CHAPTER-I

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

SECTION-A

Radical cyclization reaction: rules and applications
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 the 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

Synthetic applications of radical reactions have been investigated extensively for a wide range of applications.\textsuperscript{1–8} These protocols have gained a prominent position as tools available to organic chemists enroute to the synthesis of complex target molecules.\textsuperscript{9,10} The successful application of radical chemistry is attributable to: a) to its mild reaction conditions (for eg. formation of C–C bonds), b) their complementarity to classical reactions (see the ‘Umpolung’ of radical intermediates) and c) for the formation of multiple bonds in a single synthetic operation through cascade process. Radical cyclization protocols are particularly very useful among all the radical reactions reported so far.\textsuperscript{11–19}

1. Baldwin Rules for Ring Closure

Three rules on an empirical basis, have been found useful to predict the relative facility of ring forming reactions. Ring-forming reactions are important and common processes in organic chemistry.

\textbf{Scheme 1}

\begin{center}
\includegraphics[width=0.5\textwidth]{scheme1.png}
\end{center}

Baldwin rules will be useful to organic chemists, especially in planning the synthesis of molecules. Further, these rules also indicate certain experiments which may be helpful to define their limits more precisely. The rules are of a stereochemical in nature and likely that unambiguous case of all the possibilities are as yet unknown.
Rule 1: Tetrahedral Systems: Scheme 2
(a) 3 to 7-Exo-Tet are all favoured\textsuperscript{20} processes with many literature precedents;\textsuperscript{21}
(b) 5 to 6-Endo-Tet are disfavoured.\textsuperscript{22}

\textbf{Scheme 2:} Tetrahedral

\begin{center}
\begin{tabular}{cccc}
3-Exo-Tet & 4-Exo-Tet & 5-Exo-Tet & 6-Exo-Tet \\
\end{tabular}
\end{center}

\begin{center}
\begin{tabular}{ccc}
7-Exo-Tet & 5-Endo-Tet & 6-Endo-Tet \\
\end{tabular}
\end{center}

Rule 2: Trigonal Systems: Scheme 3
(a) 3 to 7-Exo-Trig are all favoured processes with many literature precedents;\textsuperscript{23}
(b) 3 to 5-Endo-Trig are disfavoured;\textsuperscript{24} 6 to 7-Endo-Trig are favoured.

\textbf{Scheme 3:} Trigonal

\begin{center}
\begin{tabular}{cccc}
3-Exo-Trig & 4-Exo-Trig & 5-Exo-Trig & 6-Exo-Trig \\
\end{tabular}
\end{center}

\begin{center}
\begin{tabular}{ccc}
7-Exo-Trig & 3-Endo-Trig & 4-Endo-Trig & 5-Endo-Trig \\
\end{tabular}
\end{center}

\begin{center}
\begin{tabular}{cc}
6-Endo-Trig & 7-Endo-Trig \\
\end{tabular}
\end{center}
Rule 3: Digonal Systems: Scheme 4

(a) 3 to 4-Exo-Dig are disfavoured processes; 5 to 7-Exo-Dig are favoured;\textsuperscript{25}
(b) 3 to 7-Endo-Dig are favoured.\textsuperscript{26}

Scheme 4: Digonal

Baldwin described a ring-forming process with the prefix \textit{Exo}, when the breaking bond is \textit{exo}-cyclic to the \textit{smallest so formed ring} and \textit{Endo} correspondingly, as in Scheme 1. Further, a numerical prefix was used to describe the ring size, being the number of atoms constituting the skeleton of the cycle, and finally, the suffixes \textit{Tet}, \textit{Trig}, and \textit{Dig} were used to indicate the geometry of the carbon atom undergoing the ring-closure reaction (Scheme 1). The suffixes are indicative of the tetrahedral, trigonal and digonal nature of the carbon atoms respectively. The various possibilities on \textit{exo} and \textit{endo} mode of cyclizations are shown in Schemes 2-4.

Radical reaction chemistry has shown a strong impact on the synthesis of terpenes, with special reference to the formation of five-membered rings. The pioneering work on the synthesis of hirsutene, a linear triquinane by Curran \textit{et al.}\textsuperscript{27} may be considered as an important milestone. Over the decades, free radical chemistry has emerged as a powerful method for the synthesis of carbocycles.\textsuperscript{28} The studies reported by pioneers like Wilcox,\textsuperscript{29} RajanBabu\textsuperscript{30} and Bartlett\textsuperscript{31} have established useful strategies for the preparation of chiral, polyfunctionalized cyclopentanoid molecules from readily available carbohydrate type precursors.
Heterocyclic scaffolds are found in a wide variety of naturally occurring compounds.\textsuperscript{32} The importance of heterocyclic compounds due to their pharmacological and biological activities, synthetic strategies have been developed. Radical cyclization is an established methodology for the synthesis of heterocycles,\textsuperscript{33,34} with five- and six-membered nitrogen-and oxygen-heterocycles, which are important structural units that are present in diverse biologically active and medicinally significant molecules.\textsuperscript{35,36}

The proximity effect of two reacting partners results in a considerable enhancement of the rate of an intramolecular reaction, while, the concept of tethering two reaction components to make a reaction intramolecular is a well-known synthetic strategy. This strategy is a well established for the synthesis of various compounds by radical cyclization, particularly for the synthesis of medium-sized carbocycles or heterocycles.\textsuperscript{37}

2. Reagents, Solvents, Radical Initiators, and Reactivity

Table: Reagents, solvents, radical initiators, and reactivity in radical reactions\textsuperscript{38-43}

<table>
<thead>
<tr>
<th>S. NO</th>
<th>Reagents</th>
<th>Solvent</th>
<th>Radical initiator</th>
<th>Reactivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>(n)-Bu(_3)SnH</td>
<td>Benzene, Toluene, THF, DIPEA, DME, MeCN, EtOAc, 2-Butanone, Dioxane and Pentane</td>
<td>AIBN, BF(_3), O(_2), ACCN and AMBN</td>
<td>Moderate</td>
</tr>
<tr>
<td>2.</td>
<td>(n)-Bu(_3)SnCl + NaBH(_3)CN</td>
<td>(t)BuOH and EtOH</td>
<td>AIBN</td>
<td>More</td>
</tr>
<tr>
<td>3.</td>
<td>(TMS)(_3)SiH</td>
<td>Toluene, Benzene, Hexane, water, CH(_2)Cl(_2) and THF</td>
<td>AIBN, BF(_3), O(_2), Et(_3)B, AMBN and ACCN</td>
<td>Less</td>
</tr>
<tr>
<td>4.</td>
<td>(n)-Bu(_3)GeH</td>
<td>Cyclohexane and Toluene</td>
<td>AIBN, ACCN and Et(_3)B</td>
<td>Moderate</td>
</tr>
<tr>
<td>5.</td>
<td>PhSH</td>
<td>Benzene, Toluene, (t)BuOH and Cyclohexane</td>
<td>AIBN and ACCN</td>
<td>Less</td>
</tr>
</tbody>
</table>

Copper(I) halides, manganese(III) acetate, and iron(III) chloride are also among the very useful and efficient reagents used for initiation of radical cyclization reactions.\textsuperscript{44} The triethylborane and molecular oxygen system is also used as a very good radical initiator. The use of water as a solvent is a tremendous development in the field of radical cyclization. The water-soluble initiator 2,2'-azobis[2-(2-imidazolin-2-yl)propane] dihydrochloride is used for carrying out the radical reactions in water.\textsuperscript{45}
The transferability of various atoms and groups X to tin radicals is generally in the order I > Br > SePh = OC(S)SMe > Cl > SPh. The reactivity order of various R groups toward tin hydride is aryl = vinyl > alkyl > allyl = benzyl. Primary, secondary, and tertiary alkyl radicals do not show considerable difference in their reactivity toward tin hydride. Nitriles are also useful radical acceptors. An imine functional group (oxime ether, hydrazone, imine, etc.) alters the normal electronic character of the carbonyl group. Carbonyl acceptors are usually less satisfactory as radical acceptors than alkene or imine systems. The 5-exo cyclization rate onto carbon–nitrogen double bonds is known to be more rapid than the rate for simple alkenes.

3. Mechanistic Pathways: Regio- and Stereoselectivity

Radical cyclizations involve the addition of a free radical to C(sp) or C(sp\(^2\)) bonds of alkenes, alkynes, allenes, arenes, conjugated dienes and other carbon–carbon or carbon–heteroatom multiple bonds. The typical course of this cyclization reaction involves: (i) reaction of tri(n-butyl) tin hydride and AIBN to generate \(n\)-Bu\(_3\)Sn\(^-\) radical; (ii) specific radical R’ is generated from the organic substrate RX by atom or group abstraction; (iii) addition of the radical R’ to C(sp) or C(sp\(^2\)) bonds of alkenes, alkynes, allenes, arenes, conjugated dienes, and other carbon–carbon or carbon–heteroatom multiple bonds to form a new radical; and (iv) abstraction of a radical H’ from another molecule of tri(n-butyl)tin hydride by the newly formed radical to afford the final product (Scheme 5). The overall reaction is driven by the exchange of a weaker Sn–H bond for a relatively strong Sn–X bond.

**Scheme 5**

<table>
<thead>
<tr>
<th>Initiation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bu(_3)SnH</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Propagation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bu(_3)Sn(^-) + RX</td>
</tr>
<tr>
<td>R’</td>
</tr>
<tr>
<td>Bu(_3)Sn(^-) + Bu(_3)SnH</td>
</tr>
<tr>
<td>Bu(_3)Sn(^-) + R-H</td>
</tr>
</tbody>
</table>

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4. Radical cyclization reactions used for formation of Heterocyclic compounds

Radical cyclizations have been applied more extensively to the synthesis of five-membered rings than to that of six-membered rings for several reasons. For example, cyclizations are generally faster for the formation of five-membered rings than for any other ring size – the simple 5-hexenyl radical is known to cyclize 20 times faster than the 6-heptenyl radical. Therefore, reactions forming five-membered-rings are thus least affected by competitive formation of the reduced, uncyclized byproducts. For the parent 5-hexenyl radical, 5-exo cyclization is 50 times faster than 6-endo cyclization. Radicals generated from substituted substrates often show higher selectivities. Radical cyclizations affording five-membered rings are often highly stereoselective. The major product in a 5-exo radical cyclization can be predicted by the application of Beckwith’s transition-state model. According to this model, the early transition state of a 5-exo radical cyclization – resembling a cyclohexane ring – favors the chair from over the boat, where the substituents are aligned pseudoequatorially rather than pseudoaxially. Simple model studies revealed that substitution at C-1 or C-3 of the 5-hexenyl radical gives primarily cis-disubstituted cyclopentanes, whereas substitution at C-2 or C-4 gives primarily trans-disubstituted cyclopentanes. Stereoselectivity was found to be highest for C-1 and C-4 substituted systems. Theoretical treatments and experimental results may aid in the planning of highly stereoselective reactions, and allow ‘exceptions’ to Beckwith’s guidelines.

Synthesis of Nitrogen-Heterocycles
Fuwa and Sasaki approach:

Fuwa and Sasaki reported aryl radical cyclization of 2-bromoaniline-derived enecabamates by a 5-endo-trig mode for the synthesis of 2-substituted indulines in moderate to good yields (Scheme 6).

Scheme 6

\[ \text{Br} \quad \begin{array}{c} \text{Boc} \\ \text{R} \end{array} \quad \xrightarrow{n\text{-Bu}_3\text{SnH, AIBN}} \quad \begin{array}{c} \text{Boc} \\ \text{R} \end{array} \]

1. 2 R = Ph (82%), 3 R = 4-MeOC_6H_4 (85%), 4 R = 4-ClC_6H_4 (62%)
2. 5 R = 2-MeC_6H_4 (72%), 6 R = 2-furyl (51%)
Ishibashi *et al.* approach: \(^{52}\)

Studies by Ishibashi *et al.* suggest that the *exo*- or *endo*-selectivity of radical cyclization onto the double bond of enamides can be controlled by positional change of the carbonyl group (Scheme 7).

**Scheme 7**

![Scheme 7](image)

Majumdar *et al.* approach: \(^{53}\)

Majumdar *et al.* reported the regioselective synthesis of potentially bioactive spiroheterocycles by 5-*exo*-trig aryl radical cyclization (Scheme 8).

**Scheme 8**

![Scheme 8](image)

Gharpure *et al.* approach: \(^{54}\)

Gharpure *et al.* reported the synthesis of *aza*-cage vinyltin derivative by way of two 5-*exo*-trig radical cyclizations of dienynamine (Scheme 9).
Zlotorzynska et al. approach: Zlotorzynska et al. reported the stereoselective synthesis of the polyhydroxylated alkaloid by radical cyclization of silyl enol ethers (Scheme 10).

De Kimpe et al. approach: De Kimpe et al. achieved a novel diastereoselective synthesis of [4.2.0]-bicyclic \( \beta \)-lactams by 6-\textit{exo}-trig radical cyclization of 4-(2-bromo-1, 1-dimethylethyl)azetidin-2-ones (Scheme 11).
Majumdar et al. approach:  

Majumdar et al. reported the regioselective synthesis of pentacyclic polyheterocycles by 6-endo-trig cyclization of 4-[(2'-bromoaryl)aminomethyl]-2H-pyrano[3, 2-c]coumarins (Scheme 12).

Scheme 12

\[ \text{Scheme 12} \]

\[ R^1 = H, R^2 = Me, A/B 45\%:30\%, \quad R^1 = Me, R^2 = Me, A/B 50\%:33\% \]
\[ R^1 = Et, R^2 = Me, A/B 45\%:35\%, \quad R^1 = Me, R^2 = H, A/B 40\%:35\% \]
\[ R^1 = Et, R^2 = H, A/B 42\%:37\% \]

Synthesis of Oxygen-Heterocycles

Sammis et al. approach:  

Sammis et al. reported that the oxygen-centered radical could undergo a 5-exo cyclization with either a silyl enol ether or a terminal olefin. The oxygen-centered radical addition is completely chemoselective to the silyl enol ether moiety (Scheme 13).

Scheme 13

\[ \text{Scheme 13} \]

\[ 40 \text{ (81\%, dr 69:31)} \]

\[ 74\% (1:9) \]
Majumdar et al. approach: \(^5^9\)

Majumdar et al. reported the regioselective synthesis of pentacyclic heterocyclics by 6-\textit{endo} cyclization of bioactive coumarin substrates (Scheme 14).

\textbf{Scheme 14}

\[ \begin{align*}
\text{R}^1 & = \text{R}^2 = \text{R}^3 = \text{H}, & \text{45} \\
\text{R}^1 & = \text{R}^2 = \text{R}^3 = \text{Me}, & \text{46} \\
\text{R}^1 & = \text{H}, \text{R}^2 = \text{Me}, \text{R}^3 = \text{H}, & \text{47} \\
\text{R}^1 - \text{R}^2 & = 3,4\text{-benzo}, \text{R}^3 = \text{H}, & \text{48} \\
\text{R}^1 & = \text{Me}, \text{R}^2 = \text{R}^3 = \text{H} & \text{49}
\end{align*} \]

Majumdar et al. approach: \(^6^0\)

Majumdar et al. reported the synthesis of bioactive 1,8-naphthyridine-2(1\(H\))-one-annulated benzopyran derivatives by 6-\textit{endo} cyclization of 4-(2\(^{\prime}\)-bromobenzyloxy)-1-phenyl-1,8-naphthyridin-2(1\(H\))-ones (Scheme 15).

\textbf{Scheme 15}

\[ \begin{align*}
\text{R} & \text{= H (78%)}, & \text{51} \\
\text{R} & \text{= OMe (70%)}, & \text{52}
\end{align*} \]

Gharpure et al. approach: \(^6^1\)

Gharpure et al. reported the synthesis of oxa-cage compound from aryl iodide via two tandem 5-\textit{exo}-trig cyclization (Scheme 16).
Scheme 16

Stork et al. approach: \(^{62}\)

Stork et al. reported the regioselective synthesis of cyclic acetal by 5-\textit{exo} cyclization of haloacetal derivative (Scheme 17).

Scheme 17

Srikrishna et al. approach: \(^{63}\)

Srikrishna et al. reported the regioselective synthesis of cyclic acetal by 5-\textit{exo} cyclization of haloacetal derivative (Scheme 18).

Scheme 18

Stork et al. approach: \(^{64}\)

Stork et al. examined the intermolecular trapping of the cyclized radical by terminal activated olefins (CH\(_2\)=CHX) in the presence of the tin hydride (Scheme 19).
This reaction was achieved by running the reaction with molecular oxygen as the radical trap and tin hydride as a chain transfer reagent (Scheme 20).

Lopez et al. approach:\textsuperscript{67-69}

Lopez et al. reported a preferred 6-exo cyclization in iodo ester, since it is believed to occur via chiral-axial-like transition state. The 5-exo cyclization product was observed as a minor product, due a possible less stable chair-equatorial transition state that was postulated (Scheme 21).
However, the situation is reversed due to the different configuration at the anomeric center in 66, the 5-exo cyclization process is favored to give 67 (Scheme 22).

**Scheme 22**

Stork *et al.* approach: ⁷⁰, ⁷¹

Stork *et al.* reported a method for the introduction of an angular methyl group based on the stereoselective cyclization leading to fused polycyclic compound (Scheme 23).

**Scheme 23**

Fraser-Reid *et al.* approach: ⁷²

Fraser-Reid *et al.* reported the cyclization-cyanation process by a 5-exo mode reaction (Scheme 24).
Haudrechy et al. approach:⁷³

Haudrechy et al. reported the spiroketalization based on a 5-exo radical cyclization of pyranose derivatives (Scheme 25).

Harrison et al. approach:⁷⁴,⁷⁵

Harrison et al. reported the synthesis of spiroacetal by 5-exo radical cyclization onto cyclic alkenes (Scheme 26).
Srikrishna et al. approach:\textsuperscript{76}

Srikrishna et al. reported the synthesis of spiroacetal by 5\textit{-exo}-dig radical cyclization reaction (Scheme 27).

\textbf{Scheme 27}

\begin{center}
\includegraphics[width=0.5\textwidth]{scheme27.png}
\end{center}

Sha et al. approach:\textsuperscript{77}

Sha et al. reported the synthesis of spiro compound by radical translocation-cyclization of cycloalkanones bearing a $\beta$-iodo-\textit{$\alpha$, $\beta$}-unsaturated ester or nitrile side chain (Scheme 28).

\textbf{Scheme 28}

\begin{center}
\includegraphics[width=0.5\textwidth]{scheme28.png}
\end{center}

Chattopadhyaya et al. approach:\textsuperscript{78}

Chattopadhyaya et al. reported the formation of C-C bond by 5\textit{-exo}-trig radical cyclization on carbohydrate derivatives (Scheme 29).

\textbf{Scheme 29}

\begin{center}
\includegraphics[width=0.5\textwidth]{scheme29.png}
\end{center}
De Mesmaeker et al. approach:79

De Mesmaeker et al. reported the synthesis of C-disaccharides by 5-exo radical cyclization reaction on carbohydrate derivative (Scheme 30).

**Scheme 30**
Chapter I, Section A

References

20. The words favoured and disfavoured in these Rules were chosen to imply a facility or otherwise of ring closure. Any generalization about a reaction pathway is necessarily limited by reaction conditions, e.g., at very high temperatures or under photochemical activation sufficient vibrational energy may be available to achieve otherwise sterically inaccessible conformations. For this reason a disfavoured ring closure is not an
impossible reaction, merely a process which may not compete effectively with alternative 
favoured ring closures or other reaction pathways.

23. The literature is replete with examples of 3 to 7-Exo-Trig reactions: e.g., all lactonisations 
of ω-hydroxy acids or esters are of this type, as are the formation of lactams from ω-
amino acids and their derivatives and also the Dieckmann cyclization of diesters.
25. Some examples of Exo-digonal closures are as follows: (a) 5-Exo-Dig: Kandil, S. A.; 
Dessy, R. E. J. Am. Chem. Soc. 1966, 88, 3027. (b) 6-Exo-Dig: Dillard, R. E.; Easton, N. 
26. Examples of Endo-digonal closures: (a) 4-Endo-Dig: Hekkert, G. L.; Drenth, W. Rec. 
Trav. Chim. 1961, 80, 1285. (b) 5-Endo-Dig: ref. 26 (a). (c) 6-Endo-Dig: Bottini, A. T.; 
Carson, F. P.; Bottner, E. F. J. Org. Chem. 1965, 30, 2988. (d) 7-Endo-Dig: ref. 26 (b). I 
have not found examples of 3-Endo-Dig and 7-Exo-Dig closures.
32. (a) Eicher, T.; Hauptmann, S. The Chemistry of Heterocycles: Structure, Reactions, 
Synthesis and Applications; Wiley-VCH: Weinheim, 2003. For reviews on biologically 
active nitrogen heterocycles, see: (b) Kang, E. J.; Lee, E. Chem. Rev. 2005, 105, 4348. 
Bermejo, A.; Figadere, B.; Zafra-Polo, M. C.; Barrachina, I.; Estornell, E.; Cortes, D. 
33. (a) Giese, B. Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds; 


Chapter I, Section A


CHAPTER I

SECTION-B
Radical cyclization reaction for cis-fused bicyclic systems: impact of alkyl side chains in L-Ara configuration
SECTION-B: Radical cyclization reaction for cis-fused bicyclic systems: impact of alkyl side chains in L-Ara configuration

This section deals with radical cyclization reaction for cis-fused bicyclic systems: impact of alkyl side chains in L-Ara configuration

Free radical cyclization has been applied extensively in natural product synthesis. Synthetic application of free radical cyclizations for C-C bond formation is a versatile protocol for the construction of carbon frameworks, particularly cis-fused bicyclic systems. A suitably substituted 5-hexynyl radical usually undergoes a highly regioselective ring closure by a 5-exo-dig mode preferentially. Because of the presence of often numerous chiral centers in natural products, diastereoselectivity is crucial in their synthesis, while carbohydrates have been used as “off-templates” for the stereoselective synthesis of chiral γ- and δ-lactones. Likewise, the regio- and stereoselective synthesis of bis-butyro-lactones by 5-exo-dig radical cyclization reactions on carbohydrate templates becomes yet another interesting and challenging protocol for the natural product synthesis. Such a protocol was earlier utilized by our group for the successful synthesis of several natural products containing the bis-butyro-lactone moieties (Figure 1).

Figure 1

In our earlier studies, a 5-exo-dig radical cyclization approach was efficiently utilized for the synthesis of avenaciolide (1) and other structurally related natural products 2-6. Sharma et al. proposed a general strategy on the use of radical cyclization reaction in 5-exo-dig mode to result in the cis-fused bicyclic systems with simultaneous introduction of exo-methylene group. Thus, after the introduction of side chain in DAG 7, 8a-8c were converted into radical precursors 9a-9c, which on cyclization afforded the furo-furans 11a-11c. Finally, oxidation of 11a-11c respectively furnished 1-3 (Scheme 1).
A similar strategy by the use of a C-3 radical was adopted for the synthesis of $4^{13}$ and $5$.$^{11}$ Accordingly, the xanthate esters $13\text{a}-13\text{b}$ on radical cyclization gave the bicyclic systems $15\text{a}-15\text{b}$, which on further transformations gave $4^{13}$ and $5^{11}$ respectively (Scheme 2).

The above cis-fused bicyclic systems were successfully synthesized by 5-exo-dig radical cyclization through C-2 and C-3 radical intermediates with different alkyl side chains from diacetone glucose (DAG) 7.

In further studies, a similar strategy was used for the synthesis of iso-avenaciolide$^{15}$ (1a), a structurally related natural product, which is epimeric to 1 at the side chain carbon.
However, the attempt for cyclization of the radical intermediate 19, generated either from 7 or L-arabinose derivative 16, met with failure and synthesis of 20 could not be achieved by the above protocol (Scheme 3).

Scheme 3

The successful synthesis of 1-5 and failure to attain 20 inferred that; (a) the systems with D-Xylo configuration undergo a facile cyclization and (b) the systems with L-Ara configuration resisted to do so. The above observations on the resistance of 19 to undergo radical cyclization prompted us to study the impact of the side chain on radical cyclization reactions. The study thus, was aimed at understanding the impact of alkyl side chains of furanoside ring systems with L-Ara configuration on the radical cyclization.

The retrosynthetic analysis (Scheme 4) revealed that the synthesis of cis-fused bicyclic systems 21a-21c and 22a-22c, with different lengths of alkyl side chains could be achieved through the precursor’s 23a-23c and 24a-24c, which in turn could be obtained from anomeric mixtures of 25, 26 and 27. These anomeric systems in turn could be envisaged from L-arabinose 28 as a common starting material.
Thus, the radical reaction here would perform three very important functions at one go \textit{viz.} (i) formation of \textit{cis}-fused bicyclic system (ii) concomitant introduction of a \textit{exo}-methylene group and (iii) control and induction of the required stereochemistry at C-3 during the C-C bond formation, while giving a major output on the impact of alkyl side chains on radical cyclization reactions to give bicyclic systems.

Accordingly, commercially available 28 was converted into 30 by a known procedure (Scheme 5). Alcohol 30 on reaction with PMBBr in the presence of NaH in dry THF at 0 °C to room temperature for 4 h furnished PMB ether 31 in 81% yield (Scheme 5). In the $^1$H NMR spectrum of 31 the H-3a and H-6a protons resonated at $\delta$ 5.82 and $\delta$ 4.60 ($J = 3.6$ Hz).
as two doublets, while Ar-H protons resonated at $\delta$ 6.82 and 7.22 ($J$ = 8.6 Hz) as two doublets and acetonide protons at $\delta$ 1.26 and 1.30 as two singlets. HRMS showed at $m/z$ 571.2507 for C$_{32}$H$_{40}$O$_6$SiNa (M+Na)$^+$ confirming the product 31.

**Scheme 5**

Desilylation of 31 with $n$-Bu$_4$NF (TBAF) at 0 °C to room temperature for 14 h gave alcohol 32 in 89% yield (Scheme 6). $^1$H NMR spectrum of 32 showed the disappearances of protons corresponding to TBDPS group. HRMS showed $m/z$ 333.1315 for C$_{16}$H$_{22}$O$_6$Na (M+Na)$^+$ further confirming the structure of 32.

**Scheme 6**

Reaction of 32 with $p$-toluenesulphonyl chloride and Et$_3$N in CH$_2$Cl$_2$ at 0 °C to room temperature for 4 h furnished tosylate 33 in 81% yield (Scheme 7). In the $^1$H NMR of 33, Ar-H resonated at $\delta$ 7.32 and 7.75 as two doublets ($J$ = 7.6 Hz) and Ar-CH$_3$ at $\delta$ 2.45 as a singlet confirming the tosylation. HRMS showed $m/z$ 487.1388 for C$_{23}$H$_{28}$O$_8$NaS (M+Na)$^+$ confirming the structure of 33.

Finally, deoxygenation of 33 using NaBH$_4$ in dry DMSO$^{16}$ at 160 °C for 10 min under nitrogen atmosphere gave 34a in 79% yield (Scheme 7). The $^1$H NMR of 34a indicated the disappearance of proton signals corresponding to $p$-toluenesulphonyl protons, while CH$_3$ protons resonated at $\delta$ 1.32 ($J$ = 6.7 Hz) as a doublet, H-5 proton resonated at $\delta$ 4.03 as a
multiplet, while the other proton signals appeared at the expected chemical shifts. HRMS showed m/z 317.1355 for C_{16}H_{22}O_{5}Na (M+Na)^+ confirming the product 34a.

**Scheme 7**

Further, the introduction of requisite C2 and C5 side chains on furanoside ring 32 was achieved by a three step sequence. Accordingly, alcohol 32 on oxidation with IBX and DMSO at room temperature for 3 h afforded aldehyde 35 (Scheme 8). In its $^1$H NMR spectrum the aldehyde proton resonated at $\delta$ 9.02 as a singlet, while IR showed the absorption at 1775 cm$^{-1}$ for carbonyl group.

**Scheme 8**

The C2 and C5 alkyl chains were incorporated on 35 by Wittig olefination reaction with respective phosphonium salts. Thus, 35 on reaction with (methyl)triphenyl phosphonium iodide and t-BuOK in THF afforded the olefin 36a in 49% yield, while a similar reaction of 35 with (n-butyl)triphenyl phosphonium bromide and t-BuOK in THF gave 36b in 50% yield (Scheme 8).

In the $^1$H NMR spectrum of 36a the olefinic protons resonated at $\delta$ 5.21 ($J = 10.6$ Hz) as a doublet of doublet and $\delta$ 5.94 as a multiplet. HRMS showed m/z 329.1366 for C_{17}H_{22}O_{5}Na (M+Na)^+ confirming the structure 36a. In $^1$H NMR spectrum of 36b the olefinic
protons resonated at δ 5.52-5.59 as a multiplet, while rest of the protons resonated at the expected chemical shifts. HRMS of 36b showed \( m/z \) 371.1841 for \( C_{20}H_{28}O_5Na \) (M+Na)+ confirming the structure 36b. Optical rotation values of 36a and 36b were found to be \( [\alpha]_D = -47.2 \) (c 0.68), \( [\alpha]_D = -12.0 \) (c 0.73) in chloroform respectively.

In order to reduce the double bond, olefins 36a and 36b were independently subjected to hydrogenation with PtO\(_2\) in EtOAc under hydrogen pressure (40 psi) afford 34b (89%) and 34c (75%) respectively (Scheme 9).

**Scheme 9**

\[
\begin{align*}
R &= H \\
36a & \\
R &= n-C_3H_7 \\
36b & \\
PtO_2, EtOAc & \\
2 h & \\
R &= C_2H_5 \\
34b & \\
R &= n-C_5H_11 \\
34c & \\
\end{align*}
\]

\(^1\)H NMR spectra of 34b and 34c indicated the disappearance of proton signals corresponding to olefinic protons and revealed the side chain introduction. For 34b, the terminal methyl protons appeared at δ 0.93 (\( J = 7.4 \) Hz) as a triplet, while the methylene protons resonated at δ 1.66 as a multiplet. Rest of the protons appeared at the appropriate chemical shifts in 34b. HRMS for 34b showed \( m/z \) 331.1627 for \( C_{17}H_{24}O_5Na \) (M+Na)+ further confirming the assigned structure. \(^1\)H NMR spectrum of 34c showed terminal methyl protons at δ 0.88 (\( J = 6.4 \) Hz) as a triplet, methylene protons at δ 1.49 as multiplet and rest of the protons at the expected chemical shifts. HRMS for 34c showed \( m/z \) 351.2097 for \( C_{20}H_{31}O_5 \) (M+H)+ further confirming the assigned structure.

Having introduced the C1, C2 and C5 side chains, it was next aimed at the incorporation of propargyl group at C-2 position. This assignment was achieved in two steps. Accordingly, hydrolysis of acetonide in 34a, 34b and 34c on reaction with MeOH containing 2-3 drops of conc. HCl at 0 °C to room temperature gave the diastereomeric mixtures of methyl glycosides 25 (1:1.5), 26 (1:1.5) and 27 (4.5:5.5) respectively as α- and β anomers (Scheme 10).
The predominant formation of $\beta$-methyl glycosides in all the substrates indicates that alkyl group at C-5 does not allow the attack of methoxy group from $\alpha$-side due to steric interactions. Observation of above results indicates that $\beta$-methyl glycosides formed predominantly due to the presence of both the acetonide protection and the alkyl side chain at C-5 on the $\alpha$-side, thus allowing the incoming methoxy nucleophile to attack from the less hindered $\beta$-side preferentially.

Mechanism for the methanolysis may be explained as follows. The acetal-linked oxygen gets protonated and the bond between oxygen and anomeric carbon gets weakened and removed. The carbocation thus generated is stabilized as oxonium ion and accepts the readily available methoxy nucleophile either from the topside of the cation, leading to the formation of $\beta$-methyl glycoside or from the bottom side leading to the formation of the $\alpha$-methyl glycoside as described in Scheme 11.
The alkyl side chains at C-5 of the substrates also have a prominent role to play in the formation of the $\alpha$- (or) $\beta$-methyl glycosides. Methanolysis reactions were complete in 5-6 h and longer the side chain lesser the formation of $\beta$-methyl glycoside.

After methanolysis, anomeric mixtures 25, 26 and 27 were subjected to alkylation independently with propargyl bromide (Scheme 12) in the presence of NaH in THF to furnish 37a-c and 38a-c respectively by column chromatography. From the spectral analysis, 37a-c were confirmed as $\beta$-methyl glycosides and 38a-c as $\alpha$-methyl glycosides. In the $^1$H NMR spectrum of 37a, H-5 resonated at $\delta$ 4.77 as a singlet, while in 38a H-5 appeared at $\delta$ 4.83 ($J = 4.1$ Hz) as a doublet and newly introduced propargylic protons resonated at $\delta$ 2.42 ($J = 2.2$ Hz) as a triplet corresponding to acetylenic protons, while rest of the protons resonated at the appropriate chemical shifts. HRMS showed $m/z$ 329.1354 for C$_{17}$H$_{22}$O$_{5}$Na (M+Na)$^+$ for 37a and $m/z$ 329.1367 for C$_{17}$H$_{22}$O$_{5}$Na (M+Na)$^+$ for 38a, to confirm the assigned structures. The optical rotation values for 37a and 38a in chloroform were [$\alpha$]$_D$ = -218 ($c$ 0.66) and [$\alpha$]$_D$ = +129.0 ($c$ 0.36) respectively.

**Scheme 12**
In the \(^1\)H NMR spectrum of \(37b\), H-5 proton resonated at \(\delta 4.78\) as a singlet, while in \(38b\) H-5 proton appeared at \(\delta 4.85\) \((J = 4.1\ Hz)\) as a doublet, whereas rest of the protons resonated at the appropriate chemical shifts. HRMS for \(37b\) showed \(m/z\) 343.1524 for \(\text{C}_{18}\text{H}_{24}\text{O}_{5}\text{Na} (\text{M}+\text{Na})^+\), while \(m/z\) 343.1522 for \(\text{C}_{18}\text{H}_{24}\text{O}_{5}\text{Na} (\text{M}+\text{Na})^+\) for \(38b\) further confirmed the respective structures of \(37b\) and \(38b\). The optical rotation values for \(37b\) and \(38b\) in chloroform were \([\alpha]_D = -252.8\ (c 0.54)\) and \([\alpha]_D = +119.4\ (c 0.70)\) respectively.

In the \(^1\)H NMR spectrum of \(37c\), H-5 proton resonated at \(\delta 4.77\) as a singlet, while in \(38c\), H-5 proton appeared at \(\delta 4.84\) \((J = 4.3\ Hz)\) as a doublet, whereas rest of the protons resonated at the appropriate chemical shifts. HRMS for \(37c\) showed \(m/z\) 385.1988 for \(\text{C}_{21}\text{H}_{30}\text{O}_{5}\text{Na} (\text{M}+\text{Na})^+\), while \(38c\) showed \(m/z\) 385.2003 for \(\text{C}_{21}\text{H}_{30}\text{O}_{5}\text{Na} (\text{M}+\text{Na})^+\) further confirming the assigned structures of \(37c\) and \(38c\). The optical rotation values for \(37c\) and \(38c\) in chloroform were \([\alpha]_D = -240.7\ (c 0.93)\) and \([\alpha]_D = +95.0\ (c 0.84)\) respectively.

After the successful introduction of side chains at C-4 and propargyl appendage at C-2, next it was aimed at the conversion of C-3 -OH group into xanthate esters in two steps. Accordingly, the PMB ethers \(37a\)-\(c\) and \(38a\)-\(c\) were independently subjected to oxidative deprotection with DDQ in aq. CH\(_2\)Cl\(_2\) at room temperature to give alcohols \(39a\)-\(c\) and \(40a\)-\(c\) respectively (Scheme 13). In \(^1\)H NMR spectrum of \(39a\)-\(c\) and \(40a\)-\(c\) disappearance of Ar-H of PMB and rest of the protons at the expected chemical shifts, supported the structure. HRMS of \(39a\) and \(40a\) showed \(m/z\) 209.0793 and \(m/z\) 209.0797 for \(\text{C}_9\text{H}_{14}\text{O}_4\text{Na} (\text{M}+\text{Na})^+\) respectively, to further confirm the assigned structures.

**Scheme 13**
HRMS of 39b and 40b showed \( m/z \) 223.0945 and \( m/z \) 223.0947 for \( C_{10}H_{16}NaO_4 \) (M+Na)+, to further confirm the assigned structures. HRMS of 39c and 40c showed \( m/z \) 265.1427 and \( m/z \) 265.1420 for \( C_{13}H_{22}NaO_4 \) (M+Na)+ and confirmed the assigned structures.

Thus the derived alcohols 39a-c and 40a-c on reaction with NaH and CS\(_2\) followed by MeI at room temperature for 2 h were converted into the corresponding xanthate esters 23a-c and 24a-c respectively (Scheme 14). In \(^1\)H NMR spectrum of 23a the methylthio group resonated at \( \delta \) 2.57 as a singlet, while, the acetylenic proton at \( \delta \) 2.47 as a triplet \((J = 2.2 \text{ Hz})\) and the H-3 proton resonated at a downfield at \( \delta \) 5.61 \((J = 3.3 \text{ Hz})\) as a doublet. Likewise, in the \(^1\)H NMR spectrum of 24a the methylthio group resonated at \( \delta \) 2.58 as a singlet, while acetylenic proton at \( \delta \) 2.42 as a triplet \((J = 2.2 \text{ Hz})\) and the H-3 proton at \( \delta \) 5.90 \((J = 4.1 \text{ Hz})\) as a quintet. HRMS of 23a showed \( m/z \) 299.0391 for \( C_{11}H_{16}O_4S_2Na \) (M+Na)+, while 24a showed \( m/z \) 299.0389 for \( C_{11}H_{16}O_4S_2Na \) (M+Na)+, further confirming the assigned structures of 23a and 24a. The optical rotation values for 23a and 24a in chloroform were \([\alpha]_D = -304.2\) (c 1.04) and \([\alpha]_D = +285.1\) (c 0.44) respectively.

![Scheme 14](image.png)

In \(^1\)H NMR spectrum of 23b, the methylthio group resonated at \( \delta \) 2.57 as a singlet, while the acetylenic proton at \( \delta \) 2.46 as a triplet \((J = 2.2 \text{ Hz})\) and the H-3 proton at \( \delta \) 5.67 \((J = 4.6 \text{ Hz})\) as a doublet. In the \(^1\)H NMR spectrum of 24b, the methylthio group resonated at \( \delta \) 2.58 as a singlet, while the acetylenic proton at \( \delta \) 2.48 \((J = 2.2 \text{ Hz})\) as a triplet and the H-3
proton at $\delta$ 6.12 ($J = 4.5$ Hz) as a doublet of doublet, while rest of the protons resonated at the appropriate chemical shifts. HRMS of 23b showed $m/z$ 313.0547 for C$_{12}$H$_{18}$O$_4$S$_2$Na (M+Na)$^+$ and 24b showed $m/z$ 313.0549 for C$_{12}$H$_{18}$O$_4$S$_2$Na (M+Na)$^+$, further confirming the assigned structures of 23b and 24b. The optical rotation values for 23b and 24b in chloroform were $[\alpha]_D = -370.5$ (c 0.28) and $[\alpha]_D = +206.3$ (c 1.25) respectively.

Likewise, in $^1$H NMR spectrum of 23c the methylthio group resonated at $\delta$ 2.57 as a singlet, while the acetylenic proton at $\delta$ 2.39 ($J = 2.2$ Hz) as a triplet and H-3 proton at $\delta$ 5.59 ($J = 4.7$ Hz) as a doublet.

Similarly, in the $^1$H NMR spectrum of 24c the methylthio group resonated at $\delta$ 2.58 as a singlet, while the acetylenic proton at $\delta$ 2.35 as a singlet and H-3 proton resonated at $\delta$ 6.0 ($J = 4.7$ Hz) as a triplet, while rest of the protons resonated at the appropriate chemical shifts. HRMS of 23c showed $m/z$ 355.1008 for C$_{15}$H$_{24}$O$_4$S$_2$Na (M+Na)$^+$ and 24c showed $m/z$ 355.1023 for C$_{15}$H$_{24}$O$_4$S$_2$Na (M+Na)$^+$, further confirming the assigned structures of 23c and 24c. The optical rotation values for 23c and 24c in chloroform were $[\alpha]_D = -327.0$ (c 0.4) and $[\alpha]_D = +158.9$ (c 0.58) respectively. Thus, the very important radical precursors were synthesized from L-arabinose.

According to the literature evidence, it is clear that during intramolecular radical cyclization, which results in the fused bicyclic systems, the ring fusion always will be cis (Figure 3). Furthermore, the stereochemistry of the new stereocentre is defined and derived from the stereocentre that carries the appendage. As per the synthetic plan, it was aimed at the generation of the required radical intermediates, which in situ would undergo cyclization, by Barton’s $^{17}$ deoxygenation method.

**Figure 3**

![Radical cyclization reaction](image)

The radical precursors 23a and 24a, the $\beta$- and $\alpha$-anomers with a methyl side chain (Scheme 15) were subjected to radical cyclization with $n$-tributyltin hydride in the presence of catalytic amount of AIBN in dry benzene at 80 °C for 12 h gave the single desired products 21a and 22a. The intramolecular radical cyclization was found to be successful in
giving the cis-fused bicyclic systems with concomitant introduction of the exo-methylene group and inversion at C-3 centre in accordance with the literature precedence.18

Interestingly, unlike the system with the n-octyl side chain, both 23a and 24a, the β- and α-anomers with a methyl side chain underwent cyclization to give the respective cyclized products 21a (69%) and 22a (57%) (Scheme 15).

**Scheme 15**

In $^1$H NMR spectrum of 21a, the exo-cyclic double bond protons resonated at $\delta$ 4.90 ($J = 1.5$ Hz) and $\delta$ 5.08 ($J = 2.2$ Hz) as two doublets, H-3a proton shifted to upfield and appeared at $\delta$ 3.18 ($J = 6.8$ Hz) as triplet. $^1$H NMR spectrum of 22a, showed the exo-cyclic double bond protons resonating at $\delta$ 4.89 ($J = 2.1$ Hz) and $\delta$ 5.08 ($J = 2.1$ Hz) as two doublets, H-3a proton appeared at $\delta$ 3.23 ($J = 5.8$ Hz) as a triplet. Rest of the protons resonated at the appropriate chemical shifts in both the bicyclic systems. HRMS of 21a showed m/z 171.1023 for C$_9$H$_{15}$O$_3$ (M+H)$^+$, while 22a showed m/z 193.0839 for C$_{9}$H$_{14}$O$_3$Na (M+Na)$^+$ further confirming the assigned structures of 21a and 22a. The optical rotation values for 21a and 22a in chloroform were $[\alpha]_D = -21.70$ (c 0.41) and $[\alpha]_D = -2.44$ (c 0.33) respectively.

After the successful synthesis of 21a and 22a, the study was then extended to 23b and 24b with C2 side chain. Radical cyclization reaction of 23b and 24b, with a ethyl side chain with n-tributyltin hydride in the presence of catalytic amount of AIBN in dry benzene at 80 °C for 12 h furnished cis-fused bicyclic systems 21b (71%) and 22b (60%) (Scheme 16). Intramolecular radical cyclization was found to be successful with ethyl side chain as in the case of methyl side chain.
In $^1$H NMR spectrum of 21b, the exo-cyclic double bond protons resonated at $\delta$ 4.92 ($J = 1.7$ Hz) and $\delta$ 5.06 ($J = 1.5$ Hz) as two quintets, H-3a proton appeared at $\delta$ 3.19 ($J = 7.1$ Hz) as a triplet. $^1$H NMR spectrum of 22b showed the resonances for exo-cyclic double bond protons at $\delta$ 4.91 and $\delta$ 5.06 as two singlets, H-3a proton shifted to upfield and appeared at $\delta$ 3.26 ($J = 7.3$ Hz) as a triplet. Rest of the protons in 21b and 22b resonated at the expected chemical shifts. HRMS of 21b and 22b showed $m/z$ 185.1170 and $m/z$ 185.1175 for $\text{C}_{10}\text{H}_{17}\text{O}_3$ (M+H)$^+$ further confirming the assigned structures of 21b and 22b. The optical rotation values for 21b and 22b in chloroform were $[\alpha]_D = -49.2$ (c 0.23) and $[\alpha]_D = -285.8$ (c 0.23) respectively.

A similar study was then extended to the radical precursors 23c ($\beta$-) and 24c ($\alpha$-), with a $n$-pentyl side chain (Scheme 17). Thus, the radical cyclization of 23c and 24c with $n$-tributyltin hydride in the presence of catalytic amount of AIBN in dry benzene at 80 $^\circ$C for 12 h afforded 21c (14%) and 22c (0%). Unlike in the case of two earlier systems 23a/24a and 23b/24b, interesting results were found. The $\beta$-anomer 23c gave cis-fused bicyclic system albeit in a very poor yield in 14%, however, 24c resisted to undergo radical cyclization and expected product 22c could not be synthesized.

In $^1$H NMR spectrum of 21c, the exo-cyclic double bond protons resonated at $\delta$ 4.95 and $\delta$ 5.09 as two singlets, H-3a proton appeared at $\delta$ 3.23 ($J = 6.2$ Hz) as a triplet, whereas rest of the protons resonated at the expected chemical shifts.
HRMS of 21c showed m/z 249.1456 for C_{13}H_{22}O_{3}Na (M+Na)^{+}, further confirming the assigned structure of 21c. The optical rotation value for 21c in chloroform are [\alpha]_D = -249.7 (c 0.26). The structures of compounds 21a-c and 22a-b were confirmed unambiguously from the corresponding spectral data.

The above studies amply indicate that, in case of L-Ara derived radical precursors, the length of the alkyl side chains has a role to play in radical cyclization. Thus, it is pertinent to mention that cyclization products were obtained in better yields from the \( \beta \)-anomers over the \( \alpha \)-anomers with methyl or ethyl side chains. In the case of \( n \)-pentyl side chains, the \( \alpha \)-anomer totally failed to give the cyclization product and the \( \beta \)-anomer gave the product in very poor yield. The above discussed results with 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 cyclization reactions.

**Theoretical studies on 5-exo-dig cyclizations in selected systems derived from the tetrahydro-furan skeleton**

In order to shed some light on the influence of the substituents present in precursor 23 on the efficiency of the subsequent 5-exo-dig cyclization processes, theoretical studies were undertaken for a series of radicals in which the \( \alpha \)-configuration of the methoxy group at C-5 was kept constant, while the stereochemistry and the substitution pattern at the C-2 position was allowed to vary (Scheme 18).
Scheme 18: 5-Exo-dig cyclizations in selected systems derived from the tetrahydrofuran skeleton.

The influence of the configuration at the C-2 position on the reaction barrier and reaction enthalpy for the cyclization step was first studied for R = CH₃ (Table 1). As previously anticipated we find here that the reaction barrier for cyclization of radical 41a is somewhat larger at ΔH‡₂₉₈(42a-41a) = +33.51 kJ/mol as compared to the barrier for cyclization of radical 44a with ΔH‡₂₉₈(45a-44a) = +29.10 kJ/mol at UB3LYP/6-311+G(d,p) level of theory. The higher barrier for cyclization of 41a is undoubtedly due to the all-cis stereochemistry in this system, which is also reflected in the reaction energy for formation of product 43a. Comparing the differences in barriers of ΔΔH‡₂₉₈(42a-45a) = +4.41 kJ/mol with differences in reaction energies of ΔΔH₂₉₈(43a-46a) = +9.12 kJ/mol we may also conclude that approx. 50% of the strain energy present in the product radicals is already present in the respective transition states. According to the Eyring equation, the cyclization rates depend on the activation energies in an exponential manner. Assuming identical activation entropies for both processes we can use the expression k₅₇₄/k₅₄a = exp((ΔH‡₅₇₄-ΔH‡₅₄a)/RT) = 5.8 to predict that the cyclization rate for 44a will be 5.8 times faster than that for 41a at a temperature of 298.15 K. Assuming equal intermolecular trapping rates for radicals 43a and 46a with hydrogen donors, this indicates that cyclization of 41a may be low yielding under conditions optimized for the reaction of 44a.
In Figure 4 the most stable conformers of 41a and 44a are shown together with the respective transition states and reaction products. For the cyclized product radical’s two configurations at the newly formed double bond are possible (see Scheme 18). For product 43a we find that the Z-configuration is more favourable than the E-configuration (with $\Delta H_{298}^\ddagger (Z) = -65.38 \text{ kJ/mol}$ vs. $\Delta H_{298}^\ddagger (E) = -63.95 \text{ kJ/mol}$). Similar results are also found for product radical 46a, where, formation of Z-radical is again more exothermic than formation of the respective E-radical (with $\Delta H_{298}^\ddagger (Z) = -74.45 \text{ kJ/mol}$ vs. $\Delta H_{298}^\ddagger (E) = -73.27 \text{ kJ/mol}$) at UB3LYP/6-311+G(d,p) level of theory.

Because the yield of cyclized products 21 and 22 with L-ara configuration dropped dramatically compared to the D-xylo derivatives by elongating the alkyl chain from methyl and ethyl over n-pentyl to an n-octyl group, the reaction pathways of all-cis substituted tetrahydrofuran models 41a-d were also examined varying the size of the side chain from Me, Et, n-propyl to n-butyl. At the UB3LYP/6-311+G(d,p)//UB3LYP/6-31G(d) level of theory we found that calculated cyclization barriers are exceedingly similar for all four cases, with the overall lowest barrier calculated for R = Et. The rather similar reaction barriers are accompanied by equally similar reaction energies (Table 1).

<table>
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<th>$\Delta H_{298}^\ddagger (42-41)$</th>
<th>$\Delta H_{298}^\ddagger (43-41)$</th>
<th>$\Delta H_{298}^\ddagger (45-44)$</th>
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**Table 1** Boltzmann-averaged activation and reaction enthalpies for the systems described in Scheme 19 (in kJ/mol)
Figure 4: Structures of the most stable conformers of 41a and 44a together with the corresponding transition states and reaction products as obtained at UB3LYP/6-31G(d) level of theory. Distances are given in pm and angles in degrees.

Scheme 19

Possible configuration of the σ-type product radicals 43 and 46.
Since the DFT hybrid functional UB3LYP does not take dispersion effects into account properly we also performed restricted open-shell MP2 ((RO)MP2) single point calculations using the large G3MP2large basis set.\(^\text{19}\) Reaction barriers calculated at (RO)MP2 level are uniformly lower than UB3LYP barriers by approx. 10 kJ/mol and reaction energies are larger by approx. 14 kJ/mol in all cases. However, also at ROMP2 level the barrier differences for cyclization of radicals 41a-d remain quite small. Thus, while the calculated reaction barriers and reaction energies for cyclization of radicals 41a and 44a clearly respond to the stereochemistry selected at C1, the calculations performed for cyclization of radicals 41a-d do not provide an answer for the largely different yields in cyclization reactions of radicals 41 with C-2 substituents of different length.

The above theoretical and experimental studies on the impact of the side chains at the C-2 and C-5 positions on 5-exo-dig radical cyclization reactions in radicals derived from L-arabinose, while the stereochemistry at the anomeric C-5 position remains without much consequence in the cyclization reactions, the length of the substituent at the C-2 position has a marked effect on cyclization yields: while extension of the C-2 substituent from methyl to ethyl leads to slightly increased yields, the cyclization becomes much more difficult for the n-pentyl substituted system. Theoretical studies of cyclization reactions indicate that the stereochemistry at the C-2 position has a significant impact on the cyclization barriers. The theoretical studies also indicate that variation of the substituent from methyl to ethyl leads to a minor reduction in reaction barriers, in full agreement with experiment. Further extension of the C-2 substituent to n-propyl and n-butyl does not lead to drastically altered cyclization barriers and suggests that the largely reduced reaction yields observed experimentally are due to other factors in the overall chain reaction.

**Synthesis of Ethisolide**

Ethisolide (2a), iso-avenaciolide (1a) and avenaciolide (1) are three bis-lactone secondary mold metabolites, isolated from broth of *Aspergillus* and *Penicillium* species. These have been reported to possess antifungal and antibacterial activities. Ethisolide (2a) has similar structural features like iso-avenaciolide (1a), except for an ethyl side chain. However, it differs from avenaciolide (1) and 4-epi-ethisolide (2) in being a positional isomer. During the studies, the radical reactions with different side chains, synthesis of 21b
and 22b (Scheme 16) has been achieved successfully. The conversion of 21b into ethisolide (2a) is since reported²⁰ in the literature, this study formally concludes the total synthesis of ethisolide 2a (Scheme 20).
Experimental Section:

5-tert.-Butyldiphenylsilyloxymethyl-(3R,4S,5S)-2H,3H,4H-2,3,4-furantriol (29): To a solution of 28 (6.0 g, 40.0 mmol) and imidazole (5.98 g, 88.0 mmol) in dry DMF (120 mL), TBDPSCl (10.99 g, 40.0 mmol) was added dropwise at 0 °C over 1 h and the whole mixture was stirred at room temperature for 18 h. DMF was removed from the reaction mixture and the residue obtained was diluted with water (100 mL) and extracted with EtOAc (2 x 100 mL). It was washed with brine (2 x 200 mL) and dried (Na2SO4). Combined organic layers were evaporated and purified the residue by column chromatography (60-120 Silica gel, ethyl acetate: pet. ether, 3:1). First eluted was 29a (7.55 g, 15%) as yellow syrup. 1H NMR (200 MHz, CDCl3): δ 1.08 (s, 18H, 2t-Bu), 3.69 (d, 2H, J = 5.1 Hz, H-5a, H-5b), 3.81 (d, 2H, J = 5.1 Hz, H-4, H-5), 3.92 (br.s, 1H, OH), 4.01 (br.s, 1H, OH), 4.08-4.13 (m, 1H, H-3), 5.88 (s, 1H, H-2), 7.42 (m, 12H, Ar-H), 7.51 (m, 8H, Ar-H).

The second eluted was 29 (9.40 g, 60%) as a gummy syrup. IR (neat): 3438, 2920, 2850, 1450, 1100 cm⁻¹; 1H NMR (200 MHz, CDCl3): δ 1.07 (s, 9H, t-Bu), 3.70 (d, 2H, J = 5.1 Hz, H-5a, H-5b), 3.80 (d, 2H, J = 5.1 Hz, H-4, H-5), 3.90 (br.s, 1H, OH), 4.00 (br.s, 1H, OH), 4.08-4.13 (m, 2H, H-3, OH), 5.38 (s, 1H, H-2), 7.40-7.50 (m, 10H, Ar-H); HRMS (ESI): m/z calculated for C21H28NaOSi (M⁺+Na) 411.1603, found 411.1617.

5-tert.-Butyldiphenylsilyloxymethyl-2,2-dimethyl-(3aR,5S,6S,6aR)-perhydrofuro[2,3-d][1,3]dioxol-6-ol (30): To a stirred mixture of 29 (7.5 g, 19.28 mmol) and dry CuSO4 (15 g) in dry acetone (75 mL), catalytic amount of conc. H2SO4 was added and the stirred at room temperature for 5 h. The reaction mixture was filtered and the filtrate was neutralized with solid NaHCO3 (5 g). It was filtered, evaporated the filtrate and purified the residue by column chromatography (60-120 Silica gel, ethyl acetate: pet. ether, 1:3) gave 30 (6.15 g, 74%) as a yellow syrup; [α]D = -30.16 (c 1.6, CHCl3); IR (Neat): 3460, 2930, 2850, 1480, 1390, 1130, 1020 cm⁻¹; 1H NMR (200 MHz, CDCl3): δ 1.06 (s, 9H, t-Bu), 1.26 (s, 3H, CH3), 1.30 (s, 3H, CH3), 1.90 (br.s, 1H, OH), 3.80 (d, 1H, J = 6.8 Hz, H-5), 3.95-4.18 (m, 2H, H-5a, H-5b), 4.36 (br.s, 1H, H-6), 4.50 (d, 1H, J = 4.0 Hz, H-6a), 5.83 (d, 1H, J = 4.0 Hz, H-3a), 7.36-7.42 (m, 6H, Ar-H), 7.64-7.70 (m, 4H, Ar-H); HRMS (ESI): m/z calculated for C24H32NaO5Si (M⁺+Na) 451.1916, found 451.1898.
6-(4-Methoxybenzyl-oxy)-2,2-dimethyl-(3aR,5S,6S,6aR)-perhydrofuro[2,3-d][1,3]dioxol-5-(tert-butyldiphenylsilyl)-methylether (31): A stirred suspension of sodium hydride (0.96 g, 40.28 mmol) in dry THF (30 mL) under N₂ atmosphere was treated with a solution of 30 (8.62 g, 20.14 mmol) in THF (25 ml) at 0 °C and stirred for 30 min. PMBBr (4.5 mL, 24.16 mmol) was added to the reaction mixture at 0 °C and stirred at room temperature for 4 h. Reaction mixture was quenched with aq. NH₄Cl solution (20 mL) and extracted with EtOAc (2 x 100 mL). Organic layer was washed with water (100 mL), brine (100 mL), dried (Na₂SO₄) and evaporated. Purification of the residue by column chromatography (60-120 Silica gel, ethyl acetate: pet. ether, 0.5:9.5) afforded 31 (8.94 g, 81%) as a colourless liquid; [α]D = +12.12 (c 1.25, CHCl₃); IR (Neat): 3451, 3069, 2934, 2859, 1723, 1612, 1513, 1464, 1249, 1214, 1107, 1030, 820, 704 cm⁻¹; ¹H NMR: (200 MHz, CDCl₃): δ 1.06 (s, 9H, (CH₃)₃), 1.26 (s, 3H, CH₃), 1.30 (s, 3H, CH₃), 3.70-3.80 (m, 5H, H-6, H-5a, OCH₃), 4.08-4.18 (m, 2H, H-5, H-5b), 4.42-4.54 (m, 2H, OCH₂), 4.60 (d, 1H, J = 3.6 Hz, H-6a), 5.82 (d, 1H, J = 3.6 Hz, H-3a), 6.82 and 7.22 (2d, 2H each, J = 8.6 Hz, Ar-H), 7.30-7.42 (m, 6H, Ar-H), 7.56-7.74 (m, 4H, Ar-H); ¹³C NMR (CDCl₃, 150 MHz): δ 159.3, 136.3, 135.8, 135.5 (4C), 129.6 (2C), 129.3 (2C), 127.7 (4C), 127.3, 113.9 (2C), 112.4, 105.7, 85.2 (2C), 82.4, 71.3, 63.4, 55.2, 26.9, 26.8 (3C), 26.1, 19.2; HRMS (ESI): m/z calculated for C₃₂H₄₀NaO₆Si (M⁺+Na) 571.2491, found 571.2507.

6-(4-Methoxybenzyl-oxy)-2,2-dimethyl-(3aR,5S,6S,6aR)-perhydrofuro[2,3-d][1,3]dioxol-5-yl-methanol (32): To a stirred solution of 31 (8.56 g, 15.62 mmol) in dry THF (20 mL) under N₂ atmosphere, tetra n-butyrammonium fluoride (17.2 mL, 1.0 M, 17.18 mmol) was added at 0 °C and stirred at room temperature for 14 h. Evaporation of solvent and purification of the residue by chromatography (60-120 Silica gel, ethyl acetate: pet. ether, 2:3) afforded 32 (4.30 g, 89%) as a colorless liquid; [α]D = +16.18 (c 0.85, CHCl₃); IR (Neat): 3450, 2927, 2855, 1756, 1612, 1513, 1461, 1377, 1301, 1247, 1168, 1074, 1030, 821, 517 cm⁻¹; ¹H NMR (200 MHz, CDCl₃): δ 1.35 (s, 3H, CH₃), 1.54 (s, 3H, CH₃), 1.94 (br.s, 1H, OH), 3.64 (d, 2H, J = 5.5 Hz, H-5a, H-5b), 3.82 (s, 3H, OCH₃), 3.90 (d, 1H, J = 2.4 Hz, H-6), 4.06-4.17 (m, 1H, H-5), 4.50-4.57 (m, 2H, OCH₂), 4.60 (d, 1H, J = 5.5 Hz, H-6a), 5.82 (d, 1H, J = 5.5 Hz, H-3a), 6.82, 7.22 (2d, 2H each, J = 8.6 Hz, Ar-H); ¹³C NMR (CDCl₃, 150 MHz): δ 159.3, 129.3 (3C), 113.8 (2C), 112.7, 105.5, 85.5, 85.1, 82.3, 71.4, 62.5, 55.1, 27.0, 26.2; HRMS (ESI): m/z calculated for C₁₆H₂₂NaO₆ (M⁺+Na) 333.1314, found 333.1315.
6-(4-Methoxybenzyloxy)-5-(4-methylphenylsulphonyloxy-methyl)-2,2-dimethyl-3aR,5S,6S,6aR-perhydrofuro[2,3-d][1,3]dioxole (33): A solution of 32 (2.5 g, 8.06 mmol) in dry CH₂Cl₂ (30 mL) at 0 °C was treated with Et₃N (3.2 mL, 24.19 mmol) and p-toluenesulphonyl chloride (2.3 g, 12.09 mmol) at 0 °C and stirred at room temperature for 4 h. Reaction mixture was extracted with CH₂Cl₂ (50 mL) and washed with water (2 x 50 mL), brine (50 mL) and dried (Na₂SO₄). Evaporation of solvent and purification of the residue by column chromatography (60-120 Silica gel, ethyl acetate: pet. ether, 1:9) afforded 33 (3.05 g, 81%) as colourless solid, m.p. 131 °C; [α]D = +16.18 (c 0.85, CHCl₃); IR (Neat): 3310, 2987, 1782, 1237, 1019, 765 cm⁻¹; ¹H NMR (200 MHz, CDCl₃): δ 1.27 (s, 3H, CH₃), 1.35 (s, 3H, CH₃), 2.45 (s, 3H, Ar-CH₃), 3.82 (s, 3H, OCH₃), 3.90 (d, 1H, J = 1.8 Hz, H-6), 4.08 (d, 2H, J = 6.4 Hz, H-5a, H-5b), 4.18 (dd, 1H, J = 6.4, 1.8 Hz, H-5), 4.48 (s, 2H, OCH₂), 4.53 (d, 1H, J = 4.1 Hz, H-6a), 5.82 (d, 1H, J = 4.1 Hz, H-3a), 6.87 (d, 2H, J = 8.2 Hz, Ar-H), 7.22 (d, 2H, J = 8.2 Hz, Ar-H), 7.32 (d, 2H, J = 7.6 Hz, Ar-H), 7.75 (d, 2H, J = 7.6 Hz, Ar-H); ¹³C NMR (CDCl₃, 75 MHz): δ 159.4, 144.9, 132.6, 129.8, 129.5, 128.8, 128.0, 114.0, 112.6, 105.9, 84.4, 81.8 (2C), 71.4, 68.5, 55.2, 26.6, 25.8, 21.6; HRMS (ESI): m/z calculated for C₂₃H₂₈NO₈S (M⁺+Na) 487.1402, found 487.1388.

6-(4-Methoxybenzyloxy)-2,2,5-trimethyl-(3aR,5S,6S,6aR)-perhydrofuro[2,3-d][1,3]dioxole (34a): To a stirred and cooled (0 °C) solution of 33 (8.56 g, 18.44 mmol) in dry DMSO (40 mL) under N₂ atmosphere, NaBH₄ (1.39 g, 36.89 mmol) was added and heated upto 160 °C for 10 min. The reaction mixture was cooled to room temperature and extracted into EtOAc (2 x 100 mL). Organic layer was washed with water (75 mL) and dried (Na₂SO₄). Evaporation of solvent and purification of the residue by column chromatography (60-120 Silica gel, ethyl acetate: pet. ether, 1.7:8.3) afforded 34a (4.30 g, 79%) as a colourless liquid; [α]D = -27.25 (c 1.6, CHCl₃); IR (neat): 2940, 1450, 1080, 700 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 1.32 (d, 6H, J = 6.7 Hz, 2CH₃), 1.49 (s, 3H, CH₃), 3.62 (d, 1H, J = 3.7 Hz, H-6), 3.78 (s, 3H, Ar-OCH₃), 4.03 (m, 1H, H-5), 4.40-4.56 (m, 3H, H-6a, OCH₂ Ar), 5.74 (d, 1H, J = 4.1 Hz, H-3a), 6.82 (d, 2H, J = 8.3 Hz, Ar-H), 7.19 (d, 2H, J = 8.3 Hz, Ar-H); ¹³C NMR (CDCl₃, 150 MHz): δ 159.3, 129.3 (3C), 113.8 (2C), 112.8, 105.3, 86.8, 85.6, 80.3, 71.4, 55.2, 27.1, 26.5, 19.9; HRMS (ESI): m/z calculated for C₁₆H₂₂NaO₅ (M⁺+Na) 317.1364, found 317.1355.
6-(4-Methoxybenzyloxy)-2,2-dimethyl-(3aR,5R,6R,6aR)-perhydrofuro[2,3-d][1,3]dioxol-5-carbaldehyde (35): A solution of 32 (2.5 g, 8.06 mmol) in dry DMSO (10 mL) was treated with IBX (3.38 g, 12.09 mmol) at 10 °C and stirred at room temperature for 3 h. Reaction mixture was quenched with ice cold water (10 mL) and stirred at room temperature for 15 min, filtered and extracted with EtOAc (2 x 75 mL). Organic layer was washed with aq. NaHCO₃ solution (50 mL), water (50 mL), brine (50 mL) and dried (Na₂SO₄). Solvent was evaporated to afford 35 (1.98 g, 80%) as a liquid; [α]D = -2.64 (c 0.8, CHCl₃); IR (Neat): 3290, 1765, 1214, 983 cm⁻¹; ¹H NMR (200 MHz, CDCl₃): δ 1.35 (s, 3H, CH₃), 1.54 (s, 3H, CH₃), 3.84 (s, 3H, OCH₃), 3.92 (d, 1H, J = 2.4 Hz, H-6), 4.22-4.54 (m, 3H, H-5, H-8, H-8a), 4.60 (d, 1H, J = 5.4 Hz, H-6a), 5.82 (d, 1H, J = 5.4 Hz, H-3a), 6.95 and 7.80 (2d, 2H each, J = 8.6 Hz, Ar-H), 9.02 (s, 1H, CHO).

(3aR,5S,6S,6aR)-6-(4-Methoxybenzyloxy)-tetrahydro-2,2-dimethyl-5-vinylfuro[3,2-d][1,3]dioxole (36a): To a stirred and cooled (0 °C) suspension of (methyl)triphenylphosphonium iodide (18.75 g, 46.42 mmol) in dry THF (50 mL) under N₂ atmosphere, 'BuO'K⁺ (5.19 g, 46.42 mmol) was added and stirred for 6 h. A solution of 35 (7.10 g, 23.21 mmol) in THF (30 mL) was added to the reaction mixture at 0 °C, and stirred at 0 °C for 1 h. It was warmed to room temperature and stirred for an additional 30 min. Reaction mixture was quenched with aq. NH₄Cl solution (30 mL) and extracted with EtOAc (2 x 100 mL). The organic layers were washed with water (100 mL), brine (100 mL), dried (Na₂SO₄) and evaporated. Purification of the residue by column chromatography (60-120 Silica gel, ethyl acetate: pet. ether, 0.5:9.5) afforded 36a (3.48 g, 49%) as a colorless liquid; [α]D = -47.2 (c 0.68, CHCl₃); IR (Neat): 2931, 1722, 1614, 1514, 1376, 1247, 1081, 1025, 824, 580 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 1.32 (s, 3H, CH₃), 1.48 (s, 3H, CH₃), 3.79 (s, 4H, H-6, OCH₃), 4.40-4.56 (m, 4H, H-5, H-6a, Ar-OCH₂), 5.11-5.31 (dd, 2H, J =10.6 Hz, olefinic), 5.83 (d, 1H, J = 3.81 Hz, H-3a), 5.94 (m, 1H, olefinic), 6.82 and 7.20 (2d, 2H each, J = 8.6 Hz, Ar-H); ¹³C NMR (CDCl₃, 75 MHz): δ 159.2, 136.6, 129.1 (2C), 116.1, 113.6 (2C), 112.5, 105.3, 96.0, 85.9, 85.1, 84.8, 71.2, 54.7, 27.0, 26.5; HRMS (ESI): m/z calculated for C₁₇H₂₂NaO₅ (M⁺+Na) 329.1364, found 329.1366.

(3aR,5S,6S,6aR)-6-(4-Methoxybenzyloxy)-tetrahydro-2,2-dimethyl-5-((E)-pent-1-enyl)furo-[3,2-d][1,3]dioxole (36b): To a stirred solution of 35 (7.80 g, 25.32 mmol) in THF (40 mL), (n-butyl)triphenylphosphonium bromide (30.23 g, 75.97 mmol) in dry THF (30 mL) and 'BuO'K⁺
(8.51 g, 75.97 mmol) was added and stirred at 0 °C for 6 h. Work up as described for 36a and purification of the residue by column chromatography (60-120 Silica gel, ethyl acetate: pet. ether, 0.5:9.5) gave 36b (4.40 g, 50%) as a colorless liquid; [α]D = -12.0 (c 0.73, CHCl3); IR (Neat): 2931, 1722, 1614, 1514, 1376, 1247, 1081, 1025, 824, 580 cm⁻¹; ¹H NMR (300 MHz, CDCl3): δ 0.90 (t, 3H, J = 7.3 Hz, CH₃), 1.25-1.45 (m, 8H, 2CH₃, CH₂), 1.93-2.15 (m, 2H, allylic-CH₂), 3.75-3.78 (m, 4H, H-4, OCH₃), 4.42-4.56 (m, 3H, H-5, OCH₂), 4.70-4.72 (dd, 1H, J = 3.5, 7.9 Hz, H-3), 5.52-5.59 (m, 2H, olefinic), 5.80 (d, 1H, J = 3.9 Hz, H-2), 6.81 and 7.20 (d, 2H each, J = 8.6 Hz, Ar-H); ¹³C NMR (CDCl₃, 75 MHz): δ 159.3, 135.5, 133.4, 129.3, 128.2, 127.6, 113.8, 112.6, 105.5, 86.7, 85.2, 80.7, 71.5, 55.2, 29.4, 27.0, 26.4, 22.6, 13.7; HRMS (ESI): m/z calculated for C₂₀H₂₈NaO₅(M⁺+Na) 371.1834, found 371.1841.

(3aR,5S,6S,6aR)-6-(4-Methoxybenzoyloxy)-5-ethyl-tetrahydro-2,2-dimethylfuro[3,2-d][1,3]dioxole (34b): A solution of 36a (2.80 g, 9.15 mmol) in dry EtOAc (20 mL) was treated with catalytic amount of PtO₂ (0.02 g) under H₂ atmosphere and stirred at room temperature for 2 h. It was filtered, removed solvent and purified the residue by column chromatography (60-120 Silica gel, ethyl acetate: pet. ether, 0.7:9.3) to afford 34b (2.50 g, 89%) as a colourless liquid; [α]D = -82.49 (c 1.4, CHCl₃); IR (Neat): 2941, 1450, 1100, 720 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 0.93 (t, 3H, J = 7.4 Hz, CH₃), 1.31 (s, 3H, CH₃), 1.47 (s, 3H, CH₃), 1.66 (m, 2H, allylic-CH₂), 3.67 (d, 1H, J = 3.6 Hz, H-6), 3.77 (m, 4H, H-5, OCH₃), 4.40-4.55 (m, 3H, H-6a, OCH₂), 5.76(d, 1H, J = 3.9 Hz, H-3a), 6.82 and 7.20 (d, 2H each, J = 8.4 Hz, Ar-H); ¹³C NMR (CDCl₃, 75 MHz): δ 159.2, 131.7, 129.1 (2C), 113.6 (2C), 112.5, 105.0, 96.1, 85.3 (2C), 85.0, 71.1, 54.8, 27.3, 27.0, 26.6, 10.3; HRMS (ESI): m/z calculated for C₁₇H₂₆NaO₅(M⁺+Na) 331.1624, found 331.1627.

(3aR,5S,6S,6aR)-6-(4-Methoxybenzoyloxy)-tetrahydro-2,2-dimethyl-5-pentylfuro[3,2-d][1,3]dioxole (34c): A stirred solution of 36b (2.20 g, 6.32 mmol) in dry EtOAc (15 mL) was treated with catalytic amount of PtO₂ (0.02 g) for 2 h. Work up as described for 34b and purification of the residue by column chromatography (60-120 Silica gel, ethyl acetate: pet. ether, 0.5:9.5) gave 34c (1.66 g, 75%) as a colourless liquid; [α]D = -120.1 (c 0.3, CHCl₃); IR (Neat): 2941, 1450, 1100, 720 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 0.88 (t, 3H, J = 6.4 Hz, CH₃), 1.28-1.69 (m, 14H, 2xCH₃, 4xCH₂), 3.66 (d, 1H, J = 3.4 Hz, H-6), 3.78 (s, 3H, OCH₃), 3.85 (m, 1H, H-5),
4.40-4.56 (m, 3H, H-6a, OCH$_2$), 5.75 (d, 1H, $J = 4.1$ Hz, H-3a), 6.81 and 7.21 (2d, 2H each, $J = 8.3$ Hz, Ar-H); $^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 159.2, 135.4, 131.8, 129.3, 128.2, 127.5, 113.7, 112.5, 105.1, 87.7, 87.2, 85.3 (2C), 84.5, 78.4, 71.2, 55.0, 33.9, 31.4, 27.0, 26.3, 25.5, 22.4, 13.8; HRMS (ESI): $m/z$ calculated for C$_{20}$H$_{31}$O$_5$ (M$^+$+H) 351.2093, found 351.2097.

**Hydrolysis of 34a**

To a stirred solution of 34a (1.50 g, 5.10 mmol) in dry methanol (20 mL) under N$_2$ atmosphere, 3 drops of conc. HCl was added at 0 °C and stirred for 5 h. The reaction mixture was cooled to 0 °C and neutralized with solid NaHCO$_3$ (0.3 g). It was filtered, evaporated solvent and purified the residue by column chromatography (60-120 Silica gel; ethyl acetate: pet. ether, 1.8:8.2) to afford anomeric mixture of 25 (1.23 g, 90%) in 1.5:1 ratio as a liquid; IR (neat): 3590, 3500, 2237, 1724, 1256, 867, 793 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 1.27 (t, 6H, $J = 6.1$ Hz, 2xCH$_3$), 3.33 (s, 3H, anomeric-OCH$_3$), 3.36 (m, 2H, $J = 3.2$, 6.9 Hz, 2xH-4), 3.41 (s, 3H, anomeric-OCH$_3$), 3.57 (t, 2H, $J = 6.1$ Hz, 2xH-5), 3.78 (s, 6H, 2xAr-OCH$_3$), 4.13–3.90 (m, 2H, 2xH-3), 6.82 (q, 4H, $J = 3.6, 8.2, 12.2$ Hz, Ar-H), 7.22 (d, 4H, $J = 8.19$ Hz, Ar-H); HRMS (ESI): $m/z$ calculated for C$_{14}$H$_{20}$NaO$_5$ (M$^+$+Na) 291.1208, found 291.1210.

**Hydrolysis of 34b**

To a stirred solution of 34b (1.95 g, 6.33 mmol) in dry methanol (20 mL) under N$_2$ atmosphere, 3 drops of conc. HCl was added at 0 °C and stirred for 5 h. Work up as described for 34a and purification of the residue by column chromatography (60-120 Silica gel, ethyl acetate: pet. ether, 1.8:8.2) to give 26 (1.20 g, 67%) in 1.5:1 ratio as a colourless liquid; IR (neat): 3500, 3590, 1765, 879 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 0.92 (m, 6H, 2xCH$_3$), 2.38 (bs, 2H, 2xOH), 3.32 (s, 3H, anomeric-OCH$_3$), 3.40-3.44 (m, 4H, anomeric-OCH$_3$, H-4), 3.62 (t, 1H, $J = 6.1$ Hz, H-4), 3.70-3.85 (m, 8H, 2xH-5, 2xAr-OCH$_3$), 4.06–4.17 (m, 2H, 2xH-3), 4.45–4.74 (m, 6H, 2xOCH$_2$, 2xH-2), 6.82 (d, 4H, $J = 8.3$ Hz, Ar-H), 7.21 (d, 4H, $J = 7.6$ Hz, Ar-H); HRMS (ESI): $m/z$ calculated for C$_{15}$H$_{22}$NaO$_5$ (M$^+$+Na) 305.1364, found 305.1356.

**Hydrolysis of 34c**

To a stirred solution of 34c (1.2 g, 3.42 mmol) in dry methanol (20 mL) under N$_2$ atmosphere, catalytic amount of conc. HCl was added at 0 °C and stirred for 5 h. Work up as described for 34a and purification of the residue by column chromatography (60-120 Silica gel, ethyl acetate: pet. ether, 1.8:8.2) gave 27 (0.81 g, 73%) in 5.5:4.5 ratio as a liquid; IR (neat):
3500, 3590, 2867, 1734, 1198, 867 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 0.89 (t, 6H, J = 5.4 Hz, 2xCH₃), 1.28-1.57 (m, 16H, 8xCH₂), 2.41 (d, 2H, 2xOH), 3.32 (s, 3H, anomeric-OCH₃), 3.40 (s, 3H, anomeric-OCH₃), 3.65 (t, 2H, J = 5.4 Hz, 2xH-4), 3.78 (s, 6H, 2xAr-CH₃), 3.86 (q, 2H, 2xH-5), 4.06-4.18 (m, 2H, 2xH-3), 4.47-4.58 (m, 4H, 2xOCH₂), 4.66-4.74 (m, 2H, 2xH-2), 6.81 (m, 4H, Ar-H), 7.23 (d, 4H, J = 8.4 Hz, Ar-H); HRMS (ESI): m/z calculated for C₁₈H₂₆NaO₅ (M⁺+Na) 347.1834, found 347.1846.

(2S,3S,4R,5R)-3-(4-Methoxybenzyloxy)-tetrahydro-5-methoxy-2-methyl-4-(prop-2-ynyloxy) furan (37a) and (2S,3S,4R,5S)-3-(4-methoxybenzyloxy)-tetrahydro-5-methoxy -2-methyl-4-(prop-2-ynyloxy)furan (38a): A stirred suspension of sodium hydride (0.04 g, 2.14 mmol) in dry THF (5 mL) under N₂ atmosphere was treated with a solution of 25 (0.25 g, 0.93 mmol) in THF (3 mL) at 0 °C and stirred for 15 min. Propargyl bromide (0.08 mL, 0.93 mmol) was added to the reaction mixture at 0 °C and stirred at room temperature for 4 h. Reaction mixture was quenched withaq. NH₄Cl solution (3 mL) and extracted with EtOAc (2 x 10 mL). Organic layer was washed with water (5 mL), brine (5 mL) and dried (Na₂SO₄). Solvent was evaporated and purified the residue by column chromatography. First eluted (60-120 Silica gel; ethyl acetate: pet. ether, 1.2:8.8) was 37a (0.13 g, 45%) as a liquid; [α]D = -218.2 (c 0.66, CHCl₃); IR (neat): 3451, 3282, 2924, 1720, 1611, 1513, 1248, 1100, 1065, 1050, 943, 771 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 1.25 (d, 3H, J = 6.0 Hz, CH₃), 2.42 (t, 1H, J = 2.2 Hz, acetylenic), 3.33 (s, 3H, OCH₃), 3.42-3.46 (q, 1H, J = 3.7, 7.5 Hz, H-3), 3.77 (s, 3H, Ar-OCH₃), 3.94-4.19 (m, 4H, H-2, H-4 and OCH₂), 4.43-4.62 (dd, 2H, J = 11.7 Hz, Ar-OCH₂), 4.77 (s, 1H, H-5), 6.82 (d, 2H, J = 8.3 Hz, Ar-H), 7.22 (d, 2H, J = 8.6 Hz, Ar-H); ¹³C NMR (CDCl₃, 100 MHz): δ 159.1, 129.8, 129.3 (2C), 113.7 (2C), 106.5, 88.4, 87.9, 76.6, 74.9, 71.8, 57.2, 54.6, 54.5, 18.6; HRMS (ESI): m/z calculated for C₁₇H₂₂NaO₅ (M⁺+Na) 329.1364, found 329.1354.

Second eluted (60-120 Silica gel; ethyl acetate: pet. ether, 1.2:8.8) was 38a (0.09 g, 31%) as colourless liquid; [α]D = +129.0 (c 0.36, CHCl₃); IR (neat): 3448, 3282, 1720, 1636, 771, 600 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 1.28 (d, 3H, J = 6.4 Hz, CH₃), 2.42 (t, 1H, J = 2.2 Hz, acetylenic), 3.38 (s, 3H, OCH₃), 3.78 (s, 3H, Ar-OCH₃), 3.85 (t, 1H, J = 6.4 Hz, H-3), 3.95 (p, 1H, J = 6.0, 12.4 Hz, H-2), 4.15-4.31 (m, 3H, H-4, OCH₂), 4.45-4.64 (dd, 2H, J = 11.3 Hz, Ar-OCH₂), 4.83 (d, 1H, J = 4.1 Hz, H-5), 6.82 (d, 2H, J = 8.3 Hz, Ar-H), 7.22 (d, 2H, J = 8.6 Hz, Ar-H). ¹³C NMR (CDCl₃, 75 MHz): δ 159.2, 130.1, 129.4 (2C), 113.8 (2C), 101.2, 86.4, 83.7,
(2S,3S,4R,5R)-3-(4-Methoxybenzylxylo)-2-ethyl-tetrahydro-5-methoxy-4-(prop-2-ynyloxy)furan (37b) and (2S,3S,4R,5S)-3-(4-methoxybenzylxylo)-2-ethyl-tetrahydro-5-methoxy-4-(prop-2-ynyloxy)furan (38b): A stirred suspension of sodium hydride (0.23 g, 9.75 mmol) in dry THF (12 mL) under N₂ atmosphere was treated with a solution of 26 (1.10 g, 3.90 mmol) in THF (3 mL) at 0 °C and stirred for 15 min. Propargyl bromide (0.58 mL, 3.90 mmol) was added to the reaction mixture at 0 °C and stirred at room temperature for 4 h. Worked up as described for 37a and purified by column chromatography. First eluted (60-120 Silica gel; ethyl acetate: pet. ether, 1.2:8.8) was 37b (0.54 g, 43%) as liquid; [α]D = -252.8 (c 0.54, CHCl₃); IR (neat): 3442, 2921, 1728, 1612, 1247, 1110, 1036, 894, 772 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 0.93 (t, 3H, J = 7.5 Hz, CH₃), 1.48-1.70 (m, 2H, CH₂), 2.41 (t, 1H, J = 2.2 Hz, acetylenic), 3.33 (s, 3H, OCH₃), 3.50 (m, 1H, H-3), 3.77-3.85 (m, 4H, Ar-OCH₃, H-2), 4.03-4.19 (m, 3H, OCH₂, H-4), 4.62-4.42 (dd, 2H, J = 11.7 Hz, Ar-OCH₂) 4.78 (s, 1H, H-5), 6.80 (d, 2H, J = 8.7 Hz, Ar-H), 7.20 (d, 2H, J = 8.7 Hz, Ar-H); ¹³C NMR (CDCl₃, 75 MHz): δ 159.2, 129.9, 129.4 (2C), 113.7 (2C), 106.3, 96.1, 88.0, 86.0, 81.8, 74.9, 71.6, 57.0, 55.0, 54.3, 26.1, 9.9; HRMS (ESI): m/z calculated for C₁₈H₂₄NaO₅ (M⁺+Na) 343.1521, found 343.1524.

Second eluted (60-120 Silica gel; ethyl acetate: pet. ether, 1.2:8.8) was 38b (0.36 g, 29%) as liquid; [α]D = +119.4 (c 0.70, CHCl₃); IR (neat): 3431, 2924, 1713, 1631, 1460, 776 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): ¹H NMR (300 MHz, CDCl₃): δ 0.93 (t, 3H, J = 7.2 Hz, CH₃), 1.60 (m, 2H, CH₂), 2.41 (t, 1H, J = 2.2 Hz, acetylenic), 3.37 (s, 3H, OCH₃), 3.70-3.78 (m, 4H, Ar-OCH₃, H-3), 3.89 (t, 1H, J = 6.8 Hz, H-2), 4.14-4.31 (m, 3H, OCH₂, H-4), 4.46-4.65 (dd, 2H, J = 11.3 Hz, Ar-OCH₂), 4.85 (d, 1H, J = 4.1 Hz, H-5), 6.82 (d, 2H, J = 8.6 Hz, Ar-H), 7.20 (d, 2H, J = 8.3 Hz, Ar-H); ¹³C NMR (CDCl₃, 75 MHz): δ 159.3, 130.3, 129.5 (2C), 113.8 (2C), 101.2, 96.2, 84.5, 84.0, 82.5, 75.2, 71.8, 57.3, 55.1, 54.7, 29.2, 10.2; HRMS (ESI): m/z calculated for C₁₈H₂₄NaO₅ (M⁺+Na) 343.1521, found 343.1522.

(2S,3S,4R,5R)-3-(4-Methoxybenzylxylo)-tetrahydro-5-methoxy-2-pentyl-4-(prop-2-ynyloxy)furan (37c) and (2S,3S,4R,5S)-3-(4-methoxybenzylxylo)-tetrahydro-5-methoxy-2-pentyl-4-(prop-2-ynyloxy)furan (38c): A stirred suspension of sodium hydride (0.14 g, 5.86 mmol) in
dry THF (5 mL) under N₂ atmosphere was treated with a solution of 27 (0.76 g, 2.34 mmol) in THF (3 mL) at 0 °C and stirred for 15 min. Propargyl bromide (0.34 mL, 2.34 mmol) was added to the reaction mixture at 0 °C and stirred at room temperature for 4 h. Worked up as described for 37a and purified by column chromatography. First eluted (60-120 Silica gel, ethyl acetate: pet. ether, 0.7:9.3) was 37c (0.30 g, 35%) as a liquid; [α]D = -240.7 (c 0.93, CHCl₃); IR (neat): 3279, 2929, 1712, 1525, 1050, 929, 780 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 0.88 (t, 3H, J = 6.7 Hz, CH₃), 1.27-1.63 (m, 8H, 4CH₂), 2.42 (t, 1H, J = 2.4 Hz, acetylenic), 3.33 (s, 3H, OCH₃), 3.49 (dd, 1H, J = 2.8 Hz, H-3), 3.78 (s, 3H, Ar-OCH₃), 3.84 (m, 1H, H-2), 4.02-4.20 (m, 3H, H₄, OCH₂), 4.42-4.63 (dd, 2H, J = 11.5 Hz, Ar-OCH₂), 4.77 (s, 1H, H-5), 6.81 (d, 2H, J = 8.6 Hz, Ar-H), 7.23 (d, 2H, J = 8.6 Hz, Ar-H); ¹³C NMR (CDCl₃, 75 MHz): δ 159.3, 129.9, 129.6 (2C), 113.8 (2C), 106.3, 87.9, 86.5, 80.9, 79.2, 75.0, 71.8, 57.1, 55.2, 54.5, 33.3, 31.8, 25.4, 22.5, 14.0; HRMS (ESI): m/z calculated for C₂₁H₃₀NaO₅ (M⁺+Na) 385.1990, found 385.1988.

Second eluted (60-120 Silica gel, ethyl acetate: pet. ether, 0.7:9.3) was 38c (0.26 g, 30%) as a liquid; [α]D = +95.0 (c 0.84, CHCl₃); IR (neat): 3272, 2942, 1743, 1576, 1057, 996, 732 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 0.88 (t, 3H, J = 6.6 Hz, CH₃), 1.27-1.59 (m, 8H, 4 CH₂), 2.42 (t, 1H, J = 2.4 Hz, acetylenic), 3.37 (s, 3H, OCH₃), 3.47 (dd, 1H, J = 2.8 Hz, H-3), 3.78 (s, 4H, H₄, Ar-OCH₃), 3.86 (m, 1H, H-2), 4.02-4.20 (m, 3H, H₄, OCH₂), 4.42-4.63 (dd, 2H, J = 11.5 Hz, Ar-OCH₂), 4.84 (d, 1H, J = 4.3 Hz, H-5), 6.82 (d, 2H, J = 8.6 Hz, Ar-H), 7.20 (d, 2H, J = 8.6 Hz, Ar-H); ¹³C NMR (CDCl₃, 75 MHz): δ 159.2, 130.2, 129.5 (2C), 113.8 (2C), 101.2, 85.0, 83.9, 81.3, 79.3, 75.1, 71.8, 57.4, 55.2, 54.7, 36.2, 31.6, 25.3, 22.5, 14.0; HRMS (ESI): m/z calculated for C₂₁H₃₀NaO₅ (M⁺+Na) 385.1990, found 385.2003.

(2S,3S,4R,5R)-Tetrahydro-5-methoxy-2-methyl-4-(prop-2-nyloxy)furan-3-ol (39a): To a stirred solution of 37a (0.22 g, 0.71 mmol) in aq. CH₂Cl₂ (1:19, H₂O:CH₂Cl₂, 10 mL), DDQ (0.32 g, 1.43 mmol) was added at 0 °C and stirred for 2 h. The reaction mixture was quenched with aq. NaHCO₃ solution (7 mL) and extracted with CH₂Cl₂ (2 × 15 mL). Organic layer was washed with aq. NaHCO₃ solution (10 mL), water (10 mL), brine (10 mL) and dried (Na₂SO₄). Evaporation of the solvent and purification of the residue by chromatography (60-120 Silica gel; ethyl acetate: pet. ether, 1:4) afforded 39a (0.12 g, 94%) as a liquid; [α]D = -65.2 (c 1.53, CHCl₃); IR (neat): 3447, 2925, 2854, 1741, 1219, 771 cm⁻¹; ¹H NMR (200 MHz, CDCl₃): δ 1.29 (d, 3H, J = 6.2 Hz, CH₃), 2.44 (t, 1H, J = 2.5 Hz, acetylenic), 2.66 (bd, 1H, OH), 3.36 (s, 3H,
OCH\textsubscript{3}), 3.69 (bs, 1H, H-3), 3.90 (d, 1H, J = 2.9 Hz, H-2), 3.99 (t, 1H, J = 5.8 Hz, H-4), 4.22 (t, 2H, J = 2.5 Hz, OCH\textsubscript{2}), 4.84 (s, 1H, H-5); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 75 MHz): \δ 106.4, 88.8, 80.5, 80.1, 75.0, 57.4, 54.7, 29.6, 18.6; HRMS (ESI): m/z calculated for C\textsubscript{9}H\textsubscript{14}NaO\textsubscript{4} (M\textsuperscript{+}+Na) 209.0789, found 209.0793.

(2S,3S,4R,5S)-Tetrahydro-5-methoxy-2-methyl-4-(prop-2-nyloxy)furan-3-ol (40a): A solution of 38a (0.39 g, 1.27 mmol) in aq. CH\textsubscript{2}Cl\textsubscript{2} (1:19, H\textsubscript{2}O:CH\textsubscript{2}Cl\textsubscript{2}, 10 mL) was treated with DDQ (0.58 g, 2.54 mmol) at 0 °C for 2 h. Work up as described for 39a and purification by column chromatography (60-120 Silica gel; ethyl acetate: pet. ether, 1:4) afforded 40a (0.21 g, 89%) as a liquid; [α]\textsubscript{D} = +284.1 (c 0.44, CHCl\textsubscript{3}); IR (neat): 3437, 2926, 2856, 1737, 1219, 1051, 769 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}): δ 1.33 (d, 3H, J = 6.4 Hz, CH\textsubscript{3}), 2.45 (t, 1H, J = 2.2 Hz, acetylenic), 3.38 (s, 3H, OCH\textsubscript{3}), 3.87 (p, 1H, J = 6.42, 12.8 Hz, H-3), 4.07-3.95(m, 2H, H-2, H-4), 4.16-4.38 (ddd, 2H, J = 2.2, 16.2 Hz, OCH\textsubscript{2}), 4.81 (d, 1H, J = 3.8 Hz, H-5); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 75 MHz): δ 100.7, 84.1, 79.2, 77.9, 75.2, 57.6, 54.6, 31.5, 21.0; HRMS (ESI): m/z calculated for C\textsubscript{9}H\textsubscript{14}NaO\textsubscript{4} (M\textsuperscript{+}+Na) 209.0789, found 209.0797.

(2S,3S,4R,5S)-2-Ethyl-tetrahydro-5-methoxy-4-(prop-2-nyloxy)furan-3-ol (39b): A solution of 37b (0.39 g, 1.21 mmol) in aq. CH\textsubscript{2}Cl\textsubscript{2} (1:19, H\textsubscript{2}O:CH\textsubscript{2}Cl\textsubscript{2}, 10 mL) was treated with DDQ (0.55 g, 2.43 mmol) at 0 °C for 2 h. Work up as described for 39a and purification by column chromatography (60-120 Silica gel; ethyl acetate: pet. ether, 1:4) afforded 39b (0.20 g, 82%) as a colourless liquid; [α]\textsubscript{D} = -176.5 (c 0.67, CHCl\textsubscript{3}); IR (neat): 3447, 2925, 2854, 1741, 1219, 771 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (300 MHz, CHCl\textsubscript{3}): δ 0.99 (t, 3H, J = 7.5 Hz, CH\textsubscript{3}), 1.58-1.69 (m, 2H, CH\textsubscript{2}), 2.43 (t, 1H, J = 2.2 Hz, acetylenic), 3.36 (s, 3H, OCH\textsubscript{3}), 3.77 (m, 2H, H-3, H-2), 3.89 (s, 1H, H-4), 4.38-4.16 (dd, 2H, J = 2.2, 15.8 Hz, OCH\textsubscript{2}), 4.85 (s, 1H, H-5); \textsuperscript{13}C NMR (CDCl\textsubscript{3}, 150 MHz): δ 106.2, 96.3, 88.7, 86.0, 78.9, 75.1, 57.3, 54.6, 26.4, 10.2; HRMS (ESI): m/z calculated for C\textsubscript{10}H\textsubscript{16}NaO\textsubscript{4} (M\textsuperscript{+}+Na) 223.0946, found 223.0945.

(2S,3S,4R,5S)-2-Ethyl-tetrahydro-5-methoxy-4-(prop-2-nyloxy)furan-3-ol (40b): A solution of 38b (0.38 g, 1.18 mmol) in aq. CH\textsubscript{2}Cl\textsubscript{2} (1:19, H\textsubscript{2}O:CH\textsubscript{2}Cl\textsubscript{2}, 10 mL) was treated with DDQ (0.53 g, 2.37 mmol) at 0 °C for 2 h. Work up as described 39a and purification by column chromatography (60-120 Silica gel; ethyl acetate: pet. ether, 1:4) gave 40b (0.19 g, 80%) as a
colourless liquid; $[\alpha]_D = +138.2$ (c 0.48, CHCl$_3$); IR (neat): 3437, 2926, 2856, 1737, 1219, 1051, 769 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 0.99 (t, 3H, $J = 7.5$ Hz, CH$_3$), 1.57-1.71 (m, 2H, CH$_2$), 2.21 (bs, 1H, OH), 2.45 (t, 1H, $J = 2.2$ Hz, acetylenic), 3.37 (s, 3H, OCH$_3$), 3.69 (q, 1H, $J = 6.4$, 13.2 Hz, H-2), 3.98 (m, 1H, H-3), 4.10 (t, 1H, $J = 7.1$ Hz, H-4), 4.16-4.38 (ddd, 2H, $J = 2.2$ Hz, OCH$_2$), 4.82 (d, 1H, $J = 4.1$ Hz, H-5);$^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 100.7, 96.2, 84.5, 82.7, 79.8, 75.2, 57.5, 54.5, 28.6, 9.9; HRMS (ESI): $m/z$ calculated for C$_{10}$H$_{16}$NaO$_4$ (M$^+$+Na) 223.0946, found 223.0947.

(2S,3S,4R,5R)-Tetrahydro-5-methoxy-2-pentyl-4-(prop-2-ynyloxy)furan-3-ol (39c): A solution of 37c (0.26 g, 0.71 mmol) in aq. CH$_2$Cl$_2$ (1:19, H$_2$O:CH$_2$Cl$_2$, 10 mL) was treated with DDQ (0.32 g, 1.43 mmol) at 0 $^\circ$C for 2 h. Work up as described for 39a and purification of the residue by column chromatography (60-120 Silica gel, ethyl acetate: pet. ether, 0.7:9.3) gave 39c (0.11 g, 65%) as a liquid; $[\alpha]_D = -164.8$ (c 1.30, CHCl$_3$); IR (neat): 3380, 2856, 2115, 1211, 764 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 0.90 (t, 3H, $J = 6.6$ Hz, CH$_3$), 1.25-1.60 (m, 8H, 4CH$_2$), 2.24 (d, 1H, $J = 8.1$ Hz, OH), 2.41 (t, 1H, $J = 2.2$ Hz, acetylenic), 3.36 (s, 3H, OCH$_3$), 3.74 (bs, 1H, H-3), 3.83 (q, 1H, $J = 5.6$, 12.2 Hz, H-2), 3.88 (d, 1H, $J = 2.2$ Hz, H-4), 4.22 (dd, 2H, $J = 2.0$, 15.7 Hz, OCH$_2$), 4.84 (s, 1H, H-5);$^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 106.2, 96.2, 88.6, 84.8, 79.3, 75.1, 57.4, 54.7, 33.5, 31.8, 25.6, 22.6, 14.1; HRMS (ESI): $m/z$ calculated for C$_{13}$H$_{22}$NaO$_4$ (M$^+$+Na) 265.1415, found 265.1427.

(2S,3S,4R,5S)-Tetrahydro-5-methoxy-2-pentyl-4-(prop-2-ynyloxy)furan-3-ol (40c): A solution of 38c (0.25 g, 0.70 mmol) in aq. CH$_2$Cl$_2$ (1:19, H$_2$O:CH$_2$Cl$_2$, 10 mL) was treated with DDQ (0.32 g, 1.41 mmol) at 0 $^\circ$C for 2 h. Work up as described for 39a and purification by column chromatography (60-120 Silica gel; ethyl acetate: pet. ether, 1:4) afforded 40c (0.12 g, 72%) as a liquid; $[\alpha]_D = +149.7$ (c 0.7, CHCl$_3$); IR (neat): 3378, 2860, 2215, 1223, 698 cm$^{-1}$; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 0.90 (t, 3H, $J = 6.4$ Hz, CH$_3$), 1.25-1.67 (m, 8H, 4CH$_2$), 2.45 (t, 1H, $J = 2.2$ Hz, acetylenic), 2.59 (bs, 1H, OH), 3.37 (s, 3H, OCH$_3$), 3.72 (q, 1H, $J = 6.7$, 13.2 Hz, H-3), 3.94-4.10 (m, 2H, H-2, H-4), 4.17-4.37 (ddd, 2H, $J = 2.2$, 15.8 Hz, OCH$_2$), 4.81 (d, 1H, $J = 4.1$ Hz, H-5);$^{13}$C NMR (CDCl$_3$, 75 MHz): $\delta$ 100.7, 96.1, 84.5, 81.7, 78.4, 75.3, 57.7, 54.7, 35.8, 31.7, 25.2, 22.6, 14.0; HRMS (ESI): $m/z$ calculated for C$_{13}$H$_{22}$NaO$_4$ (M$^+$+Na) 265.1415, found 265.1420.
O-(2S,3S,4R,5R)-Tetrahydro-5-methoxy-2-methyl-4-(prop-2-ynyloxy)furan-3-yl-S-methyl carbonodithioate (23a): A stirred suspension of NaH (0.05 g, 2.25 mmol) in dry THF (3 mL) under N₂ atmosphere was treated with a solution of 39a (0.14 g, 0.75 mmol) in THF (3 mL) at 0 °C and stirred at room temperature for 30 min. Carbon disulphide (0.07 mL, 1.12 mmol) was added at 0 °C and stirred at room temperature for 30 min. Methyl iodide (0.07 mL, 1.12 mmol) was added at 0 °C and stirred at room temperature for 1 h. The reaction mixture was quenched with aq. NH₄Cl solution (4 mL) and extracted with EtOAc (3 x 5 mL). Organic layer was washed with water (6 mL), brine (6 mL), dried (Na₂SO₄) and evaporated. Purification of the residue by column chromatography (60-120 Silica gel; ethyl acetate: pet. ether, 1:9) afforded 23a (0.18 g, 89%) as light yellow liquid; [α]D = -304.2 (c 1.04, CHCl₃); IR (neat): 3448, 2921, 2851, 1724, 1460, 1250, 1071, 771 cm⁻¹; ¹H NMR (400 MHz, CDCl₃): δ 1.43 (d, 3H, J = 6.2 Hz, CH₃), 2.47 (t, 1H, J = 2.2 Hz, acetyl enic), 2.57 (s, 3H, SCH₃), 3.38 (s, 4H, H-2, OCH₃), 4.19 (s, 1H, H-4), 4.30 (s, 2H, OCH₂), 5.0 (s, 1H, H-5), 5.61 (d, 1H, J = 3.3 Hz, H-3); ¹³C NMR (CDCl₃, 75 MHz): δ 214.7, 107.3, 96.3, 86.3, 84.5, 76.3, 75.3, 57.8, 55.2, 18.9, 15.8; HRMS (ESI): m/z calculated for C₁₁H₁₆NaO₄S₂ (M⁺+Na) 299.0387, found 299.0391.

O-(2S,3S,4R,5S)-Tetrahydro-5-methoxy-2-methyl-4-(prop-2-ynyloxy)furan-3-yl-S-methyl carbonodithioate (24a): A stirred suspension of NaH (0.05 g, 2.25 mmol) in dry THF (5 mL) under N₂ atmosphere was treated with a solution of 40a (0.14 g, 0.75 mmol) in THF (4 mL) at 0 °C and stirred at room temperature for 30 min. Carbon disulphide (0.07 mL, 1.12 mmol) was added at 0 °C and stirred at room temperature for 30 min. Methyl iodide (0.07 mL, 1.12 mmol) was added at 0 °C. Work up as described for 23a and purification of the residue by column chromatography (60-120 Silica gel; ethyl acetate: pet. ether, 1:9) afforded 24a (0.18 g, 86%) as light yellow liquid; [α]D = +285.1 (c 0.44, CHCl₃); IR (neat): 3285, 2924, 2858, 2120, 1712, 1446, 1210, 1064, 669 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 1.50 (d, 3H, J = 6.4 Hz, CH₃), 2.42 (t, 1H, J = 2.2 Hz, acetylenic), 2.58 (s, 3H, SCH₃), 3.44 (s, 3H, OCH₃), 4.06 (m, 1H, H-2), 4.25 (t, 2H, J = 2.2 Hz, OCH₂), 4.45 (t, 1H, J = 5.2 Hz, H-4), 4.95 (d, 1H, J = 4.5 Hz, H-5), 5.90 (q, 1H, J = 4.1 Hz, H-3); ¹³C NMR (CDCl₃, 100 MHz): δ 214.9, 106.9, 88.7, 86.3, 78.7, 78.3, 75.3, 57.7, 54.6, 19.1 (2C); HRMS (ESI): m/z calculated for C₁₁H₁₆NaO₄S₂ (M⁺+Na) 299.0387, found 299.0389.
O-(2S,3S,4R,5R)-2-Ethyl-tetrahydro-5-methoxy-4-(prop-2-ynyloxy)furan-3-yl-S-methyl carbonodithioate (23b): A stirred suspension of NaH (0.05 g, 2.37 mmol) in dry THF (5 mL) under N₂ atmosphere was treated with a solution of 39b (0.19 g, 0.95 mmol) in THF (4 mL) at 0 °C and stirred at room temperature for 30 min. Carbon disulphide (0.08 mL, 1.42 mmol) was added at 0 °C and stirred at room temperature for 30 min. Methyl iodide (0.07 mL, 1.12 mmol) was added at 0 °C. Work up as described for 23a and purification of the residue by column chromatography (60-120 Silica gel; ethyl acetate: pet. ether, 1:9) gave 23b (0.19 g, 70%) as liquid; [α]D = -370.5 (c 0.28, CHCl₃); IR (neat): 3448, 2921, 2851, 1724, 1460, 1250, 1071, 771 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 0.98 (t, 3H, J = 7.5 Hz, CH₃), 1.75 (m, 2H, CH₂), 2.46 (t, 1H, J = 2.2 Hz, acetylenic), 2.57 (s, 3H, S(CH₃)), 3.40 (s, 3H, OCH₃), 4.11-4.15 (m, 2H, H-2), 4.32 (d, 2H, J = 2.3 Hz, OCH₂), 4.98 (s, 1H, H-5), 5.67 (d, 1H, J = 4.6 Hz, H-3); ¹³C NMR (CDCl₃, 100 Hz): δ 214.9, 106.7, 87.4, 86.2, 82.9, 78.8, 75.2, 57.7, 54.5, 26.2, 19.0, 9.7; HRMS (ESI): m/z calculated for C₁₂H₁₈NaO₄S₂ (M⁺+Na) 313.0544, found 313.0547.

O-(2S,3S,4R,5S)-2-Ethyl-tetrahydro-5-methoxy-4-(prop-2-nyloxy)furan-3-yl-S-methyl carbonodithioate (24b): A stirred suspension of NaH (0.05 g, 2.06 mmol) in dry THF (5 mL) under N₂ atmosphere was treated with a solution of 40b (0.16 g, 0.82 mmol) in THF (4 mL) at 0 °C and stirred at room temperature for 30 min. Carbon disulphide (0.07 mL, 1.23 mmol) was added at 0 °C and stirred at room temperature for 30 min. Methyl iodide (0.07 mL, 1.23 mmol) was added at 0 °C. Work up as described for 23a and purification of the residue by column chromatography (60-120 Silica gel; ethyl acetate: pet. ether, 1:9) gave 24b (0.21 g, 88%) as a liquid; [α]D = +206.3 (c 1.25, CHCl₃); IR (neat): 3285, 2924, 2858, 2120, 1712, 1460, 1250, 1064, 669 cm⁻¹; ¹H NMR (300 MHz, CDCl₃): δ 0.99 (t, 3H, J = 7.3 Hz, CH₃), 1.67-2.00 (m, 2H, CH₂), 2.48 (t, 1H, J = 2.2 Hz, acetylenic), 2.58 (s, 3H, S(CH₃)), 3.46 (s, 3H, OCH₃), 3.87-3.93 (m, 1H, H-2), 4.29-4.27 (dd, 2H, J = 2.4 Hz, OCH₂), 4.48 (dd, 1H, J = 4.5 Hz, H-4), 5.01 (d, 1H, J = 4.5 Hz, H-5), 6.12 (dd, 1H, J = 4.5 Hz, H-3); ¹³C NMR (CDCl₃, 100 MHz): δ 215.1, 101.8, 88.0, 83.1, 81.9, 78.8, 75.5, 57.8, 55.2, 28.5, 19.3, 10.1; HRMS (ESI): m/z calculated for C₁₂H₁₈NaO₄S₂ (M⁺+Na) 313.0544, found 313.0549.

O-(2S,3S,4R,5R)-Tetrahydro-5-methoxy-2-pentyl-4-(prop-2-ynyloxy)furan-3-yl-S-methyl carbonodithioate (23c): A stirred suspension of NaH (0.02 g, 0.74 mmol) in dry THF (5 mL)
under N₂ atmosphere was treated with a solution of 39c (0.09 g, 0.37 mmol) in THF (4 mL) at 0 °C and stirred at room temperature for 30 min. Carbon disulphide (0.03 mL, 0.55 mmol) was added at 0 °C and stirred at room temperature for 30 min. Methyl iodide (0.03 mL, 0.55 mmol) was added at 0 °C. Work up as described for 23a and purification of the residue by column chromatography (60-120 Silica gel; ethyl acetate: pet. ether, 1:9) gave 23c (0.09 g, 73%) as light yellow liquid; \([\alpha]_D = -327.0 \ (c 0.4, \text{CHCl}_3)\); IR (neat): 3440, 2922, 2115, 1724, 1469, 1255, 1072, 778 cm⁻¹; \(^1\)H NMR (300 MHz, CDCl₃): \(\delta\) 0.89 (t, 3H, \(J = 6.6\ \text{Hz, CH}_3\)), 1.25-1.72 (m, 8H, 4 \(\text{CH}_2\)), 2.39 (t, 1H, \(J = 2.2\ \text{Hz, acetylenic}\)), 2.57 (s, 3H, SCH₃), 3.36 (s, 3H, OCH₃), 4.08-4.14 (m, 2H, H-4, H-2), 4.28 (d, 2H, \(J = 2.2\ \text{Hz, OCH}_2\)), 4.91 (s, 1H, H-5), 5.59 (d, 1H, \(J = 4.7\ \text{Hz, H-3}\)); \(^{13}\)C NMR (CDCl₃, 75 MHz): \(\delta\) 214.8, 106.8, 87.9, 86.2, 81.8, 78.9, 75.3, 57.7, 54.5, 33.3, 31.6, 25.3, 22.6, 19.1, 14.1; HRMS (ESI): \(m/z\) calculated for C₁₅H₂₄NaO₄S₂ (M⁺+Na) 355.1013, found 355.1008.

O-(2S,3S,4R,5S)-Tetrahydro-5-methoxy-2-pentyl-4-(prop-2-ynyloxy)furan-3-yl-S-methyl carbonodithioate (24c): A stirred suspension of NaH (0.02 g, 1.03 mmol) in dry THF (5 mL) under N₂ atmosphere was treated with a solution of 40c (0.10 g, 0.41 mmol) in THF (4 mL) at 0 °C and stirred at room temperature for 30 min. Carbon disulphide (0.03 mL, 0.62 mmol) was added at 0 °C and stirred at room temperature for 30 min. Methyl iodide (0.03 mL, 0.62 mmol) was added at 0 °C. Work up as described for 23a and purification of the residue by column chromatography (60-120 Silica gel; ethyl acetate: pet. ether, 1:9) gave 24c (0.11 g, 81%) as light yellow liquid; \([\alpha]_D = +158.9 \ (c 0.58, \text{CHCl}_3)\); IR (neat): 3356, 2861, 2167, 1718, 1532, 1209, 1132, 761 cm⁻¹; \(^1\)H NMR (300 MHz, CDCl₃): \(\delta\) 0.88 (t, 3H, \(J = 6.6\ \text{Hz, CH}_3\)), 1.25-1.92 (m, 8H, 4 \(\text{CH}_2\)), 2.35 (s, 1H, H-acetylenic), 2.58 (s, 3H, SCH₃), 3.45 (s, 3H, OCH₃), 3.95 (m, 1H, H-4), 4.27 (m, 2H, OCH₂), 4.46 (t, 1H, \(J = 4.9\ \text{Hz, H-4}\)), 4.99 (t, 1H, \(J = 4.5\ \text{Hz, H-5}\)), 6.0 (t, 1H, \(J = 4.7\ \text{Hz, H-3}\)); \(^{13}\)C NMR (CDCl₃, 150 MHz): \(\delta\) 215.1, 101.7, 101.1, 88.4, 82.0, 81.8, 78.6, 75.6, 57.8, 55.2, 35.5, 25.4, 22.6, 19.4, 14.1; HRMS (ESI): \(m/z\) calculated for C₁₅H₂₄NaO₄S₂ (M⁺+Na) 355.1013, found 355.1023.

(3aR,4S,6S,6aR)-Hexahydro-6-methoxy-4-methyl-3-methylene[furo[3,4-b]furan (21a): A solution of 23a (0.18 g, 0.67 mmol) in dry benzene (25 mL) under N₂ atmosphere was treated with \(n\)-Bu₃SnH (0.36 mL, 1.34 mmol) at room temperature and heated at reflux for 30 min. After
30 min, catalytic amount of AIBN was added at reflux and continued for 12 h. The reaction mixture was cooled to room temperature, benzene evaporated under reduced pressure and purification of the residue by column chromatography (60-120 Silica gel; ethyl acetate: pet. ether, 1:2:8:8) to afford 21a (0.08 g, 69%) as a colourless liquid; [α]D = -21.70 (c 0.41, CHCl3); IR (neat): 2925, 2852, 1731, 1654, 1463, 1265, 1100, 771 cm⁻¹; ¹H NMR (400 MHz, CDCl3): δ 1.25 (d, 3H, J = 9.0 Hz, CH3), 3.18 (t, 1H, J = 6.8 Hz, H-3a), 3.31-3.40 (m, 4H, H-4, OCH3), 4.19-4.30 (m, 2H, OCH2), 4.53 (d, 1H, J = 3.8 Hz, H-6a), 4.81 (s, 1H, H-6), 4.90 (d, 1H, J = 1.5 Hz, olefinic), 5.08 (d, 1H, J = 2.2 Hz, olefinic); ¹³C NMR (CDCl3, 75 MHz): δ 146.3, 107.5, 106.2, 85.2, 74.5, 73.0, 54.7, 52.8, 29.6; HRMS (ESI): m/z calculated for C9H15O3 (M+H) 171.1021, found 171.1023.

(3aR,4S,6R,6aR)-Hexahydro-6-methoxy-4-methyl-3-methylenefuro[3,4-b]furan (22a): A solution of 24a (0.85 g, 3.07 mmol) in dry benzene (25 mL) under N₂ atmosphere was treated with n-Bu₃SnH (1.65 mL, 6.15 mmol) and AIBN was added at reflux and continued for 12 h. Work up as described for 21a and purification by column chromatography (60-120 Silica gel, ethyl acetate: pet. ether, 0.7:9.3) gave 22a (0.30 g, 57%) as a colourless liquid; [α]D = -2.44 (c 0.33, CHCl3); IR (neat): 2923, 2853, 1732, 1654, 1461, 1261, 1029, 869, 723 cm⁻¹; ¹H NMR (400 MHz, CDCl3): δ 1.23 (d, 3H, J = 6.5 Hz, CH3), 3.23 (t, 1H, J = 5.8 Hz, H-3a), 3.50 (s, 3H, OCH3), 4.06 (m, 1H, H-4), 4.28-4.38 (m, 2H, OCH2), 4.61 (q, 1H, H-6a), 4.67 (d, 1H, J = 3.6 Hz, H-6), 4.89 (d, 1H, J = 2.1 Hz, olefinic), 5.08 (d, 1H, J = 2.1 Hz, olefinic); ¹³C NMR (CDCl3, 75 MHz): δ 146.3, 108.0, 105.2, 83.7, 73.9, 73.7, 57.7, 50.5, 29.6; HRMS (ESI): m/z calculated for C9H14NaO3 (M⁺Na) 193.0840, found 193.0839.

(3aR,4S,6R,6aR)-4-Ethyl-hexahydro-6-methoxy-3-methylenefuro[3,4-b]furan (21b): A solution of 23b (0.10 g, 0.34 mmol) in dry benzene (25 mL) on reaction with n-Bu₃SnH (0.18 mL, 0.68 mmol) and catalytic amount of AIBN was added at reflux and continued for 12 h. Work up as described for 21a and purification by column chromatography (60-120 Silica gel, ethyl acetate: pet. ether, 0.7:9.3) gave 21b (0.04 g, 71%) as a colourless liquid; [α]D = -49.2 (c 0.23, CHCl3); IR (neat): 3437, 2926, 2856, 1737, 1219, 1051, 769 cm⁻¹; ¹H NMR (300 MHz, CDCl3): δ 1.01 (t, 3H, J = 7.3 Hz, CH3), 1.49 (m, 2H, CH2), 3.19 (t, 1H, J = 7.1 Hz, H-3a), 3.29 (s, 3H, OCH3), 3.94 (m, 1H, H-4), 4.16 (m, 2H, J = 1.7, 3.5 Hz, OCH2 ), 4.53 (d, 1H, J = 6.4 Hz,
(3aR,4S,6S,6aR)-4-Ethyl-hexahydro-6-methoxy-3-methylenefuro[3,4-b]furan (22b): A solution of 24b (0.10 g, 0.34 mmol) in dry benzene (25 mL) was treated with n-Bu3SnH (0.18 mL, 0.68 mmol) and catalytic amount of AIBN was added at reflux and continued for 12 h. Work up as described for 21a and purification by column chromatography (60-120 Silica gel, ethyl acetate: pet. ether, 0.9:9.1) gave 22b (0.03 g, 60%) as a colourless liquid; [α]D = -285.8 (c 0.23, CHCl3); IR (neat): 3412, 2891, 2797, 1764, 1176, 1083, 804 cm⁻¹; 1H NMR (400 MHz, CDCl3): δ 1.02 (t, 3H, J = 7.3 Hz, CH3), 1.55 (m, 2H, CH2), 3.26 (t, 1H, J = 7.3 Hz, H-3a), 3.51 (s, 3H, OCH3), 3.74 (m, 1H, H-4), 4.25-4.35 (q, 2H, J = 12.1 Hz, OCH2), 4.60 (m, 1H, H-6a), 4.67 (d, 1H, J = 3.6 Hz, H-6), 4.91 (s, 1H, olefinic), 5.06 (s, 1H, olefinic); 13C NMR (CDCl3, 75 MHz): δ 147.1, 107.7, 96.2, 88.5, 80.9, 72.6, 54.1, 50.0, 24.3, 11.4; HRMS (ESI): m/z calculated for C10H17O3 (M⁺+H) 185.1177, found 185.1170.

(3aR,4S,6R,6aR)-Hexahydro-6-methoxy-3-methylene-4-pentylfuro[3,4-b]furan (21c): A solution of 23c (0.08 g, 0.24 mmol) in dry benzene (25 mL) on reaction with n-Bu3SnH (0.13 mL, 0.48 mmol) and catalytic amount of AIBN was added at reflux and continued for 12 h. Work up as described for 21a and purification by column chromatography (60-120 Silica gel, ethyl acetate: pet. ether, 0.9:9.5) gave a 21c (0.008 g, 14%) as a colourless liquid; [α]D = -249.7 (c 0.26, CHCl3); IR (neat): 3367, 2832, 2165, 1167, 762 cm⁻¹; 1H NMR (300 MHz, CDCl3): 0.89 (t, 3H, J = 6.6 Hz, CH3), 1.28-1.58 (m, 8H, alkyl chain), 3.23 (t, 1H, J = 6.2 Hz, H-3a), 3.33 (s, 3H, OCH3), 4.08 (m, 1H, H-4), 4.21 (q, 2H, J = 12.3 Hz, OCH2), 4.59 (d, 1H, J = 6.1 Hz, H-6a), 4.89 (s, 1H, H-6), 4.95 (s, 1H, olefinic), 5.09 (s, 1H, olefinic); 13C NMR (CDCl3, 150 MHz): δ 146.5, 108.0, 107.6, 88.3, 79.3, 72.5, 54.1, 49.8, 31.8, 31.0, 26.5, 22.6, 14.0; HRMS (ESI): m/z calculated for C13H22NaO3 (M⁺+Na) 249.1466, found 249.1456.
References:

SPECTRA
Spectrum 1: $^1$H NMR Spectrum of compound 34a in CDCl$_3$ (300 MHz)

$^{13}$C NMR Spectrum of compound 34a in CDCl$_3$ (75 MHz)
Spectrum 2: $^1$H NMR Spectrum of compound 37a in CDCl$_3$ (300 MHz)
$^{13}$C NMR Spectrum of compound 37a in CDCl$_3$ (100 MHz)
Spectrum 3: $^1$H NMR Spectrum of compound 38a in CDCl$_3$ (300 MHz)
$^{13}$C NMR Spectrum of compound 38a in CDCl$_3$ (75 MHz)
Spectrum 4: $^1$H NMR Spectrum of compound 23a in CDCl$_3$ (400 MHz)

$^{13}$C NMR Spectrum of compound 23a in CDCl$_3$ (75 MHz)
Spectrum 5: $^1$H NMR Spectrum of compound 24a in CDCl$_3$ (300 MHz)
$^{13}$C NMR Spectrum of compound 24a in CDCl$_3$ (100 MHz)
Spectrum 6: $^1$H NMR Spectrum of compound 21a in CDCl$_3$ (400 MHz)

$^{13}$C NMR Spectrum of compound 21a in CDCl$_3$ (75 MHz)
Spectrum 7: $^1$H NMR Spectrum of compound 22a in CDCl$_3$ (400 MHz)

$^{13}$C NMR Spectrum of compound 22a in CDCl$_3$ (75 MHz)
Spectrum 8: $^1$H NMR Spectrum of compound 34b in CDCl$_3$ (300 MHz)
$^{13}$C NMR Spectrum of compound 34b in CDCl$_3$ (75 MHz)
Spectrum 9: $^1$H NMR Spectrum of compound 37b in CDCl$_3$ (300 MHz)

$^{13}$C NMR Spectrum of compound 37b in CDCl$_3$ (75 MHz)
Spectrum 10: $^1$H NMR Spectrum of compound 38b in CDCl$_3$ (300 MHz)
$^{13}$C NMR Spectrum of compound 38b in CDCl$_3$ (75 MHz)
Spectrum 11: $^1$H NMR Spectrum of compound 23b in CDCl$_3$ (300 MHz)

$^{13}$C NMR Spectrum of compound 23b in CDCl$_3$ (100 MHz)
Spectrum 12: $^1$H NMR Spectrum of compound 24b in CDCl$_3$ (300 MHz)
$^{13}$C NMR Spectrum of compound 24b in CDCl$_3$ (100 MHz)
Spectrum 13: $^1$H NMR Spectrum of compound 21b in CDCl$_3$ (300 MHz)

$^{13}$C NMR Spectrum of compound 21b in CDCl$_3$ (75 MHz)
Spectrum 14: $^1$H NMR Spectrum of compound 22b in CDCl$_3$ (400 MHz)

$^{13}$C NMR Spectrum of compound 22b in CDCl$_3$ (75 MHz)
Spectrum 15: $^1$H NMR Spectrum of compound 34c in CDCl$_3$ (300 MHz)

$^{13}$C NMR Spectrum of compound 34c in CDCl$_3$ (75 MHz)
Spectrum 16: $^1$H NMR Spectrum of compound 37c in CDCl$_3$ (300 MHz)
$^{13}$C NMR Spectrum of compound 37c in CDCl$_3$ (75 MHz)
Spectrum 17: $^1$H NMR Spectrum of compound 38c in CDCl$_3$ (300 MHz)

$^{13}$C NMR Spectrum of compound 38c in CDCl$_3$ (75 MHz)
Spectrum 18: $^1$H NMR Spectrum of compound 23c in CDCl$_3$ (300 MHz)
$^{13}$C NMR Spectrum of compound 23c in CDCl$_3$ (75 MHz)
Spectrum 19: $^1$H NMR Spectrum of compound 24c in CDCl$_3$ (300 MHz)

$^{13}$C NMR Spectrum of compound 24c in CDCl$_3$ (150 MHz)
Spectrum 20: $^1$H NMR Spectrum of compound 21c in CDCl$_3$ (300 MHz)

$^{13}$C NMR Spectrum of compound 21c in CDCl$_3$ (150 MHz)