ABSTRACT
This thesis entitled “Radical cyclization routes to the synthesis of α-methylene cis-fused bicyclic systems, synthesis of (-)-osmundalactone, it’s epimer and butyro-lactone moiety of angiopterlactone A” is divided into three chapters.

CHAPTER I: Radical cyclization reaction rules, applications and synthesis of cis-fused bicyclic systems: impact of alkyl side chains in L-Ara configuration

This chapter deals with radical cyclization reaction rules, applications and synthesis of cis-fused bicyclic systems: impact of alkyl side chains in L-Ara configuration which was divided into two sections

Section-A: Radical cyclization reaction: rules and applications


Radical cyclization reactions, particularly on carbohydrate derived precursors, are very useful for the synthesis of furo-furan class of bicyclic systems. Such cyclizations by 5-exo-dig mode, on diacetone glucose (DAG) derived systems were earlier applied for the synthesis of several natural products containing α-methylene bis-butyro lactones, such as avenaciolide 1 (Figure 1). Similar approach used for the synthesis of iso-avenaciolide 2 (Figure 1) from L-arabinose, however, met with failure. The above observations, prompted to undertake a study on the impact of the side chain on radical cyclization reactions in systems with L-Ara configuration.

![Figure 1](image.png)

The retrosynthetic analysis (Scheme 1) revealed that the synthesis of cis-fused bicyclic systems 3a-3c and 4a-4c, with different lengths of alkyl side chains could be achieved through the precursor’s 5a-5c and 6a-6c, which in turn could be obtained from anomeric mixtures of 7, 8 and 9. These anomeric systems in turn could be envisaged from L-arabinose 10 as a common staring material.
It was firstly proposed to prepare the anomic alcohols 7-9, for the introduction of 3-carbon propargylic unit for radical cyclization. Commercially available 10 (Scheme 2) on two simple known\textsuperscript{10} chemical reactions gave 11. Reaction of alcohol 11 with PMBBr in the presence of NaH in dry THF at 0 °C to room temperature for 4 h afforded 12 in 81% yield. Desilylation of 12 with TBAF in dry THF at 0 °C to room temperature for 14 h furnished alcohol 13 (89%), which on further treatment with p-TsCl and Et$_3$N in CH$_2$Cl$_2$ at 0 °C to room temperature for 4 h gave tosylate 14 in 81% yield. Reductive deoxygenation of 14 using NaBH$_4$ in dry DMSO\textsuperscript{11} at 160 °C for 10 min under nitrogen atmosphere afforded 15a in 79% yield.

Further, the requisite C2 and C5 side chains on furanoside ring 13 were achieved by a three step sequence. Accordingly, oxidation of alcohol 13 (Scheme 2) with IBX in DMSO at room temperature gave aldehyde 16, which on Wittig olefination with (methyl)triphenylphosphonium iodide and t-BuOK in THF at -4 °C for 7 h afforded the olefin 17 (49%). A similar reaction on 16 with (n-butyl)triphenylphosphonium bromide and t-BuOK in THF at -4 °C for 7 h furnished 18 in 50% yield. Olefins 17 and 18, independently on hydrogenation with PtO$_2$ in EtOAc at room temperature for 2 h afforded 15b (89%) and 15c (75%) respectively. Methanolysis of 15a, 15b and 15c in methanol and conc. HCl (2-3 drops) at 0 °C to room temperature for 6 h gave diastereomeric mixtures of methyl glycosides 7 (1:1.5), 8 (1:1.5) and 9 (4.5:5.5) respectively as $\alpha$- and $\beta$-anomers.
Alkylation of alcohols 7, 8 and 9 independently with propargyl bromide (Scheme 3) in the presence of NaH in dry THF at room temperature for 4 h furnished the propargyl ethers 19a-c and 20a-c as β- and α-anomers respectively. Both the β-anomers 19a-c and α-anomers 20a-c were independently subjected to oxidative deprotection of the PMB group with DDQ in wet CH₂Cl₂ at room temperature for 2 h to afford alcohols 21a-c and 22a-c respectively.
Reaction of alcohols 21a-c and 22a-c with NaH, CS₂ and MeI in dry THF at 0 °C to room temperature for 2 h furnished the corresponding xanthate esters 5a-c and 6a-c respectively (Scheme 4).

Having prepared the radical precursors, the stage was set for radical cyclization reactions. Accordingly, 5a and 6a, the β- and α-anomers with a methyl side chain were subjected to radical reaction with n-Bu₃SnH in the presence of AIBN (cat.) in dry benzene at reflux for 12 h (Scheme 4). Interestingly, unlike the system with an n-octyl side chain, both 5a and 6a underwent cyclization to give the respective cyclized products 3a (69%) and 4a (57%) (Scheme 4).

Having met with success from 5a and 6a, the study was then extended to 5b and 6b, under the above conditions to furnish cis-fused bicyclic systems 3b (71%) and 4b (60%) respectively. A similar study when was conducted on the radical precursors 5c (β-) and 6c (α-), unlike in the case of 5a/5b and 6a/6b, the β-anomer 5c gave cis-fused bicyclic system albeit in a very poor yield (14%). However, 6c resisted to undergo cyclization and expected product 4c could not be synthesized.
Thus, the above studies amply indicate that, it is not the configuration (D-Xylo or L-Ara) of furanoside ring alone, but the length of alkyl side chains also has a role to play in radical cyclization. The above discussed results on the n-pentyl side chain very well compliment with the reported results with an n-octyl side chain. Thus, it is pertinent to mention that the side chain in L-Ara configuration has a role to play in the 5-exo-dig radical cyclizations.

The theoretical studies (DFT and (RO)MP2) on the above systems also indicated that variation of the substituent from methyl to ethyl leads to a minor reduction in reaction barriers, which is in full agreement with experimental results. However, the results with n-propyl and n-butyl side chains do not drastically lead to altered cyclization barriers, thus, suggesting that reduced reaction yields experimentally observed may be attributed to other factors in the overall chain reaction.

The above studies have successfully resulted in the synthesis of 3b and 4b (Scheme 4). Since, the conversion of 3b into ethisolide 2a is reported\textsuperscript{12,13} in the literature, the present study formally concludes the total synthesis of ethisolide 2a.
CHAPTER II: Radical cyclization routes for the formal synthesis of ethisolide, iso-avenaciolide and cis-fused bicyclic systems

Chapter II deals with the radical cyclization routes for the formal synthesis of ethisolide, iso-avenaciolide and cis-fused bicyclic systems which was divided into two sections.

Section-A: Radical mediated formal synthesis of ethisolide and iso-avenaciolide from diacetone glucose

Section A deals with the formal synthesis of ethisolide and iso-avenaciolide from diacetone glucose

Ethisolide $2a^{13}$ and iso-avenaciolide $2^{14}$ are $\alpha$-methylene bis-butyrolactone class of secondary metabolites, isolated from the broths of Aspergillus avenaceus and Penicillium species respectively. Both $2$ and $2a$ (Figure 1) inhibit fungal growth and have antibacterial activity$^{15}$ and thus attracted numerous synthetic efforts.$^{16}$ Structurally, $2$ and $2a$ are very similar to each other, except for the length of the side chains, wherein, $2$ has a C8 side chain, while $2a$ with a C2 side chain in their structures (Figure 1).

The retrosynthetic strategy of $2a$ and $2$ as depicted in Scheme 5 indicates, the bicyclic systems $23$ and $24$ are the late stage intermediates. These bicyclic systems could be realized from glycols $23a$ and $24a$ respectively by radical cyclization protocol. The glycols $23a$ and $24a$ inturn
could be generated from the appropriately substituted triflate derivatives 25 and 26 respectively, derived from diacetone glucose (DAG). Thus, the main synthetic strategy is: a) to generate the C-3/C-4 glycol, b) to utilize a vinyl radical for the radical cyclization to invert the C-4 stereocentre, while creating the cis-fused bicyclic systems.

Accordingly, reaction of the known diol\textsuperscript{17} 27 with Ph\textsubscript{3}P, imidazole and I\textsubscript{2} in CH\textsubscript{2}Cl\textsubscript{2} at 0 °C to room temperature for 2 h gave olefin 28 (77%), which on hydrogenation with PtO\textsubscript{2} in EtOAc at 0 °C for 2 h afforded 29 (97%). Similarly, the C8 side chain was introduced by a four step sequence. Accordingly, diol 27 on oxidative cleavage with NaIO\textsubscript{4} in CH\textsubscript{2}Cl\textsubscript{2} at 0 °C to room temperature for 3 h furnished aldehyde 30, which on reaction with n-heptylmagnesium bromide in dry THF at 0 °C to room temperature for 3 h afforded a mixture of alcohols 31 in 80% yield. Further, treatment of 31 with NaH, CS\textsubscript{2} and MeI in dry THF at 0 °C to room temperature for 2 h gave xanthate esters 32 (85%). Reductive deoxygenation of xanthate esters 32 with n-Bu\textsubscript{3}SnH and AIBN (cat.) in dry benzene at reflux for 12 h furnished 33 in 89% yield (Scheme 6).

![Scheme 6](image)

*Reagents and conditions:* (a) Ph\textsubscript{3}P, I\textsubscript{2}, Imidazole, CH\textsubscript{2}Cl\textsubscript{2}, 0 °C-rt, 2 h; (b) PtO\textsubscript{2}, EtOAc, rt, 2 h; (c) NaIO\textsubscript{4}, CH\textsubscript{2}Cl\textsubscript{2}, aq.NaHCO\textsubscript{3}, 0 °C-rt, 3 h; (d) n-C\textsubscript{3}H\textsubscript{13}Br, Mg, THF, 0 °C-rt, 3 h; (e) NaH, CS\textsubscript{2}, MeI, THF, 0 °C-rt, 2 h; (f) n-Bu\textsubscript{3}SnH, dry Benzene, AIBN (cat.), reflux 12 h.

Hydrolysis of 29 and 33 in methanol containing conc. HCl (2-3 drops) at 0 °C to room temperature for 7 h gave separable diastereomeric mixtures of methyl glycosides 34 (1:1.5) and 35 (1:2.3) respectively as \(\alpha\)-anomers and \(\beta\)-anomers. The \(\alpha\)-anomers 34a/35a and \(\beta\)-anomers...
34b/35b independently on reaction with 2,3-dibromopropene in the presence of NaH in dry THF at 0 °C to room temperature for 3 h furnished the required bromo derivatives 36a (72%)/37a (65%) and 36b (78%)/37b (64%) respectively. Oxidative deprotection of the PMB group in 36a/37a and 36b/37b with DDQ in wet CH₂Cl₂ at room temperature for 2 h to furnished alcohols 38a (72%)/39a (65%) and 38b (75%)/39b (82%) respectively (Scheme 7).

**Scheme 7**

![Scheme 7 Diagram]

Reagents and conditions: (a) MeOH, H⁺, 0 °C-rt, 7 h; (b) NaH, 2,3-dibromopropene, THF, 0 °C-rt, 3 h; (c) DDQ, CH₂Cl₂:H₂O (19:1), rt, 2 h.

Treatment of alcohols 38a/39a and 38b/39b independently with Tf₂O and pyridine in dry CH₂Cl₂ at -20 °C for 30 min furnished triflates 40a (88%)/41a (81%) and 40b (95%)/41b (93%), which on further reaction with DBU in dry DMSO at 0 °C to room temperature for 12 h afforded the glycols 42a/43a and 42b/43b respectively (Scheme 8).

Having prepared the radical precursors 42a/43a and 42b/43b, they were subjected to cyclization reaction with n-Bu₃SnH in the presence of AIBN (cat.) in dry benzene at reflux for 12 h to give cis-fused bicyclic systems 4b (60%)/3b (71%) and 44a (72%)/44b (65%) respectively.
Synopsis

Reagents and conditions: (a) Tf₂O, Pyridine, dry CH₂Cl₂, -20 °C, 30 min; (b) DBU, dry DMSO, 0 °C-rt, 12 h; (c) n-Bu₃SnH, AIBN (cat.), dry benzene, 80 °C, 12 h.

The structures of all the furo-furans (4b/3b and 44a/44b) were confirmed unambiguously from the corresponding spectral data. Further, conversion of 3b and 44b into 2a and 2, since is reported, the synthesis of 3b/44b, formally constitutes the total synthesis of 2a and 2.

Section-B: Radical mediated synthesis of cis-fused bicyclic systems from L-arabinose and D-xylose

Section B deals with radical mediated synthesis of cis-fused bicyclic systems from L-arabinose and D-xylose

As discussed in the first chapter, the side chain effect was amply evident in furanoside systems with L-Ara configuration, rather than in systems with D-Xylo configuration. The synthesis of iso-avenaciolid 2 from such a protocol was not possible in our hands. In addition to the nature’s diversity such as, ethisolide 2a and iso-avenaciolid 2, non-natural products such as iso-canadensolide 45 and iso-sporothriolid 46 were synthesized. Hence, in this study it was proposed to undertake the synthesis of cis-fused bicyclic systems from the precursors with L-Ara configuration, so that requisite side chain diversity can be introduced accordingly on these bicyclic systems for the synthesis of 45 and 46.
According to the retrosynthetic strategy, the bicyclic systems 47 and 47a could be made from the radical precursors 48 and 48a, while, the xanthate derivatives in turn could be realized from L-arabinose derivative 11 (Scheme 9).

Accordingly, alcohol 11 (Scheme 10) was subjected to alkylation with propargyl bromide in the presence of NaH in THF at room temperature for 4 h to furnish the propargyl ether 49 in 91% yield. Methanolyis of 49 with methanol containing conc. HCl (cat.) at 0 °C to room temperature for 6 h gave the α- and β-methyl glycosides 50, with concomitant hydrolysis of TBDPS group. The anomeric mixtures 50 on reaction with TBDPSCl and imidazole in dry CH2Cl2 at 0 °C to room temperature for 2 h and purification by column chromatography (60-120 Silica gel; ethyl acetate: pet. ether, 1.2:8.8) gave the α-anomer 51 (33%) and β-anomer 51a (49%).
**Scheme 10**

Reagents and conditions: (a) Propargyl bromide, NaH, THF, 0 °C-rt, 2 h; (b) MeOH, H+, 0 °C-rt, 6 h; (c) TBDPSCl, imidazole, dry CH2Cl2, 0 °C-rt, 2 h.

The β-anomer 51a on reaction with NaH, CS2 and MeI in THF at 0 °C to room temperature for 2 h furnished the xanthate ester 48 in 90% yield. Radical cyclization of 48 under standard reaction conditions using n-Bu3SnH and AIBN (cat.) in dry benzene at reflux for 12 h afforded 47 in 68% yield (Scheme 11).

**Scheme 11**

Reagents and conditions: (a) CS2, MeI, NaH, THF, 0 °C-rt, 2 h; (b) n-Bu3SnH, AIBN, dry benzene, 80 °C, 12 h.

Having successfully synthesized the cis-fused bicyclic furo-furan system 47, the study was then extended to the synthesis of the furo-furan 47a, by the use of radical generated at C-3. Accordingly, known PMB ether 12 on methanolysis (MeOH, conc. HCl) gave the desilylated glycoside mixture 52, which on silylation for 2 h furnished 52a. Alkylation of 52a with propargyl bromide in the presence of NaH in THF at room temperature for 4 h afforded the ethers 53 (34%) and 53a (50%) after chromatography purification.
Reagents and conditions: (a) MeOH, H+, 0°C-rt, 6 h; b) TBDPSCl, imidazole, dry CH₂Cl₂, 0°C-rt, 2 h; (c) propargyl bromide, NaH, THF, 0°C-rt, 4 h; (d) DDQ, CH₂Cl₂:H₂O (19:1), 0°C-rt, 2 h; (e) NaH, CS₂, MeI, THF, 0°C-rt, 2 h; (f) n-Bu₃SnH, AIBN (cat.), dry benzene, 80°C, 12 h.

Treatment of 53a with DDQ in aq. CH₂Cl₂ at room temperature for 2 h afforded the alcohol 54 (75%), which on further reaction with NaH, CS₂ and MeI in THF at 0°C to room temperature for 2 h gave the xanthate ester 48a in 85% yield. The attempted radical cyclization of 48a with n-Bu₃SnH and AIIBN (cat.) in dry benzene at reflux for 12 h met with failure to give the expected cyclic system 47a, unlike in the case of 48, which furnished 47. Based on these findings, the study was not extended to convert the α-anomer 54 into cyclized product. These findings become now very interesting, since, the resistance of the C-3 radical to undergo radical cyclization is attributable to the L-Ara configuration or to the bulkiness of the protecting group (-CH₂OTBDPS).

To understand the above discussed results, the study was extended to the synthesis of bicyclic systems having D-Xylo configuration. This study has a strong banking from nature, where, several natural products, as shown Figure 3, which have two different kinds of furo-furan moieties with D-Xylo configuration.

Figure 3

55 R = C₂H₅ Xylobovide
56 R = n-C₃H₇ Canadensolide
57 R = n-C₆H₁₃ Sporothriolide
58 R = n-C₁₀H₂₁ Discociolide

1a R = C₂H₅ Epi-ethisolidine
1 R = n-C₈H₁₇ Avenaciolide
58 R = n-C₁₀H₂₁ Discociolide
A similar retrosynthetic strategy as described in Scheme 9 was proposed for the synthesis of the bicyclic systems 59 and 59a from D-xylose derivative 61.

Scheme 13

Accordingly, the known diol\textsuperscript{20} 61 on silylation (TBDPScI, imidazole) in CH\textsubscript{2}Cl\textsubscript{2} at 0 °C to room temperature for 2 h afforded 62 (70%), which on reaction with propargyl bromide (NaH, THF) at room temperature for 4 h gave 63 (80%). The cleavage of isopropylidene functional group in 63 with acidic (conc. HCl) MeOH at 0 °C to room temperature for 6 h furnished the diol 64, which on silylation afforded β-anomer 65 (44%) as a major anomer, after chromatographic purification.

Scheme 14

Reagents and conditions: (a) TBDPScI, imidazole, dry CH\textsubscript{2}Cl\textsubscript{2}, 0 °C-rt, 2 h; (b) Propargyl bromide, NaH, THF, 0 °C-rt, 4 h; (c) MeOH, H\textsuperscript{+}, 0 °C-rt, 6 h.
Reaction of alcohol 65 with NaH, CS₂ and MeI in THF at 0 °C to room temperature for 2 h to gave xanthate ester 60 (70%) yield (Scheme 15), which on cyclization (n- Bu₃SnH and AIBN) in dry benzene at 80 °C for 12 h furnished the bicyclic system 59 in 71% yield.

**Scheme 15**

\[
\begin{align*}
\text{65} & \xrightarrow{a} \text{60} \quad \text{60 R} = \text{OCH₂TBDPS} \\
& \quad \text{(70%)} \\
& \quad \text{60} & \xrightarrow{b} \text{59} \quad \text{59 R} = \text{OCH₂TBDPS} \\
& \quad \text{(71%)}
\end{align*}
\]

*Reagents and conditions:* (a) NaH, CS₂, MeI, THF, 0 °C-rt, 2 h; (b) n-Bu₃SnH, AIBN, dry benzene, 80 °C, 12 h.

To understand the effect of D-Xylo configuration on C-3 radical cyclization, it was then extended to the C-3 radical mediated formation of bicyclic system. Accordingly, alkylation of 62 with PMBBr in the presence of NaH in dry THF furnished 66 (83%), which on methanolysis (MeOH, conc. HCl) for 6 h gave an inseparable mixture of diols 67. Silylation of 67 and alkylation of 68 with propargyl bromide with NaH in dry THF at 0 °C to room temperature for 4 h, followed by chromatographic purification furnished the β-anomer 69 (53%) as a major anomer.

**Scheme 16**

\[
\begin{align*}
\text{63} & \xrightarrow{a} \text{66} \quad \text{66 (83%)} \\
& \quad \text{PMBO} \\
& \quad \text{TBDPSO} \\
\text{69} & \xrightarrow{d} \text{68} \quad \text{68 (76%)} \\
& \quad \text{PMBO} \\
& \quad \text{TBDPSO} \\
\text{69} & \xrightarrow{e} \text{70} \quad \text{70 R} = \text{OCH₂TBDPS} \\
& \quad \text{(76%)} \\
& \xrightarrow{f} \text{60a} \quad \text{60a R} = \text{OCH₂TBDPS} \\
& \quad \text{(81%)} \\
\text{60a} & \xrightarrow{g} \text{59a} \quad \text{59a R} = \text{OCH₂TBDPS}
\end{align*}
\]

*Reagents and conditions:* (a) PMBBr, NaH, THF, 0 °C-rt, 4 h; (b) MeOH, H⁺, 0 °C-rt, 6 h; (c) TBDPSCl, imidazole, dry CH₂Cl₂, 0 °C-rt, 2 h; (d) Propargyl bromide, NaH, THF, 0 °C-rt, 4 h; (e) DDQ, CH₂Cl₂:H₂O (19:1), 0 °C-rt, 2 h; (f) NaH, CS₂, MeI, THF, 0 °C-rt, 2 h; (g) n-Bu₃SnH, AIBN, dry benzene, 80 °C, 12 h.
The β-anomer 69 on oxidative deprotection of PMB group with DDQ in wet CH₂Cl₂ at 0 °C to room temperature for 2 h gave alcohol 70 (76%). Alcohol 70 was converted corresponding xanthate ester 60a in 81% yield, which, however on radical cyclization met with failure to afford the expected bicyclic system 59a (Scheme 16).

This study on xanthate derivative 60a with D-Xylo configuration infers that the failure to undergo cyclization is not perhaps due to the C-4 (D-Xylo or L-Ara) configuration of furanoside, but may be due to the bulkyness of the side chain (-CH₂OTBDPS).

CHAPTER III: Total synthesis of (-)-osmundalactone, it’s epimer and butyro-lactone moiety of angiopterlactone A

This chapter deals with the total synthesis of (-)-osmundalactone, it’s epimer and butyro-lactone moiety of angiopterlactone A

Many natural products21-26 contain lactone rings, particularly the α, β-unsaturated δ-lactone ring systems and many of exhibit diverse biological activities and tumour promoting activity. (-)-Osmundalactone 7127 is the aglycone part of the natural glycoside osmundalin27 and occurs also in the free form28 in the edible Japanese fern species Osmunda japonica and has been found to display antifeedant activity against larvae of some insect species.28 (-)-Osmundalactone 7127 was recently isolated32 from rhizome of Angiopteris caudatiformis and shown insect antifeeding activity against Plutella xylostella and Heliothis virescens. Its enantiomer, (+)-osmundalactone 72 has also been reported as a natural product.29 Osmudalactones and the cis-diastereomers (4-epi-(+)-osmundalactone30,31) are used as O-substituted derivatives (angiopterlactone A 7432) of several natural products.33-38

The retrosynthetic strategy for 71 and its stereoisomer 73 (Scheme 17), revealed that the lactones could be obtained by cyclization of α,β-unsaturated esters 75 and 76 respectively. The
requisite 4\textit{R}, 5\textit{S}-\textit{vic} diol for 71 could be realized from 77 derived from L-arabinose, while, the \textit{vic}-diol with 4\textit{R}, 5\textit{R}-configuration could be obtained from 78, derived from D-xylose. Thus, C-6 of the target molecule comes from C-5, while C-4/C-5 stereocentres are correlated to C-3/C-4 of 77 and 78 respectively. The aldehyde generated from C-1/C-2 of 77/78 would be used for the homologation to introduce a two carbon chain.

For the synthesis of 71, the known\textsuperscript{10} alcohol 11 on desilylation with TBAF in THF at 0 \degree C to room temperature for 14 h gave diol 79 (82\%), which on tosylation with \(p\)-TsCl and Et\textsubscript{3}N in dry CH\textsubscript{2}Cl\textsubscript{2} at 0 \degree C to room temperature for 2 h furnished monotosylate 80 (75\%) (Scheme 18). Reductive deoxygenation of 80 using NaBH\textsubscript{4} in dry DMSO at 160 \degree C for 10 min under N\textsubscript{2} atmosphere gave 81 (80\%), which on further reaction with PMBBBr and NaH in dry THF at 0 \degree C to room temperature for 4 h afforded 77 (95\%). Hydrolysis of 1,2-acetanide in 77 on reaction with 60\% aq. AcOH and conc. HCl (cat.) at room temperature for 18 h furnished the lactol 82, which on oxidative cleavage with NaIO\textsubscript{4} in CH\textsubscript{2}Cl\textsubscript{2} at 0 \degree C to room temperature for 3 h gave aldehyde. Subsequently, Wittig olefination of the aldehyde with (methoxycarbonylmethylene) triphenyl phosphorane in MeOH at 0 \degree C to room temperature for 2 h gave \textit{cis}-ester as major isomer 75 in 77\% yield (8.5:1.5). Treatment of ester 75 with catalytic amount of conc. HCl (2-3 drops) in 1,4-dioxane:H\textsubscript{2}O (1:1) afforded the lactone 83 (75\%), with concomitant O-formate ester hydrolysis. Finally, oxidative deprotection of PMB group in 83 with DDQ in wet CH\textsubscript{2}Cl\textsubscript{2} furnished 71 in 72\% yield. The spectral data of synthetic 71 was comparable with the natural product data reported, \([\alpha]_D = -69.1 \text{ (c 0.38, H}_2\text{O)}\); \{ref.\textsuperscript{39} \([\alpha]_D = -68.4 \text{ (c 0.41, H}_2\text{O)}\).
Synopsis

Scheme 18

\[ \begin{align*}
11 & \xrightarrow{a} \text{HO} \quad \text{79 (82\%)} \\
& \xrightarrow{b} \text{TsO} \quad \text{80 (75\%)} \\
& \xrightarrow{c, d} \text{RO} \quad \text{81 R = H (80\%)} \\
& \text{77 R = PMB (95\%)} \\
& \xrightarrow{e} \text{PMBO} \quad \text{82 (75\%)} \\
& \xrightarrow{f} \text{OCHO} \quad \text{OPMB} \quad \text{83 (75\%)} \\
& \xrightarrow{g} \text{PMBO} \quad \text{81} \quad \text{(72\%)}
\end{align*} \]

Reagents and conditions: (a) TBAF, THF, 0 °C-rt, 14 h; (b) p-TsCl, Et\textsubscript{3}N, CH\textsubscript{2}Cl\textsubscript{2}, 0 °C-rt, 2 h; (c) NaBH\textsubscript{4}, dry DMSO, 160 °C, 10 min; (d) PMBBR, NaH, THF, 0 °C-rt, 4 h; (e) 60\% AcOH, Cat. conc. HCl, rt, 18 h; (f) NaO\textsubscript{4}, CH\textsubscript{2}Cl\textsubscript{2}, aq.NaHCO\textsubscript{3}, 0 °C-rt, 3 h; (ii) Ph\textsubscript{3}P=CHCOOME, MeOH, 0 °C-rt, 2 h; (g) 1,4-Dioxane:H\textsubscript{2}O(1:1), Cat. conc. HCl, 18 h; (h) DDQ, CH\textsubscript{2}Cl\textsubscript{2}:H\textsubscript{2}O (19:1), 0 °C-rt, 2 h.

Similar synthetic strategy was adopted for the synthesis of 4R, 5R-diastereomer from D-xylose and its conversion into 73 (Scheme 19). The spectral data was in accordance with lit. data \([\alpha]_D = -228.2 \; (c \; 0.56, \; H_2O)\); \{ref. \(40\) \([\alpha]_D = -230.0 \; (c \; 0.55, \; H_2O)\}.

Scheme 19

\[ \begin{align*}
63 & \xrightarrow{a} \text{TsO} \quad \text{84 (87\%)} \\
& \xrightarrow{b, c} \text{RO} \quad \text{85 R = H (82\%)} \\
& \text{78 R = PMB (77\%)} \\
& \xrightarrow{d} \text{PMBO} \quad \text{86 (63\%)} \\
& \xrightarrow{e} \text{OCHO} \quad \text{OPMB} \quad \text{87 (78\%)} \\
& \xrightarrow{f} \text{PMBO} \quad \text{73 (71\%)} \\
& \xrightarrow{g} \text{73 (71\%)}
\end{align*} \]

Reagents and conditions: (a) p-TsCl, Et\textsubscript{3}N, CH\textsubscript{2}Cl\textsubscript{2}, 0 °C-rt, 2 h; (b) LiAlH\textsubscript{4}, dry THF, 0 °C-rt, 18 h; (c) PMBBR, NaH, THF, 0 °C-rt, 4 h; (d) 60\% AcOH, Cat. conc. HCl, rt, 18 h; (e) NaO\textsubscript{4}, CH\textsubscript{2}Cl\textsubscript{2}, aq.NaHCO\textsubscript{3}, 0 °C-rt, 3 h; (ii) Ph\textsubscript{3}P=CHCOOEt, MeOH, 0 °C-rt, 2 h; (f) 1,4-Dioxane:H\textsubscript{2}O(1:1), Cat. conc. HCl, 18 h; (g) DDQ, CH\textsubscript{2}Cl\textsubscript{2}:H\textsubscript{2}O (19:1), 0 °C-rt, 2 h.

Having successfully synthesized the (4R, 5S)- and (4R, 5R)-lactones, 71 and 73, the study was then extended to the synthesis of angiopterlactone A 74\textsuperscript{32} (Figure 5). Angiopterlactone A 74\textsuperscript{32} is unique metabolite possessing dual-lactone skeleton, isolated from rhizome of Angiopteris
caudatiformis and having insect antifeeding activity against Plutella xylostella and Heliothis virescens and slightly cytotoxic against HeLa cells, with an IC$_{50}$ value of 68.8 µM.

**Figure 5**

According to the retroanalysis of 74 (Scheme 20), it could be fragmented into two lactones 71 and 88, wherein, the butyrolactone 88 could be made from alcohol 89. Diol 90 could be the appropriate building block for the synthesis of 89, while 90 could be made from D-Mannitol. Thus, C-2, C-3 and C-4 of D-mannitol are retained for the synthesis of 88, while C-1 on deoxyganation would give the methyl group and the C-5, C-6-diol would be converted into acetic acid moiety.

**Scheme 20**

Accordingly, known alcohol 91 on alkylation with BnCl and NaH in THF at 0 °C to room temperature for 10 h gave 92 in 60% yield. Reaction of 92 with 60% aq. AcOH at room temperature for 5 h (Scheme 21) afforded the required diol 90 (57%). Treatment of diol 90 with Ph$_3$P, imidazole and I$_2$ in CH$_2$Cl$_2$ at 0 °C to room temperature for 2 h furnished olefin 93 (32%), which on reaction with borane DMS in THF at 0 °C to room temperature for 10 h afforded 89 in 89% yield. Oxidation of alcohol 89 with TEMPO and BIAB in CH$_2$Cl$_2$:H$_2$O (1:1) at room temperature for 90 min afforded the acid 94 in 93% yield. Treatment of acid 94 with PTSA in MeOH at room temperature for 2 h underwent acetonide hydrolysis and concomitant cyclization to afford the lactone 88 in 63% yield.
Having successfully synthesized two lactones 72 and 88, the attempted etherification with BF₃·Et₂O and CH₂Cl₂ at 0 °C to room temperature for 4 h, met with failure to angiopterlactone A 74. Work was abandoned at this stage.

**Scheme 22**
References


