Journal Pre-proof

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PII: S0040-4020(20)30868-1

DOI: https://doi.org/10.1016/j.tet.2020.131661

Reference: TET 131661

To appear in: *Tetrahedron*

Received Date: 11 August 2020

Revised Date: 1 September 2020

Accepted Date: 4 September 2020

Please cite this article as: Uphade MB, Prasad KR, Total Synthesis of (+)-γ-Lycorane from Ethyl Lactate Using Iterative Claisen and Overman Rearrangement Reactions, *Tetrahedron*, https://doi.org/10.1016/j.tet.2020.131661.

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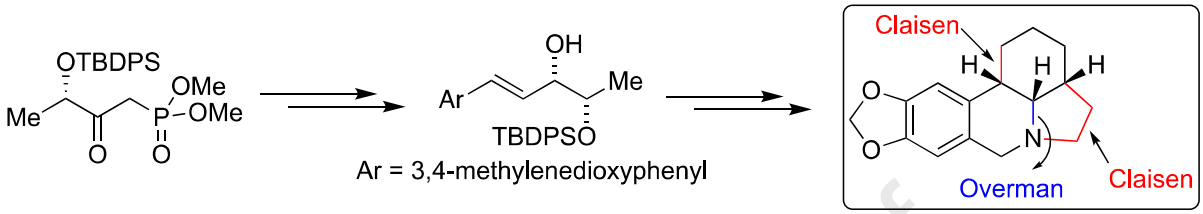

Total Synthesis of (+)-*γ*-Lycorane from Ethyl Lactate Using Iterative Claisen and Overman Rearrangement Reactions

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Abstract: Total synthesis of (+)-*γ*-lycorane is accomplished from (*S*)-ethyl lactate. Key disconnections in the synthesis involve an iterative Claisen and Overman rearrangement reactions to install the chiral centers in the tetrahydroindole moiety while, Pictet-Spengler reaction is used for the synthesis of the isoquinoline unit.

Key words: (+)-*γ*-lycorane, Sigmatropic rearrangement, (*S*)-lactic acid, Total synthesis, Alkaloids.

Lycorane alkaloids belong to the subclass of *Amaryllidaceae* alkaloids exhibiting wide range of biological activities.[1] Lycorane alkaloids possess a tetracyclic framework comprising an octahydroindole unit. Simple alkaloid in this series is *γ*- lycorane **1**, while lycorine **2**, galanthine **3** and narcissidine **4** are alkaloids comprising hydroxy substitutions and unsaturation at varied positions (Fig.1). A number of strategies were reported in the literature for the asymmetric synthesis of lycorane alkaloids.[2] Previous methods employed for the installation of the chiral amine part in lycoranes include Curtius rearrangement, reduction of oxazoloquinolones, reduction of the nitro group, Wittig rearrangement, asymmetric bromo amination and Pd-catalyzed asymmetric allylic alkylation reactions.[2] The Overman rearrangement,[3] a useful reaction for the synthesis of chiral amines involving a [3,3]-sigmatropic rearrangement of allyl alcohol and has been widely utilized for the synthesis of amine containing compounds. Herein, we report the synthesis of *γ*-lycorane **1**, using successive Claisen and Overman rearrangement reaction sequence.

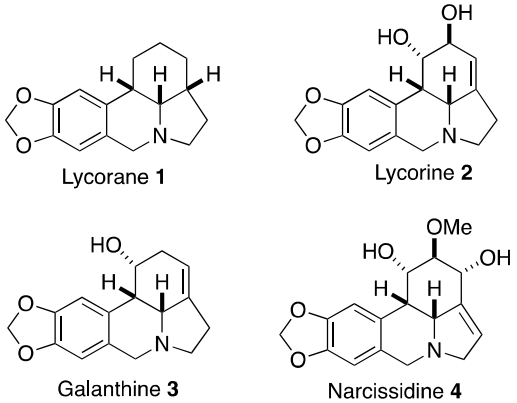
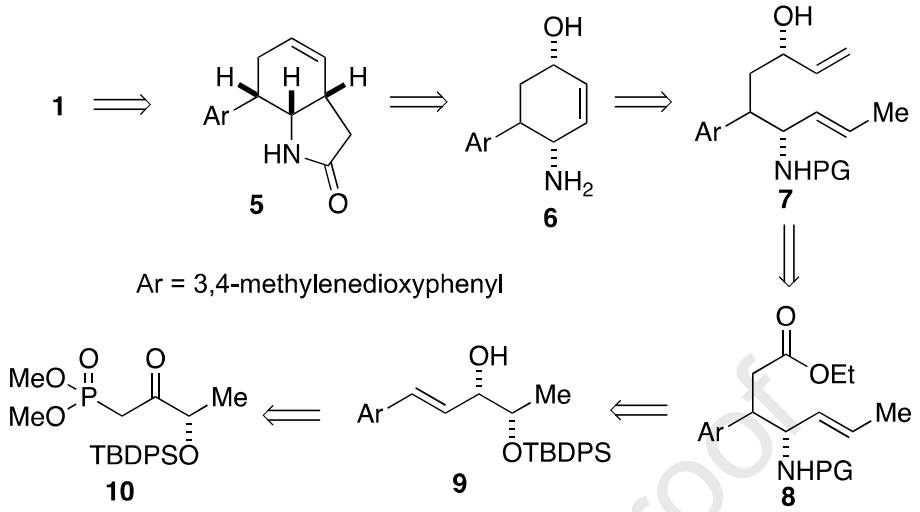


Fig. 1: Lycorane natural products

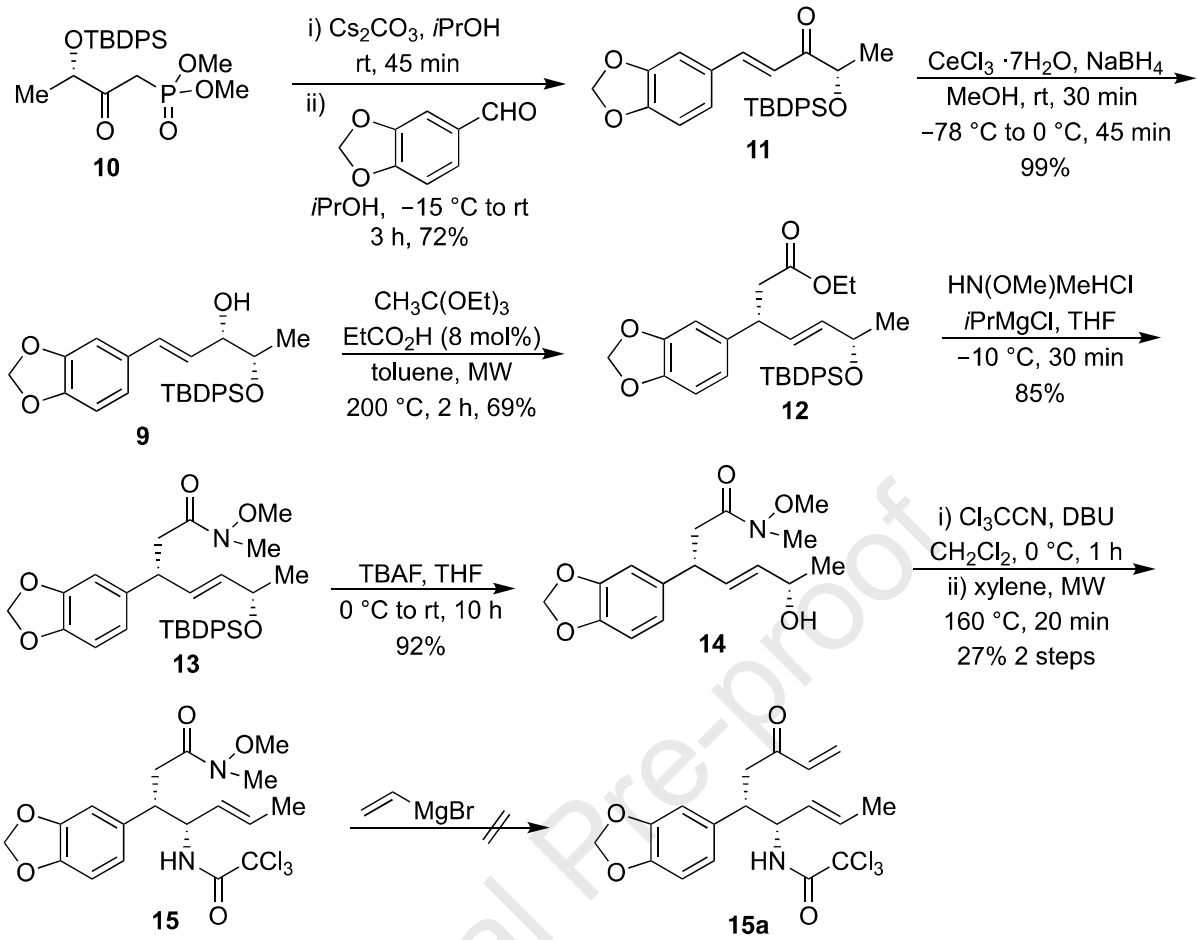
The approach for our synthesis of *γ*-lycorine is depicted in Scheme-1. We envisioned the synthesis of **1** by a late stage formation of the isoquinoline using Pictet-Spengler reaction of **5**. Synthesis of **5** is planned by Claisen rearrangement of the allyl alcohol in cyclohexenol **6** followed by lactamization. Formation of the required functionalized amino cyclohexenol **6** is planned by ring closing metathesis (RCM) of the corresponding diene **7**, the synthesis of

which is envisaged from the γ-amino ester **8**. Construction of the γ-amino ester **8** is envisioned by employing successive Claisen/ Overman rearrangements from the allyl alcohol **9** derived from β-ketophosphonate obtained from lactic acid (Scheme-1).



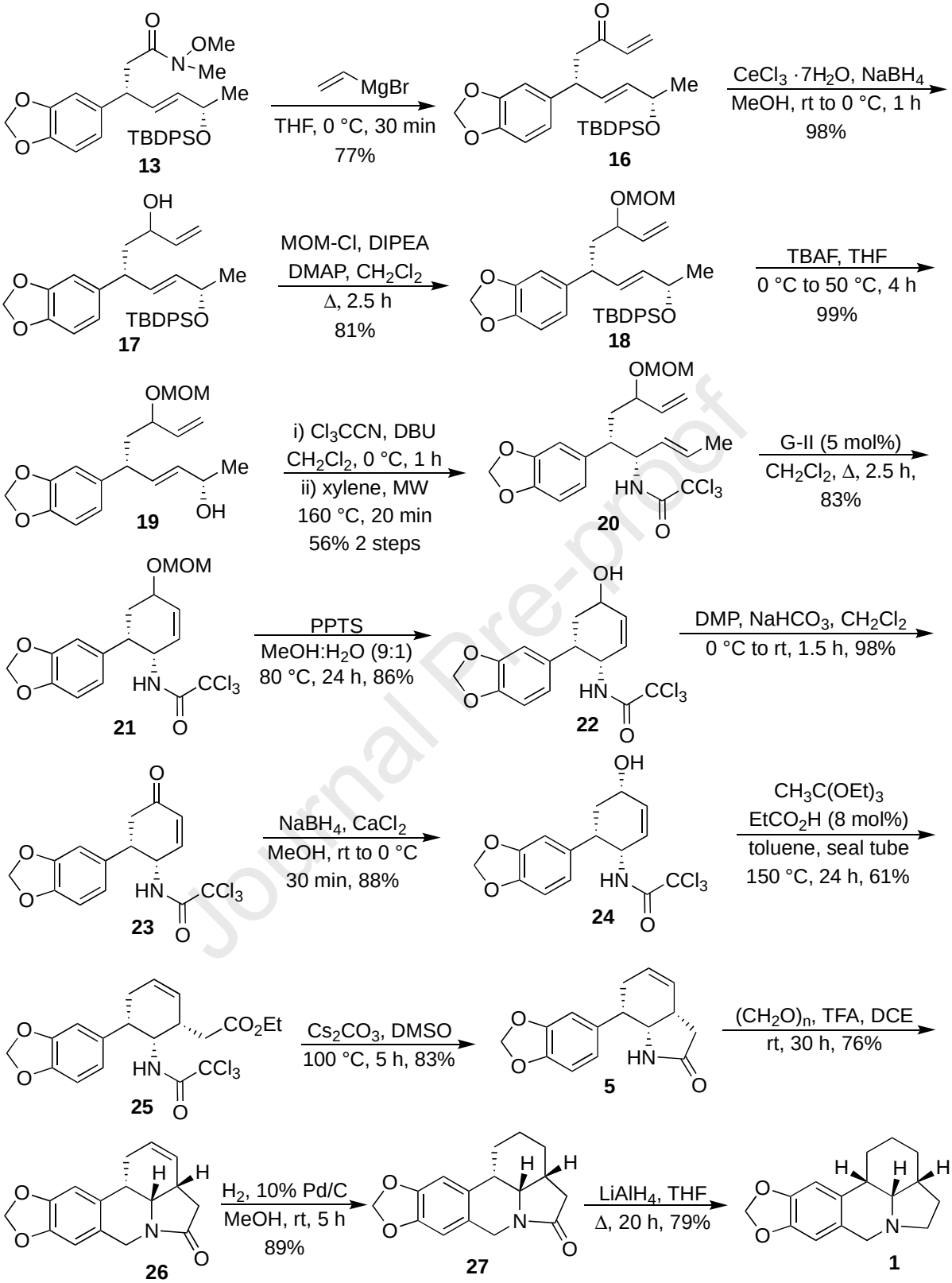
Scheme-1: Retrosynthesis for γ-lycorane **1**

Accordingly, the synthetic sequence commenced with the Horner-Wittig olefination of the known phosphonate **10**[4] derived from (*S*)-lactic acid with 3,4-methylenedioxy benzaldehyde to afford the α, β-unsaturated ketone **11** in 72% yield. Reduction of the ketone **11** under Luche condition[5] furnished the alcohol **9** in 99% yield. Claisen rearrangement[6] of the allyl alcohol **9** using triethylorthoacetate under microwave irradiation afforded the ester **12** in 69% yield. Conversion of the ester **12** to the Weinreb amide **13** was accomplished in 85% yield. Deprotection of the *tert*-butyldiphenysilyl ether in **13** with TBAF produced the free alcohol **14** which on Overman rearrangement yielded the trichloroacetyl amide **15** in mere 27% yield. Our efforts to add vinylmagnesium bromide to the Weinreb amide **15** were unsuccessful (Scheme-2).[7]



Scheme-2: Attempted synthesis of the functionalized diene **15a**

Although we failed to obtain the product enone in the addition of vinylmagnesium bromide to the Weinreb amide **15**, the reaction of the Weinreb amide **13** with vinylmagnesium bromide furnished the unsaturated ketone **16** in 77% yield. However, Luche reduction of the ketone **16** resulted in a 1:1 diastereomeric mixture of alcohols **17** in almost quantitative yield. Protection of the alcohol in **17** as the MOM ether followed by removal of the TBDPS group afforded the allyl alcohol **19** in 99% yield. Overman rearrangement of the allyl alcohol **19** produced the corresponding trichloroacetamide **20** in 56% yield. RCM of the diene containing the trichloroacetamide **20** yielded the functionalized cyclohexene **21** in 83% yield. Deprotection of the MOM ether in **21** followed by oxidation of the resultant alcohol **22** gave the cyclohexenone **23** in excellent yield. Gratifyingly, stereoselective reduction of the cyclohexenone under 1,2- reduction condition using $NaBH_4/CaCl_2$[8] resulted in the cyclohexenol **24** as a single diastereomer. Claisen rearrangement of the allyl alcohol furnished the ester **25** which on reaction with cesium carbonate afforded the known lactam **5**[9] in 83% yield. Pictet-Spengler reaction[10] of **5** with formaldehyde formed the isoquinoline **26** in 76% yield. Hydrogenation of the double bond in **26** followed by reduction of the lactam **27** with $LiAlH_4$ produced γ-lycorane **1** in 79% yield (Scheme-3). The spectral and physical data of the synthesized 3ycorine is identical with that reported in the literature.[2g, 11]

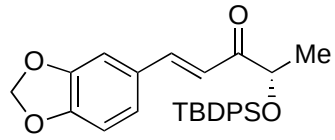


Scheme-3: Total Synthesis of γ-lycorane

In conclusion, total synthesis of γ-lycorane is accomplished from (*S*)-lactic acid using iterative Claisen-Overman rearrangement as the key reactions. Although, the present sequence is longer than some of the reported approaches, it showcased the use of sigmatropic rearrangements in construction of the required tricyclic unit. The synthesis of γ-

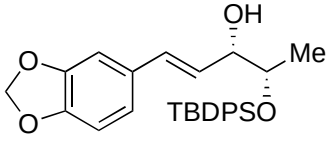
lycorane was accomplished in 2.4% overall yield in 19 linear steps from the phosphonate derived from lactic acid.

General Procedures: Column chromatography was performed on silica gel, Acme grade 100-200 mesh. TLC plates were visualized either with UV, in an iodine chamber, or with phosphomolybdic acid spray, unless noted otherwise. All reagents were purchased from commercial sources and used without additional purification. THF was freshly distilled over Na-benzophenone ketyl. Melting points were uncorrected. Unless stated otherwise, ^{1}H NMR and ^{13}C NMR spectra were recorded either on a 400 or on a 300 MHz machine in $CDCl_3$ as solvent with TMS as reference unless otherwise indicated. High-resolution mass spectra (HRMS) were recorded on a Q-TOF micromass spectrometer using electron spray ionization mode.



11

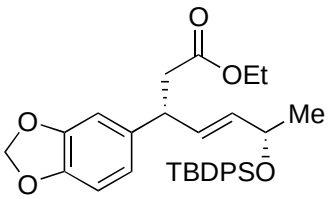
(*S*,*E*)-1-(benzo[d][1,3]dioxol-5-yl)-4-((*tert*-butyldiphenylsilyl)oxy)pent-1-en-3-one (**11**):
In a 50 ml two neck round bottom flask equipped with argon balloon was placed a solution of **10** (1.75 g, 4.2 mmol) in *i*PrOH (12 mL). Cs_2CO_3 (2.72 g, 8.4 mmol) was introduced into the flask all at once and was stirred for 45 min at room temperature. The reaction mixture was then cooled to –15 °C and a solution of the 3,4-methylenedioxy benzaldehyde (0.69 g, 4.6 mmol) in *i*PrOH (8 mL) was added dropwise. The reaction mixture was slowly warmed up to room temperature and stirred for 3 h at room temperature. After completion of the reaction (TLC), the reaction mixture was cautiously quenched by addition of aqueous solution of citric acid (10 mL), poured into water (15 mL) and extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with brine (2 × 5 mL) and dried over anhydrous Na_2SO_4. Evaporation of solvent gave crude residue, which was purified on silica gel column chromatography using petroleum ether/EtOAc (9:1) as eluent to furnish **11** (1.39 g, 72%) as a yellow oil. $[\alpha]_D^{24}$ −188.7 (*c* 1.45, $CHCl_3$). IR (Neat): ν_{max} 2956, 1686, 1591, 1492, 1110 cm^{-1}.
^{1}H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, *J* = 6.8 Hz, 2H), 7.63 (d, *J* = 6.8 Hz, 2H), 7.56 (d, *J* = 16.0 Hz, 1H), 7.50-7.28 (m, 6H), 7.16 (d, *J* = 16.0 Hz, 1H), 7.02 (m, 2H), 6.81 (d, *J* = 8.4 Hz, 1H), 6.00 (s, 2H), 4.36 (q, *J* = 6.8 Hz, 1H), 1.30 (d, *J* = 6.8 Hz, 3H), 1.13 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 201.3, 149.8, 148.3, 143.5, 135.74 (2 × C), 135.72 (2 × C), 133.5, 133.0, 129.88, 129.86, 129.3, 127.7 (2 × C), 127.67 (2 × C), 125.2, 118.6, 108.6, 106.6, 101.5, 75.2, 26.9 (3 × C), 21.2, 19.2.
HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{28}H_{30}O_4Si$+Na 481.1811; Found 481.1809.



9

(3*S*,4*S*,*E*)-1-(benzo[d][1,3]dioxol-5-yl)-4-((*tert*-butyldiphenylsilyl)oxy)pent-1-en-3-ol (9): To a stirred solution of **11** (1.38 g, 3.01 mmol) in MeOH (30 mL) was added $CeCl_3.7H_2O$ (1.68 g, 4.5 mmol) and the reaction mixture was stirred for 30 min at room temperature. The reaction mixture was cooled to −78 °C and $NaBH_4$ (0.17 g, 4.5 mmol) was added portion

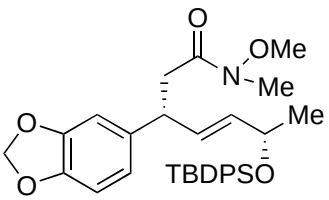
wise over a period of 5 min. The reaction mixture was slowly warmed up to 0 °C and stirred at the same temperature for 45 min. After completion of the reaction (TLC), it was quenched by addition of water (1 mL) and slowly warmed up to room temperature. Most of the solvent was evaporated off and the crude residue was diluted with water (20 mL) and extracted with EtOAc (2 × 30 mL). The combined organic layers were washed with brine (20 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave the crude residue which was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1) as eluent to furnish **9** (1.38 g, 99%) as a colorless oil. $[\alpha]_D^{24}$–64.8 (*c* 1.6, $CHCl_3$). IR (Neat): ν_{max} 3332, 2926, 1643, 1587, 1219 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.69 (d, *J* = 7.6 Hz, 4H), 7.55-7.25 (m, 6H), 6.84 (s, 1H), 6.80-6.68 (m, 2H), 6.54 (d, *J* = 16.0 Hz, 1H), 5.95 (dd, *J* = 16.0, 6.0 Hz, 1H), 5.93 (s, 2H), 4.06 (q, *J* = 5.6 Hz, 1H), 3.84 (quint, *J* = 6.0 Hz, 1H), 2.68 (d, *J* = 4.8 Hz, 1H, OH exchangeable with D_2O), 1.10-1.00 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.9, 147.2, 135.89 (2 × C), 135.86 (2 × C), 134.0, 133.3, 131.5, 131.3, 129.8, 129.7, 127.7 (2 × C), 127.5 (2 × C), 127.2, 121.1, 108.2, 105.7, 101.0, 77.1, 73.2, 27.0 (3 × C), 19.7, 19.3. HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{28}H_{32}O_4Si$+Na 483.1968; Found: 483.1970.



12

ethyl (3*R*,6*S*,*E*)-3-(benzo[d][1,3]dioxol-5-yl)-6-((*tert*-butyldiphenylsilyl)oxy)hept-4-enoate (**12):** To a solution of the allyl alcohol **9** (0.8 g, 1.74 mmol) in toluene (5 mL) were added triethyl orthoacetate (1.7 mL, 8.7 mmol) and propionic acid (0.5 M in toluene, 0.28 mL, 0.14 mmol). The resulting solution was heated at 200 °C in microwave for 2 h. After completion of the reaction (TLC), most of the solvent was evaporated off and the crude obtained which was purified by silica gel column chromatography using petroleum ether/EtOAc (9.5:0.5) as eluent to furnish **12** (0.64 g, 69%) as a colorless oil. $[\alpha]_D^{24}$–50.9 (*c* 0.9, $CHCl_3$). IR (Neat): ν_{max} 2967, 2937, 2859, 1734, 1490, 1244 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.75-7.56 (m, 4H), 7.44-7.28 (m, 6H), 6.69 (d, *J* = 8.0 Hz, 1H), 6.60-6.52 (m, 2H), 5.91 (s, 2H), 5.54 (dd, *J* = 15.6, 6.4 Hz, 1H), 5.47 (dd, *J* = 15.6, 5.2 Hz, 1H), 4.25 (quint, *J* = 6.0 Hz, 1H), 4.04 (q, *J* = 7.2 Hz, 2H), 3.68 (q, *J* = 7.6 Hz, 1H), 2.62-2.48 (m, 2H), 1.16 (t, *J* = 7.2 Hz, 3H), 1.12 (d, *J* = 6.0 Hz, 3H), 1.05 (s, 9H).

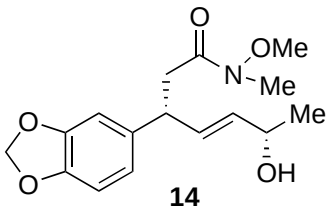
^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7, 147.6, 146.0, 136.7, 135.86 (2 × C), 135.85 (2 × C), 134.44, 134.4, 134.2, 131.1, 129.5, 129.4, 127.5 (2 × C), 127.4 (2 × C), 120.5, 108.1, 108.0, 100.8, 70.0, 60.3, 43.7, 40.7, 26.9 (3 × C), 24.4, 19.2, 14.2. HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{32}H_{38}O_5Si$+Na 553.2386; Found: 553.2387.



13

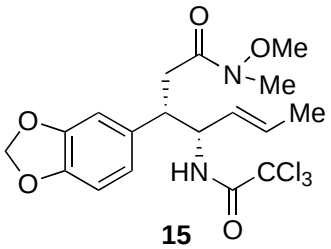
(3*R*,6*S*,*E*)-3-(benzo[d][1,3]dioxol-5-yl)-6-((*tert*-butyldiphenylsilyl)oxy)-N-methoxy-N-methylhept-4-enamide (**13)**: In a two neck round bottom flask equipped with argon balloon

was placed a solution of **12** (0.26 g, 0.49 mmol) in THF (3 mL). *N*,*O*-Dimethylhydroxylamine hydrochloride (0.1 g, 0.98 mmol) was introduced into the flask. The reaction mixture was then cooled to –10 °C and a solution of *i*PrMgCl (1.2 M in THF, 1.6 mL, 1.96 mmol) was added dropwise. The reaction mixture was stirred at the same temperature for 30 min. After completion of the reaction (TLC), the reaction mixture was cautiously quenched by addition of aqueous solution of NH_4Cl (5 mL) and extracted with EtOAc (3 × 15 mL). The combined organic layers were washed with brine (5 mL) and dried over anhydrous Na_2SO_4. Evaporation of solvent gave crude residue, which was purified on silica gel column chromatography using petroleum ether/EtOAc (7.5:2.5) as eluent to furnish **13** (0.23 g, 85%) as a colorless oil. $[\alpha]_D^{24}$–47.1 (*c* 1.05, $CHCl_3$). IR (Neat): ν_{max} 2962, 2934, 1663, 1488, 1244 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.65 (t, *J* = 6.8 Hz, 4H), 7.45-7.25 (m, 6H), 6.68 (d, *J* = 8.0 Hz, 1H), 6.65-6.60 (m, 1H), 6.57 (d, *J* = 1.2 Hz, 1H), 5.87 (s, 2H), 5.60 (dd, *J* = 15.6, 6.8 Hz, 1H), 5.49 (dd, *J* = 15.6, 6.0 Hz, 1H), 4.27 (quint, *J* = 6.0 Hz, 1H), 3.82 (q, *J* = 7.2 Hz, 1H), 3.57 (s, 3H), 3.09 (s, 3H), 2.71 (d, *J* = 6.8 Hz, 2H), 1.14 (d, *J* = 6.0 Hz, 3H), 1.05 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.3, 147.4, 145.8, 137.2, 135.8 (2 × C), 135.7 (2 × C), 134.22, 134.2, 134.0, 131.6, 129.4, 129.3, 127.33 (2 × C), 127.3 (2 × C), 120.5, 108.1, 108.0, 100.6, 69.9, 61.1, 42.9, 37.6, 31.9, 26.8 (3 × C), 24.3, 19.1. HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{32}H_{39}NO_5Si$+Na 568.2495; Found: 568.2491.



14

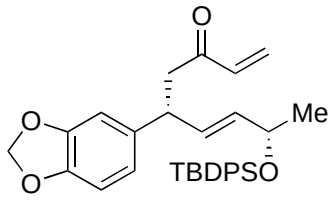
(3*R*,6*S*,*E*)-3-(benzo[d][1,3]dioxol-5-yl)-6-hydroxy-N-methoxy-N-methylhept-4-enamide (**14**): To a solution of **13** (0.15 g, 0.28mmol) in THF (3 mL) was added a solution of TBAF (0.67 mL of 1 M in THF, 0.67 mmol) at 0 °C and was allowed to stir at room temperature for 10 h. After the reaction was complete (TLC), it was diluted with cold water and extracted with EtOAc (3×10 mL). The combined organic extract was washed with brine (5 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by silica gel column chromatography using petroleum ether/EtOAc (2:8) as eluent furnished the compound **14** (0.08 g, 92%) as colorless oil. $[\alpha]_D^{24}$–22.0 (*c* 1.2, $CHCl_3$). IR (Neat): ν_{max} 3411, 2972, 2893, 1645, 1485, 1242, 1037 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.78-6.58 (m, 3H), 5.88 (s, 2H), 5.76 (dd, *J* = 15.6, 7.2 Hz, 1H), 5.51 (dd, *J* = 15.6, 6.4 Hz, 1H), 4.23 (quint, *J* = 6.4 Hz, 1H), 3.83 (q, *J* = 7.2 Hz, 1H), 3.60 (s, 3H), 3.10 (s, 3H), 2.76 (d, *J* = 7.2 Hz, 2H), 2.42 (bs, 1H), 1.20 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.4, 147.5, 145.9, 137.1, 134.4, 132.3, 120.4, 108.1, 107.9, 100.7, 68.2, 61.2, 43.2, 38.0, 32.0, 23.2. HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{16}H_{21}NO_5$+Na 330.1317; Found: 330.1315.



15

(**3*S*,4*S*,*E*)-3-(benzo[d][1,3]dioxol-5-yl)-N-methoxy-N-methyl-4-(2,2,2-trichloroacetamido)hept-5-enamide** (**15)**: To a stirred solution of the allyl alcohol **14** (0.08 g, 0.24mmol) in CH_2Cl_2 (3 mL) were added Cl_3CCN (0.06 mL, 0.53mmol) and DBU (0.01 mL, 0.05mmol) at 0 °C and was allowed to stir at same temperature for 1 h. After completion of the reaction (TLC), most of the solvent was evaporated off and the crude obtained which was purified by silica gel column chromatography (petroleum ether/EtOAc (6:4), 1% Et_3N) as eluent to furnish the imidate.

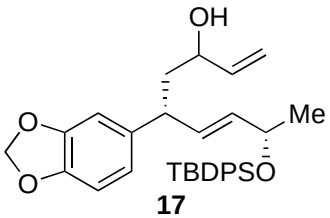
A solution of the imidate in xylene (5 mL) was heated at 160 °C in microwave for 20 min. After completion of the reaction (TLC), most of the solvent was evaporated off and the crude obtained which was purified by silica gel column chromatography using petroleum ether/EtOAc (7:3) as eluent to furnish **15** (0.03 g, 27% for 2 steps) as a colorless oil. $[\alpha]_D^{24}$−7.1 (*c* 1.5, $CHCl_3$). IR (Neat): ν_{max} 3400, 2925, 1709, 1646, 1245, 1037 cm^{-1}.^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (d, *J* = 8.4 Hz, 1H), 6.80-6.60 (m, 3H), 5.95 (s, 2H), 5.54 (sextet, *J* = 6.4 Hz, 1H), 5.24 (dd, *J* = 15.2, 6.4 Hz, 1H), 4.49 (q, *J* = 8.8 Hz, 1H), 3.62 (s, 3H), 3.42 (td, *J* = 8.8, 4.4 Hz, 1H), 3.15 (s, 3H), 2.87 (dd, *J* = 17.6, 8.4 Hz, 1H), 2.74 (dd, *J* = 17.6, 3.6 Hz, 1H), 1.60 (d, *J* = 6.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 172.9, 161.2, 147.8, 146.5, 135.0, 128.6, 127.7, 121.6, 108.4, 108.3, 101.0, 92.9, 61.2, 58.1, 44.2, 36.4, 32.2, 17.7. HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{18}H_{21}Cl_3N_2O_5$+Na 473.0414; Found: 473.0416.



16

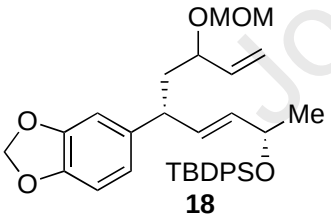
(5*R*,8*S*,*E*)-5-(benzo[d][1,3]dioxol-5-yl)-8-((*tert*-butyldiphenylsilyl)oxy)nona-1,6-dien-3-one (**16)**: To a solution of **13** (0.11 g, 0.2mmol) in THF (3 mL) was added a solution of vinylmagnesium bromide (0.25 M in THF, 1.7 mL, 0.42 mmol) dropwise at 0 °C and was allowed to stir at same temperature for 30 min. After the reaction was complete (TLC), it was quenched by addition of saturated aqueous solution of NH_4Cl (5 mL) and extracted with EtOAc (2 × 10 mL). The combined organic layers were washed with brine (5 mL) and dried over anhydrous Na_2SO_4. Evaporation of solvent gave crude residue, which was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1) as eluent to furnish **16** (0.08 g, 77%) as a colorless oil. $[\alpha]_D^{24}$−53.8 (*c* 1.25, $CHCl_3$). IR (Neat): ν_{max} 2928, 1683, 1487, 1242 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.64 (t, *J* = 8.0 Hz, 4H), 7.45-7.28 (m, 6H), 6.67 (d, *J* = 8.0 Hz, 1H), 6.57 (s, 1H), 6.52 (d, *J* = 8.0 Hz, 1H), 6.27 (dd, *J* = 17.6, 10.4 Hz, 1H), 6.13 (d, *J* = 17.2 Hz, 1H), 5.88 (bs, 2H), 5.75 (d, *J* = 10.8 Hz, 1H), 5.52 (dd, *J* = 15.6, 6.4 Hz, 1H), 5.43 (dd, *J* = 15.6, 5.6 Hz, 1H), 4.26 (quint, *J* = 6.0 Hz, 1H), 3.79 (q, *J* = 6.8 Hz, 1H), 2.88-2.72 (m, 2H), 1.13 (d, *J* = 6.4 Hz, 3H), 1.04 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.6, 147.5, 145.9, 137.0, 136.6, 135.84 (2 × C), 135.80 (2 × C), 134.31, 134.3, 134.2, 131.5, 129.5, 129.4, 128.1, 127.4 (2 × C), 127.3 (2 × C), 120.5, 108.1, 108.0, 100.8, 70.0, 45.3, 42.6, 26.9 (3 × C), 24.3, 19.1. HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{32}H_{36}O_4Si$+Na 535.2281; Found: 535.2279.



17

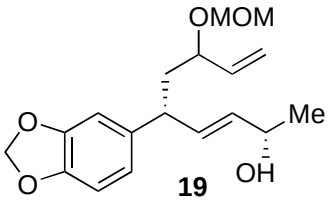
(5*R*,8*S*,*E*)-5-(benzo[d][1,3]dioxol-5-yl)-8-((*tert*-butyldiphenylsilyl)oxy)nona-1,6-dien-3-ol (**17)**: To a stirred solution of **16** (0.57 g, 1.11 mmol) in MeOH (25 mL) was added $CeCl_3.7H_2O$ (0.62 g, 1.67 mmol) and the reaction mixture was stirred for 30 min at room temperature. The reaction mixture was cooled to 0 °C and $NaBH_4$ (0.064 g, 1.67 mmol) was added portion wise over a period of 5 min. The reaction mixture stirred at the same temperature for 30 min. After completion of the reaction (TLC), it was quenched by addition of water (1 mL) and slowly warmed up to room temperature. Most of the solvent was evaporated off and the crude residue was diluted with water (15 mL) and extracted with EtOAc (2 × 25 mL). The combined organic layers were washed with brine (15 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave the crude residue which was purified by silica gel column chromatography using petroleum ether/EtOAc (8.5:1.5) as eluent to furnish **17** (0.56 g, 98%, 1:1 diastereomer) as a colorless oil. $[\alpha]_D^{24}$–76.2 (*c* 0.85, $CHCl_3$). IR (Neat): ν_{max} 3376, 2931, 2859, 1487, 1242 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.75-7.55 (m, 4H), 7.45-7.28 (m, 6H), 6.75-6.65 (m, 1H), 6.62-6.50 (m, 2H), 5.95-5.88 (m, 2H), 5.87-5.75 (m, 1H), 5.57-5.38 (m, 2H), 5.20-5.03 (m, 2H), 4.26 (sextet, *J* = 6.4 Hz, 1H), 3.95-3.80 (m, 1H), 3.42-3.22 (m, 1H), 1.82-1.72 (m, 1H), 1.71-1.62 (m, 1H), 1.14 (t, *J* = 6.8 Hz, 3H), 1.05 (bs, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.6 (4 × C), 145.8, 145.74 (2 × C), 141.2, 141.0 (2 × C), 138.2 (2 × C), 137.6, 135.9 (8 × C), 134.6, 134.4, 134.35, 134.3, 133.8, 132.8, 132.3, 129.6, 129.53, 129.5, 129.4, 127.43, 127.42, 127.4 (2 × C), 120.7, 120.3, 114.7, 114.5, 108.2 (2 × C), 108.0, 107.8, 100.8 (2 × C), 70.8, 70.6, 70.23, 70.2, 44.1, 43.9, 42.8, 42.7, 26.93 (3 × C), 26.9 (3 × C), 24.5, 24.4, 19.3 (2 × C). HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{32}H_{38}O_4Si$+Na 537.2437; Found: 537.2437.



18

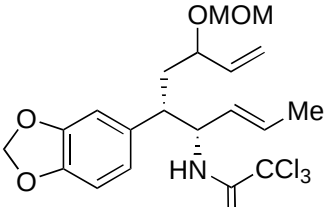
(7*R*,10*S*,*E*)-7-(benzo[d][1,3]dioxol-5-yl)-10,13,13-trimethyl-12,12-diphenyl-5-vinyl-2,4,11-trioxa-12-silatetradec-8-ene (**18)**: To a stirred solution of **17** (40 mg, 0.08 mmol) in CH_2Cl_2 (3 mL) were added diisopropylethylamine (0.16 mL, 0.96 mmol), MOMCl (0.04 mL, 0.48 mmol) and DMAP (4 mg, 0.03 mmol) at 0 °C. The reaction mixture was heated to reflux for 2.5 h. After completion of the reaction (TLC), it was allowed to cool to room temperature, quenched by addition of saturated aqueous solution of NH_4Cl (5 mL) and extracted with diethyl ether (3 × 5 mL). The combined organic layers were washed with brine (5 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave the crude residue which was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1) as eluent to furnish **18** (35 mg, 81%) as a colorless oil. $[\alpha]_D^{24}$–63.7 (*c* 1.2, $CHCl_3$). IR (Neat): ν_{max} 2931, 2889, 1487, 1242, 1034 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.70-7.55 (m, 4H), 7.45-7.35 (m, 2H), 7.35-7.25 (m, 4H), 6.70 (dd, *J* = 8.0, 4.4 Hz, 1H), 6.62-6.48 (m, 2H), 5.92 (s, 1H), 5.91 (s, 1H), 5.72-5.60 (m, 1H), 5.56-5.38 (m, 2H), 5.17 (dq, *J* = 10.4, 1.2 Hz, 1H), 5.12 (d, *J* = 17.2 Hz, 1H), 4.63 (dd, *J* = 6.4, 5.2 Hz, 1H), 4.48 (dd, *J* = 6.8, 5.2 Hz, 1H), 4.24 (q, *J* = 6.4 Hz, 1H), 3.92-

3.75 (m, 1H), 3.40-3.25 (m, 4H), 1.91 (quint, *J* = 8.0 Hz, 1H), 1.78-1.65 (m, 1H), 1.12 (dd, *J* = 6.4, 2.0 Hz, 3H), 1.09-1.00 (m, 9H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.6 (2 × C), 145.8, 145.7, 138.5, 138.2, 138.1, 137.7, 135.9 (5 × C), 134.45 (2 × C), 134.42 (2 × C), 134.3, 134.29, 134.27 (2 × C), 133.8, 132.9, 132.4, 129.48, 129.47, 129.40, 129.39, 127.42 (4 × C), 127.4 (2 × C), 127.35 (2 × C), 120.8, 120.5, 117.7, 117.1, 108.2, 108.12, 108.07, 107.9, 100.7 (2 × C), 94.3, 93.9, 75.7, 75.5, 70.11, 70.10, 55.7, 55.4, 43.6, 43.5, 41.42, 41.40, 26.9 (6 × C), 24.4 (2 × C), 19.2 (2 × C). HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{34}H_{42}O_5Si$+Na 581.2699; Found: 581.2696.



19

(2*S*,5*R*,*E*)-5-(benzo[d][1,3]dioxol-5-yl)-7-(methoxymethoxy)nona-3,8-dien-2-ol (**19)**: To a stirred solution of **18** (0.54 g, 0.97mmol) in THF (8 mL) was added a solution of TBAF (1 M in THF, 2.9 mL, 2.91 mmol) at 0 °C. The reaction mixture was slowly warmed up to 50 °C and stirred for 4 h. After the reaction was complete (TLC), it was allowed to cool to room temperature, diluted with cold water (10 mL) and extracted with EtOAc (3×20 mL). The combined organic extract was washed with brine (10 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent followed by silica gel column chromatography using petroleum ether/EtOAc (1:1) as eluent furnished **19** (0.31 g, 99%) as colorless oil. $[\alpha]_D^{24}$–31.5 (*c* 1.2, $CHCl_3$). IR (Neat): ν_{max} 3411, 2926, 1489, 1243, 1034 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.74 (dd, *J* = 8.0, 4.0 Hz, 1H), 6.70-6.60 (m, 2H), 5.93 (s, 1H), 5.92 (s, 1H), 5.78-5.60 (m, 2H), 5.58-5.46 (m, 1H), 5.25-5.10 (m, 2H), 4.65 (dd, *J* = 6.8, 4.8 Hz, 1H), 4.50 (dd, *J* = 6.8, 4.4 Hz, 1H), 4.26 (sextet, *J* = 6.8 Hz, 1H), 3.98-3.80 (m, 1H), 3.45-3.32 (m, 4H), 1.98 (quint, *J* = 7.2 Hz, 1H), 1.85-1.72 (m, 2H), 1.23 (dd, *J* = 6.4, 4.4 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 147.74, 147.73, 146.0, 145.9, 138.3, 138.1, 137.8, 137.4, 134.4, 133.91, 133.9, 133.3, 120.7, 120.4, 117.8, 117.3, 108.3, 108.2, 107.9, 107.8, 100.8 (2 × C), 94.1, 93.4, 75.6, 75.5, 68.6 (2 × C), 55.7, 55.6, 43.9, 43.8, 41.5, 41.4, 23.32, 23.3. HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{18}H_{24}O_5$+Na 343.1521; Found: 343.1519.

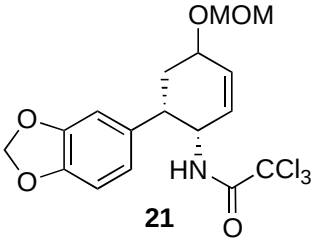


20

N-((4*S*,5*S*,*E*)-5-(benzo[d][1,3]dioxol-5-yl)-7-(methoxymethoxy)nona-2,8-dien-4-yl)-2,2,2-trichloroacetamide (**20):** To a solution of the allyl alcohol **19** (0.06 g, 0.19mmol) in CH_2Cl_2 (4 mL) were added Cl_3CCN (0.04 mL, 0.42mmol) and DBU (0.01 mL, 0.04mmol) at 0 °C and was allowed to stir at same temperature for 1 h. After completion of the reaction (TLC), most of the solvent was evaporated off and the crude obtained which was purified by silica gel column chromatography (petroleum ether/EtOAc (8.5:1.5), 1% Et_3N) as eluent to furnish the imidate.

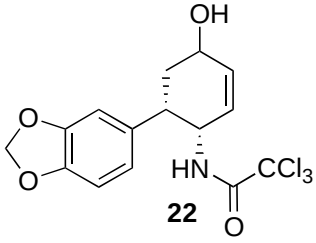
A solution of the imidate in xylene (5 mL) was heated at 160 °C in microwave for 20 min. After completion of the reaction (TLC), most of the solvent was evaporated off and the crude obtained which was purified by silica gel column chromatography using petroleum

ether/EtOAc (8.5:1.5) as eluent to furnish **20** (0.05 g, 56% for 2 steps) as colorless oil. $[\alpha]_D^{24}$–1.4 (*c* 0.9, $CHCl_3$). IR (Neat): ν_{max} 3334, 2926, 1712, 1592, 1495, 1031 cm^{-1}.
^1H NMR (400 MHz, $CDCl_3$): δ 6.77 (dd, *J* = 8.0, 2.0 Hz, 2H), 6.75-6.55 (m, 5H), 6.51 (d, *J* = 8.8 Hz, 1H), 6.05-5.90 (m, 4H), 5.72-5.54 (m, 4H), 5.34-5.18 (m, 2H), 5.18-5.10 (m, 2H), 5.06 (dd, *J* = 17.2, 0.8 Hz, 1H), 4.63 (dd, *J* = 6.8, 2.4 Hz, 2H), 4.58-4.40 (m, 4H), 3.90-3.78 (m, 2H), 3.32 (s, 3H), 3.31 (s, 3H), 3.15-3.05 (m, 1H), 2.90 (quint, *J* = 5.2 Hz, 1H), 2.10-2.00 (m, 1H), 1.98-1.90 (m, 1H), 1.88-1.75 (m, 2H), 1.74-1.60 (m, 7H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.6, 160.5, 148.0, 147.9, 146.8, 146.7, 138.1, 137.3, 133.0, 132.3, 130.1, 129.6, 126.2, 125.6, 122.5, 122.4, 118.9, 117.4, 108.68, 108.65, 108.2, 108.16, 101.1 (2 × C), 94.0, 93.6, 92.9, 92.8, 75.3, 75.2, 57.1, 56.9, 55.8, 55.3, 45.4, 44.8, 38.4, 37.4, 17.9, 17.8. HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{20}H_{24}Cl_3NO_5$+Na 486.0618; Found: 486.0615.



21

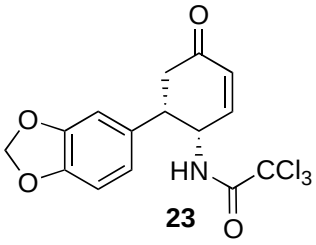
N-((1*S*,6*S*)-6-(benzo[d][1,3]dioxol-5-yl)-4-(methoxymethoxy)cyclohex-2-en-1-yl)-2,2,2-trichloroacetamide (**21)**: A solution of **20** (0.20 g, 0.43mmol) and Grubbs' 2nd generation catalyst (19 mg, 0.022mmol) in CH_2Cl_2 (21 mL) was heated to refluxed for 2.5 h. After completion of the reaction (TLC), most of the solvent was evaporated off and the crude residue obtained was purified by silica gel column chromatography using petroleum ether/EtOAc (7:3) as eluent to furnish **21** (0.15 g, 83%) as colorless oil. $[\alpha]_D^{24}$+161.1 (*c* 0.8, $CHCl_3$). IR (Neat): ν_{max} 3332, 2890, 1707, 1504, 1443, 1034 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.78-6.58 (m, 7H), 6.48 (dd, *J* = 13.6, 9.6 Hz, 2H), 6.11 (dd, *J* = 7.2, 4.4 Hz, 1H), 6.10-5.95 (m, 2H), 5.94-5.80 (m, 4H), 4.78-4.70 (m, 2H), 4.68-4.50 (m, 4H), 4.30 (t, *J* = 6.8 Hz, 1H), 4.23 (bs, 1H), 3.55-3.45 (m, 1H), 3.44-3.28 (m, 6H), 3.11 (dd, *J* = 14.0, 2.4 Hz, 1H), 2.35-2.20 (m, 1H), 2.15-1.93 (m, 2H), 1.88-1.70 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.8, 160.6, 147.6, 147.5, 146.4 (2 × C), 134.1, 133.8 (2 × C), 130.7, 129.0, 126.8, 120.7, 120.6, 108.2, 108.16, 108.08, 108.01, 100.8 (2 × C), 95.3, 95.2, 92.3 (2 × C), 72.7, 68.4, 55.3, 55.2, 49.3, 49.2, 40.9, 38.1, 29.8, 29.5. HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{17}H_{18}Cl_3NO_5$+Na 444.0148; Found: 444.0145.



22

N-((1*S*,*6S*)-6-(benzo[d][1,3]dioxol-5-yl)-4-hydroxycyclohex-2-en-1-yl)-2,2,2-trichloroacetamide (**22)**: To a stirred solution of **21** (0.34 g, 0.81 mmol) in MeOH:H_2O (9:1, 10 mL) was added PPTS (0.93 g, 3.70 mmol) at room temperature. The reaction mixture was heated at 80 °C for 24 h. After completion of the reaction (TLC), it was allowed to cool to room temperature, most of the solvent was evaporated off and the crude residue was diluted with water (10 mL) and extracted with EtOAc (2 × 20 mL). The combined organic

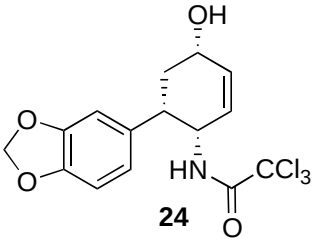
layers were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave the crude residue which was purified by silica gel column chromatography using petroleum ether/EtOAc (1:1) as eluent to furnish **22** (0.26 g, 86%) as a colorless oil. $[\alpha]_D^{24}$+140.5, (*c* 1.2, $CHCl_3$). IR (Neat): ν_{max} 3599, 1703, 1506, 1442, 1037 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.85-6.60 (m, 7H), 6.52 (d, *J* = 8.8 Hz, 1H), 6.08 (dd, *J* = 9.6, 4.4 Hz, 1H), 6.05-5.90 (m, 2H), 5.89-5.72 (m, 5H), 4.70-4.50 (m, 2H), 4.49-4.30 (m, 2H), 3.60-3.40 (m, 1H), 3.20-3.00 (m, 1H), 3.00-2.68 (bs, 2H), 2.30-2.12 (m, 1H), 2.11-1.95 (m, 2H), 1.77 (q, *J* = 12.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.1, 160.9, 147.6, 147.5, 146.4, 146.3, 136.0, 133.9, 133.7, 132.4, 128.3, 126.0, 120.8, 120.6, 108.24, 108.22, 108.13, 108.1, 100.81, 100.8, 92.3 (2 × C), 67.3, 63.2, 49.3 (2 × C), 41.0, 37.8, 32.2, 32.1. HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{15}H_{14}Cl_3NO_4$+Na 399.9886; Found: 399.9890.



23

N-((1*S*,6*S*)-6-(benzo[d][1,3]dioxol-5-yl)-4-oxocyclohex-2-en-1-yl)-2,2,2-trichloroacetamide (**23)**: To a stirred solution of **22** (88 mg, 0.23 mmol) in CH_2Cl_2 (5 mL) were added $NaHCO_3$ (58 mg, 0.69 mmol), DMP (0.15 g, 0.35 mmol) at 0 °C. The reaction mixture was stirred at same temperature for 1.5 h. After completion of the reaction (TLC), it was quenched by addition of aqueous solution of $Na_2S_2O_3$ (5 mL) and extracted with EtOAc (2 × 25 mL). The combined organic layers were washed with brine (25 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave the crude residue which was purified by silica gel column chromatography using petroleum ether/EtOAc (7:3) as eluent to furnish **23** (86 mg, 98%) as a colorless oil. $[\alpha]_D^{24}$+145.9, (*c* 0.7, $CHCl_3$). IR (Neat): ν_{max} 3319, 2904, 1681, 1506, 1443, 1245 cm^{-1}.

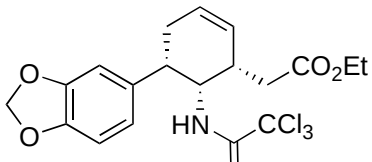
^1H NMR (400 MHz, $CDCl_3$): δ 6.96 (d, *J* = 8.8 Hz, 1H), 6.83 (dd, *J* = 10.4, 4.4 Hz, 1H), 6.72 (d, *J* = 7.6 Hz, 1H), 6.68-6.55 (m, 2H), 6.17 (d, *J* = 10.0 Hz, 1H), 5.96-5.85 (m, 2H), 5.08-4.96 (m, 1H), 3.75-3.60 (m, 1H), 2.88 (dd, *J* = 16.8, 8.8 Hz, 1H), 2.75 (dd, *J* = 16.8, 4.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.4, 161.4, 148.0, 147.1, 145.6, 131.5, 131.2, 121.4, 108.38, 108.35, 101.1, 92.0, 49.7, 45.5, 39.9. HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{15}H_{12}Cl_3NO_4$+Na 397.9730; Found: 397.9732.



24

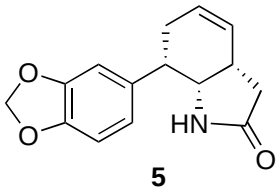
N-((1*S*,4*S*,6*S*)-6-(benzo[d][1,3]dioxol-5-yl)-4-hydroxycyclohex-2-en-1-yl)-2,2,2-trichloroacetamide (**24)**: To a stirred solution of **23** (0.25 g, 0.67 mmol) in anhydrous MeOH (25 mL) was added $CaCl_2$ (fused) (0.15 g, 1.34 mmol) and the reaction mixture was stirred for 30 min at room temperature. The reaction mixture was cooled to 0 °C and $NaBH_4$ (0.038 g, 1.01 mmol) was added. The reaction mixture stirred at the same temperature for 30 min.

After completion of the reaction (TLC), it was quenched by addition of water (1 mL) and slowly warmed up to room temperature. Most of the solvent was evaporated off and the crude residue was diluted with water (10 mL) and extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with brine (10 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave the crude residue which was purified by silica gel column chromatography using petroleum ether/EtOAc (1:1) as eluent to furnish **24** (0.22 g, 88%) as a colorless oil. $[\alpha]_D^{24}$+144.3, (*c* 0.7, $CHCl_3$). IR (Neat): ν_{max} 3415, 2884, 1702, 1504 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.84-6.64 (m, 3H), 6.59 (d, *J* = 8.8 Hz, 1H), 6.02 (d, *J* = 10.0 Hz, 1H), 5.98-5.80 (m, 3H), 4.68-4.50 (m, 1H), 4.49-4.35 (m, 1H), 3.22-3.05 (m, 1H), 2.44 (s, 1H), 2.32-2.15 (m, 1H), 1.78 (q, *J* = 12.8 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 160.9, 147.6, 146.5, 135.9, 133.9, 126.3, 120.7, 108.2, 108.1, 100.9, 92.4, 67.5, 49.3, 41.0, 32.3. HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{15}H_{14}Cl_3NO_4$+Na 399.9886; Found: 399.9882.



25

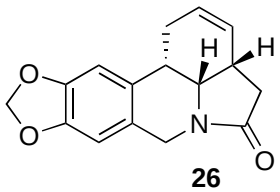
Ethyl 2-((1*S*,5*S*,6*S*)-5-(benzo[d][1,3]dioxol-5-yl)-6-(2,2,2-trichloroacetamido)cyclohex-2-en-1-yl)acetate (**25**): To a solution of the allyl alcohol **24** (0.18 g, 0.48 mmol) in toluene (5 mL) were added triethyl orthoacetate (0.45 mL, 2.4 mmol) and propionic acid (0.08 mL, 0.04 mmol). The resulting solution was heated at 150 °C in seal tube for 24 h. After completion of the reaction (TLC), most of the solvent was evaporated off and the crude obtained which was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1) as eluent to furnish **25** (0.13 g, 61%) as a colorless oil. $[\alpha]_D^{24}$+82.2 (*c* 1.05, $CHCl_3$). IR (Neat): ν_{max} 3419, 2917, 1723, 1505, 1030 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.80-6.60 (m, 4H), 6.02-5.85 (m, 3H), 5.55 (d, *J* = 9.6 Hz, 1H), 4.43 (d, *J* = 10.0 Hz, 1H), 4.22-4.05 (m, 2H), 3.30-3.15 (m, 2H), 2.52-2.35 (m, 3H), 2.29 (dd, *J* = 16.0, 8.4 Hz, 1H), 1.25 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 171.7, 161.5, 147.8, 146.5, 134.7, 127.5, 127.3, 120.2, 108.2, 107.7, 100.9, 92.9, 60.8, 52.8, 42.7, 38.0, 35.9, 26.2, 14.1. HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{19}H_{20}Cl_3NO_5$+Na 470.0305; Found: 470.0303.



5

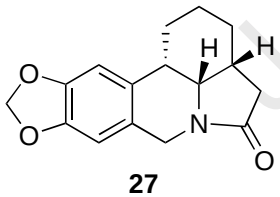
(3a*S*,7*S*,7a*S*)-7-(benzo[d][1,3]dioxol-5-yl)-1,3,3a,6,7,7a-hexahydro-2H-indol-2-one (**5**): To a stirred solution of **25** (0.02 g, 0.05 mmol) in anhydrous DMSO (2 mL) was added Cs_2CO_3 (0.05 g, 0.15 mmol) at room temperature. The reaction mixture was heated at 100 °C for 5 h. After completion of the reaction (TLC), it was allowed to cool to room temperature, cautiously quenched by addition water (5 mL) and extracted with diethyl ether (2 × 10 mL). The combined organic layers were washed with brine (5 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave the crude residue which was purified by silica gel column chromatography using petroleum ether/EtOAc (2:8) as eluent to furnish **5** (0.01 g, 83%) as a colorless oil. $[\alpha]_D^{24}$+153.1, (*c* 0.9, $CHCl_3$). IR (Neat): ν_{max} 3409, 2918, 1685, 1203 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.78 (d, *J* = 8.0 Hz, 1H), 6.73 (bs, 1H), 6.69 (d, *J* = 8.0 Hz,

1H), 5.94 (bs, 2H), 5.95-5.85 (m, 1H), 5.49 (d, *J* = 10.0 Hz, 1H), 5.32 (s, 1H), 4.05 (d, *J* = 4.4 Hz, 1H), 3.14 (bs, 1H), 2.95 (d, *J* = 10.8 Hz, 1H), 2.66 (dd, *J* = 16.8, 9.2 Hz, 1H), 2.48 (t, *J* = 14.8 Hz, 1H), 2.11 (d, *J* = 16.8 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 177.4, 148.2, 146.5, 135.9, 127.8, 126.7, 119.7, 108.6, 107.6, 101.1, 58.2, 41.1, 38.0, 35.4, 23.2. HRMS (ESI) *m/z*: $[M+Na]^+$ Calcd for $C_{15}H_{15}NO_3$+Na 280.0950; Found: 280.0948.



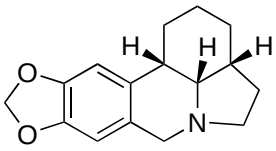
26

(3a*S*,3a1*S*,12b*S*)-3a,4,7,12b-tetrahydro-1H-[1,3]dioxolo[4,5-j]pyrrolo[3,2,1-de]phenanthridin-5(3a1H)-one (**26**): To a stirred solution of **5** (56 mg, 0.22 mmol) in dichloroethane (5 mL) were added paraformaldehyde (27 mg, 0.90 mmol) followed by TFA (0.22 mL, 2.82 mmol) dropwise at room temperature. The reaction mixture was stirred at same temperature for 30 h. After completion of the reaction (TLC), it was quenched by addition of saturated aqueous solution of $NaHCO_3$ (5 mL) and extracted with CH_2Cl_2 (2 × 25 mL). The combined organic layers were washed with brine (5 mL) and dried over anhydrous Na_2SO_4. Evaporation of the solvent gave the crude residue which was purified by silica gel column chromatography using petroleum ether/EtOAc (2:8) as eluent to furnish **26** (45 mg, 76%) as a viscous mass. $[\alpha]_D^{24}$−12.2, (*c* 1.05, $CHCl_3$). IR (KBr): ν_{max} 2908, 1670, 1483, 1429, 1213, 1033 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.61 (bs, 2H), 5.91 (d, *J* = 6.4 Hz, 2H), 5.76 (t, *J* = 9.6 Hz, 1H), 5.65-5.50 (m, 1H), 4.61 (d, *J* = 17.2 Hz, 1H), 4.28 (d, *J* = 17.6 Hz, 1H), 4.05-3.90 (m, 1H), 3.20-3.05 (bs, 1H), 2.88-2.70 (m, 2H), 2.19 (d, *J* = 17.2 Hz, 1H), 2.15-2.05 (m, 1H), 1.90-1.72 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 174.4, 146.8, 146.4, 132.0, 128.1, 125.6, 123.4, 108.3, 106.8, 101.0, 55.5, 42.9, 38.4, 37.3, 31.8, 28.1. HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{15}NO_3$+H 270.1130; Found: 270.1126.



27

(3a*R*,3a1*S*,12b*S*)-2,3,3a,4,7,12b-hexahydro-1H-[1,3]dioxolo[4,5-j]pyrrolo[3,2,1-de]phenanthridin-5(3a1H)-one (**27**): A solution of **26** (45 mg, 0.17 mmol) and 10% Pd/C (5 mg) in MeOH (8 mL) was stirred under hydrogen atmosphere for 5 h at room temperature. After completion of the reaction (TLC), most of the solvent was evaporated off and the crude obtained which was purified by silica gel column chromatography using petroleum ether/EtOAc (2:8) as eluent to furnish **27** (40 mg, 89%) as a white solid. Mp 145-150 °C $[\alpha]_D^{24}$+96.9 (*c* 0.9, $CHCl_3$), Lit[2f] $[\alpha]_D^{24}$ −96.0 (*c* 1.0, $CHCl_3$) for the enantiomer. IR (KBr): ν_{max} 2929, 1681, 1483, 1201, 1033 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.57 (d, *J* = 11.2 Hz, 2H), 5.92-5.85 (m, 2H), 4.51 (d, *J* = 17.2 Hz, 1H), 4.29 (d, *J* = 17.2 Hz, 1H), 3.80-3.68 (m, 1H), 2.85-2.68 (m, 1H), 2.55 (dd, *J* = 16.0, 6.8 Hz, 1H), 2.40 (sextet, *J* = 6.0 Hz, 1H), 2.06 (d, *J* = 16.0 Hz, 1H), 1.80-1.60 (m, 3H), 1.40-1.25 (m, 1H), 1.20-1.05 (m, 2H).^{13}C NMR (100 MHz, $CDCl_3$): δ 175.6, 146.6, 146.5, 131.5, 123.2, 108.4, 106.6, 100.9, 55.6, 42.6, 40.2, 39.8, 32.9, 30.2, 27.8, 23.5. HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{17}NO_3$+H 272.1287; Found: 272.1289.



1

γ-lycorane (1): To a stirred solution of **28** (36 mg, 0.13 mmol) in anhydrous THF (12 mL) was added $LiAlH_4$ (15 mg, 0.39 mmol) at 0 °C. The reaction mixture was heated to reflux for 20 h. After completion of the reaction (TLC), it was cooled to room temperature, cautiously quenched by addition of moist Na_2SO_4. Evaporation of the solvent gave the crude residue which was purified by silica gel column chromatography using petroleum ether/EtOAc (6:4) as eluent to furnish **1** (27 mg, 79%) as a colorless oil. $[\alpha]_D^{20}$+17.0 (*c* 0.3, EtOH), Lit[11] $[\alpha]_D^{20}$ +17.1 (*c* 0.25, EtOH). IR (Neat): ν_{max} 2924, 2854, 2778, 2626, 1481, 1233 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 6.61 (s, 1H), 6.49 (s, 1H), 5.90-5.80 (m, 2H), 4.01 (d, *J* = 14.4 Hz, 1H), 3.37 (td, *J* = 9.2, 4.0 Hz, 1H), 3.21 (d, *J* = 14.4 Hz, 1H), 2.80-2.68 (m, 1H), 2.37 (t, *J* = 4.8 Hz, 1H), 2.25-2.10 (m, 2H), 2.08-1.95 (m, 1H), 1.80-1.68 (m, 2H), 1.67-1.57 (m, 1H), 1.54-1.35 (m, 2H), 1.32-1.20 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 146.0, 145.6, 133.1, 127.3, 108.3, 106.2, 100.6, 62.9, 57.1, 53.7, 39.4, 37.3, 31.7, 30.4, 29.3, 25.2. HRMS (ESI) *m/z*: $[M+H]^+$ Calcd for $C_{16}H_{19}NO_2$+H 258.1494; Found: 258.1492. The spectral data of the synthesized lycorane were in complete agreement with that reported in the literature.[2g]

Acknowledgment

M. B. U. thanks Indian Institute of Science (IISc) Bangalore for a research fellowship.

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Total Synthesis of (+)-*γ*-Lycorane from Ethyl Lactate Using Iterative Claisen and Overman Rearrangement Reactions

Highlights of the present work:

- Total synthesis of (+)-*γ*-lycorane is accomplished from (*S*)-ethyl lactate.
- Used iterative Claisen and Overman rearrangement reactions to install the chiral centers in the tetrahydroindole moiety
- Pictet-Spengler reaction is used for the synthesis of the isoquinoline unit.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: