Chapter II

Stereoselective synthesis of (+)-Harzialactone A and its Antipode (–)-Harzialactone A via Crimmins Aldol approach:

In this chapter-II, we have described a simple, convenient and efficient approach for the synthesis of naturally occurring (+)-Harzialactone A and its antipode (–)-Harzialactone A with high enantioselectivity. The naturally available harzialactone A shows modest cytotoxicity against cultured P388 cells among the other harzialactones, makes it an attractive target in the synthetic organic community. Because of the significant anti-tumor activity and unique structural architecture, the different stereomers of harzialactone A can show different biological activities, we developed an efficient and stereoselective synthetic route via Crimmins aldol condensation approach.

Introduction

Marine environment is an exceptional reservoir of bioactive natural products, many of which exhibit structural/chemical features not found in terrestrial natural products. Marine organisms was evolved biochemical and physiological mechanisms that include the production of bioactive compounds for such purposes as reproduction, communication, and protection against predation, infection, and competition. The greatest biodiversity on Earth is found in the world’s oceans, which cover greater than 70% of earth’s surface. They contain more than 300 000 described plants and animals which represents approximately 75% of all living organisms, with 34 of the 36 phyla contain an extraordinary diversity of life present. Many marine organisms are soft bodied and have a sedentary life style necessitating chemical means of defense. To resist the ecological pressures, they have evolved the ability to synthesize toxic compounds or to obtain them from marine microorganisms. These compounds help them deter predators, competition for space, fouling of the surface; predation and successfully reproducing have required these species to develop chemical defense systems in addition to various physical defense systems they possess.

Several of these compounds show pharmacological activities and are helpful for the invention and discovery of bioactive compounds, primarily for deadly diseases like Cancer, Acquired Immuno-Deficiency Syndrome (AIDS), and Arthritis etc, while other compounds have been developed as analgesics or to treat inflammation etc. The life saving drugs is mainly found abundantly in micro-organisms, algae and invertebrates, while they
are scarce in vertebrates. Modern technologies have opened vast areas of research for the extraction of biomedical compounds from Oceans and Seas.⁴ᵃ⁻⁵

“Poison kills the poison”, the famous proverb is the basis for researchers in finding the biomedical metabolites from living organisms. Natural products released into the water are rapidly diluted, highly potent, immense biological diversity in the sea as a whole, it is increasingly recognized that a huge number of natural products and novel chemical entities exist in the oceans, with diverse biological activities that may be useful in finding drugs with greater efficacy and specificity for the treatment of many human diseases.

Marine organisms have provided an array of novel structures since the launch of Marine natural product chemistry in the late 1960s-1970s. The catalyst for the search for pharmaceutical products from the ocean came in 1969 when Weinheimer and Spraggins⁵ discovered large quantities of the prostaglandins, in the gorgonian coral *Plexaura homomalla*. Interest in the search for drugs from the sea was stimulated because the prostaglandins had previously been identified as important mediators involved in managing inflammatory diseases, pain and fever.

**Marine Organisms as Potential Source of Drugs:**

During the past 30 to 40 years, numerous novel compounds have been isolated and characterized from marine organisms. A large number of marine-derived natural products have progressed to preclinical and clinical trials for assessment in treating a range of conditions such as cancer, pain, neuropathic pain, epilepsy, inflammation and asthma. However, many do not progress to development as commercial drugs due to formulation problems, undesirable side effects or inactivity. The journey of a potential drug target from identification and structural elucidation through to clinical trials can be extremely long so there are a significant number of compounds currently under investigation as potential pharmaceutical drugs.

Much of the earlier work limited the biological testing to antimicrobial activity, but this was often extended later to testing for cytotoxic properties, which may provide useful leads for anticancer drugs. This latter area is the one that most of the compounds in various stages of clinical trials are located. Screening for other activities has, of course, also been undertaken, for example for antiviral, anti-inflammatory, anticoagulant and antiparasitic compounds.
Some examples of pharmacologically active compounds which are under clinical and preclinical trials range of structures reported and also the variety of marine animals, plants and microorganisms from which they have been isolated are described below.

**Anti-Microbial Compounds:**

The cephalosporins are good examples of antibiotic drugs which owe their origin to a marine source. Cephalosporin C 1 (Figure 1) was isolated from the marine fungus, *Cephalosporium acremonium*.6 A semi-synthetic derivative of this, cephalothin sodium, has been widely used as an antibiotic drug. Istamycins A and B (2, 3; Figure 1) produced by the marine actinomycete *Streptomyces tenjimariensis* SS-939, were reported to have *in vitro* activity against both gram-negative and gram-positive bacteria, including those with known resistance to the amino-glycoside antibiotics.7

![Chemical structure of Cephalosporin C 1](image)

**Figure 1**

**Anti-viral Compounds:**

Many marine organisms have been screened for antiviral activity and a wide range of active compounds has been isolated and characterized.8 However, the only compound reported to have significant therapeutic activity is ara-A 4 (Figure 2),9 which is a semi-synthetic substance based on the arabinosyl nucleosides isolated from the sponge *Tethya Crypta*. Other antiviral compounds include avarol 5 and avarone 6 (Figure 2) isolated from a sponge, *Disidea avara* inhibit the immunodeficiency virus, have high therapeutic indices and the ability to cross the blood-brain barrier.10
Anti-Inflammatory Compounds:

A variety of inflammatory diseases are due to the production of arachidonic acid, the precursor of prostaglandins and leukotrienes. Examples of the anti-inflammatories isolated from marine animals are sesterterpene palaulol 7 (Figure 3), from the sponge *Fascaplysinopsis sp.*\(^{11}\) and a sesquiterpene furan 8 (Figure 3) from the coelenterate, *Sinularia sp.*\(^{12}\)

Anti-Parasitic Compounds:

The active component α-kainic acid 9 (Figure 4), of *Digenia simplex*,\(^{13}\) a red alga, has been used as a vermifuge for very many years and is marketed for the treatment of parasitic round worm, whip worm and tape worm. Marine animals have been tested as source of anti-parasitic compounds for example, bengamide F 10 (Figure 4) which has anthelmintic properties.
Cytotoxic Compounds:

Many of the compounds isolated from marine organisms have been tested for cytotoxicity in search for drugs active against cancer. In this short account it is only possible to select a very few examples illustrated here. Cytotoxic compounds isolated from coelenterates include the sesquiterpene, suberosenone 11 (Figure 5), extracted from subergorgia suberosa. Examples of active compounds from tunicates are the cytotoxic alkaloids clavepictine-A 12 and –B 13 (Figure 5) reported for clavelina picta.

Harzialactone A

A variety of microorganisms were initially isolated from the sponge Halichondria okadai, collected in the Tanabe Bay of Japan. A strain of Trichoderma harzianum OUPSN 115, originally separated from the sponge Halichondria okadai showed cytotoxic activity against the P388 lymphocytic leukemia test system in culture. The Trichoderma species, found in diverse ecological niches, including marine and freshwater environments, are prolific producers of secondary metabolites many of which show biological activity against infective agents.
Figure 6. The Sponge *Halichondria okadai* and its strain *Trichoderma harzianum*

Numata and co-workers\textsuperscript{17} isolated the secondary metabolites from strain of *Trichoderma harzianum* OUPS-N 115. They are six novel metabolites, designated trichodenones A, B and C (14-16), harzialactone A 19 and B 18, along with known *R*-mevalonolactone 17 (Figure 7) showed cytotoxic activity against the P388 lymphocytic leukemia test system in cell culture.

![Chemical structures of trichodenones and harzialactones](image)

**Figure 7**

Fractionation of the crude culture filtrate resulted in the isolation of harzialactone A 19 among other lactones. The naturally available (3\text{R},5\text{R})-19 shows modest cytotoxicity against cultured P388 cells.\textsuperscript{16} The absolute stereochemistry for 19 was established using \textsuperscript{1}H NMR spectra by comparison of the observed coupling constants and NOE data with those of related compounds. Mereyala et al. have synthesized harzialactone A 19 from *D*-glucose\textsuperscript{18} and assigned the absolute configuration as (3\text{R},5\text{R}). The absolute configuration
of 19 was confirmed by its synthesis from D-glucose$^{18a}$ and D-xylose$^{18b}$ by Mereyala and coworkers.

There are four possible stereo isomers for the harzialactone A 19, viz. (3R,5R)-harzialactone A 19, (3S,5S)-harzialactone A 20, (3S,5R)-harzialactone A 21, (3R,5S)-harzialactone A 22 (Figure- 8).

![Figure 8](image)

**Previous synthetic approaches:**

Due to their potent biological activities and unique structures, the (3R,5R)-harzialactone A 19 and its stereo isomers (3S,5S)-20, (3S,5R)-21, (3R,5S)-22 has attracted the many chemists to synthesize in few methods.

**Mereyala’s first approach:**

Mereyala and his co-workers$^{18a}$ have synthesized the harzialactone A 19 for studying the structure–activity relationship starting from easily available homochiral sugars. Commercially available monoacetone-D-glucose 23, on oxidation with NaIO$_4$ affords aldehyde that without purification was immediately treated with phenyl magnesium bromide at 0 °C to furnish diastereomeric mixture of diol (3:1) 24. The diol 24 was reacted with NaH/CS$_2$/MeI to obtain the methyl xanthate derivative 25, which was treated with Bu$_3$SnH to afford dideoxy derivative 26. Compound 26 was treated with 60% aqueous HOAc/cat. H$_2$SO$_4$ at 45 °C to produce diol 27. Finally oxidation of 27 with Ag$_2$CO$_3$/Celite resulted in the formation of (3R,5R)-harzialactone A 19 along with the undesired diketo compound 28 (Scheme 1).
Mereyala’s second approach:

Mereyala and his co-workers\textsuperscript{18b} have reported the synthesis of all possible stereoisomers of harzialactone A\textsuperscript{19}, viz. (3S,5R)-21, (3R,5S)-22 and (3S,5S)-20, respectively, by a similar chiron approach starting from diacetone-D-glucose\textsuperscript{29}. The diacetone-D-glucose\textsuperscript{29} was transformed into the diol 24 by well established methods,\textsuperscript{19a} which was converted to methyl xanthate 25 derivative by reaction with NaH-CS\textsubscript{2}-MeI in THF and was subjected to radical deoxygenating (Bu\textsubscript{3}SnH/cat. AIBN) in refluxing toluene to produce the dideoxy derivative 26, followed by deprotection of acetonide affords the diol 27. Oxidation of the diol 27 with Ag\textsubscript{2}CO\textsubscript{3} resulted in the isolation of harzialactone A\textsuperscript{19}. Thus, reaction of 19 with DEAD/p-NO\textsubscript{2}C\textsubscript{6}H\textsubscript{4}CO\textsubscript{2}H:Ph\textsubscript{3}P in THF gave the p-nitrobenzoate 30. Compound 30 on reaction with a catalytic amount of NaOMe in MeOH:DCM (1:1) strictly at −20 °C resulted in the isolation of (3S,5R)-harzialactone 21 as a crystalline solid (Scheme 2).
Scheme 2

Synthesis of hydroxylactone (3R,5S)-22 was achieved starting from diacetone-D-glucose 29. Compound 29 was converted to the 3-deoxy diol derivative 31 by literature methods\textsuperscript{19b} and reacted with NaIO₄ to obtain the corresponding aldehyde that was immediately reacted with phenyl magnesium bromide to isolate the alcohol 32. Compound 32 was converted to the methyl xanthate ester 33 and deoxygenated to obtain the dideoxyfuranose derivative 34 in good yield. Reaction of 34 with aq. acetic acid containing a catalytic amount of conc. H₂SO₄ resulted in the isolation of diol 35, that on further regioselective oxidation with Ag₂CO₃/Celite in benzene:DMF (8:1) at reflux temperature gave the hydroxylactone (3R,5S)-22. The synthesis of hydroxylactone (3S,5S)-20 was achieved from 22 by inverting the configuration at the C-3 hydroxyl. Thus, the Mitsunobu reaction of 22 (DEAD:\textit{p}−NO₂C₆H₄CO₂H:Ph₃P) gave the \textit{p}-nitrobenzoyl ester derivative 36, which on further reaction with a catalytic amount of NaOMe in MeOH and dichloromethane (1:1) at −20 °C gave (3S,5S)-20 (Scheme 3).
Y. J. Jian’s approach:

Y. J. Jian and his co-workers\cite{20} have synthesized the antipode of harzialactone A \textbf{20} by making use of starting material \textbf{37}, which is derived from \textit{L}-malic acid. First they converted compound \textbf{37} into the corresponding acid halide by treatment with \textit{SOCl}_{2}. To this crude acid halide a benzyl group was introduced under \textit{PhCH}_{2}ZnBr/PdCl\textsubscript{2}(PPh\textsubscript{3})\textsubscript{2} conditions, and got product ketone \textbf{38}, which on treatment with \textit{p-TsOH} in MeOH, giving acetyl deprotected \textbf{39}. This ketone carbonyl compound \textbf{39} on reduction with \textit{NaBH}_{4}/Et\textsubscript{2}BOMe affords a mixture \textit{syn-} and \textit{anti-}diols which are inseperable. This crude diol was directly cyclized by treatment with a catalytic amount of \textit{p-TsOH} in DCM. By separating the isomers derived from the \textit{syn-} and \textit{anti-}diols furnished the target molecule antipode of harzialactone \textbf{20} (Scheme 4).
S. P. Kotkar’s approach:

S. P. Kotkar and his co-workers\textsuperscript{21} reported the synthesis of the harzialactone A 19 via L-proline-catalyzed sequential aminooxylation–olefination of the aldehydes. Thus, 3-phenylpropanal 40 was subjected to $\alpha$-aminooxylation with nitrosobenzene followed by in situ Horner–Wadsworth–Emmons (HWE) olefination with LiCl and DBU (Masamune–Roush protocol) to furnish aminooxy olefinic ester 41. Simultaneous reduction of both the C=C bond and the anilinoxy group in ester 41 was achieved with 10\% Pd/C, H\textsubscript{2} (1 atm) to produce $\gamma$-hydroxy ester 42. Intramolecular cyclization of hydroxyl ester 42 gave lactone 43. Finally, diastereoselective $\alpha$-hydroxylation of lactone 43, with KHMDS and 2-[(4-methylphenyl)sulfonyl]-3-phenyloxaziridine (Davis oxaziridine) affords harzialactone A 19 (Scheme 5).

\begin{scheme}
\centering
\includegraphics[width=\textwidth]{scheme4}
\caption{Scheme 4}
\end{scheme}

A. N. Kumar’s approach:

A. N. Kumar and his co-workers\textsuperscript{22} have synthesized the harzialactone A 19 and its stereo isomers in chemoenzymatic route. The allylation of commercially available, 2-phenylacetaldehyde 44 in the presence of Al-powder/SnCl\textsubscript{2}.2H\textsubscript{2}O in
MeOH/H₂O/CH₃COOH provided the racemic homoallylic alcohol 45 which was resolved with a combination of Novozyme 435/vinyl acetate in diisopropyl ether gave the (S)-46 and (R)-acetate 47. The compound (S)-46 on dihydroxylation with polymer-bound OsO₄ reagent produces a mixture of triol epimers 48, these are separated after monosilylation of primary hydroxygroup. Next, by acetonide protection of 1,3-diol of compound 49 followed by desilylation gave the alcohol 51, which on Swern oxidation afforded the aldehyde 52. Finally the aldehyde was oxidized with NaClO₂ and acidic work-up furnished directly the lactone (3R,5R)-19 (Scheme 6). The synthesis of (3S,5S)-20 was also accomplished in an identical manner starting from (R)-47.

![Scheme 6](image-url)
Sabitha’s approach:

Sabitha and her co-workers\(^\text{23}\) synthesized the \((3R,5R)\)-harzialactone A \(19\) and its \((3R,5S)\)-isomer \(22\) by the opening of epoxide \(54\) with thiacetal \(53\). The starting material epoxide \(54\) is commercially available and the thiacetal \(53\) is prepared by the treatment of 2-phenylacetaldehyde \(44\) with 1,3-propanedithiol in the presence of \(\text{BF}_3\cdot\text{Et}_2\text{O}\) in DCM. The epoxide \(54\) was coupled with the acyl anion equivalent \(53\), prepared by metellation with \(n\)-butyllithium in the presence of \(\text{BF}_3\cdot\text{Et}_2\text{O}\) at \(-78\) °C to obtain \(55\). By removal of dithioketal using \(\text{HgCl}_2/\text{CaCO}_3\) in \(\text{CH}_3\text{CN}/\text{H}_2\text{O}\) (4:1) provided the corresponding hydroxyketone \(56\), this on treatment with \(\text{NaBH}_4\) and \(\text{MeOBEt}_2\) stereo selectively formed the \(\text{syn}\) diol \(57\). The diol \(57\) was transformed into the isopropylidene derivative \(58\) by treatment with 2,2-dimethoxypropane and a catalytic amount of PPTS in DCM. Deprotecting the benzyl group of compound \(58\) using \(\text{Li/liq. NH}_3\) produce alcohol \(59\). Oxidation of alcohol \(59\) under Swern conditions and further oxidation of the resulting aldehyde using \(\text{NaH}_2\text{PO}_4, \text{NaClO}_2\) in DMSO/H\(_2\)O furnished the target hydroxylactone \((3R,5R)\)-harzialactone A \(19\) (Scheme 7).

\[
\begin{align*}
\text{CHO} & \quad \text{HS(CH}_2\text{)_2SH, BF}_3\cdot\text{Et}_2\text{O} \quad \text{DCM, } -10\text{ °C to rt} \quad 6\text{ h, 90}\% \\
\text{44} & \quad \text{+} \quad \text{O} \quad \text{O} \quad \text{Bn} \\
\text{CHO} & \quad \text{CaCO}_3, \text{HgCl}_2 \quad \text{CH}_3\text{CN}/\text{H}_2\text{O (4:1)} \quad \text{rt, 1 h, 82}\% \\
\text{55} & \quad \text{OH} \quad \text{Bn} \\
\text{OH} & \quad \text{2,2-DMP, PPTS} \quad \text{DCM, 92}\% \\
\text{57} & \quad \text{Bn} \\
\text{OH} & \quad \text{i) (COCl)}_2, \text{Et}_3\text{N, 1.5 h, 95}\% \\
\text{59} & \quad \text{ii) NaH}_2\text{PO}_4, \text{NaClO}_2 \quad \text{DMSO}/\text{H}_2\text{O, 3 M HCl} \\
\text{Bn} & \quad \text{Ph} \\
\text{OH} & \quad \text{OH} \\
\text{19} & \quad \text{PH}\end{align*}
\]
Similarly the isomer (3R,5S)-harzialactone A 22 was also accomplished in the above manner. For this isomer the anti-diol 60 was prepared by asymmetric reduction of hydroxyketone 56 with Me₄NBH(OAc)₃ at 0 °C. This anti-diol 60 which was converted to the stereoisomer (3R,5S)-21 via acetonide protection, debenzylation and by the further functional group transformations (Scheme 8).

Scheme 8

He, Lei’s approach:

He, Lei and his co-workers²⁴ have synthesized the (−)-harzialactone A 20 begins with epoxy chiral building blocks.

Scheme 9
The epoxy alcohol 63 was treated with PhMgCl in the presence of CuI at $-20 \, ^\circ\text{C}$, leading to diol 64, in which the alcohol groups are protected as TBS ether 65 followed by the hydrolysis of acetonide group affords the compound 66. The diol 66 was then cleaved with NaIO$_4$ in THF:H$_2$O (V:V=5:1) to deliver the intermediate aldehyde, which was immediately oxidized into the corresponding carboxylic acid 67 with NaClO$_2$. On treatment with $p$-TsOH in DCM at ambient temperature, the TBS protecting groups were readily cleaved and the resultant diol underwent spontaneous cyclization, affording the end product lactone (−)-harzialactone A 20 (Scheme 9).

Alternatively, the lactone (−)-harzialactone A 20 was also accessed through the route shown in Scheme 10. Protection of the hydroxyl group in chiral building block 63 as reported previously led to benzyl ether 68, which was treated with PhMgCl/CuI to afford the alcohol 69. The terminal acetonide protecting group was then hydrolyzed with 50% aq CF$_3$CO$_2$H to produce compound 70. The desired carboxylic group was released through oxidative cleavage of vicinal diol of compound 70 with NaIO$_4$/SiO$_2$ and the subsequent oxidation of the intermediate aldehyde with NaClO$_2$. Finally, atmospheric pressure hydrogenolysis of the benzyl protecting group over 10% Pd-C delivered the end product (−)-harzialactone A 20 (Scheme 10).
Present Work

In combination of both the biological significance and necessity of developing versatile approaches to access of these lactones, we were interested in making a chiral template that meets the requirement. Our salient feature of the synthesis is the construction of chiral building block C by Crimmins aldol condensation and subsequent Grignard reaction followed by reduction to deliver the intermediate B which upon chaping and oxidation followed by cyclization would provide the natural lactone A. Appropriate choice of base quantity in Crimmins aldol condensation to make compound C and the proper reducing agent for keto group can make clear path to any of the aforementioned lactones (Figure 9).

![Diagram showing the synthesis process]

Figure 9

Since in the present work, Crimmins aldol condensation have been involved, therefore brief methodologies and mechanism were described herein.

A brief review on Crimmins aldol approach:

The asymmetric aldol addition mediated by chiral auxiliaries is one of the most important and general methods for asymmetric carbon-carbon bond formation.\(^\text{25}\) The utility of the asymmetric aldol addition has been adequately demonstrated through a multitude of synthetic applications.\(^\text{26}\) Dibutylboron enolates and titanium enolates of N-acyl oxazolidinones, pioneered by Evans, are the most commonly utilized enolates and are highly effective for the preparation of Evans syn products with high diastereoselectivity in asymmetric aldol additions.\(^\text{27}\)

Recently Crimmins group has investigated the aldol addition using inexpensive TiCl\(_4\), sparteine/DIPEA and chiral N-acyl thiazolidinethiones to afford two different diastereomers depending on the amount of base employed. The syn aldol product 73b was obtained in high diastereomeric ratio when using 1or 2 eq of Lewis acid and 1 eq of base.
The *anti* aldol product 73a was obtained preferentially when 1 or 2 eq of Lewis acid and 2 eq of base were employed especially for unsaturated aldehydes. When less base is employed, the thiacarbonyl of the auxiliary coordinates to the titanium center and exposes the transition state of the reaction to a different diastereomeric face of the auxiliary to yield *syn* aldol product in high diastereomeric ratio. However excess base generates an open transition state where the thiacarbonyl of the chiral auxiliary is not coordinated to the metal to afford *anti* aldol product (Figure 10).28

![Figure 10. Suggested transition states for the titanium mediated aldol reactions.](image)

**Retro Synthesis:**

The retro synthetic analysis of (+)-harzialactone A 19 and its antipode (−)-harzialactone A 20 is shown in Scheme 11. We envisioned that these targets might be forged via cyclization of acids came from 74a and 74b respectively. The olefinic compounds 74a and 74b could be accessed from the respective aldol products 73a and 73b by successive Grignard vinylation29 and reduction. We planned to prepare the aldol products *anti* isomer 73a and *syn* isomer 73b by Crimmins aldol condensation28 of commercially available aldehyde phenyl ethanol 44 with chiral auxiliary 75.
Results and Discussion

We started our synthesis firstly by preparing the chiral auxiliary \(N\)-acetyl-4-benzylthiazolidinethione \(75\), with the readily available \((S)-2\)-amino-3-phenylpropanoic acid \(L-\)phenylalanine \(76\). Accordingly, reduction of \((S)-2\)-amino-3-phenylpropanoic acid \((L-\text{Phenylalanine})\) \(76\) with NaBH\(_4\) and I\(_2\) in THF following Meyers method\(^{30a}\) afforded \((S)-2\)-amino-3-phenylpropan-1-ol \((L-\text{Phenylalaninol})\) \(77\) in 92% yield (Scheme 12) and the physical characteristics were in excellent agreement with those reported in the literature\(^{28d}\).

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{OH} \\
\text{Ph} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{H}_2\text{N} & \quad \text{OH}
\end{align*}
\]

Scheme 12

The thiazolidinethione \(78\) was prepared in 88 % yield from \((S)-2\)-amino-3-phenylpropan-1-ol \((L-\text{Phenylalaninol})\) \(77\) by refluxing in the presence of aq. KOH and CS\(_2\) by a modification of the Corre’s procedure\(^{31}\) and the physical characteristics were in excellent agreement with those reported in the literature\(^{28d}\) (Scheme 13).

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{OH} \\
\text{Ph} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{H}_2\text{N} & \quad \text{HN} \ 
\end{align*}
\]

Scheme 13
Acylation of the thiazolidinethione 78 was accomplished with n-butyl lithium and acetyl chloride to furnish the required N-acetyl-4-benzyl-thiazolidinethione 75\textsuperscript{2nd} in 96% yield (Scheme 14), which is yellow crystalline compound and readily purified by recrystallization. The imide 75 in its \textsuperscript{1}H NMR spectrum showed the presence of a singlet at \( \delta \) 2.78 integrating for three protons corresponding to methyl group along with the chiral moiety signals at their respective positions confirms the acylation. The \textsuperscript{13}C NMR spectrum of compound 75 showing the presence of –C=S, –C=O carbons at \( \delta \) 201.57 and 170.03 respectively, also LCMS peak at \( m/z \) 274 [M+Na]\textsuperscript{+} and IR spectrum showing strong absorptions at 1702 cm\textsuperscript{-1} due to –C=O stretching further supported the formation of the product 75 (Scheme 14).

![Scheme 14](image)

Next, we commenced the synthesis key intermediates 73a and 73b with Crimmins aldol condensation of phenyl ethanal 44 and titanium enolate of N-acetyl-4-benzyl-thiazolidinethione 75 under different equivalent amounts of base DIPEA as shown in scheme 15. The \textit{anti} aldol product 73a was obtained as major diastereomer in 82% combined isolated yield with diastereomeric ratio (73a/73b = \textit{anti}:\textit{syn} = 85:15), when 1 eq of Lewis acid TiCl\textsubscript{4} and 2 eq of base DIPEA were used. The \textit{syn} aldol product 73b was obtained preferential diastereomer in 82% combined isolated yield with diastereomeric ratio (73a/73b = \textit{anti}:\textit{syn} = 15:85), when 1 eq of Lewis acid TiCl\textsubscript{4} and 1 eq of base DIPEA were used. The \textit{anti-} and \textit{syn-}diastereomers 73a and 73b were easily separated by flash column chromatography in 68.8% and 68% isolate yields. The less polar \textit{anti}-aldol product 73a showed \textsuperscript{1}H NMR chemical shift signals for the corresponding \( \alpha \)-protons at \( \delta \) 3.62–3.57 (m, 2H). The \textit{syn}-aldol product 73b showed characteristic \textsuperscript{1}H NMR chemical shift signals for the \( \alpha \)-protons at \( \delta \) 3.56 (dd, \( J = 17.9, 2.2 \text{ Hz}, 1\text{H} \)) for the less shielded proton and at \( \delta \) 3.22 (dd, \( J = 17.9, 8.6 \text{ Hz}, 1\text{H} \)) for the more shielded proton along with other peaks in their respective positions. ESI mass spectral analysis showing peak at \( m/z \) 394 [M+Na]\textsuperscript{+} and IR
spectrum of compound 73a showing strong absorptions at 3448 cm\(^{-1}\) and 1616 cm\(^{-1}\) due to –OH and –C=O stretching respectively also supported the required transformation.

\[
\begin{align*}
\text{Ph} & \quad 75 \quad 44 \\
\text{Ph} & \quad 73a
\end{align*}
\]

**Scheme 15**

Alternatively, compound 79a can be prepared according to the route depicted in Scheme 16. Transamidation\(^{33}\) of the \(\beta\)-hydroxy \textit{anti} amide 73a with 2 eq of \(N,O\)-dimethylhydroxylamine hydrochloride and 5 eq of imidazole in DCM under nitrogen atmosphere for 6 h gave the corresponding Weinreb amide 79a in 97% yield. The \(^1\)H NMR spectra of compound 79a showed the absence of protons for thiazolidine moiety and presence characteristic peaks of –NO\(_2\) and –NCH\(_3\) protons at δ 3.68 (s, 3H) and 3.20 (s, 3H) as singlets integrating for three protons each respectively proving the product formation. The peak obtained in the ESI mass spectra at \(m/z\) 246 [M+H]\(^+\) further confirmed the assigned structure.

\[
\begin{align*}
\text{Ph} & \quad \text{OH} \quad \text{N} \quad \text{OMe} \\
\text{Ph} & \quad 79a
\end{align*}
\]

**Scheme 16**
In the similar way shown in scheme 16 the Weinreb amide 79b was obtained from the β-hydroxy syn amide 73b. Also the $^1$H NMR spectra of compound 79b showed the absence of protons for thiazolidine moiety and presence characteristic peaks of –NOCH$_3$ and –NCH$_3$ protons at δ 3.70 (s, 3H) and 3.18 (s, 3H) as singlets integrating for three protons each respectively proving the product formation. The structure was also confirmed by the peak at $m/z$ 246 [M+H]$^+$ in the ESI mass spectra of Weinreb amide 79b.

The addition of 3 eq of vinylmagnesium bromide in THF to a stirred solutions of Weinreb amide 79a in THF at −78 °C under nitrogen atmosphere afforded the corresponding β-hydroxy vinyl ketone 80a in 95% yield (Scheme 17).$^{29}$ The compound 80a was confirmed by its $^1$H NMR spectra which showed the absence of characteristic peaks of –NOCH$_3$ and –NCH$_3$ protons at δ 3.68 (s, 3H) and 3.20 (s, 3H) and the presence three olefinic protons of vinyl double bond in the region δ 6.27–6.20 (m, 2H) as multiplet, 5.96 (dd, $J = 17.2$, 10.5 Hz, 1H) as doublet of doublet. It was further characterized by its $^{13}$C NMR spectrum showing two more peaks in the region of δ 140 and 125 corresponding to vinylic carbons and shifting of carbonyl carbon signal to down field at δ 201.52 along with other relative peaks indicating the successful formation of vinyl ketone. ESI mass spectral analysis showing peak at $m/z$ 213 corresponding to [M+Na]$^+$ further confirmed the assigned structure.

![Scheme 17](image)

The Weinreb amide 79b was converted to vinyl ketone 80b under similar conditions shown in scheme 17. The structure of the compound 80b is confirmed by its $^1$H NMR spectra, in which the characteristic peaks at δ 3.70 (s, 3H) and 3.18 (s, 3H) of –NOCH$_3$ and –NCH$_3$ protons are absent and three olefinic protons of vinyl double bond in the region 6.29 (dd, $J = 17.2$, 10.5 Hz, 1H) as doublet of doublet and 6.18 (d, $J = 17.2$ Hz, 1H), 5.99 (d, $J = 10.5$ Hz, 1H) as doublets are present. It was further characterizes by its
$^{13}$C NMR spectrum showing two more peaks in the region of $\delta$ 140 and 125 corresponding to vinylic carbons and shifting of carbonyl carbon signal to down field at $\delta$ 201.71 along with other relative peaks indicating the successful formation of vinyl ketone. ESI mass spectral analysis showing peak at $m/z$ 213 corresponding to the [M+Na]$^+$ further confirmed the assigned structure.

The syn-selective reduction of the oxo functionality was achieved with DIBAL-H; this gave 1,3-syn-diol in good yield and good selectivity. Thus the reduction of $\beta$-hydroxy vinyl ketone 80a using 2.5 eq of 20% solution of DIBAL-H in toluene at $-78 \degree C$ under nitrogen atmosphere afforded the required syn-1,3-diol 81a along with its diastereomer 81$^1$a (syn:anti, 94:6) in 79% of desired isomer 81a which is separated by column chromatography (Scheme 18). Stereochemistry was assumed to be in anticipated line as it was well examined and established previously.

High diastereo selectivity has been explained that a stable chelated complex would be formed when a $\beta$-hydroxy homoallylic ketone 80a is converted to the corresponding dialkylaluminium ester and that it would be sufficiently rigid to control the direction of the attack of nucleophiles to the carbonyl group. They further hypothesized that the intermediate aluminium ester is of a chair like confirmation such that the axial hydrogen of the $\alpha$-carbon prevents the approach of a reducing agent from the bottom side. Hence DIBAL-H attacks preferentially from the top side, resulting the major syn isomer.

**Scheme 18**

The structure of syn-1,3-diol 81a was confirmed by its $^1$H NMR spectra which showed the presence of two $-$OH protons at $\delta$ 3.33, 2.78 as broad singlet. The absence of peak at $\delta$ 201.52 corresponding to the carbonyl carbon in $^{13}$C NMR spectra confirms the
reduction. In addition, molecular formula of 81a was confirmed by showing peak at m/z 215 corresponding to the [M+Na]^+ in its ESI mass spectrum.

In the similar way, as shown in scheme 19, by the addition of 2.5 eq of 20% solution of DIBAL-H in toluene to the solution of 80b in THF at −78 °C under nitrogen atmosphere affords the 1,3-Syn diol 81b along with its anti diastereomer 81b (syn:anti, 94:6) in 79% of desired isomer 81b which is separated by column chromatography. Stereochemistry was assumed to be in anticipated line as it was well examined and established previously.34

![Scheme 19](image)

Also the structure of syn-1,3-diol 81b was confirmed by its ^1H NMR spectra which showed the presence of two –OH protons at δ 3.48 (br s, –OH, 1H), 2.55 (br s, –OH, 1H) as broad singlets proving the product formation. In addition the absence of peak at δ 201.71 in ^13C NMR spectra confirms the reduction. The peak at m/z 215 corresponding to the [M+Na]^+ in ESI mass spectrum also confirms the molecular formula of 81b.

The syn diols 81a and 81b were subsequently converted into the corresponding acetonide 74a and 74b in 95% and 93% yields respectively, by treatment with 2 eq of 2,2-dimethoxypropane and 0.1 eq of PPTS in DCM for 2.5 h at room temperature35 (Scheme 20). The structures of 74a and 74b was confirmed by their ^1H NMR spectra which showed the absence of characteristic two –OH protons and the presence of characteristics of methyl protons resonance at δ 1.49 (s, 6H), 1.47 (s, 6H) respectively in 74a and 74b as singlet proving the acetonide protection. In addition to this, a signal at m/z 233 [M+H]^+ provided the satisfying support for the acetonide protection.
The syn and anti relative configuration of the hydroxy groups was confirmed based on Rychnovsky’s analogy. The stereochemistry of syn, anti-1,3-acetonide was confirmed by the \(^{13}\)C NMR chemical shifts of the 6 membered acetonide. \(^{13}\)C NMR spectra of syn-1,3-diol acetonide 74a show an axial methyl at \(\delta 29.75\) and an equatorial methyl group at \(\delta 19.87\). \(^{13}\)C NMR chemical shifts of the ketal carbons follow a stereo regular pattern where the syn-diol acetonides resonate at \(\delta 98.26\), were consistent with those found in chair confirmation, which is indicative of a 1,3-syn-diol disposition. In the previous reports of 1,3-anti aldol acetonide product, the \(^{13}\)C NMR spectra of anti-1,3-diol acetonide show ketal carbon resonate above \(\delta 100\) and both the acetonide methyxl resonates above \(\delta 24\) confirming the anti-diol were consistent with those found in twist boat confirmation, which is indicative of a 1,3-anti-diol (Figure 11).

Figure 11. Characteristic conformations and \(^{13}\)C NMR chemical shift values for syn- and anti-1,3-diols.

In the similar way we can explain, the \(^{13}\)C NMR spectra of syn-1,3-diol acetonide 74b show an axial methyl at \(\delta 29.93\) and an equatorial methyl group at \(\delta 19.95\). \(^{13}\)C NMR chemical shifts of the ketal carbons follow a stereo regular pattern where the syn-diol acetonides resonate at \(\delta 99.65\), were consistent with those found in chair confirmation, which is indicative of a 1,3-syn-diol disposition.
Conversion of compound 74a to the final molecule 19 requires a three-step procedure. Firstly the double bond in 74a was dihydroxylated with OsO₄ to give diol, which without further purification the diol was cleaved with NaIO₄ to give the aldehyde 82a. Finally, the aldehyde compounds 82a on oxidation with NaClO₂, NaH₂PO₄ and DMSO to give the acid compound which on acidified work up with 3 N HCl results in the deprotection of acetonide group and subsequent lactonisation furnished the target molecules (3R,5R)-harzialactone A 19 in 74% yield (Scheme 21). The spectral and analytical data were comparable to the previously reported literature data.\(^{18a,b}\)

![Scheme 21](image)

The compound 19 was confirmed by its \(^1\)H NMR and \(^{13}\)C NMR spectrums, which shows the disappearance of peaks corresponding to the acetonide and vinylic groups. In addition, the appearance of proton attached to lactone hydroxy which shifted downfield at δ 4.93–4.88 (m, 1H), also other methylene proton attached to the sec hydroxyl shifted down field at δ 4.10 (t, \(J = 7.3\) Hz, 1H) and a broad singlet at δ 3.37 corresponding to alcoholic proton in the \(^1\)H NMR spectrum of compound 19 further confirms the lactonization. The compound 19 was further confirmed by its \(^{13}\)C NMR spectrum, which shows disappearance of acetonide, vinyl carbons and appearance of lactone carbonyl carbon which shifted up field at δ 177.66.

Likewise the double bond in 74b was dihydroxylated with OsO₄ to give diol, without further purification the diol was cleaved with NaIO₄ to give the aldehyde 82b. Finally, the aldehyde compound 82b on oxidation with NaClO₂, NaH₂PO₄ and DMSO to give the acid compound which on acidified work up with 3 N HCl results in the deprotection of acetonide group and subsequent lactonisation furnished the target molecule (3S,5S)-harzialactone A 20 in 73% yield (Scheme 22). The spectral and analytical data were comparable to the previously reported literature data.\(^{18a,b}\)
Also the compound 20 was confirmed by its $^1$H NMR and $^{13}$C NMR spectra. Appearance of proton attached to lactone hydroxy which shifted downfield at $\delta$ 4.93–4.88 (m, 1H), also other methylene proton attatched to the sec hydroxyl shifted down field at $\delta$ 4.04 (t, $J = 7.3$ Hz, 1H) and a broad singlet at $\delta$ 2.79 corresponding to alcoholic proton in the $^1$H NMR spectrum of compound 20 confirms the lactonization. The compound 20 was further confirmed by its $^{13}$C NMR spectrum, which shows disappearance of acetonoide, vinyl carbons and appearance of lactone carbonyl carbon which shifted up field at $\delta$ 177.22.

Appearance of a broad signal at 1771 and 1774 cm$^{-1}$ in the respective IR spectrums of 19 and 20 indicates the presence of $\gamma$-lactone system. Presence of signal at $m/z$ 215 corresponding to [M+Na]$^+$ in the ESI mass spectrum further supported the formation of the products. In addition to this, a signal at $m/z$ 215.0674 corresponding to [M+Na]$^+$ (calcd 215.0679) in the high resolution ESI mass spectrum also suggested the success of the reaction.

**Conclusion**

In summary, we have described a simple, convenient and efficient approach towards the synthesis of harzialactone 19 and its antipode 20 involving a sequence of reactions starting from N-acetyl-4-benzyl-thiazolidinethione 78. This approach offers high stereo selectivity and readily available starting material at low cost and simple experimental conditions, which makes it a useful and attractive process.
Experimental Section

(S)-2-Amino-3-phenylpropan-1-ol (77):

To a stirred solution of (S)-2-amino-3-phenylpropanoic acid 76 (8.25 g, 50.0 mmol) and NaBH₄ (9.45 g, 250.0 mmol) in THF (120 mL) at 0 °C was added slowly the solution of I₂ (31.75 g, 125.0 mmol) in the reaction mixture was allowed to stir at rt until the evolution of H₂ gas ceased. Then the reaction mixture was heated to reflux for 18 h. After completion of the reaction, the reaction mixture was cooled to 0 °C and quenched by adding MeOH (25 mL) drop wise till the reaction mixture turns homogenous and allowed to attain rt. The solvent was then evaporated under reduced pressure and the residue was dissolved in 20% aq KOH (75 mL) solution and stirred for 4 h at rt. The reaction mixture was diluted with CH₂Cl₂ (250 mL) and the organic layer was separated, washed successively with water (2×200 mL), brine (1×200 mL), dried over anhydrous Na₂SO₄, filtered and concentrated in vacuo. Recrystallization (hot EtOAc followed by hexane, 1:4) afforded the pure compound 77 (6.94 g) as white solid. Yield: 92%; Melting range: 89–91 °C.

\[\alpha\]D²² : −19.10 (c 1.0, CHCl₃);

IR (KBr) : \(\nu_{\text{max}}\) 3352, 3294, 3080, 2934, 2929, 2855, 1598, 1449, 1252, 1218, 1086, 1028 cm⁻¹;

\(^1\)H NMR (300 MHz, CDCl₃) : \(\delta\) 7.32–7.14 (m, 5H, ArH), 3.68 (dd, \(J = 11.7, 3.5\) Hz, 1H), 3.32 (dd, \(J = 11.7, 7.0\) Hz, 1H), 3.14 (m, 1H), 2.75 (dd, \(J = 13.2, 4.8\) Hz, 1H), 2.54 (dd, \(J = 13.2, 9.3\) Hz, 1H), 2.10–1.92 (br s, 3H, –NH₂, –OH);

\(^{13}\)C NMR (75 MHz, CDCl₃) : \(\delta\) 138.27, 129.25, 128.53, 126.73, 66.14, 54.17, 40.07;

MS-ESI : \(m/z\) 174 [M+Na]+;

(S)-4-Benzylthiazolidin-2-thione (78):
To a magnetically stirred solution of compound 77 (5 g, 33.11 mmol) in EtOH (40 mL) at rt were added slowly CS$_2$ (5.2 mL, 86.08 mmol) and a solution of KOH (5.01 g, 89.39 mmol) in water (25 mL). The resulting reaction mixture was refluxed for 72 h. After cooling to rt, ethanol was evaporated under reduced pressure and extracted with DCM (3×75 mL). The combined organic extracts were washed with 1M HCl (75 mL), water (75 mL), saturated aqueous NaCl (75 mL), dried over anhydrous Na$_2$SO$_4$, filtered and concentrated in vacuo. The crude residue thus obtained was purified by silica gel column chromatography using EtOAc–hexane (1:9) to get the compound 78 (6.09 g) as colorless solid. Yield: 88%; Melting range: 85–90 °C.

[$\alpha$]$_{D}^{30}$: $-119 \ (c \ 1.5, \ \text{CHCl}_3)$;

IR (KBr) : $\nu_{\text{max}}$ 3154, 2954, 1455, 1438, 1328, 1289, 1252, 1218, 1086, 1028 cm$^{-1}$;

$^1$H NMR (300 MHz, CDCl$_3$) : $\delta$ 7.75 (bs, 1H), 7.36–7.21 (m, 5H, ArH), 4.45 (m, 1H), 3.54 (dd, $J = 11.7, 7.0$ Hz, 1H), 3.31 (dd, $J = 11.7, 6.8$ Hz, 1H), 3.14 (dd, $J = 13.2, 7.6$ Hz, 1H), 2.97 (dd, $J = 13.2, 6.8$ Hz, 1H);

$^{13}$C NMR (75 MHz, CDCl$_3$) : $\delta$ 200.38, 135.46, 129.04, 128.07, 126.94, 65.09, 39.73, 38.46;

MS-ESI : $m/z$ 210 [M+H]$^+$;

(S)-1-(4-benzyl-2-thioxothiazolidin-3-yl)ethanone (75):

To a stirred solution of (S)-4-Benzyl-thiazolidine-2-thione 78 (3 g, 14.35 mmol) in dry THF (30 mL) at 0 °C under nitrogen atmosphere was added slowly n-BuLi (6.9 mL, 17.2 mmol, 2.5 M) and stirred for 30 min at the same temperature. Then acetyl chloride (1.35 g, 17.2 mmol) was added slowly at 0 °C and stirred for 1 h. After completion of the reaction, the reaction mixture was quenched with saturated aq. NH$_4$Cl (15 mL). The organic layer was separated and the aqueous layer was extracted with EtOAc (3×25 mL). The combined organic layers were washed with water (2×30 mL), brine (2×30 mL), dried over anhydrous Na$_2$SO$_4$, filtered and concentrated in vacuo. The residue was purified by silica gel column...
chromatography using EtOAc–hexane (1:19) to afford (S)-1-(4-benzyl-2-thioxothiazolidin-3-yl)-ethanone 75 (3.45 g) as bright yellow crystals, Yield: 96%; Melting range: 87–90 °C.

\[^{25}\text{[a]}\] \text{D} : +247 (c 1.5, CHCl\(_3\));

\text{IR (KBr)} : \nu_{\text{max}} 3025, 2925, 2919, 1702, 1495, 1435, 1362, 1215, 1018 cm\(^{-1}\);

\(^1\)\text{H NMR (300 MHz, CDCl\(_3\))} : \delta 7.33–7.22 (m, 5H), 5.36–5.32 (m, 1H), 3.37 (dd, \(J = 11.5, 7.3\) Hz, 1H), 3.22 (dd, \(J = 13.1, 3.6\) Hz, 1H), 3.06–2.99 (m, 1H), 2.88 (d, \(J = 11.5\) Hz, 1H), 2.78 (s, 3H);

\(^{13}\)\text{C NMR (75 MHz, CDCl\(_3\))} : \delta 201.57, 170.03, 136.73, 129.67, 127.78, 127.25, 31.77, 26.91;

\text{MS-ESI} : \text{m/z 274 [M+Na]\(^{+}\)};

\((R)-1-(\text{(S)-4-benzyl-2-thioxothiazolidin-3-yl})-3\text{-hydroxy-4-phenylbutan-1-one (73a):}\)

To a dry roundbottomed flask under nitrogen atmosphere was added (S)-1-(4-benzyl-2-thioxothiazolidin-3-yl)ethanone 75 (2.0 g, 7.96 mmol) dissolved in dry DCM (50 mL). The solution was cooled to 0 °C and TiCl\(_4\) (0.86 mL, 7.90 mmol) was added dropwise. The thick suspension was stirred for 10 min upon which DIPEA (2.80 mL, 15.92 mmol) was added dropwise at 0 °C and stirring was continued. After 10 min the reaction mixture was cooled to −78 °C and to this was added phenylacetaldehyde 44 (1.14 g, 9.56 mmol) dissolved in DCM (5 mL). After 10 min the reaction mixture was quenched with half-saturated aq. ammonium chloride solution (15 mL) and warmed to rt. The organic layer was separated and the aqueous layer was extracted with CH\(_2\)Cl\(_2\) (2×60 mL). The combined organic extracts were washed with 80 mL of a half-saturated aq. NH\(_4\)Cl (2×60 mL), water (2×60 mL), brine (2×60 mL), dried over anhydrous Na\(_2\)SO\(_4\), filtered and concentrated \textit{in vacuo}. The residue was purified by silica gel column chromatography using EtOAc–hexane (1:19) over silica gel (100–200 mesh), to afford major \textit{anti}-diastereomer 73a (2.03 g) as a yellow oil, Yield: 68.8%;
|α|b\(^{25}\) : \(-5.1\) (c 1.0, CHCl\(_3\));

IR (neat) : \(\nu_{\text{max}}\) 3416, 2943, 2831, 1745, 1616, 1413 cm\(^{-1}\);

\(^1\)H NMR (300 MHz, CDCl\(_3\)) : \(\delta\) 7.32–7.22 (m, 10H), 5.37–5.33 (m, 1H), 4.58–4.52 (m, 1H), 4.38 (m, 1H), 4.05 (m, 1H), 3.89–3.86 (m, 1H), 3.62–3.57 (m, 2H), 3.34 (dd, \(J = 13.2, 3.8\) Hz, 1H), 3.18 (dd, \(J = 13.2, 10.8\) Hz, 1H), 3.00 (dd, \(J = 11.5\) Hz, 1H), 2.85 (m, 1H);

\(^13\)C NMR (75 MHz, CDCl\(_3\)) : \(\delta\) 201.38, 170.48, 137.42, 136.59, 129.94, 129.43, 128.90, 128.39, 127.65, 126.72, 71.36, 68.80, 67.54, 48.39, 36.38, 32.21;

MS-ESI : \(m/z\) 394 [M+Na]\(^+\);

HRMS (ESI) : \(m/z\) calcld for C\(_{20}\)H\(_{21}\)NO\(_2\)S\(_2\)Na: 394.1096; found: 394.1091;

(S)-1-((S)-4-benzyl-2-thioxothiazolidin-3-yl)-3-hydroxy-4-phenylbutan-1-one (73b):

To a dry round bottomed flask under nitrogen atmosphere was added (S)-1-((4-benzyl-2-thioxothiazolidin-3-yl)ethanone 75 (2.0 g, 7.96 mmol) dissolved in dry DCM (50 mL). The solution was cooled to 0 °C and TiCl\(_4\) (0.86 mL, 7.90 mmol) was added drop wise. The thick suspension was stirred for 10 min upon which DIPEA (1.40 mL, 7.90 mmol) was added drop wise at 0 °C and stirring was continued. After 10 min the reaction mixture was cooled to −78 °C and to this was added crude 2-phenylacetaldehyde 44 (1.14 g, 9.56 mmol) dissolved in DCM (5 mL). After 10 min the reaction mixture was quenched with half-saturated aq. ammonium chloride solution (20 mL) and warmed to rt. The organic layer was separated and the aqueous layer was extracted with CH\(_2\)Cl\(_2\) (2×60 mL). The combined organic extracts were washed with 80 mL of a half-saturated aq. NH\(_4\)Cl (2×60 mL), water (2×60 mL), brine (2×60 mL), dried over anhydrous Na\(_2\)SO\(_4\), filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography using EtOAc–hexane (2:18) to afford major syn-diastereomer (S)-1-((S)-4-benzyl-2-thioxothiazolidin-3-yl)-3-hydroxy-4-phenylbutan-1-one 73b (2.01 g) as a yellow oil.
Yield: 68%;

$\frac{[\alpha]}{D}^{25}$: +46.2 (c 1.0, CHCl$_3$);

IR (neat) : $\nu_{\text{max}}$ 3448, 2923, 2853, 1728, 1639, 1461 cm$^{-1}$;

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.35–7.17 (m, 10H), 5.42–5.35 (m, 1H), 4.44–4.39 (m, 1H), 4.12 (br s, 1H), 3.97 (m, 1H), 3.82–3.77 (m, 1H), 3.56 (dd, $J = 17.9$, 2.2 Hz, 1H), 3.45–3.39 (m, 1H), 3.31–3.28 (m, 1H), 3.22 (dd, $J = 17.3$, 8.6 Hz, 1H), 3.08–3.03 (m, 1H), 2.95 (m, 1H);

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 201.86, 170.90, 137.64, 136.59, 130.17, 129.66, 129.08, 128.49, 127.90, 126.84, 71.74, 68.98, 67.88, 48.63, 36.95, 32.47.

MS-ESI : m/z 394 [M+Na]$^+$;

(R)-3-hydroxy-N-methoxy-N-methyl-4-phenylbutanamide (79a):

Imidazole (0.92 g, 13.47 mmol) and MeNH(OMe).HCl (0.522 g, 5.39 mmol) were added sequentially to a stirred solution of (R)-1-((S)-4-benzyl-2-thioxothiazolidin-3-yl)-3-hydroxy-4-phenylbutan-1-one 73a (1.0 g, 2.69 mmol) in dry DCM (15 mL) under N$_2$. The reaction was allowed to stir for 6 h at rt and then quenched with saturated aq. NH$_4$Cl (5 mL). The organic layer was separated and the aqueous layer was extracted with DCM (3×20 mL). The combined organic extracts were washed with brine (1×30 mL), dried over anhydrous Na$_2$SO$_4$, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography using EtOAc–hexane (15:85) to afford (R)-3-hydroxy-N-methoxy-N-methyl-4-phenylbutanamide 79a (0.64 g) as a pale yellow oil, Yield: 97%;

$\frac{[\alpha]}{D}^{25}$: +32.7 (c 1.0, CHCl$_3$);

IR (neat) : $\nu_{\text{max}}$ 3346, 2943, 2841, 1745, 1619, 1463 cm$^{-1}$;

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.31–7.15 (m, 5H), 4.01–3.93 (m, 1H), 3.68 (s, 3H), 3.57 (br s, 1H), 3.20 (s, 3H), 2.84 (d, $J = 10.8$ Hz, 1H), 2.73 (m, 1H), 2.56 (m, 1H), 2.39–2.34 (m, 1H);
$^{13}$C NMR (75 MHz, CDCl$_3$) : $\delta$ 173.15, 138.02, 129.46, 128.40, 127.60, 71.61, 67.44, 62.06, 38.48, 37.95;

MS-ESI : $m/z$ 246 [M+H]$^+$;

(S)-3-hydroxy-N-methoxy-N-methyl-4-phenylbutanamide (79b):

\[ \begin{array}{c}
\text{Ph} \quad \text{OH} \\
\text{O} \quad \text{NOMe}
\end{array} \]

$[\alpha]_{D}^{25}$ : $-11.7$ (c 1.0, CHCl$_3$);

IR (neat) : $\nu_{\text{max}}$ 3448, 2923, 2853, 1728, 1639, 1461 cm$^{-1}$;

$^1$H NMR (300 MHz, CDCl$_3$) : $\delta$ 7.33–7.24 (m, 5H), 4.04–3.93 (m, 1H), 3.70 (s, 3H), 3.64 (br s, 1H), 3.18 (s, 3H), 2.87 (dd, $J = 10.8$ Hz, 1H), 2.75 (m, 2H), 2.45 (dd, $J = 11.2$, 2.4 Hz, 1H);

$^{13}$C NMR (75 MHz, CDCl$_3$) : $\delta$ 173.86, 138.55, 128.27, 127.56, 127.43, 71.36, 67.33, 62.70, 38.67, 37.02;

MS-ESI : $m/z$ 246 [M+H]$^+$;

(R)-5-hydroxy-6-phenylhex-1-en-3-one (80a):

\[ \begin{array}{c}
\text{Ph} \quad \text{OH} \\
\text{O}
\end{array} \]

A 1.0 M solution of vinylmagnesium bromide in THF (6.12 mL, 6.12 mmol) was added to a stirred solution of 79a (0.50 g, 2.04 mmol) in dry THF (10 mL) at $-78^\circ$C under N$_2$. The mixture was stirred at $-78^\circ$C for 3 h, and then quenched with saturated aq. NH$_4$Cl (5 mL), and extracted with EtOAc (3×20 mL). The combined organic extracts were washed with brine (1×30 mL), dried over anhydrous Na$_2$SO$_4$, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography using EtOAc–hexane (15:85) to afford pure 80a (0.368 g) as a pale yellow oil, Yield: 95%;

$[\alpha]_{D}^{25}$ : $+16.7$ (c 1.0, CHCl$_3$);

IR (neat) : $\nu_{\text{max}}$ 3416, 2923, 2851, 1727, 1625, 1113 cm$^{-1}$;

$^1$H NMR (300 MHz, CDCl$_3$) : $\delta$ 7.31–7.23 (m, 5H), 6.27–6.20 (m, 2H), 5.96 (dd, $J = 17.2$, 10.5 Hz, 1H), 4.03–3.98 (m, 1H), 3.56 (br s, 1H), 3.34–3.30 (m, 1H), 3.11–3.08 (m, 2H), 2.82 (m, 1H);
13C NMR (75 MHz, CDCl3):  δ 201.52, 137.55, 136.64, 129.39, 128.81, 128.27, 126.89, 71.27, 67.35, 45.21;

MS-ESI: m/z 213 [M+Na]+;

(S)-5-hydroxy-6-phenylhex-1-en-3-one (80b):

(2R,4R)-1-phenylhex-5-ene-2,4-diol (81a):

A 20% solution of DIBAL-H in toluene (2.80 mL, 3.94 mmol) was added drop wise to a stirred solution of 80a (0.30 g, 1.57 mmol) in dry THF (30 mL) at –78 °C under N2. The resulting mixture was stirred at –78 °C for 2 h. Then the reaction mixture was quenched with saturated aq. NH4Cl (5 mL) and extracted with Et2O (3×10 mL). The combined organic extracts were washed with brine (1×20 mL), dried over anhydrous Na2SO4, filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography using EtOAc–hexane (15:85) to afford pure 81a (0.240 g) pale yellow oil, Yield: 79%

[α]D25: −6.7 (c 1.0, CHCl3);

IR (neat): νmax 3316, 2934, 2813, 1445, 1279, 1123 cm⁻¹;
$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.34–7.24 (m, 5H), 5.92–5.84 (m, 1H), 5.28 (m, 1H), 5.11 (m, 1H), 4.11–4.05 (m, 1H), 3.68 (m, 1H), 3.33 (br s, 1H), 2.92 (m, 1H), 2.78 (br s, 1H), 2.58 (m, 1H), 1.86 (m, 2H);

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 138.75, 137.59, 129.38, 128.24, 127.22, 114.25, 73.61, 72.51, 71.39, 40.32;

MS-ESI: $m/z$ 215 [M+Na]$^+$;

(2S,4S)-1-phenylhex-5-ene-2,4-diol (81b):

![Chemical Structure]

$[\alpha]_D^{25}$ : $+13.5$ (c 1.0, CHCl$_3$);

IR (neat) : $\nu_{\text{max}}$ 3348, 2927, 2853, 1454, 1274, 1126 cm$^{-1}$;

$^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 7.33–7.24 (m, 5H), 5.85–5.77 (m, 1H), 5.40 (m, 1H), 5.17 (m, 1H), 4.04–3.98 (m, 1H), 3.67–3.64 (m, 1H), 3.48 (br s, 1H), 2.89–2.82 (m, 1H), 2.72 (dd, $J = 11.8$, 5.6 Hz, 1H), 2.55 (br s, 1H), 1.83 (m, 2H);

$^{13}$C NMR (75 MHz, CDCl$_3$): $\delta$ 139.69, 137.86, 129.61, 128.60, 127.82, 114.71, 73.62, 72.40, 71.62, 40.56;

MS-ESI: $m/z$ 215 [M+Na]$^+$;

(4R,6R)-4-benzyl-2,2-dimethyl-6-vinyl-1,3-dioxane (74a):

![Chemical Structure]

A solution of 1,3-diol 81a (0.2 g, 1.04 mmol), 2,2-DMP (0.217 g, 2.08 mmol) and PPTS (0.026 g, 0.10 mmol) in DCM (1 mL) was stirred at rt for 2.5 h. The reaction mixture was diluted with Et$_2$O, the organic layer was washed with 10% aqueous NaHCO$_3$, water and brine, dried over anhydrous Na$_2$SO$_4$, filtered and concentrated in vacuo followed by silica gel column chromatography using EtOAc–hexane (3:47) afforded pure 74a (0.230 g) as colourless oil, Yield: 95%;

$[\alpha]_D^{25}$ : $-8.2$ (c 1.0, CHCl$_3$);
IR (neat) \( : \nu_{\text{max}} 2963, 2874, 1445, 1319, 1262, 1173 \text{ cm}^{-1};\)

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \( : \delta 7.29–7.15 \text{ (m, 5H)}, 5.88–5.81 \text{ (m, 1H)}, 5.33 \text{ (m, 1H)}, 5.17 \text{ (m, 1H)}, 4.24 \text{ (m, 1H)}, 4.08 \text{ (m, 1H)}, 2.90 \text{ (m, 1H)}, 2.76 \text{ (m, 1H)}, 1.84 \text{ (m, 2H)}, 1.49 \text{ (s, 6H)};\)

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( : \delta 139.31, 138.51, 129.29, 128.87, 127.71, 114.88, 98.26, 81.67, 80.84, 71.62, 41.58, 29.75, 19.87;\)

MS-ESI \( : m/z 233 \text{ [M+H]}^+;\)

\((4S,6S)\)-4-benzyl-2,2-dimethyl-6-vinyl-1,3-dioxane (74b):

\[\alpha\] \(\text{D}^25 \): +22.7 \( \text{(c 1.0, CHCl}_3\);\)

IR (neat) \( : \nu_{\text{max}} 1415, 1317, 1253 \text{ cm}^{-1};\)

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \( : \delta 7.25–7.14 \text{ (m, 5H)}, 5.81–5.76 \text{ (m, 1H)}, 5.40 \text{ (dd, } J = 13.5 \text{ Hz, 1H)}, 5.16 \text{ (dd, } J = 17.5, 2.8 \text{ Hz, 1H)}, 4.48 \text{ (m, 1H), 4.28–4.19 \text{ (m, 1H)}, 2.87 \text{ (dd, } J = 11.5 \text{ Hz, 1H)}, 2.73 \text{ (dd, } J = 11.5 \text{ Hz, 1H)}, 1.84 \text{ (m, 2H)}, 1.47 \text{ (s, 6H)};\)

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( : \delta 139.68, 138.92, 129.51, 128.76, 127.88, 114.85, 99.65, 81.67, 81.00, 71.44, 41.71, 29.93, 19.95;\)

MS-ESI \( : m/z 233 \text{ [M+H]}^+;\)

\((3R,5R)\)-5-benzyl-3-hydroxydihydrofuran-2(3H)-one (19):

To a solution of compound 74a (0.20 g, 0.862 mmol) in acetone:H\(_2\)O (3:1, 10 mL) were added OsO\(_4\) (0.5 mol%) and NMO (0.30 g, 2.58 mmol) at rt. The mixture was stirred for 6 h, and then the reaction was quenched with solid NaHSO\(_4\) (0.62 g, 5.17 mmol) and the mixture was stirred for 15 min. Solid particles were separated by filtration and the filtrate was concentrated. The residue was dissolved in THF:H\(_2\)O (4:1, 10 mL), and NaIO\(_4\) (0.55 g, 2.58 mmol) was added. After 30 min, the mixture was filtered, dried over anhydrous Na\(_2\)SO\(_4\), filtered and concentrated in vacuo to give the crude aldehyde.
Oxidation of the aldehyde (0.17 g, 0.72 mmol) with NaClO₂ (0.098 g, 1.08 mmol, 80% purity) and NaH₂PO₄ (25 mg) in DMSO (0.75 mL) and water (1.75 mL) followed by acidic work-up with 3 N HCl and purification furnished (3R,5R)-19 (0.122 g) as a white solid, Yield: 74%; Melting range: 79–82 °C. lit. value: Melting range: 78–79 °C.¹⁸b

\[ [\alpha]_D^{25} \] : +39.7 (c 0.5, CHCl₃); lit. Value: \[ [\alpha]_D = 38 \] (c 0.3, CHCl₃).¹⁸b

IR (neat) : \( v_{\text{max}} 3319, 1771, 1607, 1444, 1249 \text{ cm}^{-1} \);

\(^1\)H NMR (300 MHz, CDCl₃) : \( \delta 7.31–7.19 \) (m, 5H), 4.93–4.88 (m, 1H), 4.10 (t, \( J = 7.3 \) Hz, 1H), 3.37 (br s, 1H), 2.96 (d, \( J = 6.1 \) Hz, 1H), 2.36–2.22 (m, 2H);

\(^1\)C NMR (75 MHz, CDCl₃) : \( \delta 177.66, 135.22, 129.51, 128.70, 127.03, 78.39, 67.14, 41.01, 34.49 \);

MS-ESI : \( m/z 215 \) [M+Na]⁺;

HRMS (ESI) : \( m/z \) calcd for C₁₆H₂₄O₃Na: 215.0679; found: 215.0674;

(3S,5S)-5-benzyl-3-hydroxydihydrofuran-2(3H)-one (20):

White solid
Yield : 73% (0.120 g);

Melting Point : 72–75 °C. lit. value: Melting range: 71–74 °C.¹⁸b

\[ [\alpha]_D^{25} \] : – 40.2 (c 0.3, CHCl₃); lit. Value: \[ [\alpha]_D = – 38 \] (c 1.1, CHCl₃).¹⁸b

IR (neat) : \( v_{\text{max}} 3314, 1774, 1607, 1449, 1219 \text{ cm}^{-1} \);

\(^1\)H NMR (300 MHz, CDCl₃) : \( \delta 7.32–7.21 \) (m, 5H), 4.93–4.88 (m, 1H), 4.04 (t, \( J = 7.3 \) Hz, 1H), 2.94 (d, \( J = 6.4 \) Hz, 1H), 2.79 (br s, 1H), 2.41–2.26 (m, 2H);

\(^1\)C NMR (75 MHz, CDCl₃) : \( \delta 177.22, 135.40, 129.94, 128.79, 127.41, 78.34, 67.02, 41.25, 34.53 \);

MS-ESI : \( m/z 215 \) [M+Na]⁺;

HRMS (ESI) : \( m/z \) calcd for C₁₆H₂₄O₃Na: 215.0679; found: 215.0674;
References


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