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Graphical Abstract

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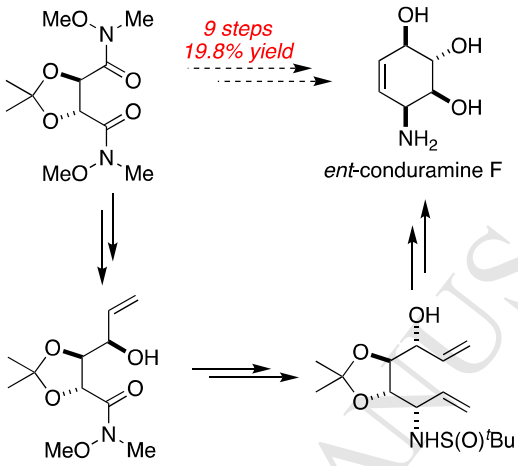
Department of Organic Chemistry, Indian Institute of Science, Bangalore 560012, INDIA



Efficient Enantiospecific Synthesis of *ent*-Conduramine F-1

Kavirayani R. Prasad* and Vipin Ashok Rangari
Department of Organic Chemistry, Indian Institute of Science, Bangalore 560012, INDIA
E-mail: prasad@iisc.ac.in; FAX: +91-80-23600529

Abstract: An efficient enantiospecific total synthesis of *ent*-conduramine F-1 (aminocyclohexenetriol) was accomplished starting from the *bis*-Weinreb amide of tartaric acid. Key reactions in the synthesis include the desymmetrization of tartaric acid amide with vinylmagnesium bromide and installation of the required amine using Ellman sulfinimine. Ring closing metathesis was used to synthesize the required alkene in the cyclohexene.

Keywords: amino cyclohexenetriols, *ent*-conduramine F-1, chiral pool, sulfinimines, total synthesis

Introduction

Aminocyclitols are important classes of compounds in medicinal chemistry. Aminocyclitol (**1**) is also a key structural unit in bio-active natural products minosaminomycin (**8**) and hygromycin A (**9**).[1] Conduramines (**3-5**), the dehydro analogues of amino cyclitols are synthetic derivatives of naturally occurring conduritols in which one of the allylic hydroxy groups is replaced with an amine. Conduramines not only exhibit interesting biological profiles, but also serve as precursors for the synthesis of aminocyclitols and the *Amaryllidaceae* alkaloids such as lycoricidine (**7**) (Fig.1).[2]

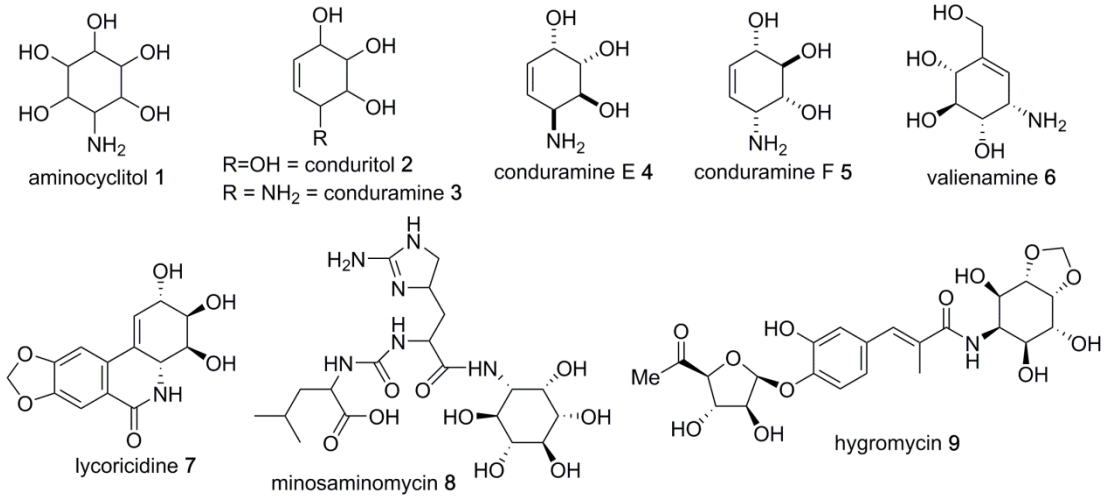
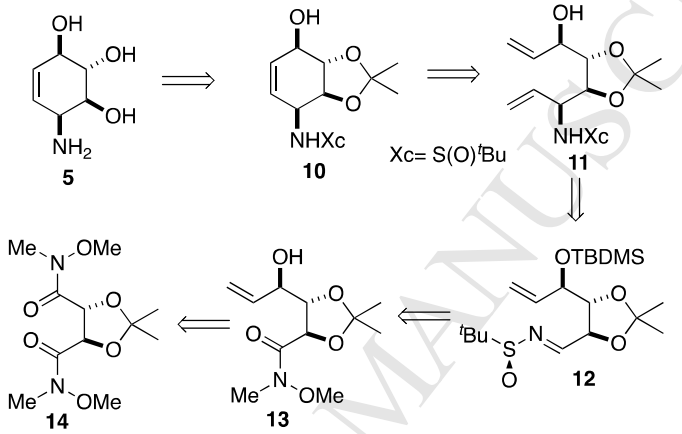


Fig.1. Aminocyclitol containing natural products and conduramines

While a number of methods were reported in literature for the synthesis of conduramines,[2] formation of the double bond of the cyclohexene by Ring Closing Metathesis (RCM) reaction is the most desirable. Of the RCM reaction used for the synthesis of conduramines, Yan's group disclosed the synthesis of tetraacetates of conduramine A and E from tartaric acid using RCM reaction and 3,3-sigmatropic rearrangement of allylic azide as the key step.[3] Rao *et. al*. disclosed the synthesis of *N*-benzyl conduramine E and F from mannitol using RCM strategy.[4] They failed to produce the conduramines by deprotection of the benzyl group instead synthesized the dihydroconduramines. Similar difficulties in the debenzylation and purification of *N*-benzyl conduramines were encountered by Vogel's group in their synthesis of conduramines.[5] Partha and Shaw disclosed a formal synthesis of both enantiomers of conduramine E using RCM,[6] however the precursor was synthesized in a multi-step sequence from the sugars galactose and mannose using Petasis reaction as the key step. Ham *et. al.* synthesized conduramine F-1 employing RCM

using their trademark chiral oxazine as the starting point.[7] We have been involved in the use of tartaric acid in the total synthesis of natural products for a decade. We have established that the γ-oxo-amides derived from tartaric acid amides serve as excellent building blocks for the synthesis of diverse oxygenated natural products. The strategy involves the desymmetrization of the Weinreb amide/ dimethyl amide derived from tartaric acid with various Grignard reagents and further transformations.[8] In continuation of our efforts, herein, we report the total synthesis of *ent*-conduramine F-1 (**5**) starting from L-tartaric acid.[9] We reasoned that *ent*-conduramine F-1 (**5**) can be accessed from the protected aminol **10**. Addition of vinylmagnesium bromide to the Weinreb amide **14** will lead to the mono keto amide, the subsequent reduction of which should form the required allylic alcohol **13**. Addition of vinyl Grignard reagent to the sulfinimine **12** obtained from the elaboration of **13** should install the amine part with requisite stereochemistry thus leading to the RCM precursor **11**. The introduction of sulfinimine not only controls the diastereoselective formation of the amine but also can easily be deprotected (Scheme-1), a problem that was encountered with the benzyl protection can be circumvented.



Scheme-1: Retrosynthesis for *ent*-conduramine F-1 (**5**)

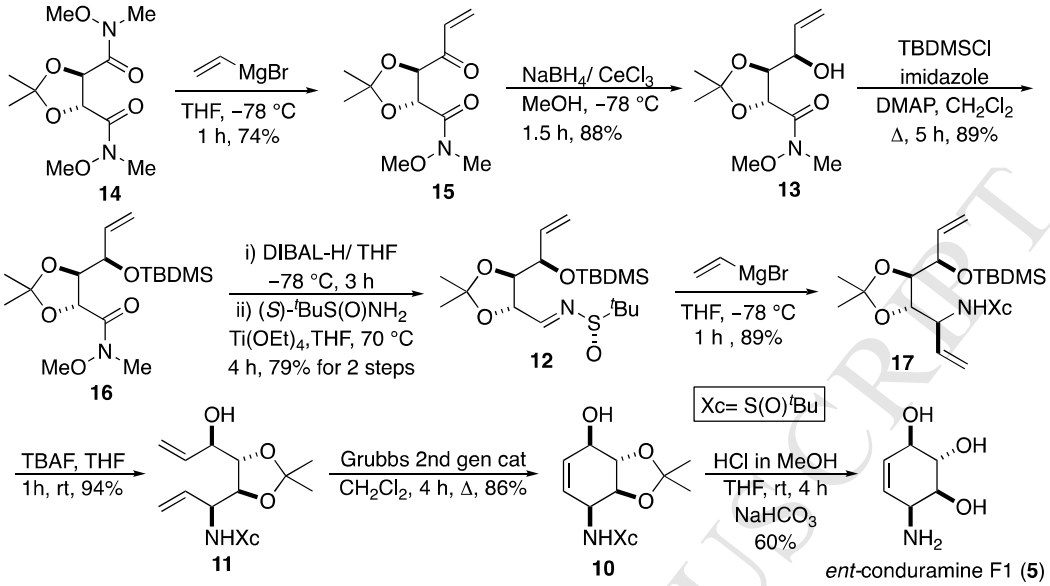
Results and Discussion

Thus, the synthetic sequence commenced with the addition of vinylmagnesium bromide to the bis-Weinreb amide **14**[10] derived from tartaric acid to afford the mono ketoamide **15** in 74% yield.[11] Stereoselective reduction of the ketone in **15** under Luche conditions furnished the alcohol **13** in 88% yield.[12] Protection of the hydroxy group in **13** as the *tert*-butyldimethylsilyl ether **16** was accomplished in 89% yield. Treatment of **16** with DIBAL-H transformed the Weinreb amide to the corresponding aldehyde, which on condensation with the (*S*)-*tert*-butylsulfinamide[13] afforded the sulfinimine **12** in 79% yield for two steps. Addition of vinylmagnesium bromide to the sulfinimine **12** yielded the sulfinamide **17** in 89% yield.[14] Interestingly, the sense of induction is not controlled by the chirality of the sulfinimine but is more influenced by the inherent tartrate moiety. Deprotection of the TBS ether in **17** furnished the diene containing amino alcohol **11** in 94% yield. Treatment of the diene **11** with Grubbs' second-generation catalyst[15] cleanly afforded the masked aminotrihydroxycyclohexene **10** in 86% yield. Deprotection of the acetonide as well as the sulfinyl group in **10** with HCl in MeOH and further neutralization with $NaHCO_3$ produced *ent*-conduramine F-1 (**5**) in 60% yield (Scheme-2). Physical and spectral characteristics of the synthesized sample is in complete agreement with that reported in the literature.[9b]

Conclusion

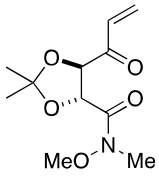
In conclusion, an efficient enantiospecific total synthesis of *ent*-conduramine F-1 (amino trihydroxycyclohexene) was accomplished from the bis-Weinreb amide of tartaric acid in 9 steps and in 19.8% overall yield. Key features of the synthesis include the formation of the cyclohexene

core by RCM reaction and stereoselective reduction of a vinyl ketone and addition of vinyl Grignard reagent to the sulfinimine derived from tartaric acid to install the required alcohol and amine stereogenic centers respectively.



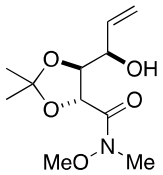
Scheme-2: Total synthesis of *ent*-conduramine F1

Experimental: General Information: 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 recorded using melting point apparatus in capillary tubes and are uncorrected. Unless stated otherwise, ^{1}H (400 MHz) and ^{13}C (100 MHz) spectra were recorded on 400 MHz spectrophotometers in $CDCl_3$ as solvent with TMS as reference. High-resolution mass spectra (HRMS) were recorded on a Q-TOF micromass spectrometer using electron spray ionization mode.

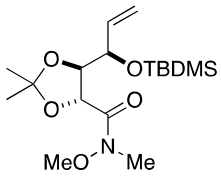


Preparation of (*4R*,*5R*)-5-acryloyl-*N*-methoxy-*N*,2,2-trimethyl-1,3-dioxolane-4-carboxamide (15): To a stirred solution of the diamide **14** (1.0 g, 3.62 mmol) in THF (20 mL) at −78 °C, under argon atmosphere was added vinylmagnesium bromide solution (14 mL of 0.35 M in THF, 4.9 mmol) dropwise for 5 min. The reaction mixture was allowed to stir for 45 min at the same temperature. After completion of the reaction (TLC), the reaction mixture was poured into a cold (0°C) solution of 1N HCl and diethyl ether (30 mL,1:1). The aqueous layer was extracted with EtOAc (2×20 mL). The combined organic layer was washed with brine (20 mL), dried over sodium sulphate and concentrated under vacuum. Purification of the residue thus obtained on silica gel column chromatography using EtOAc:Hexane (3:7) as eluent yielded the compound **15** (0.65g, 74%) as colourless oil. Rf (1:1, EtOAc:Hexane) 0.6; $[\alpha]_D^{24}$ +2.40 (*c* 1.5, $CHCl_3$); IR (Neat) 2987, 1671, 1607, 1379 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.74 (dd, *J* = 17.6 Hz, 10.8 Hz, 1H), 6.47 (dd, *J* = 17.6 Hz, 1.2 Hz, 1 H), 5.92 (dd, *J* = 10.8 Hz, 1.2 Hz,1 H), 5.16 (d, *J* = 4.4 Hz, 1H), 5.04 (d, *J* = 4.8 Hz, 1H), 3.71 (s, 3 H), 3.24 (bs, 3H), 1.53 (s, 3H), 1.43 (s, 3H);^{13}C NMR (100 MHz, $CDCl_3$) δ 196.5, 169.9, 132.2, 130.9,

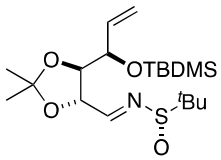
113.0, 81.1, 74.2, 61.6, 32.5, 26.6, 26.3. HRMS (ESI) $[M+Na]^+$ found: 266.1005. $C_{11}H_{17}NO_5Na$ requires 266.1004.



Preparation of (*4R,5S*)-5-((R)-1-hydroxyallyl)-*N*-methoxy-*N*,2,2-trimethyl-1,3-dioxolane-4-carboxamide (13): To a stirred solution of the amide **15** (0.63 g, 2.6 mmol) in MeOH (20 mL) at −78 °C, was added a pre-mixed suspension of $CeCl_3.7H_2O$ (3.67 g, 9.82 mmol) and $NaBH_4$ (0.325 g, 8.85 mmol) in MeOH (10 mL) dropwise for 10 min. The reaction mixture was allowed to stir for 1.5 h at the same temperature. After completion of the reaction (TLC), most of the solvent was evaporated off. The residue thus obtained was dissolved in H_2O (20mL) and was extracted with EtOAc (2×20 mL). The combined organic layer was washed with brine (20 mL), dried over Na_2SO_4.and concentrated. Purification of the residue obtained on silica gel column chromatography using EtOAc:Hexane (1:1) as eluent yielded the compound **13** (0.56 g, 88%) as colourless oil with 99:1 *dr*. Rf (1:1, EtOAc:Hexane) 0.5; $[\alpha]_D^{24}$ +2.36 (*c* 1.1, $CHCl_3$); IR (Neat) 3446, 2987, 2934, 1600 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.93 (ddd, *J* = 17.2 Hz, 10.8 Hz, 5.6 Hz, 1H), 5.48 (d, *J* = 17.2 Hz, 1 H), 5.26 (d, *J* = 10.4 Hz, 1 H), 4.76 (bs, 1H), 4.50 (bs, 1H), 4.24 (bs, 1H), 3.75 (s, 3H), 3.24 (bs, 3H), 2.45 (bs, 1H), 1.50 (s, 3H), 1.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.2, 136.8, 116.8, 111.4, 80.5, 73.7, 71.8, 61.7, 32.4, 27.0, 26.1. HRMS (ESI) $[M+Na]^+$ found 268.1159. $C_{11}H_{19}NO_5Na$ requires 268.1161.

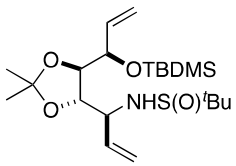


Preparation of (*4R,5R*)-5-((*R*)-1-((tert-butyldimethylsilyl)oxy)allyl)-*N*-methoxy-*N*,2,2-trimethyl-1,3-dioxolane-4-carboxamide (16): To a stirred solution of the alcohol **13** (0.26 g, 1.06 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added TBSCl (0.47 g, 3.1 mmol), imidazole (0.37 g. 5.45 mmol), and DMAP (0.013 g, 0.11 mmol) successively. The reaction mixture was heated to reflux for 5 h. After completion of the reaction (TLC), the reaction mixture was diluted with EtOAc (20 mL) and was poured into water (20 mL). The organic layer was separated, and the aqueous layer was extracted with EtOAc (2×10 mL). The combined organic layer was washed with sat. solution of brine (10 mL) and dried over sodium sulphate. Evaporation of the solvent gave crude residue which was purified by silica gel column chromatography using EtOAc:Hexane (1:9) as eluent to yield the compound **16** (0.34 g, 89%) as colourless oil. Rf (2:8, EtOAc:Hexane) 0.6; $[\alpha]_D^{24}$ +7.58 (*c* 1.3, $CHCl_3$); IR (Neat) 2993, 1672, 1466, 1254 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.97 (ddd, *J* = 17.2 Hz, 10.8 Hz, 5.2 Hz, 1H), 5.33 (dd, *J* = 17.2 Hz, 1.6 Hz, 1 H), 5.23 (dd, *J* = 10.8 Hz, 1.2 Hz, 1 H), 4.70 (s, 1H), 4.60 (s, 1H), 4.41 (d, *J* = 4.8 Hz, 1H), 3.72 (s, 3H), 3.20 (bs, 3H), 1.44 (s, 6H), 0.87 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$).δ 170.3, 136.5, 116.4, 111.4, 80.3, 72.5, 72.2, 61.7, 32.2, 27.0, 26.3, 25.7 (3C), 18.2, −4.8, −5.1. HRMS (ESI) $[M+Na]^+$ found 382.2023. $C_{17}H_{33}NO_5SiNa$ requires 382.2026.

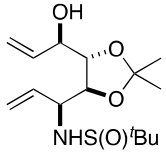


Preparation of (*E*)-*N*-(*tert*-butyl(λ^1-oxidanyl)-λ^3-sulfanyl)-1-((*4S,5R*)-5-((*R*)-1-((tert-butyldimethylsilyl)oxy)allyl)-2,2-dimethyl-1,3-dioxolan-4-yl)methanimine (12): To a stirred

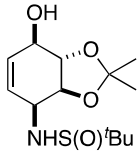
solution of the amide **16** (0.8 g. 2.22 mmol) in THF (20 mL) at –78 °C, was added DIBAL-H (7.3 mL of 1M, 7.23 mmol). The reaction mixture was stirred for 1 h at the same temperature. After completion of the reaction, (TLC), the reaction mixture was diluted with Et_2O (10 mL) and saturated aqueous solution of potassium sodium tartrate (10 mL) was added. The reaction mixture was stirred vigorously at rt for 1.5 h. The organic layer was separated and the aqueous layer was extracted with EtOAc (2×20 mL). The combined organic layer was washed with sat. solution of brine (10 mL), and was dried over sodium sulphate. The crude aldehyde obtained after evaporation of the solvent was used in the next step without further purification. The crude aldehyde obtained above was dissolved in THF (20 mL), and *(S)-ter*t-butanesulfinamide (0.385 g, 3.17 mmol), $Ti(OEt)_4$ (1 mL, 4.88 mmol) were added successively. The reaction mixture was refluxed for 4h. After completion of the reaction (TLC), sat. solution of brine (5 mL) was added, and stirred vigorously at rt for 15 min. The resulting solid cake filtered through a short pad of celite. The crude residue obtained after evaporation of solvent was purified by silica gel column chromatography using EtOAc:Hexane (1:9) as eluent to yield the compound **12** (0.71 g, 79% for 2 steps) as a colourless oil. Rf (1:9, EtOAc:Hexane) 0.6; $[\alpha]_D^{24}$ +126.4 (*c* 1.1, $CHCl_3$); IR (Neat) 2955, 2858, 1741, 1622 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 4.0 Hz, 1H), 5.93 (ddd, *J* =16.8 Hz, 10.4 Hz, 5.6 Hz, 1H), 5.31 (d, *J* = 17.2 Hz, 1H), 5.22 (d, *J* = 10.8 Hz, 1H), 4.71 (dd, *J* =6.8 Hz, 4.0 Hz, 1H), 4.31 (t, *J* =5.2 Hz, 1H), 4.11 (dd, *J* = 6.8 Hz, 4.4 Hz, 1H), 1.47 (s, 3H), 1.38 (s, 3H), 1.21 (s, 9H), 0.90 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$).δ: 168.2, 136.8, 116.9, 111.1, 82.4, 78.0, 73.1, 57.1, 26.7, 26.6, 25.8 (3C), 22.4 (3C), 18.3, –4.5, –4.9. HRMS(ESI) $[M+Na]^+$ found 426.2109. $C_{19}H_{37}NO_4SSiNa$ requires 426.2110.



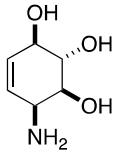
Preparation of 1-*tert*-butyl-*N*-((*S*)-1-((*4S,5R*)-5-((*R*)-1-((*tert*-butyldimethylsilyl)oxy)allyl)-2,2-dimethyl-1,3-dioxolan-4-yl)allyl)-1-(λ ^{1}-oxidanyl)- λ ^{3}-sulfanamine (17): To a stirred solution of the imine **12** (0.07 g, 0.17 mmol) in THF (5 mL) at –78 °C, under argon atmosphere was added dropwise a solution of vinylmagnesium bromide (0.2 M solution in THF, 1.5 mL, 0.3 mmol). The resulting reaction mixture was stirred at the same temperature for 45 min. After completion of the reaction (TLC), the reaction mixture was cautiously quenched by addition of aqueous solution of NH_4Cl and was slowly warmed upto room temperature. The reaction mixture was extracted with EtOAc (2×10 mL). Combined organic layer was washed with brine (5 mL) and dried over sodium sulphate. Residue obtained after evaporation of the solvent was purified by silica gel chromatography using EtOAc:Hexane (1:1) as eluent to yield the compound **17** (0.065 g, 89%) with 99:1 *dr.* Rf (1:1, EtOAc:Hexane) 0.4; $[\alpha]_D^{24}$ +28.0 (*c* 1.2, $CHCl_3$); IR (Neat) 3308, 2931,1591, 1251 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.91 (ddd, *J* = 17.2 Hz, 10.4 Hz, 6.4 Hz, 1H), 5.76 (ddd, *J* = 17.2 Hz, 10.4 Hz, 8.4 Hz, 1H), 5.40–5.18 (m, 4H), 4.28–4.17(m, 2H), 4.10 (quint, *J* = 4.4 Hz, 1H) 3.91 (d, *J* = 8 Hz, 4 Hz, 1H), 3.81 (d, *J* = 4.4 Hz, 1H) 1.38 (s, 6H), 1.22 (s, 9H), 0.91 (s, 9H), 0.06 (s, 3H), 0.05 (s, 3H), ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.2, 134.0, 119.8, 116.8, 109.8, 80.2, 79.2, 74.0, 58.8, 55.8, 27.3, 27.0, 25.9 (3C), 22.6 (3C), 18.3, –4.5, –4.8. HRMS (ESI) $[M+Na]^+$ found 454.2424. $C_{21}H_{41}NO_4SSiNa$ requires 454.2423.



Preparation of (*R*)-1-((*4S,5S*)-5-((*S*)-1-((*tert*-butyl(λ ^{1}-oxidanyl)- λ ^{3}-sulfanyl)amino)allyl)-2,2-dimethyl-1,3-dioxolan-4-yl)prop-2-en-1-ol (11): To a stirred solution of compound **17** (0.06 g, 0.15 mmol) in THF (3 mL) at 0 °C, under argon atmosphere was added TBAF in THF (1.0 M in THF, 0.2 mL, 0.19 mmol). The reaction mixture was stirred at room temperature for 45 min. After completion of the reaction (TLC), it was concentrated under vacuum and the residue thus obtained was purified by silica gel chromatography using EtOAc as eluent to yield **11** (0.041g, 93%) as colourless oil. Rf (9:1, EtOAc:Hexane) 0.4; $[\alpha]_D^{24}$: +58.4 (*c* 0.75, $CHCl_3$); IR (Neat): 3462, 3437, 1592, 1219cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.92 (ddd, *J* = 16.8 Hz, 10.4 Hz, 5.2 Hz, 1H), 5.76 (ddd, *J* = 17.2 Hz, 10.4 Hz, 6.8 Hz, 1H), 5.47 – 5.22 (m, 4H), 4.33 (bs, 1H), 4.17 (d, *J* = 4.0 Hz, 1H) 4.12 (dd, *J* = 6.8 Hz, 4.0 Hz, 1H), 4.04–3.91 (m, 2 H) 1.41 (s, 6H), 1.23 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.9, 135.2 , 119.1, 117.1, 109.6, 80.5, 79.0, 71.5, 60.0, 56.0, 27.1, 27.0, 22.7 (3C). HRMS (ESI) $[M+Na]^+$ found 340.1556. $C_{15}H_{27}NO_4SNa$ requires 340.1558.



Preparation of (3a*S*,4*R*,7*S*,7a*S*)-7-((*tert*-butyl(λ^{1}-oxidanyl)- λ ^{3}-sulfanyl)amino)-2,2-dimethyl-3a,4,7,7a-tetrahydrobenzo[d][1,3]dioxol-4-ol (10): To a stirred solution of compound **11** (0.04 g, 0.12 mmol) in CH_2Cl_2 (6 mL) under argon atmosphere was added Grubbs'-2nd gen. catalyst (5 mg, 0.006 mmol). The resulting solution was heated to reflux for 3 h. After completion of the reaction (TLC), most of the solvent was evaporated and the crude residue thus obtained was purified by silica gel column chromatography using EtOAc:MeOH (95:5) as eluent to yield the compound **10** (0.031g, 86%) Rf (9:1, EtOAc: MeOH) 0.6; IR (Neat) 3583, 3449, 2926, 1586 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.99 (dd, *J* = 10.0 Hz, 4.8 Hz, 1H), 5. 90–5.75 (m, 1H), 4.40 (d, *J* = 8.0 Hz, 1H), 4.28 (s, 1H), 3.95–3.75 (m, 2H), 3.61 (dd, *J* = 9.6 Hz, 4.4 Hz,1 H), 2.75 (s, 1H), 1.47 (s, 3H), 1.44 (s, 3H), 1.21 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 133.9, 125.9, 111.0, 76.7, 75.8, 71.4, 56.0, 48.9, 27.1, 26.6, 22.5 (3C). HRMS (ESI) $[M+Na]^+$ found 312.1247. $C_{13}H_{23}NO_4SNa$ requires 312.1245.



Preparation of (1*S*,2*S*,3*R*,6*S*)-6-aminocyclohex-4-ene-1,2,3-triol [(+)-*ent*-conduramine F-1] (5): To a stirred solution of compound **10** (0.020 g, 0.069 mmol) in THF (2 mL) was added a saturated solution of HCl in MeOH (1mL) at 0 °C and was stirred for 2 h at room temperature. The reaction mixture was quenched with sat. solution of $NaHCO_3$ and concentrated. The crude residue thus obtained was purified by silica gel column chromatography using CH_2Cl_2:MeOH (1:1) to yield (+)-*ent*-conduramine F-1 **(5)** (6 mg) in 60% yield) Rf (1:1, MeOH:CH_2Cl_2) 0.1: $[\alpha]_D^{24}$ +50.0 (*c* 0.2, MeOH) [lit[9b] +50.8 (*c* 1.3, MeOH)], IR (Neat): 3178, 2924, 1483, 1240, cm^{-1}; ^{1}H NMR (400 MHz, CD_3OD) δ 5.76 (dd, *J* = 8.4, Hz, 4.8 Hz, 1H), 5.68–5.58 (m, 1H) 3.92 (bs, 1H), 3.51–3.46 (m, 2H), 3.38 (bs, 1H), ^{13}C NMR (100 MHz, CD_3OD) δ 132.5, 129.2 ,73.7 (2C), 71.9, 51.5. HRMS (ESI) $[M+H]^+$ found 146.0820. $C_6H_{11}NO_3$+H requires 146.0817.

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