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PAPER

Antituberculosis agent diaportheone B: synthesis, absolute configuration assignment, and anti-TB activity of its analogues†

Pandrangi Siva Swaroop,[a] Gajanan N. Raut,[a] Rajesh G. Gonnade,[b] Priyanka Verma,[c] Rajesh S. Gokhale[c,d] and D. Srinivasa Reddy*[a]

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First synthesis of diaportheone B, an antituberculosis agent isolated from endophytic fungus *Diaporthe sp.* P133 is reported using two complementary routes, a one step and a three-step sequence. The absolute configuration of diaportheone B was determined by using X-ray crystal structure analysis of its dibromo derivative. In addition, we have prepared several close analogues of diaportheone B and determined their anti-TB potential using Alamar-blue assay ($H_{37}Rv$).

Introduction

With the increased need for ways to fight against multidrug-resistant tuberculosis (TB), there is an urgent need for novel antimicrobials due to the emergence of organisms that are resistant to existing antimicrobials.[1] Natural products isolated from various sources have been providing novel chemotypes for medicinal chemists as lead compounds for the development of new drugs.[2] Along these lines, very recently, a group from Philippines reported two benzopyranones, diaportheone A (**1**) and B (**2**) using bioassay-guided isolation of the secondary metabolites from the endophytic fungus *Diaporthe sp.* P133.[3] The structures and relative stereochemistry of these compounds were determined by the authors with the help of NMR spectroscopy (Fig. 1). However, the absolute configuration was not determined by them. Both the diaportheones A and B showed antituberculosis activity against the virulent strain of *Mycobacterium tuberculosis* $H_{37}Rv$ with MICs of 101 μM and 3.5 μM, respectively. The diaportheone B is a good starting point for a medicinal chemistry program as it is only 14-fold less potent than marketed TB-drug rifampin (MIC 0.25 μM) and is structurally a more simple molecule. In addition, compound **2** has a low molecular weight (220) and *c*log*P* value (1.38) which are perfect for medicinal chemists during lead optimization to develop a druggable candidate following the Lipinski rule of five (Fig. 2).[4,5] Hence, we decided to synthesize and determine the absolute configuration of the natural product diaportheone B (**2**) followed by the preparation of close analogues of this attractive target to evaluate their anti-TB potential. The synthesis planning, optimization of conditions, execution, analogue synthesis, and biological activity are described in this paper.

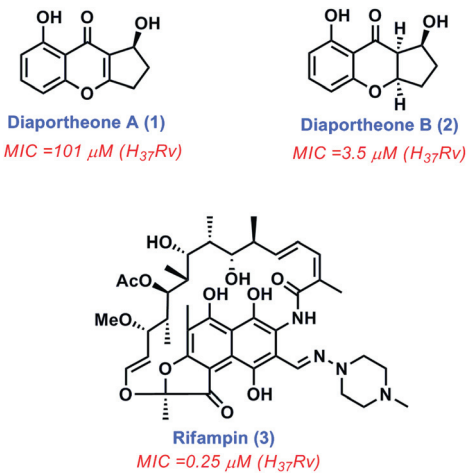


Fig. 1 Structures and activity of diaportheones and rifampin.

Results and discussion

Retrosynthetically, we planned the target molecule **2** using a single domino-reaction sequence with the help of an organocatalyst starting from commercially available 2,6-dihydroxyacetophenone **4** and succinaldehyde **5**. A plausible rationale for the

[a]*Division of Organic Chemistry, CSIR-National Chemical Laboratory, Dr. Homi Bhabha Road, Pune, 411008, India. E-mail: ds.reddy@ncl.res.in; Fax: +91 20 25902629; Tel: +91 20 25902445*
[b]*Center for Material Characterization, CSIR-National Chemical Laboratory, Dr. Homi Bhabha Road, Pune, 411008, India*
[c]*National Institute of Immunology, New Delhi 110 067, India*
[d]*CSIR-Institute of Genomics and Integrative Biology, Delhi 110 007, India*

†Electronic supplementary information (ESI) available: Optimization tables, ^1H and ^{13}C NMR data comparison table for the natural product diaportheone B, copies of spectra for all the new compounds, selected HPLC chromatograms, details of X-ray crystal structure analysis, and CIF files for three X-ray crystal structures of compounds. CCDC 859789–859791. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob25831e

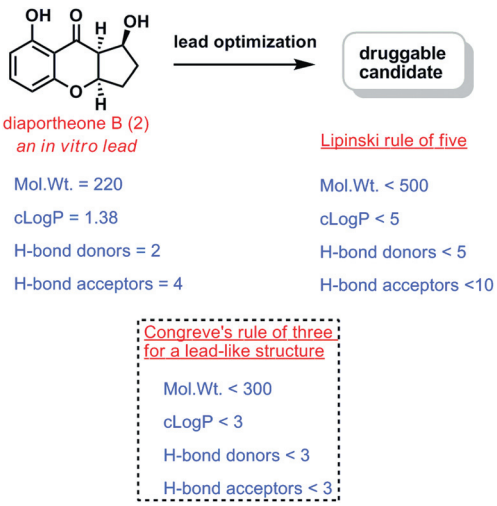
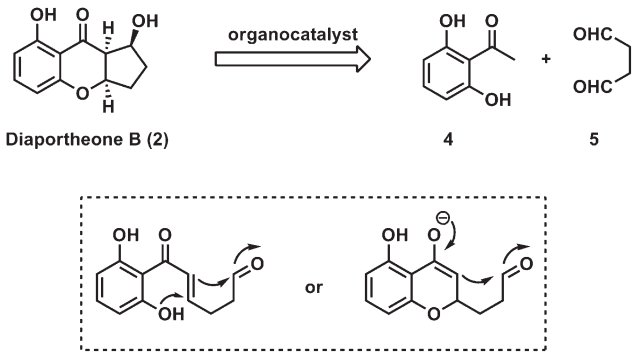
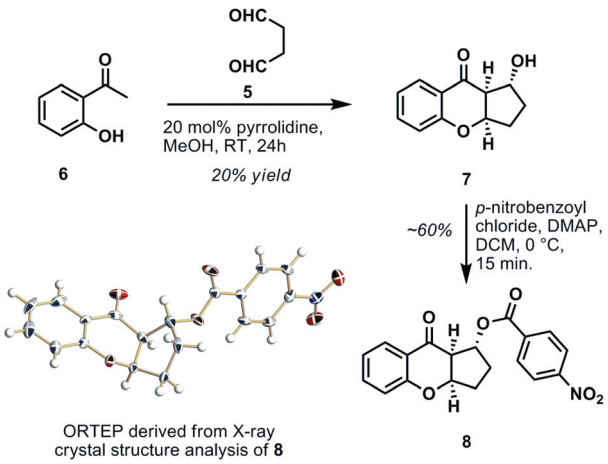


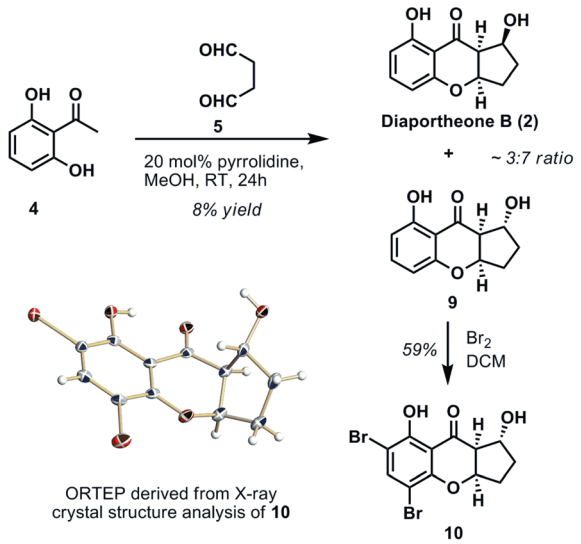
Fig. 2 Diaportheone B is an "*ideal in vitro lead*" for optimization.



Scheme 1 A plausible rationale for the planned transformation.



Scheme 2 Initial attempt of cascade-reaction approach.



Scheme 3 Cascade-reaction approach to diaportheone B.

desired transformation is shown in Scheme 1. Ultimately, our goal was to use a chiral organocatalyst to access enantiopure material of natural product **2** and its analogues.

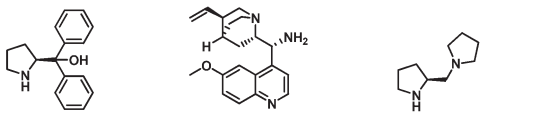
Initially, we attempted the reaction on *o*-hydroxyacetophenone **6** with succinaldehyde **5** in the presence of 20 mol% of pyrrolidine to obtain the desired tricyclic core structure. In this reaction, the compound **7** was obtained as the major product along with trace amounts of its epimer.[6,7] To determine the relative stereochemistry of the three newly formed chiral centers, we converted compound **7** to its corresponding *p*-nitrobenzoyl ester **8** as shown in Scheme 2. The stereochemistry was unambiguously proved with the help of X-ray crystal structure analysis of **8**. Although we tried a few attempts[8] with no significant improvements at this stage, we thought of putting more effort into the actual substrate which can deliver the target natural product diaportheone B. Having seen a positive result using *o*-hydroxyacetophenone **6**, we reacted the 2,6-dihydroxyacetophenone **4** with **5** under similar conditions to furnish the natural product diaportheone B (**2**) along with its epimer **9**. The spectral data of the synthetic diaportheone B (**2**) is identical with that of the natural one in all respects.[3] The relative stereochemistry of compound **9** was proved with the help of X-ray crystal structure analysis of its dibromo derivative **10** as shown in Scheme 3. Selected efforts to improve the yield and selectivity of the reaction to favour the natural product are compiled in Table 1. Unfortunately, all efforts (changing base, solvent, temperature *etc.*) were in vain.[8] The chiral organocatalysts (entries 5–11) also did not produce positive results. We suspected instability/polymerization associated with the succinaldehyde under the reaction conditions and attempted a few efforts to address this but were not successful.[9]

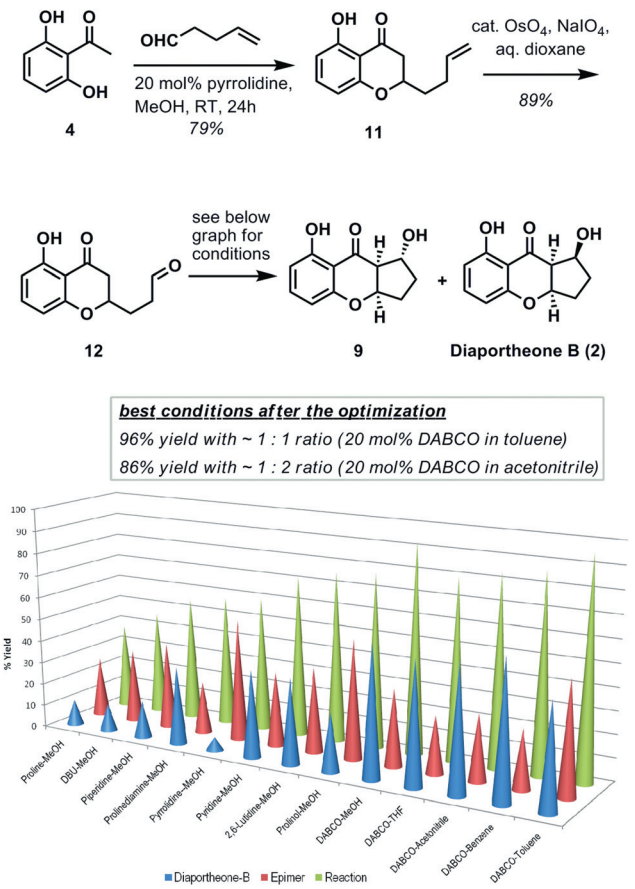
Although we could achieve the first synthesis of diaportheone B (**2**) using a one-step procedure with bench-top chemicals (Scheme 3), we were still interested in improving the yield of natural product **2** by following an alternate route. We carried out the synthesis of **2** and its diastereomer **9** as described in Scheme 4. The reaction of dihydroxyacetophenone **4** with 4-pentenal in the presence of pyrrolidine (20 mol%) resulted in benzopyranone **11** in 79% yield. Olefin cleavage to produce aldehyde **12** followed by exposure to 20 mol% of pyrrolidine furnished the compounds **9** and **2** in ~9 : 1 ratio. To improve the yield and ratio to favour the natural product, we explored various conditions by changing the base, solvent, *etc.* which are summarized as a graphical representation in Scheme 4 and the details are

Table 1 Selected conditions for cascade-reaction optimization

Entry	Base/acid	Solvent	Time (h)	Temp (°C)	Observation[a]
1	Pyrrolidine	MeOH	24	50	~3 : 7 ratio
2	KOH	DMSO	24	50	Complex mixture
3	NaOEt	EtOH	24	50	No desired Product
4	Amberlyst15	MeOH	24	50	No desired Product
5	CSA	MeOH	24	50	No desired Product
6	Proline	MeOH	24	25	Complex mixture
7	Base-1[b]	MeOH	24	25	Complex mixture
8	Base-2[b]	ACN	48	25	No desired Product
9	Base-2	DMSO	48	25	No desired Product
10	Base-3[b]	ACN	24	25	No desired Product
11	Base-3	DMSO	48	25	No desired Product

[a] Observations were made using TLC. [b] Structures of the bases.





Scheme 4 Synthesis of diaportheone B using a three-step method and optimization during the final aldol reaction.

shown in Table 2. After the optimization, we found that 20 mol % of DABCO in acetonitrile resulted in a higher ratio (~1 : 2) favouring diaportheone **2** and that 20 mol% of DABCO in toluene furnished the highest yield (96%) of the reaction. Also, we made a few unsuccessful attempts to convert the epimer **9** to the natural product diaportheone **2** which mostly resulted in eliminated product **15**.

As part of our goal to establish the absolute configuration of the natural diaportheone (+)-isomer, we decided to separate both the enantiomers of racemic diaportheone **2**. After few attempts, we were successful in separating all the four possible stereoisomers from **2** (**2** plus *ent*-**2**) and its epimer **9** (**9** plus *ent*-**9**) using chiral HPLC.[10] The natural enantiomer **(+)-2** was converted to its dibromo derivative **13**. The absolute configuration of **(+)-2** was determined by single-crystal X-ray diffraction analysis[10,11] of **13** as (*1S,3aR,9aS*)-*1,8-dihydroxy-1,2,3,3a tetrahydro-cyclopenta*[*b*]*chromen-9(9aH)-one* (Scheme 5). As the diaportheone A (**1**) is closely related to compound **2** and isolated from same species, we presume the absolute configuration of diaportheone A **1** as shown in Fig. 1 ((*S*)-*1,8-dihydroxy-2,3-dihydrocyclopenta*[*b*]*chromen-9(1H)-one*).

Analogue synthesis

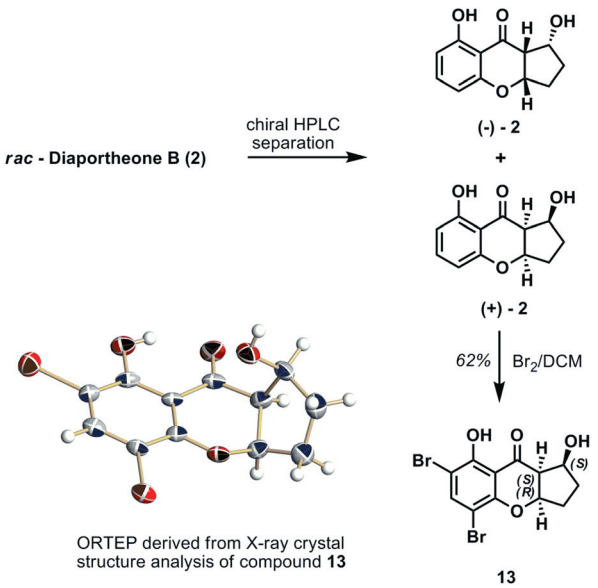
Having developed methods to the ready access of natural product **2** and its epimer **9**, we were interested in synthesis of their close analogues to evaluate their antituberculosis potential. The synthesis of the dehydro analogues **15** and **16** was accomplished using 20 mol% pyrrolidine in toluene at 80 °C for 3 h. This transformation can also be achieved by conducting the reaction in MeOH for prolonged time (Scheme 6).

To incorporate a substitution on the 5-membered ring, olefins **11** and **17** were subjected to Wacker oxidation to produce the corresponding methylketones **18** and **19**, respectively. Cyclization of **18** and **19** using pyrrolidine in toluene resulted in the desired analogues **20** and **21** in good yields. Allylic oxidation (SeO_2) of the methyl groups on **20** and **21** resulted in the corresponding aldehydes **22** and **23**. Methoxy analogues **24** and **25** were synthesized by treating phenols **15** and **20** with potassium carbonate–methyl iodide in acetone (Scheme 7).

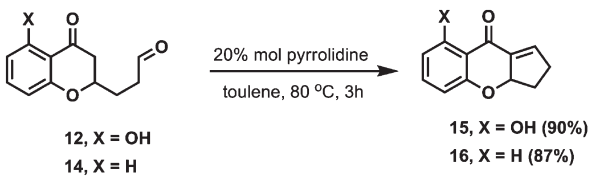
Table 2 Conditions used for aldol-reaction optimization[a]

Base	Solvent	Yield[b] %	Ratio of **9** : **2**	Base	Solvent	Yield[b] %	Ratio of **9** : **s2**
Proline	MeOH	38	70 : 30	Prolinol	MeOH	79	67 : 33
DBU	MeOH	46	73 : 27	DABCO	MeOH	93	37 : 63
Piperidine	MeOH	55	70 : 30	DABCO	THF	80	32 : 68
Base-3	MeOH	58	40 : 60	DABCO	ACN	86	34 : 66
Pyrrolidine	MeOH	60	90 : 10	DABCO	Benzene	87	30 : 70
Pyridine	MeOH	72	46 : 54	DABCO	MeOH	93	37 : 63
2,6-Lutidine	MeOH	76	50 : 50	DABCO	Toluene	96	52 : 48

[a] All the above reactions were conducted at 25 °C. [b] Based on recovered starting material.



Scheme 5 Determination of absolute stereochemistry.

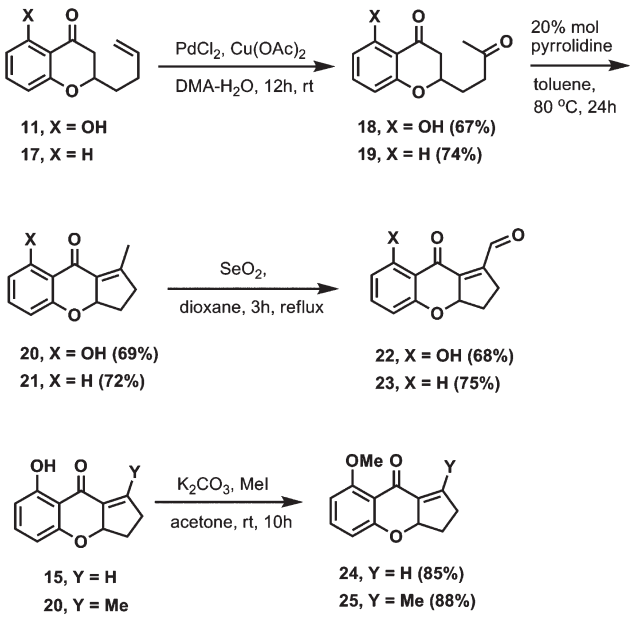


Scheme 6 Synthesis of dehydro analogues.

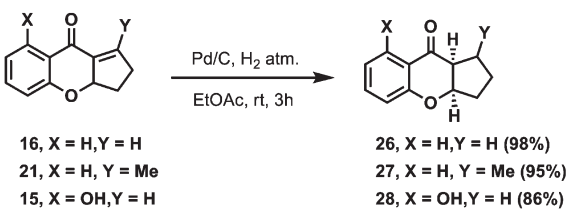
Hydrogenation of the double bond present in compounds **16**, **21**, and **15** using 10% Pd/C under a hydrogen atmosphere (using balloon pressure) produced the corresponding saturated analogues **26**, **27**, and **28** in good yields, respectively (Scheme 8).

Biological activity

The natural product diaportheone B (**2**), its isomers, and all other synthesized analogues of **2** were tested for antitubercular activity through inhibition of growth of the virulent strain of *Mycobacterium tuberculosis* $H_{37}Rv$ using the Alamar-blue assay method. The results are compiled in Table 3. The natural isomer **(+)-2**, its enantiomer **(−)-2**, and ***rac*-2** showed very similar activity (10–12.5 μg ml^{-1}).[12] Out of all the tested analogues, methoxy



Scheme 7 Synthesis of substituted analogues.



Scheme 8 Hydrogenation of unsaturated analogues.

Table 3 Anti-TB activity[a] of synthesized compounds

Compound	MIC[b] (μg ml^{-1})	Compound	MIC[b] (μg ml^{-1})	Compound	MIC (μg ml^{-1})
rac-2	12.5	**13**	25	**24**	6.25
(+)-2	10	**15**	12.5	**25**	>200
(−)-2	12.5	**16**	25	**26**	>200
***rac*-9**	12.5	**20**	50	**27**	>200
(+) 9	25	**21**	100	**28**	>200
(−) 9	25	**22**	200		
7	50	**23**	100		

[a] Through inhibition of *Mycobacterium tuberculosis* $H_{37}Rv$ growth. [b] Minimum inhibitory concentration (90%).

analogue **24** showed superior activity compared to diaportheone B, **2**. Based on limited SAR on its anti-TB activity, this novel scaffold seems promising, with potential that needs further systematic exploration with a larger number of compounds.

Conclusions

In short, we have disclosed a first and short synthesis of antituberculosis agent diaportheone B (**2**) following two complementary methods starting from bench-top chemicals. We have determined the absolute configuration of the natural isomer through X-ray crystal structure analysis of its dibromo derivative **13**. We have initiated a medchem program on this scaffold to understand structure–activity relationships (SARs) with respect to their anti-TB potential and to identify the exact mechanism of action/target. Along these lines, we have synthesized several close analogues of diaportheone B and screened for their antitubercular activity. Although, we did not see significant improvement in potency, we did observe similar activity with some of the analogues suggesting that this new chemotype can be explored further towards the development of novel and better antituberculosis agents.

Experimental

General

All reactions were carried out in oven-dried glassware under a positive pressure of argon or nitrogen unless otherwise mentioned with magnetic stirring. Air sensitive reagents and solutions were transferred *via* syringe or cannula and were introduced to the apparatus *via* rubber septa. All reagents, starting materials, and solvents were obtained from commercial suppliers and used as such without further purification. Reactions were monitored by thin layer chromatography (TLC) with 0.25 mm pre-coated silica gel plates (60 F_{254}). Visualization was accomplished with either UV light, or by immersion in an ethanolic solution of phosphomolybdic acid (PMA), Para anisaldehyde stain or, $KMnO_4$ followed by heating with a heat gun for ~15 s. Column chromatography was performed on silica gel (100–200 or 230–400 mesh size). Deuterated solvents for NMR spectroscopic analyses were used as received. All ^1H NMR and ^{13}C NMR spectra were obtained using a 200 MHz, 400 MHz, or 500 MHz spectrometer. Coupling constants were measured in Hertz. All chemical shifts were quoted in ppm, relative to $CDCl_3$, using the residual solvent peak as a reference standard. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. HRMS Mass spectra were recorded on MALDI-TOF using 2,5-dihydroxybenzoic acid as the solid matrix. Infrared (IR) spectra were recorded on a FT-IR spectrometer as a thin film. Optical rotation values were recorded on polarimeter at 589 nm. Chemical nomenclature was generated using ChemDraw. Melting points of solids were measured in melting point apparatus. HPLC was carried out on standard HPLC system and the data was processed by using appropriate software.

General procedure for tandem aldol reaction

To a mixture of succinaldehyde (**5**) (2 mmol) and hydroxy acetophenone (1 mmol) in dry methanol (4 mL), was added a catalytic amount of pyrrolidine (0.2 mmol) dropwise at room temperature. The reaction mixture was warmed to 50 °C and stirring continued for 24 h. Methanol from the reaction mixture was removed under vacuum and the crude mixture was diluted with ethyl acetate (10 mL) and water (10 mL). The aqueous layer was extracted with ethyl acetate (1 × 10 mL) and the combined organic extracts were washed with 1 N HCl (1 × 2 mL), water (1 × 5 mL), brine (1 × 2 mL), dried over Na_2SO_4, and concentrated to a crude mixture which was further purified by flash column chromatography (230–400 mesh) by using ethyl acetate–pet ether to afford pure compound along with the recovery of unreacted acetophenone.

(1*R**,3a*R**,9a*S**)-1-Hydroxy-1,2,3,3a-tetrahydrocyclopenta[*b*]-chromen-9(9a*H*)-one (7))

Prepared from *o*-hydroxy acetophenone (200 mg, 1.47 mmol), succinaldehyde (**5**) (252 mg, 2.94 mmol), pyrrolidine (0.02 mL, 0.29 mmol) by following the general procedure described above, yielding **7** (60 mg, 20%) as colorless solid. M.p. 58–60 °C; IR ν_{max} (film): cm^{-1} 3684, 3611, 3020, 1677, 1607, 1464; ^1H NMR (400 MHz, $CDCl_3$): δ 7.88 (1H, dd, J = 7.8, 1.7 Hz), 7.47 (1H, m), 7.00 (1H, t, J = 7.8 Hz), 6.91 (1H, d, J = 8.3 Hz), 5.02 (1H, td, J = 5.1, 1.9 Hz), 4.59 (1H, m), 2.73 (1H, dd, J = 7.6, 5.0 Hz), 2.43–2.31 (1H, m), 2.30–2.22 (1H, m), 2.15–2.08 (1H, m), 1.82–1.73 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 193.3, 160.7, 136.4, 126.9, 121.5, 119.5, 118.2, 81.8, 75.1, 59.0, 31.8, 30.3; HRMS calculated for $C_{12}H_{12}O_3$, $[M + Na]^+$: 227.0683 found 227.0694.

(1*R**,3a*R**,9a*R**)-9-Oxo-1,2,3,3a,9,9a-hexahydrocyclopenta[*b*]-chromen-1-yl 4-nitrobenzoate (8)

To a mixture of **7** (50 mg, 0.24 mmol) and DMAP (88 mg, 0.73 mmol) in DCM (2 mL) at 0 °C was added *p*-nitrobenzoyl chloride‡ in DCM (2 mL) and allowed to stir for 15 min. After the completion of reaction, water was added to the reaction mixture and the aqueous layer was separated and extracted with DCM (1 × 5 mL). The combined organic extracts were washed with 1 N HCl (1 × 5 mL), water (1 × 10 mL), brine (1 × 2 mL), dried over Na_2SO_4, concentrated to a crude mixture and the compound purified by silica gel column chromatography (100–200 mesh) using ethyl acetate–pet ether (1 : 9) to afford **8** (51 mg, 60%) as white crystals. M.p. 136–138 °C; IR ν_{max} (film): cm^{-1} 3155, 2929, 2254, 1727, 1686, 1608, 1529, 1464, 1350; ^1H NMR (400 MHz, $CDCl_3$): δ 8.28 (2H, d, J = 8.7 Hz), 8.21 (2H, d, J = 8.7 Hz), 7.88 (1H, dd, J = 7.7, 1.5 Hz), 7.50 (1H, m), 7.03 (1H, t, J = 7.7 Hz), 6.95 (1H, d, J = 8.2 Hz), 5.71 (1H, m), 5.12 (1H, m), 3.14 (1H, dd, J = 7.2, 4.7 Hz), 2.70–2.60 (1H, m), 2.30–2.22 (2H, m), 1.97–1.89 (1H, ddd, J = 14.3, 10.0,

‡*Note*: *p*-nitrobenzoyl chloride was freshly prepared by addition of oxalyl chloride (0.12 mL, 1.47 mmol) to a solution of *p*-nitrobenzoic acid (122 mg, 0.73 mmol) in DCM and catalytic amount of DMF, left for 45 min.

5.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.0, 164.1, 160.3, 150.6, 136.6, 135.2, 130.8 (2C overlapped), 127.1, 123.5 (2C overlapped), 121.8, 119.1, 118.1, 81.3, 77.8, 55.4, 30.3, 29.9.

(1*S,3a*R**,9a*S**)-1,8-Dihydroxy-1,2,3,3a-tetrahydrocyclopenta[*b*]-chromen-9(9a*H*)-one (2)**

Prepared from 2,6-dihydroxy acetophenone (200 mg, 1.31 mmol), succinaldehyde (**5**) (226 mg, 2.63 mmol), pyrrolidine (0.02 mL, 0.26 mmol) by following the general procedure described above, yielding a mixture of **2** and **9** (3 : 7) (23 mg, 8%). The diastereomeric mixture of **2** and **9** was separated by silica gel column chromatography using DCM (100%) giving **2** and **9** as colorless solids. ***rac*-2**: M.p. 93–95 °C; IR ν_{max} (film): cm^{-1} 3445, 3020, 2980, 2940, 1731, 1635, 1578, 1462; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.86 (1H, s), 7.33 (1H, t, J = 8.2 Hz), 6.48 (1H, d, J = 8.2 Hz), 6.39 (1H, d, J = 8.2 Hz), 4.95 (1H, m), 4.74 (1H, br m), 2.78 (1H, dd, J = 6.2, 5.2 Hz), 2.32–2.41 (1H, m), 2.21–2.29 (1H, m), 1.98–2.09 (3H, complex multiplet); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.3, 161.9, 161.2, 138.5, 109.5, 109.2, 107.6, 81.7, 75.4, 55.4, 33.7, 31.7 (Spectral data is identical with natural diaportheone-B in all respects).[3]

(1*R,3a*R**,9a*S**)-1,8-Dihydroxy-1,2,3,3a-tetrahydrocyclopenta-[*b*]chromen-9(9a*H*)-one (9)**

M.p. 92–96 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 11.76 (1H, s), 7.33 (1H, t, J = 8.2 Hz), 6.45 (1H, d, J = 8.2 Hz), 6.35 (1H, d, J = 8.2 Hz), 4.97 (1H, td, J = 4.7, 1.7 Hz), 4.63 (1H, dd, J = 13.5, 7.5 Hz), 2.74 (1H, dd, J = 7.5, 5.0 Hz), 2.41–2.32 (1H, m), 2.29–2.20 (1H, m), 2.15–2.07 (1H, m), 1.74–1.83 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.9, 162.3, 160.6, 138.7, 109.4, 107.5, 106.5, 81.7, 75.6, 58.3, 32.1, 30.4; HRMS calculated for $C_{12}H_{12}O_4$, $[M + Na]^+$: 243.0628 found 243.0635.

2-(But-3-enyl)-5-hydroxychroman-4-one (11)

To a mixture of **4** (33 mmol, 5 g) and 4-penten-1-al (66 mmol, 6.5 mL) in dry methanol (200 mL) was added pyrrolidine (6.6 mmol, 0.5 mL) dropwise at room temperature. The reaction mixture was warmed to 50 °C and was further allowed to stir for 24 h at the same temperature. Methanol was removed under vacuum and the reaction mixture was diluted with water (100 mL) and extracted with ethyl acetate (2 × 100 mL). The organic layer was washed with 1 N HCl (1 × 20 mL), water (1 × 20 mL), brine (1 × 10 mL), dried over Na_2SO_4, and concentrated under vacuum to give a crude residue which was further purified by silica gel column chromatography (100–200 mesh) using ethyl acetate–pet ether (2 : 98) affording 4.3 g of compound as yellow oil (75% yield based on the recovered starting material of 1 g). IR ν_{max} (film): cm^{-1} 3079, 3019, 2933, 1647, 1628, 1463; ^{1}H NMR (200 MHz, $CDCl_3$): δ 11.68 (1H, s), 7.34 (1H, t, J = 8.3 Hz), 6.48 (1H, dd, J = 8.3, 0.8 Hz), 6.42 (1H, dd, J = 8.2, 0.8 Hz), 5.83 (1H, ddt, J = 20.2, 10.2, 6.5 Hz), 5.05 (2H, m), 4.43 (1H, m), 2.70 (2H, m), 2.29 (2H, m), 1.96 (1H, m), 1.78 (1H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ 198.4, 162.0, 161.5, 138.1, 137.0, 115.7, 109.1, 108.1, 107.2, 76.5, 42.1, 33.8, 28.9. HRMS calculated for $C_{13}H_{14}O_3$ $[M + H]^+$: 219.1021 found 219.1029.

3-(5-Hydroxy-4-oxochroman-2-yl)propanal (12)

To a mixture of **11** (0.2 g 0.9 mmol) in dioxane–water (4 : 1, 10 mL) was added 2,6-lutidine (1.8 mmol, 0.2 mL), OsO_4 (cat) (0.01 mmol) and $NaIO_4$ (3.7 mmol, 0.78 g). The reaction was stirred at 25 °C for 1 h. After completion of the reaction (monitored by TLC), water (10 mL) and DCM (4 mL) were added. The organic layer was separated and the water layer was extracted with DCM (3 × 4 mL). The combined organic extracts were washed with 1 N HCl (4 mL), brine (2 mL) and dried over Na_2SO_4. The solvent was removed under vacuum, and the crude mixture was purified on silica gel column (100–200 mesh) using ethyl acetate–pet ether (20 : 80) affording 0.18 g of pure compound **12** (89%) as an opaque low melting solid. M.p. 68–69 °C; IR ν_{max} (film): cm^{-1} 3020, 2932, 2832, 2731, 1726, 1647, 1629, 1463, 1357; ^{1}H NMR (500 MHz, $CDCl_3$): δ 11.61 (1H, s), 9.81 (1H, s), 7.30 (1H, t, J = 8.2 Hz), 6.46 (1H, d, J = 8.2 Hz), 6.35 (1H, d, J = 8.2 Hz), 4.42 (1H, m), 2.72 (3H, m), 2.65 (1H, dd, J = 17.0, 3.6 Hz), 2.08 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 200.7, 197.8, 161.9, 161.0, 138.1, 109.3, 107.9, 107.1, 76.1, 42.1, 39.1, 27.0; HRMS calculated for $C_{12}H_{12}O_4$, $[M + H]^+$: 221.0814 found 221.0823.

3-(4-Oxochroman-2-yl) propanal (14)

Prepared from **17** (4 g, 19.80 mmol), 2,6-lutidine (4.60 mL, 39.60 mmol), OsO_4 (cat) and $NaIO_4$ (16.87 g, 79.20 mmol) by following the procedure described for the synthesis of **12** yielding **14** (3.59 g, 89%). IR ν_{max} (film): cm^{-1} 3020, 2831, 2730, 1724, 1691, 1609, 1465; ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.84 (1H, s), 7.84 (1H, d, J = 7.8 Hz), 7.45 (1H, m), 6.99 (1H, m), 6.94 (1H, d, J = 8.2 Hz), 4.47 (1H, m), 2.71 (4H, m), 2.11 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 200.9, 191.8, 161.1, 136.0, 126.9, 121.4, 120.8, 117.7, 76.6, 42.9, 39.3, 27.2. HRMS calculated for $C_{12}H_{12}O_3$, $[M + Na]^+$: 227.0683 found 227.0669.

(3a*R*,9a*S*)-1,8-Dihydroxy-1,2,3,3a-tetrahydrocyclopenta[*b*]-chromen-9(9a*H*)-one

To a solution of **12** (1 mmol) in a specified solvent (Table 2) (5 mL mmol^{-1}) at room temperature, was added amine (0.2 mmol) dropwise and the reaction mixture was allowed to stir for the required time, after a considerable amount of starting material had been consumed with no further improvement in the product formation (TLC monitoring), the solvent was removed under vacuum from the reaction mixture and diluted with ethyl acetate (10 mL). The organic layer was washed with 1 N HCl (1 × 2 mL), water (1 × 5 mL), brine (1 × 2 mL), dried over Na_2SO_4, and concentrated to a crude mixture. The crude diastereomeric mixture was filtered through a silica gel pad (100–200 mesh) and the diastereomeric ratio was determined by HPLC method.

Separation of enantiomers of 2 and 9

The chiral separation of ***rac*-2** was done by normal phase HPLC method using Kromasil 5-AmyCoat chiral column (250 × 4.6 mm) using mobile phase of IPA–*n*-hexane (15 : 85). Specific rotation of natural **2** was found to be $[\alpha]_D^{24}$ = (+) 177.8° (*c* = 1.2, $CHCl_3$) and its enantiomer specific rotation (98% pure) was $[\alpha]_D^{24}$ = (−) 170.8° (*c* = 1.2, $CHCl_3$). The chiral separation of ***rac*-9** was done by normal phase HPLC method using Chiralcel-OD chiral column (250 × 4.6 mm) using mobile phase of IPA–*n*-hexane (9 : 91). Specific rotation of (+) isomer of **9** was found to be $[\alpha]_D^{23}$ = (+) 85.6° (*c* = 0.5, $CHCl_3$) and its enantiomer specific rotation was $[\alpha]_D^{23}$ = (−) 88.9° (*c* = 0.5, $CHCl_3$).

General procedure for bromination reaction

A solution of bromine (1 mmol) in DCM (5 mL) was slowly added to the compound (1 mmol), in dry DCM (5 mL) and allowed to stir for 15 min at 0 °C. The reaction mixture was treated with saturated aq. solution of $Na_2S_2O_5$ (5 mL) followed by addition of water (5 mL). The organic phase was separated and aq. phase was extracted with DCM (1 × 5 mL) and the combined organic extracts were washed with water (1 × 5 mL), brine (1 × 2 mL), dried over Na_2SO_4 and concentrated to a crude mixture. The crude mixture was purified by flash column chromatography (230–400 mesh) to obtain a yellow colored solid.

(1*R**,3a*R**,9a*S**)-5,7-Dibromo-1,8-dihydroxy-1,2,3,3a-tetrahydrocyclopenta[*b*]chromen-9(9a*H*)-one (10)

Prepared from **9** (5 mg, 0.022 mmol) and bromine (2.30 µl, 0.045 mmol) following the general procedure for the bromination reaction described above yielding **10** (5 mg, 58%) as a yellow solid. M.p. 136–140 °C; IR ν_{max} (film): cm^{-1} 3585, 3019, 2931, 1638, 1606, 1448; ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.51 (1H, s), 7.83 (1H, m), 5.09 (1H, td, *J* = 4.7, 2.0 Hz), 4.63 (1H, m), 2.84 (1H, dd, *J* = 7.5, 4.7 Hz), 2.45–2.36 (2H, m), 2.34–2.20 (2H, m), 1.86–1.76 (1H, m); ^{13}C NMR (50 MHz, $CDCl_3$): δ 198.5, 157.9, 155.9, 143.0, 107.3, 101.7, 99.8, 82.9, 75.5, 57.8, 32.1, 30.3.

(1*S*,3a*R*,9a*S*)-5,7-Dibromo-1,8-dihydroxy-1,2,3,3a-tetrahydrocyclopenta[*b*]chromen-9(9a*H*)-one (13)

Prepared from **9** (10 mg, 0.04 mmol) and bromine (4.60 µl, 0.09 mmol) following the general procedure for the bromination reaction described above yielding **13** (10.6 mg, 62%) as a yellow solid. IR ν_{max} (film): cm^{-1} 3584, 3019, 2930, 1641, 1607, 1448; ^{1}H NMR (400 MHz, $CDCl_3$): δ 12.61 (1H, s), 7.82 (1H, m), 5.05 (1H, m), 4.79 (1H, br m), 2.85 (1H, app t, *J* = 5.7 Hz), 2.56–2.49 (1H, m), 2.33–2.24 (1H, m), 2.16–2.03 (2H, m), 1.81 (1H, br d, *J* = 6.0 Hz); ^{13}C NMR (50 MHz, $CDCl_3$): δ 198.0, 157.5, 155.5, 143.0, 109.9, 101.6, 99.8, 82.8, 75.6, 54.9, 33.8, 32.0. $[\alpha]_D^{25}$ = (+) 107.3° (*c* = 1, $CHCl_3$).

General procedure for the synthesis of substituted 3,3a-dihydrocyclopenta[*b*]chromen-9(2*H*)-ones

To a solution of aldehyde (1 mmol) in dry toluene (20 mL) at room temperature, was added pyrrolidine (0.2 mmol) dropwise. The reaction mixture was heated to 80 °C and stirred for 12 h. After completion of the reaction, solvent was removed under vacuum from the reaction mixture and diluted with ethyl acetate. The organic layer was washed with 1 N HCl (5 mL), water (10 mL), brine (2 mL), dried over Na_2SO_4, concentrated under vacuum and the crude residue was purified by silica gel column chromatography (100–200 mesh) eluting with ethyl acetate–pet ether as eluent to afford a pure compound.

8-Hydroxy-3,3a-dihydrocyclopenta[*b*]chromen-9(2*H*)-one (15)

Prepared from **12** (140 mg, 0.63 mmol) and pyrrolidine (0.02 mL, 0.12 mmol) in toluene (10 mL) by following the general procedure described above yielding **15** (115 mg, 90%) as a yellow viscous mass. IR ν_{max} (film): cm^{-1} 3020, 2982, 2932, 2867, 1635, 1619, 1459; ^{1}H NMR (200 MHz, $CDCl_3$): δ 12.13 (1H, s), 7.33 (1H, t, *J* = 8.3 Hz), 6.98 (1H, m), 6.50 (1H, dd, *J* = 8.3, 0.8 Hz), 6.41 (1H, dd, *J* = 8.3, 0.8 Hz), 5.41 (1H, m), 2.84–2.43 (3H, m), 2.27–2.09 (1H, m); ^{13}C NMR (50 MHz, $CDCl_3$): δ 186.0, 163.2, 161.3, 142.3, 138.2, 137.8, 109.6, 109.3, 107.6, 84.0, 31.6, 31.1; HRMS calculated for $C_{12}H_{10}O_3$ $[M + H]^+$: 203.0708 found 203.0720.

3,3a-Dihydrocyclopenta[*b*]chromen-9(2*H*)-one (16)

Prepared from **14** (50 mg, 0.24 mmol) and pyrrolidine (0.04 mL, 0.05 mmol) in toluene (2 mL) by following the general procedure described above yielding **16** (40 mg, 87%) as a yellow viscous mass. IR ν_{max} (film): cm^{-1} 2979, 3019, 1667, 1638, 1607, 1462; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.96 (1H, dd, *J* = 7.83, 1.77 Hz), 7.51–7.42 (1H, ddd, *J* = 8.3, 7.2, 1.7 Hz), 7.05 (1H, m), 6.97 (2H, m), 5.46 (1H, m), 2.82–2.65 (2H, m), 2.62–2.43 (1H, m), 2.30–2.11 (1H, m). ^{13}C NMR (50 MHz, $CDCl_3$): δ 180.9, 161.1, 141.3, 139.0, 135.8, 127.6, 122.7, 121.6, 118.2, 84.4, 31.6, 30.8; HRMS calculated for $C_{12}H_{10}O_2$ $[M + H]^+$: 187.0759 found 187.0754. Compound **16** was reported in the literature[13] but the data is not available.

2-(But-3-enyl)chroman-4-one (17)

Prepared from **6** (10 g, 73.53 mmol), 4-penten-1-al (21.6 mL, 220.58 mmol) and pyrrolidine (1.2 mL, 14.71 mmol) by following the procedure described for the synthesis of **11** as a yellow oil (13 g, 92% based on the recovery of starting material 0.5 g) as a yellow liquid. The spectral data matched according to the literature report.[15]

8-Hydroxy-1-methyl-3,3a-dihydrocyclopenta[*b*]chromen-9(2*H*)-one (20)

Prepared from **18** (1.8 g, 7.69 mmol) and pyrrolidine (0.12 mL, 1.53 mmol) in toluene (50 mL) by following the general procedure described above yielding **20** (1.15 g, 69%) as a yellow crystalline solid. M.p. 102–104 °C; IR ν_{max} (film): cm^{-1} 3020, 2981, 2946, 2867, 2840, 1655, 1633, 1610; ^{1}H NMR (500 MHz, $CDCl_3$): δ 12.39 (1H, s), 7.29 (1H, t, *J* = 8.2 Hz), 6.48 (1H, d, *J* = 8.2 Hz), 6.38 (1H, d, *J* = 8.2 Hz), 5.37 (1H, br m), 2.66–2.60 (1H, m), 2.60–2.50 (2H, m), 2.26 (3H, s),

2.14–2.07 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$): δ 187.7, 163.3, 161.0, 158.7, 137.5, 129.1, 109.8, 109.5, 107.4, 85.0, 37.1, 29.9, 16.6; HRMS calculated for $C_{13}H_{12}O_3$ $[M + H]^+$: 217.0864 found 217.0859.

1-Methyl-3,3a-dihydrocyclopenta[*b*]chromen-9(2*H*)-one (21)

Prepared from **19** (500 mg, 0.23 mmol) and pyrrolidine (0.37 mL, 0.46 mmol) in toluene (10 mL) by following the general procedure described above yielding **21** (330 mg, 72%) as a yellow crystalline solid. M.p. 98–99 °C; IR ν_{max} (film): cm^{-1} 3019, 2979, 2945, 2867, 2842, 1669, 1638, 1605, 1462; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.95 (1H, dd, J = 7.9, 1.5 Hz), 7.43 (1H, t, J = 8.2 Hz), 7.01 (1H, t, J = 7.9 Hz), 6.93 (1H, d, J = 8.2 Hz), 5.42 (1H, m), 2.64–2.59 (1H, m), 2.56–2.50 (2H, m), 2.25 (3H, s), 2.14–2.10 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 182.3, 160.8, 157.2, 135.5, 130.3, 127.4, 123.6, 121.4, 118.0, 85.6, 36.8, 29.6, 16.4; HRMS calculated for $C_{13}H_{12}O_2$ $[M + H]^+$: 201.0915 found 201.0930.

General procedure for the Wacker oxidation of olefin

A suspension of alkene (5 mmol), $PdCl_2$ (0.5 mmol) and $Cu(OAc)_2{\cdot}H_2O$ (7.5 mmol) in dimethylacetamide–water (4 : 1) (75 mL), was placed under oxygen (1 atm) and the green colored mixture was allowed to stir for 12 h at room temperature. The crude mixture was diluted with ether (10 mL), filtered through celite bed and washed with additional amount of ether (30 mL) and the filtrate was poured into water, extracted with ether (3 × 10 mL). The combined organic extracts were washed with brine (1 × 10 mL), dried over Na_2SO_4, and concentrated under vacuum. The crude residue was purified by silica gel column chromatography (100–200 mesh) using ethyl acetate–pet ether as eluent to afford the pure compound.

5-Hydroxy-2-(3-oxobutyl)chroman-4-one (18)

Prepared from **11** (2 g, 9.17 mmol), $PdCl_2$ (162 mg, 0.91 mmol) and $Cu(OAc)_2$ (2.50 g, 1.37 mmol) by following the general procedure for Wacker oxidation described above yielding **18** (1.80 g, 83%) as a white solid. M.p. 82–83 °C; IR ν_{max} (film): cm^{-1} 3017, 2929, 1716, 1648, 1629, 1578, 1463, 1225, 1054, 771; ^{1}H NMR (200 MHz, $CDCl_3$): δ 11.66 (1H, s), 7.33 (1H, t, J = 8.3 Hz), 6.48 (1H, dd, 8.3, 0.7 Hz), 6.39 (1H, dd, 8.2, 0.7 Hz), 4.42 (1H, m), 2.82–2.62 (4H, m), 2.19 (3H, s), 2.03 (2H, m); ^{13}C NMR (50 MHz, $CDCl_3$): δ 207.4, 198.1, 162.0, 161.2, 138.1, 109.3, 108.0, 107.1, 76.2, 42.2, 38.5, 30.0, 28.4; HRMS calculated for $C_{13}H_{14}O_4$ $[M + Na]^+$: 257.0789 found 257.0768.

2-(3-Oxobutyl)chroman-4-one (19)

Prepared from **17** (2.0 g, 9.90 mmol), $PdCl_2$ (175 mg, 0.99 mmol) and $Cu(OAc)_2$ (2.72 g, 15 mmol) by following the general procedure for Wacker oxidation described above yielding **19** (1.90 g, 87%) as a grey colored solid. IR ν_{max} (film): cm^{-1} 3020, 1715, 1689, 1608, 1465, 1215; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (1H, d, J = 8.3 Hz), 7.45 (1H, t, J = 7.2 Hz), 6.99 (1H, t, J = 7.2 Hz), 6.93 (1H, d, J = 8.3 Hz), 4.45 (1H, m), 2.79–2.64 (4H, m), 2.19 (3H, s), 2.06 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 207.4, 192.0, 161.2, 135.9, 126.9, 121.3, 120.9, 117.7, 76.7, 43.0, 38.6, 30.0, 28.6; HRMS calculated for $C_{13}H_{14}O_3$, $[M + Na]^+$: 241.0840 found 241.0848.

General procedure for the SeO_2 mediated allylic oxidation

To a stirred solution of compound (0.25 mmol) in 1,4-dioxane (2 mL) was added selenium dioxide (0.4 mmol) and the reaction mixture was refluxed for 3 h. After completion of reaction, the reaction mixture was allowed to cool to room temperature. The deposited selenium metal was filtered off and the residue was washed with dioxane (10 mL). The filtrate was concentrated and diluted with ethyl acetate (5 mL) and water (5 mL). The organic layer was separated and the aqueous layer was extracted with ethyl acetate (2 × 2 mL) and the combined organic extracts were washed with saturated solution of $NaHCO_3$ (2 mL), water (2 mL), brine (2 mL), dried over Na_2SO_4 and concentrated to a crude mixture which was further purified by silica gel column chromatography using ethyl acetate–pet ether to afford pure compound.

8-Hydroxy-9-oxo-2,3,3a,9-tetrahydrocyclopenta[*b*]chromene-1-carbaldehyde (22)

Prepared from **20** (90 mg, 0.41 mmol) and SeO_2 (74 mg, 0.67 mmol) by following the general procedure for SeO_2 mediated allylic oxidation described above yielding **22** (65 mg, 68%) as a yellow solid. M.p. 180–183 °C; IR ν_{max} (film): cm^{-1} 3020, 2954, 2874, 1715, 1681, 1634, 1615, 1459; ^{1}H NMR (500 MHz, $CDCl_3$): δ 11.95 (1H, s), 10.56 (1H, s), 7.41 (1H, t, J = 8.2 Hz), 6.56 (1H, dd, J = 8.2, 0.9 Hz), 6.46 (1H, dd, J = 8.2, 0.6 Hz), 5.54 (1H, m), 3.00–2.93 (1H, m), 2.71–2.60 (2H, m), 2.22–2.14 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 189.7, 185.4, 163.6, 161.0, 149.8, 143.7, 139.3, 110.2, 109.9, 107.7, 84.8, 30.0, 28.0; HRMS calculated for $C_{13}H_{10}O_4$ $[M + H]^+$: 231.0657 found 231.0651.

9-Oxo-2,3,3a,9-tetrahydrocyclopenta[*b*]chromene-1-carbaldehyde (23)

Prepared from **21** (50 mg, 0.25 mmol) and SeO_2 (44 mg, 0.40 mmol) by following the general procedure for SeO_2 mediated allylic oxidation described above yielding **23** (40 mg, 75%) as a yellow solid. M.p. 118–120 °C; IR ν_{max} (film): cm^{-1} 3020, 1680, 1633, 1608; ^{1}H NMR (200 MHz, $CDCl_3$): δ 10.56 (1H, s), 8.00 (1H, dd, J = 7.9, 1.6 Hz), 7.54 (1H, m), 7.09 (1H, m), 7.02 (1H, m), 5.57 (1H, m), 3.05–2.87 (1H, m), 2.78–2.53 (2H, m), 2.30–2.09 (1H, m); ^{13}C NMR (50 MHz, $CDCl_3$): δ 190.3, 180.5, 161.1, 149.0, 144.9, 136.9, 127.7, 122.5, 122.2, 118.3, 85.2, 30.0, 27.7; HRMS calculated for $C_{13}H_{10}O_3$ $[M + H]^+$: 215.0708 found 215.0697.

8-Methoxy-3,3a-dihydrocyclopenta[*b*]chromen-9(2*H*)-one (24)

To a solution of **15** (100 mg, 0.46 mmol) in acetone (2 mL) was added oven dried potassium carbonate (254 mg, 1.85 mmol) and methyl iodide (0.12 mL, 1.85 mmol) and the reaction mixture

was stirred at rt for 10 h. After completion of reaction, acetone was evaporated and residue was diluted with ethyl acetate (2 mL). The organic layer was washed with water, brine, dried over Na_2SO_4, concentrated and purified by column chromatography, eluting the crude mixture with ethyl acetate–pet ether (8 : 92) to afford 90 mg of pure compound (85%) as a white powdery solid. M.p. 175–178 °C; IR ν_{max} (film): cm^{-1} 3019, 3931, 1664, 1636, 1602, 1471; ^1H NMR (400 MHz, $CDCl_3$): δ 7.37 (1H, t, J = 8.2 Hz), 6.89 (1H, m), 6.57 (1H, d, J = 8.2 Hz), 6.53 (1H, d, J = 8.2 Hz), 5.35 (1H, br m), 3.91 (3H, s), 2.73–2.59 (2H, m), 2.54–2.45 (1H, m), 2.20–2.11 (1H, m); ^{13}C NMR (100 MHz): δ 180.0, 163.1, 161.6, 140.4, 140.1, 135.7, 113.5, 110.5, 104.4, 83.9, 56.2, 31.5, 30.8; HRMS calculated for $C_{13}H_{12}NaO_3$ $[M + Na]^+$: 239.0683 found 239.0658.

8-Methoxy-1-methyl-3,3a-dihydrocyclopenta[*b*]chromen-9(2*H*)-one (25)

Prepared from **20** (100 mg, 0.46 mmol), K_2CO_3 (127 mg, 0.92 mmol) and methyl iodide (0.12 mL, 1.85 mmol) by following the procedure for the synthesis of **24** yielding **25** (94 mg, 88%) as a yellow solid. M.p. 145–147 °C; IR ν_{max} (film): cm^{-1} 3019, 2944, 2842, 1667, 1634, 1601, 1470; ^1H NMR (400 MHz, $CDCl_3$): δ 7.31 (1H, t, 8.2 Hz), 6.53 (2H, m), 5.31 (1H, br m), 3.90 (3H, s), 2.57–2.45 (3H, m), 2.24 (3H, s), 2.11–2.01 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 181.7, 162.8, 161.5, 156.6, 135.2, 130.9, 114.2, 110.3, 104.2, 85.2, 56.1, 37.1, 29.4, 16.2; HRMS calculated for $C_{14}H_{14}NaO_3$ $[M + Na]^+$: 253.0840 found 253.0830.

General procedure for the reduction of 3,3a-dihydrocyclopenta-[*b*]chromen-9(2*H*)-ones

To a solution of chromenone (1 mmol) in ethyl acetate (3 mL) was added a catalytic amount of 5% Pd on activated charcoal (10 mg) and catalytic amount of triethylamine (0.01 mL). The reaction mixture was stirred under H_2 (1 atm) for 0.5–3 h. After completion of reaction, the reaction mixture was filtered through a short celite bed. The filtrate was concentrated under vacuum and the crude mixture was purified by silica gel column chromatography (100–200 mesh) eluting with ethyl acetate–pet ether to give pure compound.

(3a*R**,9a*S**)-1,2,3,3a-Tetrahydrocyclopenta[*b*]chromen-9(9a*H*)-one (26)

Prepared from **16** (80 mg, 0.43 mmol) and 5% Pd/C (cat) under hydrogen atmosphere (1 atm) by following the general procedure described above yielding **26** (79 mg, 98%) as a colorless viscous mass. The spectral data matched according to the literature reported data.[14]

(1*R**,3a*R**,9a*S**)-1-Methyl-1,2,3,3a-tetrahydrocyclopenta[*b*]-chromen-9(9a*H*)-one (27)

Prepared from **21** (100 mg, 0.50 mmol) and 5% Pd/C (cat) under hydrogen atmosphere (1 atm) by following the general procedure described above yielding **27** (96 mg, 95%) as a colorless liquid. The spectral data matched according to the literature reported data.[15]

(3a*R**,9a*S**)-8-Hydroxy-1,2,3,3a-tetrahydrocyclopenta[*b*]-chromen-9(9a*H*)-one (28)

Prepared from **15** (100 mg, 0.49 mmol) and 5% Pd/C (cat) under hydrogen atmosphere (1 atm) by following the general procedure described above yielding **28** (87 mg, 86%) as a colorless mass. IR ν_{max} (film): cm^{-1} 3020, 2929, 2877, 1641, 1578, 1555, 1462; ^1H NMR (200 MHz, $CDCl_3$): δ 11.90 (1H, s), 7.32 (1H, t, J = 8.3 Hz), 6.46 (1H, dd, J = 8.3, 0.8 Hz), 6.36 (1H, dd, J = 8.3, 0.8 Hz), 4.90 (1H, br m), 2.76–2.65 (1H, m), 2.30–2.10 (2H, m), 2.07–1.75 (4H, m); ^{13}C NMR (50 MHz, $CDCl_3$): δ 200.6, 162.4, 160.6, 138.2, 109.1, 107.3, 106.1, 82.9, 50.3, 32.9, 28.0, 22.5; HRMS calculated for $C_{12}H_{12}O_3$ $[M + Na]^+$: 227.0683 found 227.0668.

Details of biological assay

MIC values of various antibiotics against $H_{37}Rv$ were determined in 7H9-OADC media supplemented with 0.5% glycerol and 1 mg ml^{-1} tryptone at 37 °C in 96-well microtiter plates using the colorimetric resazurin microtiter assay, and growth was measured by visual readout. Rifampicin was used as a positive drug control.

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Notes and references

1 (*a*) A. Koul, E. Arnoult, N. Lounis, J. Guillemont and K. Andries, *Nature*, 2011, **469**(7331), 483; (*b*) Z. Ma, C. Lienhardt, H. Mcilleron, A. J. Nunn and X. Wang, *Lancet*, 2010, **375**(9731), 2100; (*c*) World Health Organization. Global tuberculosis control: a short update to the 2009 report, Geneva, Switzerland, WHO/HTM/TB/2009, 426; (*d*) K. R. Foster and H. Grundmann, *PLoS Med.*, 2006, **3**, e29; (*e*) K. M. Overbye and J. F. Barrett, *Drug Discovery Today*, 2005, **10**, 45.
2 (*a*) F. E. Koehn and G. T. Carter, *Nat. Rev. Drug Discovery*, 2004, **4**, 206; (*b*) D. J. Newman and G. M. Cragg, *J. Nat. Prod.*, 2007, **70**, 461; (*c*) J. W.-H. Li and J. C. Vederas, *Science*, 2009, **325**, 161; (*d*) A. L. Harvey, *Drug Discovery Today*, 2008, **13**, 894.
3 M. E. Bungihan, M. A. Tan, M. Kitajima, N. Kogure, S. G. Franzblau, T. E. E. dela Cruz, H. Takayama and M. G. Nonato, *J. Nat. Med.*, 2011, **65**, 606.
4 (*a*) D. C. Rees, M. Congreve, C. W. Murray and R. Carr, *Nat. Rev. Drug Discovery*, 2004, **10**, 660; (*b*) R. A. E. Carr, M. Congreve, C. W. Murray and D. C. Rees, *Drug Discovery Today*, 2004, **10**, 987; (*c*) T. I. Oprea, *J. Chem. Inf. Comput. Sci.*, 2001, **41**, 1308; (*d*) S. J. Teague, A. M. Davis, P. D. Leeson and T. Oprea, *Angew. Chem., Int. Ed.*, 1999, **38**, 3743; (*e*) H. J. Verheij, *Mol. Diversity*, 2006, **10**, 377.

5 (*a*) C. A. Lipinski, F. Lombardo, B. W. Dominy and P. J. Feeney, *Adv. Drug Delivery Rev.*, 2001, **46**, 3; (*b*) M. C. Wenlock, R. P. Austin, P. Barton, A. M. Davis and P. D. Leeson, *J. Med. Chem.*, 2003, **46**, 1250; (*c*) D. F. Veber, S. R. Johnson, H. Y. Cheng, B. R. Smith, K. W. Ward and K. D. Kopple, *J. Med. Chem.*, 2002, **45**, 2615; (*d*) M. P. Gleeson, *J. Med. Chem.*, 2008, **51**, 817.

6 For selected reviews on organocatalytic cascade reactions, see: (*a*) D. B. Ramachary and Y. V. Reddy, *Eur. J. Org. Chem.*, 2012, 865; (*b*) D. B. Ramachary and S. Jain, *Org. Biomol. Chem.*, 2011, **9**, 1277; (*c*) J. Yu, F. Shi and L.-Z. Gong, *Acc. Chem. Res.*, 2011, **44**, 1156; (*d*) C. Grondal, M. Jeanty and D. Enders, *Nat. Chem.*, 2010, **2**, 167; (*e*) W. Notz, F. Tanaka and C. F. Barbas, III, *Acc. Chem. Res.*, 2004, **37**, 580; (*f*) J. Seayad and B. List, *Org. Biomol. Chem.*, 2005, **3**, 719.

7 For related cascade reactions for the synthesis of benzopyranone derivatives, see selected refs: (*a*) J. D. Butler, W. E. Conrad, M. W. Lodewyk, J. C. Fettinger, D. J. Tantillo and M. J. Kurth, *Org. Lett.*, 2010, **12**, 3410; (*b*) K. Mori, G. Audranb and H. Monti, *Synlett*, 1998, 259; (*c*) P.-Y. Chen, T. P. Wang, M. P. Chiang, K.-S. Huang, C.-C. Tzeng, Y.-L. Chen and E.-C. Wang, *Tetrahedron*, 2011, **67**, 4155; (*d*) H.-F. Wang, H. Xiao, X.-W. Wang and G. Zhao, *Tetrahedron*, 2011, **67**, 5389; (*e*) S. Klutchko, M. Von Strandtmann, J. R. Shavel, *US Patent*, 3862141, 1975; (*f*) S. Hintza, J. Mattay, R. Eldik and W.-F. Fu, *Eur. J. Org. Chem.*, 1998, 1583; (*g*) J. E. Yeo, X. Yang, H. J. Kim and S. Koo, *Chem. Commun.*, 2004, 236.

8 See the ESI† for the various conditions we have explored.

9 Selected efforts are (i) use of excess succinaldehyde, (ii) slow addition of components (iii) change of aldehyde to 1,5-pentanedial or *o*-phthaldehyde and (iv) protection of hydroxyl group as OMe.

10 Details are available in ESI.†

11 (*a*) H. D. Flack and G. Bernardinelli, *Chirality*, 2008, **20**, 681; (*b*) H. D. Flack, *Acta Chim. Slov.*, 2008, **55**, 689 and refs cited therein.

12 Diaportheone B showed slightly lower activity in our hands compared to literature report.

13 J. E. Yeo, X. Yang, H. J. Kim and S. Koo, *Chem. Commun.*, 2004, 236.

14 A. V. Dubrovskiy and R. C. Larock, *Org. Lett.*, 2010, **12**, 3117.

15 S. Hintza, J. Mattay, R. V. Eldikb and W.-F. Fu, *Eur. J. Org. Chem.*, 1998, 1583.

