Supporting Information

Diastereoselective Synthesis of Substituted Hexahydrobenzo[de]isochromans and their Evaluation as Antileishmanial activity

Sabera Sultana,1 Ngangbam Renubala Devi,1 Manash J. Deka,1 Kartikeya Tiwari2 Vikash K. Dubey2* and Anil K. Saikia1*

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Synthesis of starting materials

\[ \text{OH} \quad \text{O} \quad \text{Br} \quad + \quad \text{LDA, -78 °C, ref. 1} \quad \text{THF} \quad \text{OH} \quad \text{O} \quad \text{LiAlH}_4 \quad \text{ether 0°C-rt} \]

\[ \text{R} \quad \text{R} \quad \text{R} \quad \text{NMM, ref. 2} \quad \text{CH}_2\text{Cl}_2/\text{rt} \quad \text{OH} \quad \text{COOEt} \]

\[ \text{1} \quad \text{2} \quad \text{3} \quad \text{4} \quad \text{5} \quad \text{70-80%} \quad \text{70-78%} \quad \text{70-78%} \quad \text{40-50%} \]

General procedure for the synthesis of α-substituted carboxylic acids (3)

To a solution of i-Pr_2NH (1.7 mL, 12 mmol) in THF (40 mL) was added n-BuLi (1.6 M in hexane, 6.9 mL, 11 mmol) drop-wise at –78 °C, and the reaction mixture was stirred for 30 minutes. To this reaction mixture, a solution of 2-arylacetic acid (10 mmol) in THF (5 mL) was added dropwise at –78 °C. After stirring at the same temperature for 1 h, 1-bromo-3-methyl-2-butene (1.4 mL, 12 mmol) was added at –78 °C. The reaction was warmed to room temperature and stirred for 5 h. The reaction was quenched with saturated aqueous NH_4Cl, and extracted with diethyl ether. The organic layer was washed with brine, dried over anhydrous MgSO_4 and concentrated under vacuum. The residue was purified by column chromatography on silica gel to give 3 as oil.

General procedure for the synthesis of alcohols (4)

A solution of acid 3 (1.0 equiv) in dry ether was added to a stirred suspension of LiAlH_4 (1.0 equiv) in dry ether at 0 °C. The reaction mixture was stirred at room temperature for 1h, after which the reaction mixture was quenched with 2 N NaOH, passed through a celite pad, and washed with ethyl acetate. The mixture was treated with brine and extracted with ethyl acetate, and the organic extract was dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuum. The crude product was purified using column chromatography on silica gel to give compound 4.

General procedure for the synthesis of enol-ether (5)

To a solution of alcohol (1.0 equiv) 4 in dry dichloromethane was added N-methylmorpholine (0.7 equiv) and ethylpropiolate (0.7 equiv), and the reaction mixture was stirred for 5 h. The mixture was extracted with ethyl acetate. The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and concentrated. The residue was purified by column chromatography on silica gel to give 5.

General procedure for the synthesis of (7)

A solution of aldehyde 6 (1.0 equiv) in dry THF was added to a stirred solution of sodium hydride (1.2 equiv) in dry THF under an inert atmosphere at 0 °C. After complete evolution of hydrogen gas, substituted 1-bromo-3-methyl-2-butene 2 (1.0 equiv) in dry THF was added drop wise for 10 min, and the reaction was stirred at room temperature for 1 h. After completion of the reaction, brine solution was added to the reaction mixture, and the reaction mixture was extracted with ethyl acetate. The organic layer was further washed with brine solution. The organic layer was dried over Na2SO4 and concentrated in a rotary evaporator. The crude product thus obtained was subjected to column chromatography over silica gel to give the corresponding product 7.


General procedure for the synthesis of (8)

To an ice cooled solution of aldehyde 7 (1.0 equiv) in methanol was added sodium borohydride (1.2 equiv) pinch wise and stirred as such for half an hour. After completion of the reaction, 1N HCl was added to make the solution acidic (pH 6 or below) and the reaction mixture was extracted with ethyl acetate. The organic layer was further washed with brine solution. The organic layer was dried over Na2SO4 and concentrated in a rotary evaporator. The crude product was subjected to column chromatography over silica gel to give the corresponding product 8.
General procedure for the synthesis of (9)

As discussed in the general procedure for 5.

General procedure for the synthesis of (10)

To an ice cooled solution of aldehyde 7 (1.0 equiv) in ether was added Grignard reagent (1.2 equiv) and stirred at room temperature for 3 h. The reaction mixture was quenched with saturated aqueous NH₄Cl, and the mixture was extracted with ether. The organic layer was washed with brine, dried over anhydrous Na₂SO₄ and concentrated. The residue was purified by column chromatography on silica gel to give 10.

General procedure for the synthesis of (11)

As discussed in the general procedure for 5.

General procedure for the synthesis of (13)

To a solution of i-Pr₂NH (1.7 mL, 12 mmol) in THF (40 mL) was added n-BuLi (1.6 M in hexane, 6.9 mL, 11.0 mmol) drop wise at −78 °C, and the reaction mixture was stirred for 30 minutes. To this reaction mixture, a solution of aldehyde 6' (10 mmol) in THF (5 mL) was added dropwise at −78 °C. After stirring at the same temperature for 1 h, cinnamyl bromide (10 mmol) was added at −78 °C. It was then warmed to room temperature and stirred for 1 h. The reaction mixture was quenched with saturated aqueous NH₄Cl, and extracted with ether. The organic layer was washed with brine, dried over anhydrous Na₂SO₄ and concentrated. The residue was purified by column chromatography on silica gel to give 13.

General procedure for the synthesis of (14) and (15)

As discussed in general procedure for synthesis of 5 and 8.

General procedure for the synthesis of (16) and (17)

As discussed in general procedure for synthesis of 5 and 10.

General procedure for the synthesis of (20)

A solution of amino alcohol 18 (1.0 equiv) in acetone was added to a stirred solution of K$_2$CO$_3$ (1.2 equiv) in acetone followed by addition of substituted allyl bromide (1.0 equiv) and the reaction was refluxed for 12 h. After completion of the reaction, the mixture was extracted with ethyl acetate and dried over Na$_2$SO$_4$ and concentrated in a rotary evaporator. The crude product was subjected to column chromatography over silica gel to give corresponding product 20.


General procedure for the synthesis of (21)

As discussed in the general procedure for the synthesis of 5.
$^1$H and $^{13}$C NMR spectra of 1a

\[
\text{\begin{center}
\includegraphics[width=\textwidth]{nmr_spectrum.png}
\end{center}}
\]
$^1$H and $^{13}$C NMR spectra of 1b
$^1\text{H}$ and $^{13}\text{C}$ NMR spectra of 1c
$^1$H and $^{13}$C NMR spectra of 1d
$^1$H and $^{13}$C NMR spectra of 1e
$^1$H and $^{13}$C NMR spectra of 1f
$^1$H and $^{13}$C NMR spectra of 1g
$^1$H and $^{13}$C NMR spectra of 1h
\( ^1H \) and \( ^{13}C \) NMR spectra of \( \text{i} \)

\[
\text{\textbf{S14}}
\]
$^1$H and $^{13}$C NMR spectra of 1j
$^1$H and $^{13}$C NMR spectra of 1k

![NMR spectra diagram]
$^1$H and $^{13}$C NMR spectra of 11

![NMR Spectra Images]
$^1$H and $^{13}$C NMR spectra of 1m
$^{1}H$ and $^{13}C$ NMR spectra of $\text{In}$
$^1$H and $^{13}$C NMR spectra of 10
$^{1}$H and $^{13}$C NMR spectra of 1p
$^1$H and $^{13}$C NMR spectra of 1q
$^1$H and $^{13}$C NMR spectra of 2a
$^1$H and $^{13}$C NMR spectra of 2b
$^1$H and $^{13}$C NMR spectra of 2c
$^1$H and $^{13}$C NMR spectra of 2d
$^1$H and $^{13}$C NMR spectra of 2e

![NMR spectra image]
$^1$H and $^{13}$C NMR spectra of 2f
$^1$H and $^{13}$C NMR spectra of 2g
$^1$H and $^{13}$C NMR spectra of 2h
$^1\text{H}$ and $^{13}\text{C}$ NMR spectra of 2i
$^1$H and $^{13}$C NMR spectra of 2j
$^1$H and $^{13}$C NMR spectra of 2k
$^1$H and $^{13}$C NMR spectra of 21

![NMR Spectrum](image)

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S34
$^1$H and $^{13}$C NMR spectra of 2m
$^1$H and $^{13}$C NMR spectra of 2n
$^1$H and $^{13}$C NMR spectra of 2o
$^1$H and $^{13}$C NMR spectra of $2p$
$^1$H and $^{13}$C NMR spectra of 2q
DEPT and HMQC spectra of 2i
NOE spectrum of 2i
NOE spectrum of 2b
NOE spectrum of 2d