alcohol 33 as colorless oil.

\textbf{Yield:} 11.87 g, 89%.

\textbf{Mol. Formula:} C\textsubscript{11}H\textsubscript{16}O\textsubscript{3}

\textbf{IR (CHCl\textsubscript{3}, cm\textsuperscript{-1})}: \nu\text{max} 3410, 2940, 2863, 1612, 1513, 1249, 1175, 1098.

\[ ^{1}H\text{ NMR (500 MHz, CDCl}_{3})\text{: }\delta \text{ }7.29\text{-}7.24\text{ }\text{(m, 2H)}, \text{ }6.92\text{-}6.88\text{ }\text{(m, 2H)}, \text{ }4.47\text{ }\text{(s, 2H)}, \text{ }3.82\text{-}3.72\text{ }\text{(m, 5H)}, \text{ }3.67\text{-}3.62\text{ }\text{(m, 2H)}, \text{ }2.57\text{ }\text{(brs, 1H)}, \text{ }1.92\text{-}1.81\text{ }\text{(m, 2H)}.\]

\[ ^{13}C\text{ NMR (125 MHz, CDCl}_{3})\text{: }\delta \text{ }159.1, \text{ }130.0, \text{ }129.2, \text{ }113.7, \text{ }72.7, \text{ }68.7, \text{ }61.4, \text{ }55.1, \text{ }31.9.\]

\[ \text{LC–MS: } m/z =219\ [M+Na]^+.\]

1-((4-Methoxybenzyl)oxy)hex-5-en-3-ol (34):
To a solution of oxalyl chloride (3.33 mL, 38.21 mmol) in dry CH₂Cl₂ (50 mL) at –78 °C was added dropwise dry DMSO (5.42 mL, 76.43 mmol) in CH₂Cl₂ (20 mL). After 30 min, alcohol 33 (5.0 g, 25.47 mmol) in CH₂Cl₂ (20 mL) was added over 10 min giving copious white precipitate. After stirring for 1 h at –78 °C, the reaction mixture was brought to –60 °C and Et₃N (15.62 mL, 112.24 mmol) was added slowly and stirred for 30 min allowing the reaction mixture to warm to room temperature. The reaction mixture was then diluted with water (100 mL) and CH₂Cl₂. The organic layer was separated and washed with water and brine, dried over Na₂SO₄ and passed through short pad of celite. The filtrate was concentrated to give the aldehyde as pale yellow oil, which was used as such for the next step without purification.

Allylmagnesium bromide (commercial 1 M solution in Et₂O, 38.24 mL, 38.24 mmol) was added dropwise under N₂ via syringe to a solution of the crude aldehyde (4.95 g, 25.00 mmol) in dry Et₂O (50 mL) at 0 °C and stirred for 30 min allowing the reaction mixture to warm to room temperature. The reaction mixture was quenched with a saturated aqueous solution of NH₄Cl and extracted with Et₂O. The extract was washed with brine, dried over Na₂SO₄, and concentrated. Purification of crude product by silica gel column chromatography using petroleum ether/EtOAc (70:30) as eluent afforded 34 as a colorless liquid.

Yield: 4.8 g, 80%.

Mol. Formula: C₁₄H₂₀O₃

IR (CHCl₃, cm⁻¹): ν_max 3386, 1640, 1603, 1493, 1453, 1243.

¹H NMR (200 MHz, CDCl₃): δ 7.29-7.24 (ms, 2H), 6.93-6.87 (m, 2H), 5.96-5.75 (m, 1H), 5.18-5.07 (m, 2H), 4.47 (s, 2H), 3.94-3.85 (m, 1H), 3.82 (s, 3H), 3.77-3.58 (m,2H), 2.97 (brs, 1H), 2.29-2.23 (m, 2H), 1.81-1.72 (m, 2H).

¹³C NMR (50 MHz, CDCl₃): δ 159.2, 134.8, 129.9, 129.2, 117.4, 113.7, 77.0, 72.8, 70.3, 68.5, 55.2, 41.8, 35.7

LC–MS: m/z =259 (M+Na)⁺.
3-((tert-Butyldimethylsilyl)oxy)hex-5-en-1-ol (36)

To a stirred solution of alcohol 34 (2 g, 8.46 mmol) in CH₂Cl₂ was added imidazole (0.86 g, 12.7 mmol). To this solution tert-butyl dimethylchlorosilane (1.53 g, 10.00 mmol) was added at 0 °C and the reaction was stirred at rt for 5 h. The reaction mixture was quenched with a saturated aqueous solution of NH₄Cl and extracted with CH₂Cl₂. The extract was washed with brine, dried over Na₂SO₄, and concentrated. Purification of crude product by silica gel column chromatography using petroleum ether/EtOAc (95:5) as eluent afforded 35 as a colorless liquid.

Yield: 2.67 g, 90%.

Mol. Formula: C₂₀H₃₄O₃Si

To a stirring solution of PMB ether 35 (2 g, 5.68 mmol) in CH₂Cl₂/H₂O (30:2) was added DDQ (1.55 g, 6.84 mmol). The resulting mixture was stirred for 30 min at 0 °C. The mixture was poured into saturated aqueous NaHCO₃ and further diluted with CH₂Cl₂. The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (2 x 15 mL). The combined organic layers were dried (Na₂SO₄), filtered, and concentrated. The solvents were removed under reduced pressure to give the crude product mixture as yellow oil. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (95:5) as eluent gave 36 as a colorless liquid.

Yield: 1.23 g, 94%.

Mol. Formula: C₁₂H₂₆O₂Si

IR (CHCl₃, cm⁻¹): ν_max 3460, 2959, 2857, 1640, 1448, 1376, 1255, 1078.

¹H NMR (400 MHz, CDCl₃): δ 5.30-5.09 (m, 1H), 4.54-4.45 (m, 2H), 3.44-3.37 (m, 1H), 3.27-3.09 (m, 2H), 2.23 (brs, 1H), 1.76-1.70 (m, 2H), 1.32-0.98 (m, 2H), 0.34-0.31 (m, 9H), –0.47- –0.53 (m, 6H)

¹³C NMR (100 MHz, CDCl₃): δ 134.5, 114.2, 70.8, 59.8, 41.6, 37.8, 30.6, 25.7, 25.6, –4.5, –4.9.
LC–MS: m/z =253 (M+Na)^+. 

3-((tert-Butyldimethylsilyl)oxy)hex-5-enoic acid (23)

To a solution of alcohol 36 (1.0 g, 4.34 mmol) in EtOAc (10 mL) was added IBX (3.64 g, 13.01 mmol) in one portion and the reaction mixture was refluxed for 3 h. The reaction mixture was filtered through a pad of celite and filtrate was concentrated to give the crude aldehyde, which was used for the next step without purification.

A solution of 79% NaClO$_2$ (0.725 g, 6.5 mmol) in 2.5 mL of water was added dropwise to a stirred solution of above crude aldehyde (0.99 g, 4.33 mmol) in 2.5 mL of DMSO and NaH$_2$PO$_4$ (0.584 g, 4.9 mmol) in 2.5 mL of water in 5 min at room temperature. The mixture was left overnight at room temperature, and then 5% aqueous solution of NaHCO$_3$ was added. The aqueous phase was extracted 3 times with CH$_2$Cl$_2$ and washed with brine, dried (Na$_2$SO$_4$), and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (9:1) as eluent gave the acid 23 as a syrupy liquid.

**Yield:** 0.84 g, 80%.

**Mol. Formula:** C$_{12}$H$_{24}$O$_3$Si

**IR** (CHCl$_3$, cm$^{-1}$): $\nu_{\text{max}}$ 3310, 3078, 2856, 1714, 1642, 1515, 1361, 1091, 939, 837, 776.

$^1$H NMR (CDCl$_3$, 200 MHz): $\delta$ 5.82-5.73 (m, 1H), 5.09-5.06 (m, 2H), 4.20-4.16 (m, 1H), 2.53-2.43 (m, 2H), 2.30-2.28 (m, 2H), 0.87 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H);

$^{13}$C NMR (CDCl$_3$, 50 MHz): $\delta$ 177.2, 133.7, 118.1, 68.9, 41.9, 41.7, 25.7, 17.9, -4.5, -4.9

LC–MS: m/z =267 (M+Na)^+. 

(2R,4S)-4-((2-Methoxyethoxy)methoxy)hex-5-en-2-yl 3-((tert-butyldimethylsilyl)oxy)hex-5-enoate (21)
To a solution of acid 23 (500 mg, 2.04 mmol) in THF, was added triethyl amine (0.4 mL, 3.07 mmol) and 2, 4, 6-trichlorobenzoyl chloride (0.48 mL, 3.07 mmol) under nitrogen atmosphere at 0 ºC and the reaction mixture was allowed to stir under this condition for 1 h. To this, alcohol 22 (0.33 g, 1.6 mmol) in THF (5 mL) and catalytic amount of 4-dimethyl aminopyridine (DMAP) were added successively at 0 ºC. Stirring was continued for additional 20 h at rt. The reaction mixture was quenched with water and extracted with ethyl acetate (3 x 50 mL). The combined organic layers were thoroughly washed with saturated sodium bicarbonate solution, brine, dried (Na₂SO₄), and concentrated to afford the crude product which was purified by silica gel column chromatography using petroleum ether/EtOAc (95:5) as eluent to afford the ester 21 as a colorless syrupy liquid.

**Yield:** 0.78 g, 89%

**Mol. Formula:** C₂₂H₄₂O₆Si

[α]₀⁺²⁵ = −36.17 (c 3.19, CHCl₃).

**IR** (CHCl₃, cm⁻¹): νmax 2926, 2855, 1735, 1647, 1463, 1258, 1096, 837, 759.

**¹H NMR** (CDCl₃, 200 MHz): δ 5.89-5.55 (m, 2H), 5.28-5.05 (m, 4H), 5.02-4.91 (m, 1H), 4.80-4.71 (m, 1H), 4.63-4.56 (m, 1H), 4.24- 4.00 (m, 2H), 3.83-3.67 (m, 1H), 3.65-3.58 (m, 1H), 3.55- 3.46 (m, 2H), 3.35 (s, 3H), 2.48-2.38 (m, 2H), 2.02-1.83 (m, 2H), 1.79-1.69 (m, 2H), 1.18 (d, J = 6.32 Hz, 3H), 0.84 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H).

**¹³C NMR** (CDCl₃, 50 MHz): δ 171.4, 137.6, 134.2, 127.9, 117.6, 92.7, 74.2, 71.7, 68.7, 67.8, 58.9, 42.1, 41.9, 41.8, 25.7, 20.6, 17.9, -4.6, -4.8.

**LC–MS:** m/z =453 (M+Na)⁺.

**(2R, 4S)-4-((2-Methoxyethoxy)methoxy)hex-5-en-2-yl 3-hydroxyhex-5-enoate (38)**
To a solution of ester 21 (0.6 g, 1.39 mmol) in THF (7 mL) was added TBAF (2.06 mL, 2.09 mmol, 1.0 M solution in THF) at room temperature. The reaction mixture was stirred for 6 h and then diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried (Na₂SO₄) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (80:20) as eluent gave alcohol 38 as a colorless liquid.

**Yield:** 0.33 g, 75%

**Mol. Formula:** C₁₆H₂₈O₆

[α]₀²⁵: −55.12 (c 1.25, CHCl₃).

**IR (CHCl₃, cm⁻¹):** νₘₐₓ 3462, 2930, 2868, 1740, 1647, 1455, 1304, 1110, 865, 745.

**¹H NMR** (200 MHz, CDCl₃): δ 5.94-5.57 (m, 2H), 5.27-5.08 (m, 5H), 4.77-4.73 (m, 1H), 4.63-4.59 (m, 1H), 4.17-4.02 (m, 2H), 3.84-3.71 (m, 1H), 3.63-3.49 (m, 3H), 3.37 (s, 3H), 2.50-2.41 (m, 2H), 2.33-2.24 (m, 2H), 1.82-1.73 (m, 2H), 1.24 (d, J = 6.4 Hz, 3H).

**¹³C NMR** (50 MHz, CDCl₃): δ 172.4, 137.5, 134.0, 117.8, 117.5, 92.8, 73.8, 71.7, 71.6, 68.0, 67.3, 58.9, 41.8, 41.2, 41.0, 20.4.

**LC–MS:** m/z =339 (M+Na)⁺.

(8S, 10R)-4-Hydroxy-8-((2-methoxyethoxy)methoxy)-10-methyl-3,4,5,8,9,10-hexahydro-2H-oxecin-2-one (39)

A mixture of 38 (0.15 g, 0.04 mmol) in anhydrous CH₂Cl₂ (100 mL) and Grubbs’ First generation catalyst (80 mg, 20 mol%) was refluxed for 14 h. Solvent was removed
under reduced pressure to leave highly dark brown colored residue. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (3:2) as eluent afforded compound 39 as a colorless liquid.

**Yield:** 112 mg, 82%

**Mol. Formula:** $C_{14}H_{24}O_6$

$[\alpha]_D^{25} = -42.89$ (c 0.88, CHCl$_3$).

**IR** (CHCl$_3$, cm$^{-1}$): $\nu_{\text{max}}$ 3450, 3019, 2944, 2880, 1720, 1680, 1647, 1110.

$^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 5.73-5.54 (m, 2H), 5.25-5.07 (m, 2H), 4.75-4.71 (m, 1H), 4.62-4.57 (m, 1H), 4.21-4.04 (m, 2H), 3.81-3.68 (m, 1H), 3.59-3.48 (m, 2H), 3.36 (s, 3H), 2.79 (brs, 1H), 2.52-2.38 (m, 2H), 2.30-2.15 (m, 2H), 1.78-1.65 (m, 2H), 1.22 (d, $J = 6.35$ Hz, 3H).

$^{13}$C NMR (50 MHz, CDCl$_3$): $\delta$ 172.1, 137.5, 129.2, 92.8, 73.8, 71.7, 71.6, 68.1, 67.3, 58.9, 41.8, 41.4, 39.8, 20.4.

**LC–MS:** m/z = 311 (M+Na)$^+$. 

**(8R, 10R)-4-Hydroxy-8-((2-methoxyethoxy)methoxy)-10-methyloxecan-2-one (40)**

To compound 39 (0.1 g, 0.35 mmol) in Ethanol was added Pd-C (10%) under hydrogenation condition and the reaction mixture was allowed for 2 h. On completion of reaction, the mixture was filtered through a pad of celite and concentrated in vacuo. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (3:2) as eluent afforded compound 40 as a colorless liquid.

**Yield:** 0.09 g, 90%

**Mol. Formula:** $C_{14}H_{26}O_6$

$[\alpha]_D^{25} = -32.92$ (c 0.40, CHCl$_3$).

**IR** (CHCl$_3$, cm$^{-1}$): $\nu_{\text{max}}$ 3459, 3015, 2932, 1729, 1462, 1378, 1253, 1179, 1042.
1H NMR (CDCl₃, 200 MHz): δ 5.11-5.02 (m, 1H), 4.75-4.63 (m, 2H), 3.98 (brs, 1H), 3.71-3.66 (m, 2H), 3.53-3.51 (m, 2H), 3.36 (s, 3H), 2.44-2.31 (m, 3H), 1.56-1.43 (m, 8H), 1.24 (d, J = 6.19 Hz, 3H).

13C NMR (CDCl₃, 50 MHz): δ 172.7, 94.7, 71.7, 68.4, 67.9, 67.3, 59.0, 42.1, 40.4, 36.4, 27.1, 20.6, 9.06.

LC–MS: m/z =313 (M+Na)+.

(8R, 10R)-8-((2-Methoxyethoxy)methoxy)-10-methyloexcane-2,4-dione (41)

Dess–Martin periodinane (0.11 g, 0.26 mmol) was added to a solution of compound 40 (0.07 g, 0.24 mmol) in CH₂Cl₂ (0.7 ml) at 0 °C. The reaction was stirred at rt for 30 min, before being quenched with saturated aqueous Na₂S₂O₃ and saturated aqueous NaHCO₃. The organic layer was washed with satd NaCl solution and dried over Na₂SO₄ and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (7:3) as eluent gave alcohol 41 as a colorless liquid.

Yield: 0.06 g, 80%

Mol. Formula: C₁₄H₂₄O₆

[α]D²⁵: –29.88 (c 0.25, CHCl₃).

IR (CHCl₃, cm⁻¹): νmax 3016, 2968, 2893, 1745, 1701, 1452, 1265, 1076, 970.

1H NMR (200 MHz, CDCl₃): δ 4.77-4.66 (m, 2H), 4.24-4.13 (m, 1H), 3.71-3.66 (m, 2H), 3.60-3.47 (m, 3H), 3.39-3.35 (m, 4H), 2.64-2.42 (m, 2H), 2.39-2.12 (m, 1H), 1.78-1.72 (m, 3H), 1.60 -1.50 (m, 3H), 1.27 (d, J = 6.4 Hz, 3H).

13C NMR (50 MHz, CDCl₃): δ 202.3, 166.8, 94.7, 75.2, 71.7, 69.5, 67.3, 58.9, 49.5, 42.6, 40.5, 37.1, 22.6, 20.6.

LC–MS: m/z =311 (M+Na)+.
Decarestrictine J (3a)

To a solution of 41 (0.05 g, 0.17 mmol) in anhydrous CH$_2$Cl$_2$ (1.5 mL) under nitrogen at 0 °C was added TiCl$_4$ (0.33 g, 0.19 mL, 1.73 mmol). After 30 min, excess of reagent was quenched with water, extracted with CH$_2$Cl$_2$, washed with water, dried (Na$_2$SO$_4$), evaporated. The reaction mixture was purified on silica gel by eluting with EtOAc to afford decarestrictine J 3a.

Yield: 0.027 g, 78%

M.P.: 50–55 °C, lit.$^8$ 54–55 °C

Mol. Formula: C$_{10}$H$_{16}$O$_4$

[$\alpha$]$_D^{25}$: $-152.4$ (c 0.1, MeOH), [lit$^8$ [$\alpha$]$_D^{23}$ = $-154.0$ (c 0.1, MeOH)].

IR (neat, cm$^{-1}$): $\nu_{\text{max}}$ 3430, 2912, 2850, 1745, 1701, 1452, 1265, 1076, 970

$^1$H NMR (200 MHz, CDCl$_3$): $\delta$ 5.12-5.06 (m, 1H), 3.69-3.67 (m, 1H), 3.39 (m, 2H), 2.55-2.53 (m, 1H), 2.37-2.13 (m, 1H), 2.07-1.97 (m, 1H), 1.92-1.79 (m, 2H), 1.59-1.56 (m, 3H), 1.27 (d, $J=6.19$ Hz, 3H).

[lit$^8$ $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 5.22-5.15 (m, 1H), 3.72-3.65 (m, 1H), 3.38 (d, $J=2.8$ Hz, 2H), 2.76-2.66 (m, 1H), 2.34-2.25 (m, 1H), 2.08-2.00 (m, 1H), 1.92-1.83 (m, 2H), 1.74-1.51 (m, 3H), 1.30 (d, $J=6.2$ Hz, 3H)]

LC–MS: m/z =223 (M+Na)$^+$. 
### 2.1.7. Spectra

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<th>Spectra Description</th>
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<td>$^1$H and $^{13}$C spectra of compound 31</td>
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<td>$^1$H and $^{13}$C spectra of compound 32</td>
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<td>$^1$H spectra of compound 3a</td>
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Figure 2.14:  

**OTBSOH**

32

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**OTBSOH**

32
Chapter 2: Section A

Chloroform-d

![Chemical Structure](image)

**OH**

**OMEM**

22

---

**Figure Caption:**

Diagram showing the chemical structure of a compound in chloroform-d. The spectrum appears to show various peaks at different chemical shifts, indicating the presence of different chemical elements or groups. The specific peaks and their chemical shifts are not detailed in the text.
Chapter 2: Section A

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MEMO

38

MEMO

38

Chloroform-d

O

O

OH

MEMO

38

O

O

OH

MEMO

38
Chapter 2: Section A

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Chapter 2: Section A

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Chloroform-d

MEMO

41

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Chloroform-d

MEMO

41
Chapter 2: Section A

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Chloroform-d

decaestricine J 3a

Diagram of decaestricine J 3a
2.1.8. References


2.2 Section B

FIRST ASYMMETRIC TOTAL SYNTHESIS OF ASPINOLIDE A

2.2.1. Introduction

Aspinonene (1) and aspyrone (2) are the main polyketide metabolites of *Aspergillus ochraceus* (DSM-7428).\(^1,\)\(^2\) Evaluation of their biosynthesis revealed a close relationship: A carbon-skeleton rearrangement leads to a branched pentaketide,\(^3\) and then the hypothetic aldehyde intermediate is either reduced or oxidised, yielding 1 and 2, respectively, after finishing the biosynthetic cascade. Surprisingly, the pathways could be directed towards 2 by using increased dissolved oxygen concentrations during fermentation.\(^2\) The analysis of the extracts of *Aspergillus ochraceus* grown under different culture conditions by chemical screening method\(^4,\)\(^5\) resulted in the isolation of seven new pentaketide metabolites, which are produced in varying amounts (Table 1).

**Table 1.** Yields of the pentaketide metabolites of *Aspergillus ochraceus*, resulting from altered fermentation conditions (isolated yields in mg/l, + = detectable on TLC plates)\(^a\)

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<th>Compound</th>
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<td></td>
<td></td>
<td>1bar</td>
<td>2.5bar</td>
<td>5bar</td>
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<td>Aspinonene (1)</td>
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<td>+</td>
<td>10</td>
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<td>12</td>
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<td>+</td>
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<td>7.0</td>
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<td>94</td>
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<td>Aspinolide B (4)</td>
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<td>Aspinolide C (5)</td>
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</tbody>
</table>
Chapter 2 Section 2

1. Static surface culture (1..5-1 P flask); 2. 300 ml Erlenmeyer flasks; 2a. addition of ancymidol; 3. 1 l stirring fermentor; 4. 50 l stirring fermentor; 5. 1 l airlift-loop fermentor.

The fermentation, purification and structure elucidation of these compounds have been discussed in the next section. The results are the base for a comprehensive discussion of the biosynthetic pathways of the strain and led to some further experiments to verify the assumptions.

**Fermentation and Isolation**

Fermentation of *Aspergillus ochraceus* was carried out in the optimised medium by using different culture vessels and aeration conditions (Table 1). The interesting metabolites of each fermentation were found in the culture filtrate only, which was separated from the mycelium by filtration and was successively extracted with chloroform and ethyl acetate to furnish two crude evaporation residues. Besides aspinonene (1) and aspyrone (2), the 10-membered lactones aspinolide A-C (3-5) were isolated by column chromatography. Their *R*, values and colour reactions on TLC plates with different staining reagents are given in Table 2.

**Aspinolides**

The colourless aspinolides A (3) and B (4) were produced in stirred or shaken cultures in amounts of 2-8 mg/l. They could not be detected in static cultures. Aspinolide C (5) was present in one culture only.

The molecular formula C10H16O3 of aspinolide A (3) was deduced from an HREI mass spectrum (*m/z* = 184.1099 [M⁺]). The elimination of CO₂ results in a characteristic peak at *m/z* = 140 [M⁺ - 44]. The IR spectrum displays a CO-ester absorption band at 3 = 1730 cm⁻¹. The ¹³C-NMR spectrum shows the expected 10 signals, which could be assigned to an unstrained lactone CO (δ_C = 175.5), two olefinic methine groups, two methine groups attached to oxygen, three methylene groups and a methyl group. In
the \(^1\)H-NMR spectrum (\(\text{CDCl}_3\), 500 MHz) signals of 16 protons can be seen, which could be assigned to the C atoms by \(^1\)H-\(^{13}\)C shift correlations.

**Table 2.** \(R_f\) values and colour reactions of the isolated pentaketide metabolites\(^a\)

<table>
<thead>
<tr>
<th>Compound</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>A</th>
<th>B</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.26</td>
<td>0.06</td>
<td>0.54</td>
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<td>brown</td>
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<tr>
<td>2</td>
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<td>0.24</td>
<td>0.71</td>
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<tr>
<td>3</td>
<td>0.60</td>
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<td>0.69</td>
<td>Dark/pink</td>
<td>Blue</td>
</tr>
<tr>
<td>4</td>
<td>0.46</td>
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<td>brown</td>
</tr>
<tr>
<td>5</td>
<td>0.77</td>
<td>0.64</td>
<td>0.65</td>
<td>Dark/pink</td>
<td>Blue</td>
</tr>
</tbody>
</table>

\(^a\)Solvent systems: (I) \(\text{CHCl}_3/\text{MeOH} = 9:1\); (II) pentane/ethyl acetate = 1 : 1, (III) acetic acid/1-butanol/water (upper layer) = 1 :4:5. - Staining reagents: (A) vanillin/sulfuric acid, (B) anisaldehyde/sulfuric acid.

The connectivities between the proton-bearing groups were revealed by a \(^1\)H-\(^1\)H COSY experiment. Due to three double-bond equivalents a required cyclization leads
to a lactone. Its ring size was confirmed by characterising 5-O-(2-
 bromobenzoyl)aspinolide A (3a), the 5-H signal of which appears at $\delta_H = 5.32$ and is shifted 1.34 ppm downfield compared with that of 3. Thus, aspinolide A (3) is a 10-
 membered lactone with an (E) double bond and two centres of chirality. The (R) configuration of the secondary alcohol (C-5) was assigned by applying the Helmchen method$^6$. The significant highfield shifts of the neighbouring protons in the 5-O-[(53-
 2-phenylbutyryl)- (3b) and the 5-O-[(R)-2-phenylbutyryl]aspinolide B (3c) are reported. The (R) configuration of C-9 is assumed by analogy with aspinolide B (4).
2.2.2. PRESENT WORK

Objective

As a part of our research programme aimed at developing enantioselective synthesis of biologically active natural products and having successfully completed the synthesis of decaerstrictine J we considered attempting an yet another structurally related 10-membered lactone called, aspinolide A. Herein we describe our successful endeavour towards the first total synthesis of employing HKR and ring-closing metathesis (RCM) as key steps.

The HKR method involves the readily accessible cobalt based chiral salen complex as catalyst and water to resolve a racemic epoxide into an enantiomerically enriched epoxide and diol, which serve as useful precursor in the synthesis of various compounds of biological importance.

Our retrosynthetic analysis for synthesis of aspinolide A is based on convergent approach as outlined in Scheme 1. We envisioned that the ring-closing could be effected by ring-closing metathesis of diene. Diene could be prepared by EDCI coupling of the alcohol and acid. Alcohol could be obtained from rac-propylene oxide via HKR, while acid fragment could be prepared from 1,5-pentane diol.

Scheme 1. Retrosynthetic analysis of Aspinolide A

2.2.3. Results and Discussion

Synthesis of fragment 5

The synthesis of fragment 5 is already been documented in section A of chapter 2 (page no. 37).
Synthesis of fragment 6

The synthesis of acid fragment 6 started from commercially available 1,5-pentanediol 8 as illustrated in Scheme 2. Thus selective monoprotection of 8 with p-methoxybenzyl bromide gave PMB ether 9. The $^1$H NMR spectrum gave benzylic protons at $\delta$ 4.44 (singlet, two protons) and aromatic protons at $\delta$ 7.29-7.25 (multiplet) and 6.91-6.87 (multiplet). The IR spectrum gave hydroxyl absorption at 3415 cm$^{-1}$. The compound 9 was subjected to Swern oxidation$^{11}$ followed by Corey Chaykovsky reaction$^{12}$ with dimethylsulfoxonium methylide to afford the racemic epoxide 10 in 75% yield. The epoxide peaks appeared at $\delta$ 2.89-2.84 (multiplet, one proton), 2.73-2.69 (multiplet, one proton) and 2.54-2.41 (multiplet, one proton) in $^1$H NMR spectrum. Compound 10 was subjected to Jacobsen’s hydrolytic kinetic resolution using $(R,R)$-salen-Co-OAc catalyst to give (R)-epoxide 10 in $>99\%$ ee,$^{13}$ which was easily separated from the (S)-dial 11 by column chromatography. Epoxide (R)-10 on reaction with dimethylsulfoxonium methylide$^{14}$ afforded the required allylic alcohol 12 in 75% yield. The IR spectrum of 12 gave broad hydroxyl absorption at 3386 cm$^{-1}$. The $^1$H NMR spectrum of 12 gave olefin peaks at $\delta$ 5.95-5.78 (multiplet, one protons) and 5.27-5.08 (multiplet, two proton).

Scheme 2: Synthesis of acid fragment 6.
Protection of hydroxy group of 12 as TBS ether followed by deprotection of PMB group\(^\text{15}\) by DDQ gave the primary alcohol 14 in 95% yield. The IR spectra of 14 showed hydroxyl absorption at 3460 cm\(^{-1}\). In the \(^1\)H NMR spectra, the peaks owing to PMB group disappeared. The alcohol 14 was oxidised to aldehyde using IBX followed by subsequent oxidation using NaClO\(_2\) to give the required acid fragment 6 in 80% yield. The IR spectra of 6 showed hydroxyl absorption at 3442 cm\(^{-1}\) and acid carbonyl at 1713 cm\(^{-1}\). The \(^1\)H NMR and \(^{13}\)C NMR spectra of 6 were compatible with the assigned structure.

**Coupling of Acid fragment 6 and Alcohol fragment 5 and The Synthesis of Aspinolide A**

With substantial amount of both the fragments in hand the coupling of alcohol 5 and acid 6 was achieved by using EDCI to afford diene 15 in 90% yield. The IR spectra of 15 showed ester carbonyl at 1732 cm\(^{-1}\). In \(^{13}\)C NMR, peak owing to carbonyl carbon was present at \(\delta\) 173.1. Ring-closing metathesis of 15 under various conditions using Grubbs\(^1\)st & 2\(^\text{nd}\) generation catalyst failed to provide the required ten-membered lactone. In order to circumvent the problem, we thought it appropriate to first deprotect the TBS group and then use the ring-closing metathesis for macrocyclization. Thus the TBS group of diene 15 was deprotected to get the alcohol 4 which on ring-closing metathesis by using Grubb’s first generation catalyst under high dilution conditions furnished a 10:1 (\(E:Z\)) mixture, which on chromatographic purification gave the target molecule 3 in 82% yield. The IR spectrum of 3 showed carbonyl group of lactone at 1729 cm\(^{-1}\). The appearance of internal olefin at \(\delta\) 5.46-5.41 and 4.93-4.87 in \(^1\)H NMR confirmed the product. The olefinic carbons appeared at \(\delta\)139.3 and 130.9 in \(^{13}\)C NMR spectrum. The prepared synthetic aspinolide A is identical (IR, \(^1\)H NMR, \(^{13}\)C NMR) with the natural product and also has an optical rotation \([\alpha]_D^{25} = -41.6 (c\ 0.25, \text{MeOH})\) which is in good agreement with the literature value \([\text{lit}^2] [\alpha]_D^{23} = -43.8 (c\ 0.3, \text{MeOH})\]. Thus, the absolute stereochemistry of aspinolide A 3 was established as 5\(R\) and 9\(R\).
Scheme 3: Completion of synthesis of aspinolide A 3 by coupling of acid fragment 6 and alcohol fragment 5.

2.2.4. Conclusion

In conclusion, a convergent and efficient first total synthesis of aspinolide A, with high enantioselectivities has been accomplished and its absolute stereochemistry has been fixed. The stereocentres were generated by means of Jacobsen’s hydrolytic kinetic resolution and cyclization was achieved by ring closing metathesis. This approach could be used for synthesis of other members of aspinolide family for structure–activity relationship. Currently work is in progress in this direction.

2.2.5. Experimental Section

General information:

All reactions were carried out under argon or nitrogen in oven-dried glassware using standard gas-light syringes, cannulas and septa. Solvents and reagents were purified and dried by standard methods prior to use. Optical rotations were measured at room temperature. IR spectra were recorded on an FT-IR instrument. $^1$H NMR spectra were recorded on 200 MHz, 300 MHz and 500 MHz and are reported in parts per million (δ) downfield relative to CDCl$_3$ as internal standard and $^{13}$C NMR spectra were recorded at 50 MHz, 75 MHz and 125 MHz and assigned in parts per million (δ) relative to CDCl$_3$. Column chromatography was performed on silica gel (100-200 and 230-400 mesh) using a mixture of petroleum ether and ethyl acetate as the eluent.
5-((4-Methoxybenzyl)oxy)pentan-1-ol (9):

![Structure of compound 9]

To a solution of 1,3-pentanediol 8 (5.0 g, 48.07 mmol) in dry THF (200 mL) was added sodium hydride (60%, 2.53 g, 52.8 mmol) at 0 °C. The reaction mixture was then stirred at room temperature for 30 min after which it was again cooled to 0 °C. To this was added slowly p-methoxybenzyl bromide (10.61 g, 52.8 mmol) and catalytic amount tetrabutylammonium iodide with further stirring for 6 h at the same temperature. The reaction mixture was quenched with addition of cold water at 0 °C. The two phases were separated and the aqueous phase was extracted with EtOAc (3 x 100 mL). The combined organic layers were washed with water (3 x 100 mL), brine, dried over Na₂SO₄ and concentrated. The residual oil was purified by silica gel column chromatography using petroleum ether/EtOAc (6:4) as eluent to furnish the mono-PMB protected alcohol 9 as colorless oil.

Yield: 9.58 g, 89%.

**Mol. Formula:** C₁₃H₂₀O₃

**IR (CHCl₃, cm⁻¹):** νmax 3415, 2950, 2905, 1630, 1513, 1256, 1190, 1110.

**¹H NMR (500 MHz, CDCl₃):** δ 7.29-7.25 (m, 2H), 6.91-6.87 (m, 2H), 4.44 (s, 2H), 3.81 (s, 3H), 3.64 (t, J=6.19 Hz, 2H), 3.46 (t, J=6.32 Hz, 2H), 1.64/1.47 (m, 6H).

**¹³C NMR (125 MHz, CDCl₃):** δ 158.9, 130.4, 129.1, 113.6, 72.3, 69.8, 69.8, 62.2, 55.0, 32.2, 29.2, 22.2.

**LC–MS:** m/z =247 [M + Na]⁺.

2-(4-((4-Methoxybenzyl)oxy)butyl)oxirane (10):

![Structure of compound 10]

**(i) Swern oxidation.** To a solution of oxalyl chloride (2.36 mL, 27.14 mmol) in dry CH₂Cl₂ (50 mL) at -78 °C was added dropwise dry DMSO (3.84 mL, 54.3 mmol) in CH₂Cl₂ (20 mL). After 30 min, alcohol 9 (4.0 g, 18.1 mmol) in CH₂Cl₂ (20 mL) was added over 10 min giving copious white precipitate. After stirring for 2 h at -78 °C,
the reaction mixture was brought to -60 °C and Et₃N (11.36 mL, 81.44 mmol) was added slowly and stirred for 30 min allowing the reaction mixture to warm to room temperature. The reaction mixture was then diluted with water (100 mL) and CH₂Cl₂. The organic layer was separated and washed with water and brine, dried over Na₂SO₄ and passed through short pad of celite. The filtrate was concentrated to give the aldehyde as pale yellow oil, which was used as such for the next step without purification.

(ii) To a solution of trimethylsulfoxonium iodide (4.32 g, 19.62 mmol) in dry DMSO was added NaH (0.78 g, 19.62 mmol). After 1 h, aldehyde (3.96 g, 17.8 mmol) dissolved in THF was added at 25 °C. After stirring for 5 h ice was added to the reaction mixture and the reaction mixture was extracted with water, brine, dried over Na₂SO₄. Solvent was removed under pressure and the crude product was purified by silica gel column chromatography using pet ether/EtOAc (95:5) to get pure epoxide 10 as colorless liquid.

**Yield:** 3.16 g, 75%.

**Mol. Formula:** C₁₄H₂₀O₃

**IR (CHCl₃, cm⁻¹):** νₘₐₓ 3490, 2940, 2863, 1612, 1513, 1249, 1175, 1098.

**¹H NMR (200 MHz, CDCl₃):** δ 7.25-7.21 (m, 2H), 6.87-6.81 (m, 2H), 4.40 (s, 2H), 3.77 (s, 3H), 3.42 (t, J=6.32 Hz, 2H), 2.89-2.84 (m, 1H), 2.73-2.69 (m, 1H), 2.54-2.41 (m, 1H), 1.61-1.45 (m, 6H).

**¹³C NMR (50 MHz, CDCl₃):** δ 159.1, 130.6, 129.2, 113.7, 72.5, 69.8, 55.0, 52.2, 47.1, 32.2, 29.5, 22.7.

**LC–MS:** m/z =259 [M + Na]^⁺.

(R)-2-(4-((4-Methoxybenzyl)oxy)butyl)oxiran (R-10):

A solution of epoxide 10 (3.0 g, 12.7 mmol) and (R,R)-salen-Co(III)-OAc (42 mg, 0.063 mmol) in THF (125 µL) was stirred at 0 °C for 5 min, and then distilled water (125 µL, 6.98 mmol) was added. After stirring for 14 h, it was concentrated and
purified by silica gel column chromatography using pet ether: EtOAc (19:1) to afford \( R-10 \) as a pale yellow color liquid. Continued chromatography with pet ether/EtOAc (3:2) provided the diol 11 as a yellow liquid as a single enantiomer.

Yield: 1.4 g, 48%.

\([\alpha]_D^{25}\): 2.77 (c 1.05, CHCl_3).

\((R)-7-((4\text{-}\text{Methoxybenzyl}oxy)\text{hept}-1\text{-en}-3\text{-ol}) (12)\)

To a suspension of trimethylsulfonium iodide (6.85 g, 5.43 mmol) in dry THF (20 mL) at \(-20 \, ^\circ C\) was added \( n\)-BuLi (22.34 mL, 1.6 M solution in hexane, 35.7 mmol) dropwise over 20 min and stirred for 30 min. Then the epoxide \( R-10 \) (1.3 g, 5.5 mmol) in dry THF (10 mL) was added to the above reaction mixture and stirred for 2 h. After consumption of the starting material the reaction mixture was quenched with \( \text{H}_2\text{O} \) (20 mL) and extracted with EtOAc (4 × 10 mL). The combined extracts were washed with brine, dried over \( \text{Na}_2\text{SO}_4 \) and concentrated. The column chromatography of crude product using pet ether:ethyl acetate (90:10) gave 12 as a colorless liquid.

Yield: 1.03 g, 75%.

Mol. Formula: \( \text{C}_{15}\text{H}_{22}\text{O}_3 \)

\([\alpha]_D^{25}\): –5.45 (c 0.94, CHCl_3).

IR (CHCl_3, cm\(^{-1}\)): \( \nu_{\text{max}} \) 3386, 1640, 1603, 1493, 1453, 1243.

\(^1\text{H NMR (200 MHz, CDCl}_3\)): \( \delta \) 7.29-7.24 (m, 2H), 6.91-6.86 (m, 2H), 5.95-5.78 (m, 1H), 5.27-5.08 (m, 2H), 4.44 (s, 2H), 4.15-4.06 (m, 1H), 3.81 (s, 3H), 3.49-3.42 (m, 2H), 1.92 (brs, 1H), 1.68-1.42 (m, 6H).

\(^{13}\text{C NMR (50 MHz, CDCl}_3\)): \( \delta \) 158.9, 141.2, 130.5, 129.1, 114.3, 113.6, 72.8, 72.4, 69.8, 55.1, 36.6, 29.4, 21.9.

LC–MS: \( m/z =273 \ [\text{M + Na}]^+ \).

\((R)-5-((\text{tert\text{-}Butyldimethylsilyl}oxy)\text{hept}-6\text{-en}-1\text{-ol}) (14)\)
To a stirred solution of alcohol 12 (5 g, 21.86 mmol) in CH$_2$Cl$_2$ was added imidazole (0.53 g, 7.8 mmol). To this solution $t$-butyl dimethylchlorosilane (0.73 g, 4.79 mmol) was added at 0 °C and the reaction was stirred at rt for 4 h. The reaction mixture was quenched with a saturated aqueous solution of NH$_4$Cl and extracted with CH$_2$Cl$_2$. The extract was washed with brine, dried over Na$_2$SO$_4$, and concentrated, which was used as such for the next step without purification.

To a stirring solution of PMB ether (1.44 g, 3.95 mmol) in CH$_2$Cl$_2$/H$_2$O (18:1) was added DDQ (1.08 g, 4.74 mmol) at 0 °C . The resulting mixture was stirred for 10 min at r. t. The mixture was poured into saturated aqueous NaHCO$_3$ and further diluted with CH$_2$Cl$_2$. The layers were separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (2 x 10 mL). The combined organic layers were dried (Na$_2$SO$_4$), filtered, and concentrated. The solvents were removed under reduced pressure to give the crude product mixture as yellow oil. Silica gel column chromatography of the crude product using pet ether:ethyl acetate (96:4) as eluent gave 14.

**Yield:** 0.92 g, 95%.

**Mol. Formula:** C$_{13}$H$_{28}$O$_2$Si

$[\alpha]_D^{25}$ − 6.67 (c 0.28, CHCl$_3$).

**IR (CHCl$_3$, cm$^{-1}$):** $\nu_{\text{max}}$ 3460, 2959, 2857, 1640, 1448, 1376, 1255, 1078.

**H NMR (200 MHz, CDCl$_3$):** δ 5.86/5.69 (m, 1H), 5.17/4.98 (m, 2H), 4.09/4.03 (m, 1H), 3.65/3.59 (m, 2H), 1.59/1.37 (m, 6H), 0.88 (s, 9H), 0.03/0.02 (m, 6H).

**C NMR (50 MHz, CDCl$_3$):** δ 141.6, 113.6, 73.7, 62.8, 37.7, 32.7, 25.8, 21.2, 18.2, −4.4, −4.8.

**LC–MS:** m/z =263 [M + Na]$^+$. 

*(R)-5-((tert-Butyldimethylsilyl)oxy)hept-6-enoic acid (6)*
To a solution of alcohol 14 (0.45 g, 8.19 mmol) in EtOAc (5 mL) was added IBX (1.72 g, 24.5 mmol) in one portion and the reaction mixture was refluxed for 3 h. The reaction mixture was filtered through a pad of celite and filtrate was concentrated to give the crude aldehyde, which was used for the next step without purification.

A solution of 79% NaClO₂ (0.315 g, 2.78 mmol) in 1.0 mL of water was added dropwise to a stirred solution of above crude aldehyde (0.45 g, 1.85 mmol) in 1.0 mL of DMSO and NaH₂PO₄ (0.167 g, 1.39 mmol) in 1.0 mL of water in 5 min at room temperature. The mixture was left overnight at room temperature, and then 5% aqueous solution of NaHCO₃ was added. The aqueous phase was extracted 3 times with CH₂Cl₂ and washed with brine, dried (Na₂SO₄), and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (4:1) as eluent gave the acid 6 (1.25 g, 80%) as a syrupy liquid.

**Yield:** 0.38 g, 80%.

**Mol. Formula:** C₁₃H₂₆O₃Si

\[ [\alpha]_D^{25} = -6.56 \text{ (c 1.15, CHCl}_3) . \]

**IR** (CHCl₃, cm⁻¹): νₘₐₓ 3442, 2930, 2858, 1713, 1463, 1254, 1087, 923

**¹H NMR** (200 MHz, CDCl₃): \( \delta \) 5.86-5.69 (m, 1H), 5.18-5.00 (m, 2H), 4.15-4.09 (m, 1H), 2.39-2.32 (m, 2H), 1.76-1.49 (m, 5H), 0.88 (s, 9H), 0.04 (m, 6H).

**¹³C NMR** (50 MHz, CDCl₃): \( \delta \) 179.9, 141.3, 113.9, 73.4, 37.1, 34.0, 29.7, 25.8, 20.3, –4.4, –4.8.

**LC–MS:** m/z =281 [M + Na]⁺.

**(R)-(R)-Pent-4-en-2-yl 5-((tert-butyldimethylsilyl)oxy)hept-6-enoate (15)**

\[
\begin{align*}
\text{O} & \quad \text{OTBS} \\
\text{C} & \quad 15
\end{align*}
\]

To a solution of the carboxylic acid 6 (0.77 g, 2.99 mmol) in CH₂Cl₂ (10 ml) was added EDCI.HCI (0.835 g, 4.35 mmol), DMAP (35 mg, 0.29 mmol) and the hydroxy amide 5 (0.25 g, 2.90 mmol) at 0 °C, and the mixture was stirred at 0 °C for 5 h. The mixture was diluted with Et₂O and successively washed with H₂O, saturated aqueous
NaHCO₃, and saturated brine, and then dried over MgSO₄ and concentrated in vacuo. Silica gel column chromatography of the crude product using petroleum ether: EtOAc (5:1) as eluent afforded compound 15 as pale yellow oil.

**Yield:** 0.876 g, 90%

**Mol. Formula:** C₁₈H₃₄O₃Si

\[ [\alpha]_{D}^{25} = -14.9 \text{ (c 0.50, CHCl}_3) \].

**IR (CHCl₃, cm⁻¹):** ν_max 2931, 2864, 1732, 1655, 1466, 1425, 1218, 1170, 781.

**¹H NMR (200 MHz, CDCl₃):** δ 5.81-5.68 (m, 2H), 5.15-5.00 (m, 4H), 4.98-4.91 (m, 1H), 4.10-4.06 (m, 1H), 2.35-2.21 (m, 4H), 1.64-1.58 (m, 5H), 1.52-1.44 (m, 2H), 1.20 (d, J = 6.53 Hz, 3H), 0.88 (s, 9H), 0.04-0.01 (m, 6H).

**¹³C NMR (50 MHz, CDCl₃):** δ 173.1, 141.4, 133.7, 117.6, 113.8, 73.5, 69.8, 40.3, 37.3, 34.6, 25.9, 20.8, 19.5, 18.2, −4.4, −4.8.

**LC–MS:** m/z =349 [M + Na]^+.

**(R)-(R)-Pent-4-en-2-yl 5-hydroxyhept-6-enoate (4)**

To a solution of olefin 15 (0.255 g, 0.78 mmol) in THF (3 mL) was added TBAF (1.17 mL, 1.17 mmol, 1.0 M solution in THF) at room temperature. The reaction mixture was stirred for 6 h and then diluted with water and extracted with EtOAc. The organic layer was washed with brine, dried (Na₂SO₄) and concentrated. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (7:3) as eluent gave alcohol 4 as a colorless liquid.

**Yield:** 0.124 g, 75%

**Mol. Formula:** C₁₂H₂₀O₃

\[ [\alpha]_{D}^{25} = -10.2 \text{ (c 0.3, CHCl}_3) \].

**IR (CHCl₃, cm⁻¹):** ν_max 3438, 2933, 1731, 1645, 1424, 1380, 1245, 1061
**H NMR (200 MHz, CDCl$_3$):** $\delta$ 5.93-5.62 (m, 2H), 5.26-5.02 (m, 4H), 4.97-4.91 (m, 1H), 4.14-4.05 (m, 1H), 2.33-2.24 (m, 4H), 1.79 (brs, 1H), 1.71-1.52 (m, 4H), 1.20 (d, $J$=6.32 Hz, 3H).

**13C NMR (50 MHz, CDCl$_3$):** $\delta$ 173.1, 140.9, 133.7, 117.7, 114.8, 72.6, 69.9, 40.3, 36.2, 34.3, 20.7, 19.5.

**LC–MS:** m/z =235 [M + Na]$^+$. 

**Aspinolide A 3**

![Aspinolide A 3 structure](image)

A mixture of 4 (50 mg, 0.23 mmol) in anhydrous CH$_2$Cl$_2$ (20 mL) and Grubbs’ first generation catalyst (39 mg, 0.047 mmol) was degassed with argon for 15 min, and refluxed for 14 h. Solvent was removed under reduced pressure to leave highly dark brown colored residue. Silica gel column chromatography of the crude product using petroleum ether/EtOAc (9:1) as eluent afforded aspinolide A (3) as a colorless oil.

**Yield:** 35 mg, 82%

**Mol. Formula:** C$_{10}$H$_{16}$O$_3$

$[\alpha]_D^{25}$ = –41.6 ($c$ 0.25, MeOH), $[\text{lit}^2 \ [\alpha]_D^{23}$ = –43.8 ($c$ 0.3, MeOH)]

**IR (CHCl$_3$, cm$^{-1}$):** $\nu_{\text{max}}$ 3435, 2925, 2854, 1729, 1462, 1275, 1073, 971

**1H NMR (200 MHz, CDCl$_3$):** $\delta$ 5.46-5.41 (m, 1H), 4.93-4.87 (m, 1H), 3.71 (q, $J$=6.48 Hz, 1H), 2.49 (t, $J$=7.03 Hz, 2H), 2.30-2.26 (m, 2H), 1.88-1.84 (m, 2H), 1.60-1.55 (m, 2H), 1.18 (d, $J$=6.27 Hz, 3H).

**13C NMR (50 MHz, CDCl$_3$):** $\delta$ 172.7, 139.3, 130.9, 70.3, 68.5, 42.5, 38.9, 37.1, 22.6, 18.9.

**LC–MS:** m/z =207 [M + Na]$^+$. 

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### 2.2.6. Spectra

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Chapter 2 Section 2

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**Acquisition Time (sec)**

- 7.9167

**Comment**

- Partha

**Date**

- 26/09/2008 10:07:08

**Frequency (MHz)**

- 200.13

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**Nucleus**

- 1H

**Original Points Count**

- 32768

**Points Count**

- 32768

**Sweep Width (Hz)**

- 4139.07

**Temperature (grad C)**

- 0.000

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**Acquisition Time (sec)**

- 1.0486

**Date**

- 16/03/2009 21:01:12

**Frequency (MHz)**

- 125.76

**Nucleus**

- 13C

**Original Points Count**

- 32768

**Points Count**

- 32768

**Sweep Width (Hz)**

- 31250.00

**Temperature (grad C)**

- 0.000

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**Chloroform-d**

- 6.15 3.08 2.18 2.08 2.05 1.98 1.01 1.00

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**Chloroform-d**

- 22.69 29.50 32.25 47.07 52.22 55.24 69.77 72.55 77.00

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**PMBO**

- 3

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**PMBO**

- 10
Chapter 2 Section 2
$^{19}$F spectrum of Mösher ester of 12
2.2.7. References

10 For various application of HKR in synthesis of bioactive compounds, see review, a) Kumar, P.; Naidu, S. V.; Gupta, P. *Tetrahedron* **2007**, 63, 2745; account, b) Kumar, P.; Gupta, P. *Synlett* **2009**, 1367.
The enantiomeric excess was determined by converting homoallylic alcohol 12 into its Mösher ester and analyzing the $^{19}\text{F}$ spectrum.
