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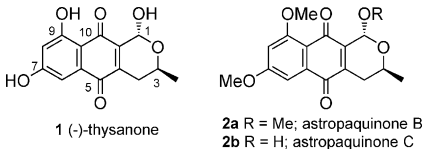
Formal Synthesis of the Human Rhinovirus 3C Protease Inhibitor (−)-Thysanone

Sandip V. Mulay, Sachin P. Gholap, and Rodney A. Fernandes*[a]

Abstract: A strategy based on Dötz benzannulation and an oxa-Pictet-Spengler reaction toward the formal synthesis of a human rhinovirus (HRV) 3C protease inhibitor, the pyranonaphthoquinone (−)-thysanone, is presented.

Introduction

The pyranonaphthoquinone antibiotic (−)-thysanone **1** was isolated from the solid-state fermentation of the fungus *Thysanophora penicilloides* (MF 5636, Merck Culture Collection).[1] (−)-Thysanone **1** (Figure 1) shows potent (IC_{50} = 13 μg mL^{-1}) activity against human rhinovirus (HRV) 3C protease, which is responsible for afflictions such as polio, hepatitis A and foot-and-mouth disease.[2a] In the western world, HRVs are leading causative agents of the common cold and currently only symptomatic treatment is available to medicate rhinoviral infections. In addition to being attributed to the common cold, HRV infections are associated with acute and chronic bronchitis.[2b] More than 100 serotypes of these viruses are known and they typically infect upper respiratory tract in humans and target nasal epithelial cells.[3] HRV 3C protease, a cysteine protease, is responsible for the polypeptide cleavage between Q-G amino acids and plays a critical role in the replication cycle of HRVs.[4] It constitutes a potential therapeutic target for the control of HRVs and common cold. The structure of thysanone was established by NMR spectroscopic studies and further confirmed by single crystal X-ray analysis of the methyl acetal derivatives. Donner and Gill[5b] established the structure and absolute stereochemistry of **1** by direct spectroscopic and circular dichroism comparison of the synthetic and natural product and their respective methyl acetals.



1 (-)-thysanone

2a R = Me; astropaquinone B
2b R = H; astropaquinone C

Figure 1. Structure of thysanone **1** and related molecules.

Due to its significant biological profile, several approaches for the synthesis of (−)-thysanone and its analogues have been reported.[5–8] Yang and co-workers achieved the synthesis of thysanone-related pyranonaphthoquinones by a combination of Diels–Alder and Pd-catalyzed alkoxycarbonylative annulation reactions.[9] The syntheses of multisubstituted aromatic moieties remains one of the challenging tasks in natural products chemistry.[10] In continuation of our research program aimed at the stereoselective synthesis of pyranonaphthoquinones and related compounds[11] by using Dötz benzannulation[12] as a key step, we aimed to target (−)-thysanone **1**. During the synthesis of (−)-thysanone **1**, Brimble and co-workers[6a,b] showed that the Lewis-acid-mediated demethylation of the C7 OMe group was problematic. Recently, they reported an iridium-catalyzed C–H borylation to install the C7 OH group in (±)-thysanone.[6c] To overcome these difficulties, we planned to choose isopropyl ether as a protecting group for the C7 OH group, which is more labile than a methyl ether[13] and bulky enough to prevent the dimerization at the C6 position in oxidation step, which occurred in the synthesis of (+)-astropaquinones **2**.[11k]

Results and Discussion

Our retrosynthetic plan for (−)-thysanone **1** is shown in Scheme 1. Thysanone **1** could be obtained from compound **3** by oxidative demethylation and dealkylation. Compound **3** can be synthesized from **4** by oxa-Pictet-Spengler reaction[14] and the latter could be derived from the known naphthol **5**[11k] prepared by Dötz benzannulation of Fischer carbene **6** with alkyne **7**.

The naphthol **5** was prepared by Dötz benzannulation of Fischer carbene **6** and alkyne **7**[11e] as reported earlier[11k] (Scheme 2). The methylation of naphthol **5** under mild condi-

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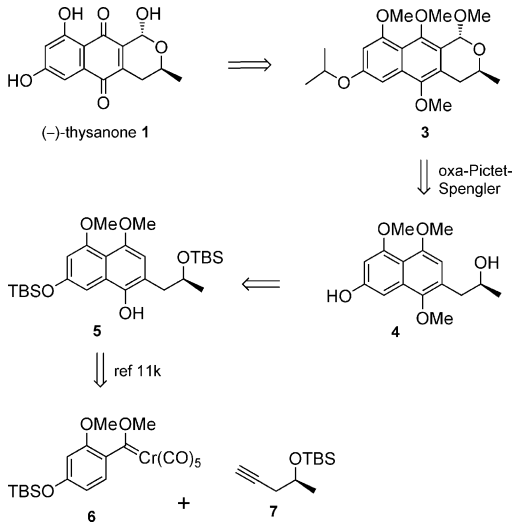
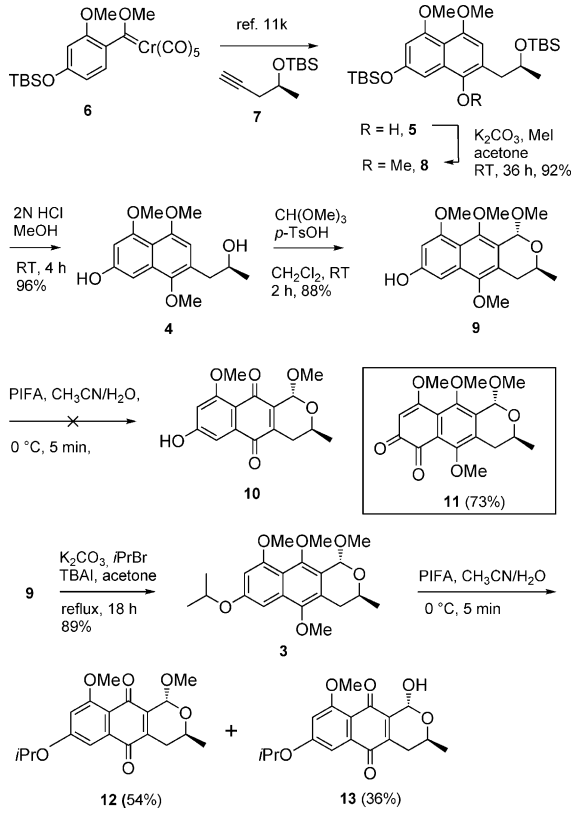


Scheme 1. Retrosynthetic plan for (−)-thysanone **1**. TBS = *tert*-butyldimethylsilyl.

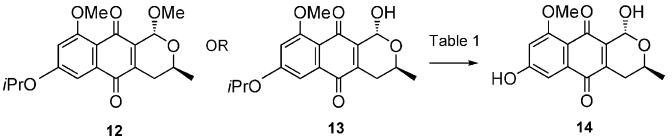


Scheme 2. Synthesis of quinones **12** and **13**. TBAI = tetra-*n*-butylammonium iodide.

tions (K_2CO_3, MeI, and acetone) gave **8** in 92% yield without affecting the TBS group.[11k,15] The removal of both TBS groups with 2 N HCl afforded the alcohol **4** in an excellent yield of 96%. The oxa-Pictet-Spengler reaction of **4** with trimethyl orthoformate in the presence of catalytic amount of *para*-toluenesulfonic acid monohydrate (*p*-TsOH·H_2O) delivered exclusively *trans*-configured pyran **9** in an excellent yield of 88%. The *trans* stereochemistry was established by a downfield shift of both C1 and C3 hydrogens in the ^{1}H NMR spectrum of **9** compared with similar known *syn* compounds synthesized in our laboratory.[11] The stereochemistry was further confirmed at later stage by comparison of the spectral data of methoxythysanone **14** with thysanone. A similar *trans*-pyran formation was reported by She and co-workers.[14d] At this stage if a selective oxidation of **9** to 5,10-quinone **10** occurs, the C7 OH group needs no protection. Thus the oxidation of **9** with phenyliodine bis(trifluoroacetate) (PIFA) was expected to give **10**, but unfortunately we isolated the orthoquinone **11** in 73% yield. Hence the protection of the C7 OH group became inevitable (as isopropyl ether, Scheme 1). Thus **9** was converted into compound **3** in 89% yield. The oxidation of **3** with PIFA now resulted in the formation of expected quinone **12** along with the C1 demethylated lactol quinone **13** in 54% and 36% isolated yields, respectively, which are easily separable by column chromatography. All that remained in the synthesis was the removal of all the *O*-alkyl protecting groups to give (−)-thysanone **1**.

When we subjected **12** or **13** to Lewis-acid-mediated dealkylation ($AlCl_3$, BBr_3, BCl_3, or $TiCl_4$), we only isolated compound **14** (Table 1). Increasing the concentration of Lewis acids or harsh

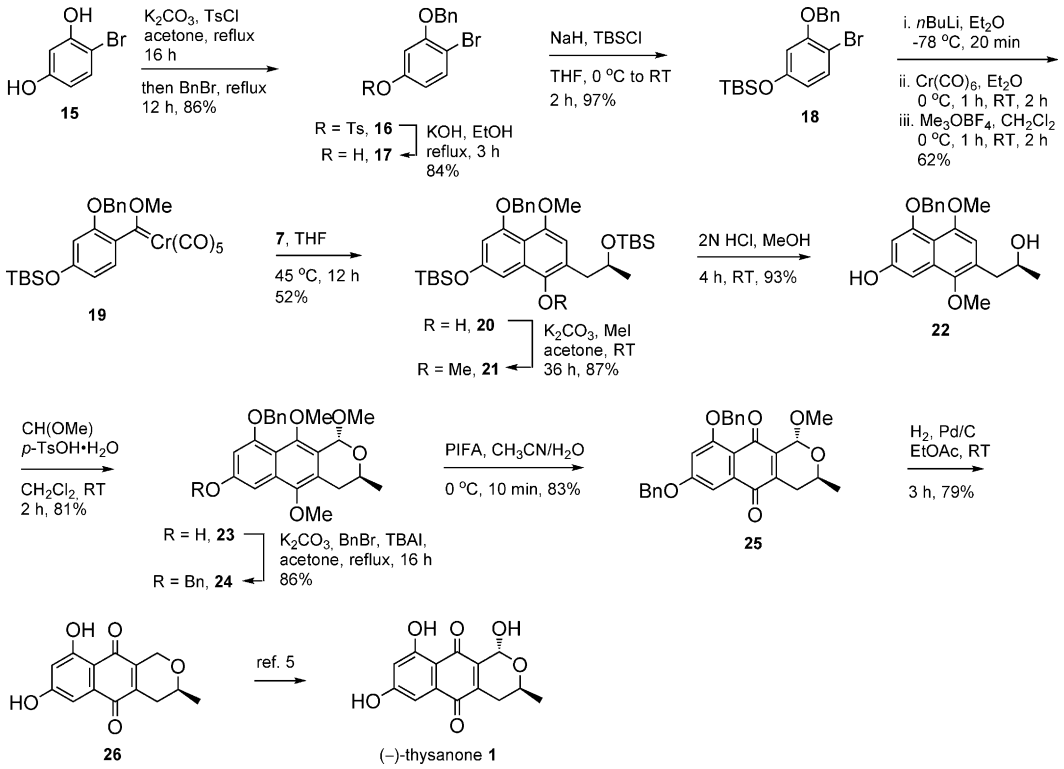
Table 1. Reaction conditions for dealkylation of **12** and **13** using Lewis acids.



Entry	Reaction conditions[a]	Yield of **14**
1	**12**, $AlCl_3$ (4.5 equiv.), 0 °C, 15 min, RT, 2 h	63%
2	**13**, $AlCl_3$ (3.0 equiv.), 0 °C, 15 min, RT, 2 h	69%
3	**13**, $AlCl_3$ (4.5 equiv.), 0 °C, 15 min, RT, 2 h	41%
4	**12**, $AlCl_3$ (6.0 equiv.), 0 °C, 15 min, RT, 1 h, reflux 1 h	decomposed
5	**13**, $AlCl_3$ (4.5 equiv.), 0 °C, 15 min, RT, 1 h, reflux 1 h	decomposed
6	**12**, BBr_3 (4.5 equiv.), −60 °C to 0 °C, 5 h	34%
7	**12**, BCl_3 (4.5 equiv.), −60 °C to 0 °C, 5 h	39%
8	**12**, $TiCl_4$ (4.5 equiv.), 0 °C, 15 min, RT, 1.5 h	32%
9	**14**, $AlCl_3$ (3.0 equiv.), 0 °C, 15 min, RT, 4 h	82% recovered
10	**14**, BCl_3 (3.0 equiv.), 0 °C, 15 min, RT, 3 h	76% recovered

[a] Reactions were carried out in CH_2Cl_2.

reaction conditions, such as reflux, resulted in decomposition of the starting material. It is surprising that the C9 OMe group resisted the demethylation with the common Lewis acids tested. In contrast, the C9 OMe was quite selectively demethylated in the presence of the C7 OMe group using BCl_3 in our ventiloquinone L synthesis.[11j] We also treated isolated **14** with $AlCl_3$. However partial decomposition and recovery of **14** (82%) occurred (Table 1, entry 9). Similar results were obtained with BCl_3 (entry 10, 76% recovery of **14**). Compound **14** is the methyl analogue of **1**. Since excess Lewis acids were used, we did not recover any starting material (**12** or **13**, entries 1–3 and 6–8), which might have partially decomposed, nor did we isolate any other compounds.



Scheme 3. Formal synthesis of (−)-thysanone **1**. Bn = benzyl.

We next considered a different strategy based on benzyl as the protecting group, which could be removed by hydrogenolysis. The revised strategy is shown in Scheme 3. The one-pot regioselective tosylation of **15** followed by benzylation gave **16** in 86% yield. Hydrolysis of aryl tosylate **16** afforded the bromophenol **17** in 84% yield, which, on subsequent TBS protection, delivered **18** in 97% yield, which is a precursor for Fischer carbene synthesis. The Fischer carbene **19** was prepared from **18** in a good yield of 62% yield. The Dötz benzannulation reaction of **19** with alkyne **7** gave the naphthol **20** in a moderate yield of 52%. Methylation of naphthol **20** under mild conditions (K_2CO_3, MeI, and acetone) at room temperature provided **21** in 87% yield. Removal of both TBS groups from **21** gave the desired alcohol **22** in 93% yield. The alcohol **22** was subjected to an oxa-Pictet-Spengler reaction with trimethyl orthoformate in the presence of catalytic amount of *p*-TsOH·H_2O to provide the *trans*-configured pyran **23** exclusively in excellent an yield of 81%. Protection of the C7 OH group of **23** as its benzyl ether under reflux conditions furnished **24** in 86% yield. It might appear as if dibenzylated compound from **15** could be used directly to get **24**. However, we have observed in our laboratory from earlier work that the dibenzyl or the dimethyl ether of **15** gives lower yields in the Dötz benzannulation reaction.[11i]

The oxidation of **24** with PIFA resulted in quinone **25** in a good yield of 83%. Hydrogenolysis of **25** with H_2 in the presence of Pd/C gave the hydroxyquinone **26** in 79% yield with unexpected demethoxylation at the C1 position. The spectral data of **26** was in excellent agreement with that reported.[5b,6a,b] Reducing the reaction time of hydrogenolysis resulted in incomplete reactions and lower yields of **26** with the recovery of unreacted **25**. The demethoxylation is more facile than the debenzylation. Nevertheless, compound **26** is an intermediate reported by Donner and Gill,[5] and recently by Brimble and coworkers,[6c] and can be converted efficiently through bromination-hydrolysis into (−)-thysanone **1**. Thus, this completes the formal synthesis of (−)-thysanone **1**.

Conclusions

In conclusion, a concise formal synthesis of (−)-thysanone has been achieved. The synthetic strategy features an efficient combination of Dötz benzannulation of a Fischer carbene with a chiral alkyne to construct the naphthalene unit, and an oxa-Pictet-Spengler reaction to install the pyran ring as the key steps. The synthesis also contains substrate-specific reactions, such as *ortho*-quinone formation (from compound **9**), resistance to demethylation of compounds **12** or **13**, and C1 OMe demethylation (compound **25**).

Experimental Section

Flasks were oven- or flame-dried and cooled in a desiccator. Anhydrous reactions were carried out under an atmosphere of Ar or N_2. Solvents and reagents were purified by standard methods. Thin layer chromatography was performed on EM 250 Kieselgel 60 F254 silica gel plates. The spots were visualized by staining with $KMnO_4$ or by UV lamp. ^{1}H NMR and ^{13}C NMR spectroscopy were recorded at 400 and 100 MHz, respectively, and chemical shifts are based on the tetramethylsilane signal at $\delta = 0.00$ ppm for ^{1}H NMR and $CDCl_3$

signal at $\delta = 77.00$ ppm (t) in ^{13}C NMR. IR samples were prepared by evaporation from $CHCl_3$ on CsBr plates. High-resolution mass spectra were obtained using positive electrospray ionization mode. Compound **5** was prepared by a literature procedure reported by us.[11k]

(*S*)-*tert*-Butyl{1-[7-(*tert*-butyldimethylsilyloxy)-1,4,5-trimethoxynaphthalen-2-yl]propan-2-yloxy}dimethylsilane (8): To a stirred solution of **5** (0.5 g, 0.986 mmol) in anhydrous acetone (15 mL) were added K_2CO_3 (0.34 g, 2.465 mmol, 2.5 equiv.) and MeI (0.15 mL, 2.465 mmol, 2.5 equiv.). The reaction mixture was stirred for 36 h at room temperature. The solvent was concentrated under reduced pressure and the residue was diluted with water and EtOAc (1:1, 20 mL). The separated aqueous layer was extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1–4:1) as eluent to afford **8** (0.435 g, 92%) as a colorless oil; $[\alpha]_D^{25} = +15.4$ ($c = 0.65$, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 2956$, 2931, 2858, 1603, 1586, 1507, 1471, 1464, 1455, 1404, 1379, 1255, 1192, 1154, 1124, 1085, 1045, 998, 981, 939, 859, 838, 777, 667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS): $\delta = -0.16$ (s, 3H), −0.05 (s, 3H), 0.28 (s, 6H), 0.83 (s, 9H), 1.02 (s, 9H), 1.19 (d, $J = 6.1$ Hz, 3H), 2.77 (dd, $J = 13.1$, 5.8 Hz, 1H), 2.90 (dd, $J = 13.1$, 7.1 Hz, 1H), 3.80 (s, 3H), 3.91 (s, 3H), 3.93 (s, 3H), 4.15–4.21 (m, 1H), 6.42 (d, $J = 2.2$ Hz, 1H), 6.53 (s, 1H), 6.99 ppm (d, $J = 2.2$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -4.9$, −4.9, −4.3, 18.1, 18.3, 23.9, 25.8, 25.9, 40.7, 56.3, 56.6, 61.2, 69.2, 102.1, 107.4, 113.2, 128.4, 131.9, 146.8, 153.0, 154.3, 158.6 ppm; HRMS: *m/z*: calcd for $[C_{28}H_{48}O_5Si_2+K]^+$: 559.2677; found: 559.2670.

(*S*)-7-(2-Hydroxypropyl)-4,5,8-trimethoxynaphthalen-2-ol (4): To a stirred solution of **8** (0.43 g, 0.825 mmol) in CH_3OH (10 mL) was added 2 N HCl (1 mL) at room temperature and then stirred for 4 h at the same temperature. The solvent was evaporated under reduced pressure and the residue was diluted with water and EtOAc (1:1, 20 mL). The separated aqueous layer was extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (3:1–1:1) as eluent to afford **4** (0.232 g, 96%) as a colorless amorphous solid; $[\alpha]_D^{25} = +39.3$ ($c = 0.8$, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 3409$, 3011, 2966, 2935, 2841, 1621, 1607, 1594, 1515, 1464, 1455, 1408, 1383, 1360, 1270, 1241, 1192, 1177, 1150, 1117, 1082, 1036, 1004, 934, 840 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS): $\delta = 1.30$ (d, $J = 6.2$ Hz, 3H), 2.89 (d, $J = 5.9$ Hz, 2H), 3.35 (s, 1H, *OH*), 3.75 (s, 3H), 3.91 (s, 6H), 4.14–4.21 (m, 1H), 6.43 (s, 1H), 6.48 (d, $J = 2.3$ Hz, 1H), 6.89 ppm (d, $J = 2.3$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 23.1$, 40.3, 56.1, 56.5, 60.1, 69.0, 96.6, 98.6, 105.9, 112.5, 127.5, 132.1, 146.0, 153.6, 155.6, 158.7 ppm; HRMS: *m/z*: calcd for $[C_{16}H_{20}O_5+H]^+$: 293.1389; found: 293.1379.

(1*R*,3*S*)-1,5,9,10-Tetramethoxy-3-methyl-3,4-dihydro-1*H*-benzo[*g*]isochromen-7-ol (9): To a solution of alcohol **4** (0.2 g, 0.684 mmol) in CH_2Cl_2 (10 mL) were added trimethyl orthoformate (0.74 mL, 6.84 mmol, 10.0 equiv.) and *p*-TsOH·H_2O (11 mg, 0.0684 mmol, 0.1 equiv.). The reaction mixture was stirred at room temperature for 2 h. It was then quenched with sat. aq. $NaHCO_3$ (8 mL) and the solution extracted with CH_2Cl_2 (3×15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1–4:1) as eluent to afford **9** (0.202 g, 88%) as a colorless solid; m.p. 81–83 °C; $[\alpha]_D^{25} = -69.8$ ($c = 0.7$, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 3367$, 3014, 2971, 2936, 2842, 1623, 1588, 1507, 1467, 1452, 1434, 1416, 1390, 1353, 1337, 1265, 1236, 1194, 1130, 1116, 1082, 1066, 1045, 977, 949, 846, 667 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS): $\delta = 1.42$ (d, $J = 6.2$ Hz, 3H), 2.54 (dd, $J = 17.0$, 11.6 Hz, 1H), 3.01 (dd, $J = 17.0$, 3.2 Hz, 1H), 3.59 (s, 3H), 3.73 (s, 3H), 3.84 (s, 3H), 3.85 (s, 3H), 4.33–4.39 (m, 1H), 5.84 (s, 1H), 6.41 (d, $J = 2.0$ Hz, 1H), 6.92 ppm (d, $J = 2.0$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.5$, 30.1, 54.9, 55.8, 60.2, 61.9, 63.0, 96.0, 96.2, 98.1, 114.8, 122.2, 124.7, 131.7, 147.1, 150.9, 154.9, 158.1 ppm; HRMS: *m/z*: calcd for $[C_{18}H_{22}O_6+Na]^+$: 357.1314; found: 357.1320.

(1*R*,3*S*)-1,5,9,10-Tetramethoxy-3-methyl-3,4-dihydro-1*H*-benzo[*g*]isochromene-6,7-dione (11): To a stirred solution of **9** (15 mg, 0.045 mmol) in CH_3CN (3 mL) and water (3 mL) was added phenyliodine bis(trifluoroacetate) (PIFA, 29 mg, 0.068 mmol, 1.5 equiv.). The reaction mixture was stirred at 0 °C for 5 min. It was then diluted with EtOAc (10 mL) and the organic layer separated. The aqueous layer was extracted with EtOAc (3×5 mL) and the combined organic extracts were washed with water and brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (4:1–3:1) as eluent to afford **11** (11.4 mg, 73%) as a yellow solid; m.p. 168 °C (decomp.); $[\alpha]_D^{25} = -87.3$ ($c = 0.2$, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 3020$, 2928, 2854, 1744, 1651, 1624, 1601, 1560, 1463, 1289, 1261, 1163, 1070, 1039, 941, 862, 844, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS): $\delta = 1.42$ (d, $J = 6.2$ Hz, 3H), 2.42 (dd, $J = 18.1$, 11.5 Hz, 1H), 2.92 (dd, $J = 18.1$, 3.4 Hz, 1H), 3.58 (s, 3H), 3.82 (s, 3H), 3.84 (s, 3H), 4.02 (s, 3H), 4.22–4.30 (m, 1H), 5.61 (s, 1H), 5.96 ppm (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.2$, 29.8, 55.3, 57.1, 61.5, 61.7, 63.6, 94.7, 102.7, 122.1, 123.0, 136.4, 138.6, 152.8, 157.5, 170.4, 179.2, 179.5 ppm; HRMS: *m/z*: calcd for $[C_{18}H_{20}O_7+Na]^+$: 371.1107; found: 371.1112.

(1*R*,3*S*)-7-Isopropoxy-1,5,9,10-tetramethoxy-3-methyl-3,4-dihydro-1*H*-benzo[*g*]iso-chromene (3): To a stirred solution of **9** (160 mg, 0.48 mmol) in anhydrous acetone (10 mL) were added K_2CO_3 (166 mg, 1.20 mmol, 2.5 equiv.), isopropyl bromide (0.092 mL, 0.98 mmol, 2.0 equiv.), and TBAI (cat.). The reaction mixture was refluxed for 18 h. The solvent was evaporated under reduced pressure and the residue was diluted with water and EtOAc (1:1, 20 mL). The separated aqueous layer was extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1–4:1) as eluent to afford **3** (160 mg, 89%) as a colorless amorphous solid; $[\alpha]_D^{25} = -53.0$ ($c = 0.4$, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 2972$, 2928, 2853, 1619, 1601, 1583, 1465, 1451, 1384, 1369, 1337, 1259, 1232, 1196, 1161, 1116, 1083, 1046, 992, 916, 668 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS): $\delta = 1.40$–1.43 (m, 9H), 2.54 (dd, $J = 17.0$, 11.6 Hz, 1H), 3.02 (dd, $J = 17.0$, 3.3 Hz, 1H), 3.58 (s, 3H), 3.81 (s, 3H), 3.85 (s, 3H), 3.96 (s, 3H), 4.32–4.40 (m, 1H), 4.70–4.79 (m, 1H), 5.83 (s, 1H), 6.47 (d, $J = 2.1$ Hz, 1H), 6.93 ppm (d, $J = 2.1$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.6$, 21.9, 22.0, 30.2, 54.9, 55.9, 60.3, 61.9, 63.1, 69.6, 94.3, 96.1, 99.6, 115.0, 122.5, 124.7, 131.7, 147.5, 150.9, 156.6, 157.8 ppm; HRMS: *m/z*: calcd for $[C_{21}H_{28}O_6+H]^+$: 377.1964; found: 377.1959.

(1*R*,3*S*)-7-Isopropoxy-1,9-dimethoxy-3-methyl-3,4-dihydro-1*H*-benzo[*g*]isochromene-5,10-dione (12) and (1*R*,3*S*)-1-Hydroxy-7-isopropoxy-9-methoxy-3-methyl-3,4-dihydro-1*H*-benzo[*g*]iso-chromene-5,10-dione (13): To a stirred solution of **3** (140 mg, 0.372 mmol) in CH_3CN (5 mL) and water (5 mL) was added PIFA (192.8 mg, 0.446 mmol, 1.2 equiv.). The reaction mixture was stirred at 0 °C for 5 min. It was then diluted with EtOAc (10 mL) and the organic layer separated. The aqueous layer was extracted with EtOAc (3×10 mL) and the combined organic extracts were washed with water and brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (4:1–3:1) as eluent to afford **12** (69.6 mg, 54%) as a yellow solid. Further elution with petroleum ether/EtOAc (3:1–

1:1) as eluent gave **13** (44.5 mg, 36%) as a yellow solid. Data for **12**: m.p. 103–105 °C; $[\alpha]_D^{25} = +44.5$ ($c = 0.5$, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu}$ = 2926, 2853, 1743, 1660, 1594, 1559, 1464, 1347, 1315, 1275, 1196, 1162, 1111, 1093, 1052, 1020, 969, 926, 821, 693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS): $\delta = 1.35$–1.38 (m, 9H), 2.20 (ddd, $J = 19.2$, 11.2, 0.7 Hz, 1H), 2.63 (dd, $J = 19.2$, 3.5 Hz, 1H), 3.55 (s, 3H), 3.93 (s, 3H), 4.16–4.21 (m, 1H), 4.72–4.78 (m, 1H), 5.52 (s, 1H), 6.68 (d, J = 2.4 Hz, 1H), 7.18 ppm (d, $J = 2.4$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 20.9$, 21.9, 28.9, 56.2, 56.3, 62.0, 70.8, 93.7, 104.2, 105.6, 113.7, 135.6, 140.3, 140.9, 162.1, 163.0, 180.7, 185.0 ppm; HRMS: *m/z*: calcd for $[C_{19}H_{22}O_6+Na]^+$: 369.1309; found: 369.1306. Data for **13**: m.p. 128–130 °C; $[\alpha]_D^{25} = +58.3$ ($c = 1.0$, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu}$ = 3453, 3092, 3010, 2978, 2931, 1651, 1641, 1591, 1558, 1463, 1417, 1381, 1349, 1317, 1273, 1197, 1161, 1111, 1083, 1030, 1008, 960, 923, 850, 810, 729, 682 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS): δ = 1.39 (d, $J = 6.2$ Hz, 3H), 1.40 (d, $J = 6.1$ Hz, 6H), 2.22 (ddd, $J = 19.1$, 11.1, 0.8 Hz, 1H), 2.69 (dd, $J = 19.1$, 3.2 Hz, 1H), 3.72 (d, $J = 3.5$ Hz, 1H, *OH*), 3.95 (s, 3H), 4.28–4.35 (m, 1H), 4.74–4.4.80 (m, 1H), 6.03 (d, $J = 2.5$ Hz, 1H), 6.70 (d, $J = 2.4$ Hz, 1H), 7.22 ppm (d, $J = 2.4$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 20.9$, 21.8, 28.8, 56.2, 62.5, 70.8, 86.8, 104.3, 105.3, 113.3, 135.4, 140.0, 142.1, 162.0, 163.1, 181.5, 184.6 ppm; HRMS: *m/z*: calcd for $[C_{18}H_{20}O_6+Na]^+$: 355.1152; found: 355.1149.

(1*R*,3*S*)-1,7-Dihydroxy-9-methoxy-3-methyl-3,4-dihydro-1*H*-benzo[*g*]isochromene-5,10-dione (14): To a solution of **12** (20 mg, 0.058 mmol) in anhydrous CH_2Cl_2 (10 mL) was added $AlCl_3$ (35 mg, 0.261 mmol, 4.5 equiv.) in portions at 0 °C and the reaction mixture was stirred for 15 min. The ice bath was removed and stirring was continued at room temperature for 2 h. It was then quenched with water (5 mL) and the solution extracted with CH_2Cl_2 (5×15 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel flash column chromatography using petroleum ether/EtOAc (3:1–1:1) as eluent to provide **14** (10.6 mg, 63%) as a yellow solid; m.p. 173–175 °C; $[\alpha]_D^{25} = +14.0$ ($c = 0.16$, $CHCl_3$); IR (KBr_3): $\tilde{\nu}$ = 3449, 3204, 2967, 2928, 2853, 1777, 1656, 1626, 1601, 1561, 1465, 1429, 1365, 1334, 1350, 1294, 1276, 1197, 1162, 1121, 1078, 1031, 963, 923, 833 cm^{-1}; ^1H NMR (400 MHz, CD_3OD): $\delta = 1.32$ (d, $J = 6.3$ Hz, 3H), 2.11 (dd, $J = 18.7$, 11.1 Hz, 1H), 2.60 (dd, $J = 18.7$, 3.4 Hz, 1H), 3.89 (s, 3H), 4.21–4.26 (m, 1H), 5.87 (s, 1H), 6.72 (d, $J = 2.3$ Hz, 1H), 7.03 ppm (d, $J = 2.3$ Hz, 1H); ^{13}C NMR (100 MHz, CD_3OD): $\delta = 21.4$, 30.1, 56.9, 63.0, 87.6, 105.3, 107.7, 113.7, 137.1, 141.7, 143.5, 164.0, 165.3, 182.5, 186.0 ppm; HRMS: *m/z*: calcd for $[C_{15}H_{14}O_6+K]^+$: 329.0422; found: 329.0424.

3-(Benzyloxy)-4-bromophenyl 4-methylbenzenesulfonate (16): To a stirred solution of 4-bromoresorcinol (**15**, 2.0 g, 10.58 mmol) in anhydrous acetone (60 mL) were added K_2CO_3 (7.31 g, 52.91 mmol, 5.0 equiv.) and TsCl (2.12 g, 11.1 mmol, 1.05 equiv.). The reaction mixture was refluxed for 16 h and then cooled to room temperature. To the reaction mixture was added BnBr (1.88 mL, 15.87 mmol, 1.5 equiv.) and reflux was continued for 12 h. It was then cooled to room temperature and the precipitated solid was filtered off. The filtrate was concentrated under reduced pressure and the residue diluted with water and EtOAc (1:1, 50 mL). The separated aqueous layer was extracted with EtOAc (3× 30 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1–4:1) as eluent to afford 3-(benzyloxy)-4-bromophenyl 4-methylbenzenesulfonate (**16**, 3.94 g, 86%) as a white solid; m.p. 95–96 °C; IR ($CHCl_3$): $\tilde{\nu}$ = 3066, 3034, 2924, 2868, 1597, 1479, 1414, 1377, 1274, 1193, 1180, 1141, 1121, 1093, 1044, 1020, 965, 854, 815, 791, 729, 669 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS): $\delta = 2.43$ (s, 3H), 5.02 (s, 2H), 6.40 (dd, $J = 8.6$, 2.6 Hz, 1H), 6.69 (d, $J = 2.6$ Hz, 1H), 7.29 (d, $J = 8.0$ Hz, 1H), 7.31–7.43 (m, 6H), 7.65 ppm (d, $J = 8.3$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.7$, 70.9, 108.4, 110.6, 115.5, 127.0, 128.1, 128.5, 128.6, 129.8, 131.9, 133.3, 135.6, 145.6, 149.4, 155.5 ppm; HRMS: *m/z*: calcd for $[C_{20}H_{17}O_4BrS+Na]^+$: 454.9923; found: 454.9924.

3-(Benzyloxy)-4-bromophenol (17): To a stirred solution of 3-(benzyloxy)-4-bromophenyl 4-methylbenzenesulfonate (**16**, 3.9 g, 9.00 mmol) in ethanol (30 mL) was added KOH (1.0 g, 18.0 mmol, 2.0 equiv.). The reaction mixture was refluxed for 3 h and then cooled to room temperature. The solvent was evaporated under reduced pressure and the residue was diluted with water and EtOAc (1:1, 50 mL). The separated aqueous layer was extracted with EtOAc (3×30 mL). The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (4:1–7:3) as eluent to afford 3-(benzyloxy)-4-bromophenol (**17**, 2.11 g, 84%) as a colorless oil; IR ($CHCl_3$): $\tilde{\nu}$ = 3400, 3060, 3033, 2927, 1605, 1586, 1486, 1447, 1381, 1295, 1265, 1176, 1128, 1042, 1025, 971, 829, 738, 696 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS): $\delta = 5.06$ (s, 2H), 5.54 (s, 1H, *OH*), 6.32 (dd, $J = 8.5$, 2.7 Hz, 1H), 6.45 (d, $J = 2.7$ Hz, 1H), 7.28–7.45 (m, 5H), 7.37 ppm (d, $J = 8.6$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 70.7$, 102.2, 102.9, 109.0, 126.9, 127.9, 128.6, 133.4, 136.2, 155.7, 156.0 ppm; HRMS: *m/z*: calcd for $[C_{13}H_{11}O_2Br+Na]^+$: 300.9835; found: 300.9835.

[3-(Benzyloxy)-4-bromophenoxy](*tert*-butyl)dimethylsilane (18): To a solution of 3-(benzyloxy)-4-bromophenol (**17**, 2.0 g, 7.16 mmol) in anhydrous THF (30 mL) was added NaH (0.223 g, 9.31 mmol, 1.3 equiv.) at 0 °C and stirred for 15 min. TBSCl (1.62 g, 10.74 mmol, 1.5 equiv.) was added at 0 °C, then the mixture was slowly warmed to room temperature and stirred for 2 h. After completion of the reaction, it was quenched with sat. aq. $NaHCO_3$ (20 mL). The solvent was evaporated under reduced pressure and the aqueous layer was extracted with EtOAc (3×20 mL). The combined organic layers were washed with water and brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9.5:0.5–9:1) as eluent to afford **18** (2.73 g, 97%) as a colorless oil; IR ($CHCl_3$): $\tilde{\nu}$ = 2956, 2931, 2886, 2859, 1583, 1484, 1471, 1414, 1380, 1300, 1256, 1182, 1121, 1048, 1018, 989, 908, 842, 782, 736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS): $\delta = 0.12$ (s, 6H), 0.9 (s, 9H), 5.12 (s, 2H), 6.35 (dd, $J = 8.6$, 2.6 Hz, 1H), 6.42 (d, $J = 2.6$ Hz, 1H), 7.29–7.49 ppm (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -4.6$, 18.2, 25.6, 70.7, 103.8, 106.9, 113.7, 126.9, 127.9, 128.6, 133.1, 136.4, 155.4, 156.0 ppm; HRMS: *m/z*: calcd for $[C_{19}H_{25}BrO_2Si+Na]^+$: 415.0699; found: 415.0698.

Fischer carbene 19: To a solution of **18** (1.0 g, 2.54 mmol) in anhydrous Et_2O (25 mL) at −78 °C was added *n*BuLi (1.75 mL 2.79 mmol, 1.1 equiv., 1.6 M solution in hexane) and the reaction mixture was stirred for 20 min. It was then transferred to a suspension of $[Cr(CO)_6]$ (0.67 g, 3.05 mmol, 1.2 equiv.) in anhydrous Et_2O (25 mL) at 0 °C. The reaction mixture was stirred for 1 h at 0 °C and then at room temperature for 2 h. Et_2O was evaporated and the residue was dissolved in anhydrous CH_2Cl_2 (25 mL). To this solution was added Me_3OBF_4 (0.563 g, 3.81 mmol, 1.5 equiv.) in portions at 0 °C and the reaction mixture was stirred for 1 h. It was then warmed to room temperature and stirred for 2 h. The red-colored reaction mixture was concentrated and the residue was purified by silica gel column chromatography using petroleum ether/CH_2Cl_2 (9:1–4:1) as eluent to give **19** (0.86 g, 62%) as red amorphous solid. This was used immediately in the next step.

(*S*)-5-(Benzyloxy)-7-(*tert*-butyldimethylsilyloxy)-2-(2-(*tert*-butyl dimethylsilyloxy)propyl)-4-methoxynaphthalen-1-ol (20): To a solu-

tion of freshly prepared Fischer carbene **19** (0.86 g, 1.57 mmol) in anhydrous and degassed THF (15 mL) was added a solution of alkyne **7** (0.62 g, 3.14 mmol, 2.0 equiv.) in anhydrous and degassed THF (5 mL). The reaction mixture was heated to 45 °C for 12 h and then allowed to cool to room temperature, exposed to air, and stirred further for 1 h. THF was removed and the residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1–4:1) as eluent to afford **20** (0.475 g, 52%) as a yellow oil; $[\alpha]_D^{25} = -7.9$ ($c = 0.75$, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 3273$, 2955, 2930, 2858, 1605, 1508, 1464, 1390, 1375, 1327, 1258, 1187, 1158, 1124, 1089, 1067, 1035, 969, 839, 782 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS): $\delta = -0.09$ (s, 3H), 0.05 (s, 3H), 0.23 (s, 3H), 0.24 (s, 3H), 0.89 (s, 9H), 1.00 (s, 9H), 1.24 (d, $J = 6.0$ Hz, 3H), 2.89 (d, $J = 5.2$ Hz, 2H), 3.86 (s, 3H), 4.23–4.30 (m, 1H), 5.17 (s, 2H), 6.41 (s, 1H), 6.52 (d, $J = 2.4$ Hz, 1H), 7.30 (d, $J = 7.4$ Hz, 1H), 7.32 (d, $J = 7.4$ Hz, 1H), 7.40 (t, $J = 7.5$ Hz, 2H), 7.60 (d, $J = 7.5$ Hz, 2H), 8.06 ppm (s, 1H, *OH*); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -5.2$, −4.8, −4.4, −4.37, 18.0, 18.3, 23.2, 25.77, 25.8, 41.8, 57.4, 71.1, 71.8, 103.3, 104.5, 109.0, 114.0, 118.9, 127.0, 127.4, 128.3, 129.7, 137.5, 144.2, 150.3, 153.4, 156.6 ppm; HRMS: *m/z*: calcd for $[C_{33}H_{50}O_5Si_2+K]^+$: 621.2828; found: 621.2815.

(*S*)-{4-(Benzyloxy)-7-[2-(*tert*-butyldimethylsilyloxy)propyl]-5,8-dimethoxynaphthalen-2-yloxy}(*tert*-butyl)dimethylsilane (21): The title compound was prepared from **20** (0.45 g, 0.772 mmol) by similar procedure as described for conversion of **5** into **8** to give **21** (0.4 g, 87%) as a yellow oil; $[\alpha]_D^{25} = +7.4$ ($c = 1.0$, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 2955$, 2931, 2858, 1621, 1603, 1583, 1507, 1463, 1409, 1374, 1255, 1178, 1154, 1126, 1091, 1046, 998, 939, 867, 837, 778, 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS): $\delta = -0.13$ (s, 3H), −0.03 (s, 3H), 0.24 (s, 6H), 0.84 (s, 9H), 1.00 (s, 9H), 1.19 (d, $J = 6.0$ Hz, 3H), 2.77 (dd, $J = 13.1$, 6.0 Hz, 1H), 2.92 (dd, $J = 13.1$, 6.9 Hz, 1H), 3.81 (s, 3H), 3.89 (s, 3H), 4.17–4.22 (m, 1H), 5.17 (s, 2H), 6.50 (d, $J = 2.2$ Hz, 1H), 6.54 (s, 1H), 7.02 (d, $J = 2.2$ Hz, 1H), 7.30 (t, $J = 7.3$ Hz, 1H), 7.40 (t, $J = 7.5$ Hz, 2H), 7.58 ppm (d, $J = 7.5$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = -4.93$, −4.91, −4.46, −4.32, 18.1, 18.3, 23.9, 25.6, 25.7, 25.8, 40.7, 56.4, 61.2, 69.2, 71.2, 102.7, 104.4, 107.4, 113.3, 113.8, 126.9, 127.5, 128.3, 128.4, 131.9, 137.4, 146.7, 153.1, 154.2, 157.5 ppm; HRMS: *m/z*: calcd for $[C_{34}H_{52}O_5Si_2+H]^+$: 597.3426; found: 597.3417.

(*S*)-4-(Benzyloxy)-7-(2-hydroxypropyl)-5,8-dimethoxynaphthalen-2-ol (22): The title compound was prepared from **21** (0.35 g, 0.586 mmol) by similar procedure as described for conversion of **8** into **4** to give **22** (0.201 g, 93%) as a colorless amorphous solid; $[\alpha]_D^{25} = +26.3$ (*c* 0.4, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 3401$, 2965, 2931, 2851, 1621, 1607, 1594, 1454, 1415, 1374, 1313, 1270, 1240, 1178, 1151, 1120, 1084, 1070, 1037, 1004, 977, 935, 844, 753, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS): $\delta = 1.30$ (d, $J = 6.2$ Hz, 3H), 2.90 (d, $J = 5.8$ Hz, 2H), 3.76 (s, 3H), 3.88 (s, 3H), 4.16–4.21 (m, 1H), 5.14 (s, 2H), 6.44 (s, 1H), 6.55 (s, 1H), 6.92 (s, 1H), 7.32 (t, $J = 7.3$ Hz, 1H), 7.39 (t, $J = 7.4$ Hz, 2H), 7.55 ppm (d, $J = 7.5$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 23.2$, 40.5, 56.5, 61.0, 69.1, 71.1, 97.1, 100.3, 106.2, 113.3, 126.9, 127.55, 127.6, 128.3, 132.1, 137.2, 146.1, 154.0, 155.2, 158.1 ppm; HRMS: *m/z*: calcd for $[C_{22}H_{24}O_5+K]^+$: 407.1255; found: 407.1250.

(1*R*,3*S*)-9-(Benzyloxy)-1,5,10-trimethoxy-3-methyl-3,4-dihydro-1*H*-benzo[*g*]isochromen-7-ol (23): The title compound was prepared from **22** (0.150 g, 0.407 mmol) by similar procedure as described for conversion of **4** into **9** to give **23** (0.135 g, 81%) as a light-yellow solid; m.p. 102–103 °C; $[\alpha]_D^{25} = -97.8$ (*c* 1.0, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 3359$, 2972, 2935, 2846, 1621, 1585, 1507, 1448, 1418, 1378, 1336, 1287, 1264, 1235, 1167, 1129, 1086, 1063, 1044, 972, 840, 699 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS): $\delta = 1.42$ (d, $J = 6.2$ Hz, 3H), 2.54 (dd, $J = 17.0$, 11.6 Hz, 1H), 3.01 (dd, $J = 17.0$, 3.2 Hz, 1H), 3.56 (s, 3H), 3.72 (s, 3H), 3.74 (s, 3H), 4.32–4.43 (m, 1H), 5.05 (dd, $J = 18.6$, 11.5 Hz, 2H), 5.85 (s, 1H), 6.36 (s, 1H), 6.51 (d, $J = 2.0$ Hz, 1H), 6.95 (d, $J = 2.0$ Hz, 1H), 7.30–7.40 (m, 3H), 7.48 ppm (d, $J = 7.0$ Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.4$, 30.1, 54.7, 60.1, 61.9, 63.3, 71.0, 96.0, 96.6, 99.7, 115.0, 122.2, 124.7, 127.7, 127.9, 128.4, 131.9, 136.3, 147.0, 151.1, 154.9, 157.2 ppm; HRMS: *m/z*: calcd for $[C_{24}H_{26}O_6+K]^+$: 449.1366; found: 449.1362.

(1*R*,3*S*)-7,9-Bis(benzyloxy)-1,5,10-trimethoxy-3-methyl-3,4-dihydro-1*H*-benzo[*g*]isochromene (24): To a stirred solution of **23** (80 mg, 0.195 mmol) in anhydrous acetone (10 mL) were added K_2CO_3 (67 mg, 0.487 mmol, 2.5 equiv.), benzyl bromide (34.7 μL, 0.292 mmol, 1.5 equiv.), and TBAI (cat.). The reaction mixture was refluxed for 16 h. The solvent was evaporated under reduced pressure and the residue was diluted with water and EtOAc (1:1, 20 mL). The separated aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (9:1–3:1) as eluent to afford **24** (97.5 mg, 86%) as a colorless solid; m.p. 123–125 °C; $[\alpha]_D^{25} = +92.2$ (*c* 0.5, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 3031$, 2972, 2932, 1619, 1600, 1583, 1499, 1455, 1429, 1371, 1339, 1260, 1233, 1165, 1133, 1087, 1064, 1046, 1006, 972, 911, 829, 698 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS): $\delta = 1.43$ (d, $J = 6.2$ Hz, 3H), 2.55 (dd, $J = 17.0$, 11.6 Hz, 1H), 3.02 (dd, $J = 17.0$, 3.3 Hz, 1H), 3.56 (s, 3H), 3.73 (s, 3H), 3.75 (s, 3H), 4.31–4.47 (m, 1H), 5.13–5.21 (m, 4H), 5.84 (s, 1H), 6.67 (d, $J = 2.2$ Hz, 1H), 7.03 (d, $J = 2.2$ Hz, 1H), 7.32–7.55 ppm (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.5$, 30.2, 54.7, 60.2, 61.8, 63.4, 71.0, 71.2, 94.2, 96.0, 100.4, 115.7, 123.0, 124.9, 127.7, 127.9, 128.1, 128.5, 128.6, 129.8, 131.6, 136.6, 136.8, 147.7, 151.1, 156.9, 157.4 ppm; HRMS: *m/z*: calcd for $[C_{31}H_{32}O_6+Na]^+$: 523.2091; found: 523.2093.

(1*R*,3*S*)-7,9-Bis(benzyloxy)-1-methoxy-3-methyl-3,4-dihydro-1*H*-benzo[*g*]isochromene-5,10-dione (25): To a stirred solution of **24** (50.0 mg, 0.10 mmol) in CH_3CN (5 mL) and water (5 mL) was added PIFA (51.6 mg, 0.12 mmol, 1.2 equiv.). The reaction mixture was stirred at 0 °C for 10 min. It was then diluted with EtOAc (10 mL) and the organic layer was separated. The aqueous layer was extracted with EtOAc (3 × 10 mL) and the combined organic extracts were washed with water and brine, dried (Na_2SO_4), and concentrated. The residue was purified by silica gel column chromatography using petroleum ether/EtOAc (4:1–3:1) as eluent to afford **25** (39.0 mg, 83%) as a yellow solid; m.p. 187–188 °C; $[\alpha]_D^{25} = +41.9$ (*c* 0.3, $CHCl_3$); IR ($CHCl_3$): $\tilde{\nu} = 3065$, 3014, 2973, 2930, 2829, 1659, 1594, 1567, 1498, 1455, 1384, 1318, 1275, 1168, 1125, 1092, 1051, 1034, 965, 925, 875, 845, 820, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$/TMS): $\delta = 1.38$ (d, $J = 6.3$ Hz, 3H), 2.22 (ddd, $J = 19.1$, 11.2, 0.7 Hz, 1H), 2.66 (dd, $J = 19.1$, 3.5 Hz, 1H), 3.58 (s, 3H), 4.11–4.25 (m, 1H), 5.12 (s, 2H), 5.22 (s, 2H), 5.58 (s, 1H), 6.79 (d, $J = 2.5$ Hz, 1H), 7.31 (d, $J = 2.4$ Hz, 1H), 7.32–7.53 ppm (m, 10H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 20.9$, 29.0, 56.1, 61.9, 70.6, 70.8, 93.6, 104.4, 106.6, 114.8, 126.7, 127.7, 127.9, 128.5, 128.7, 135.6, 136.0, 140.5, 140.9, 160.8, 163.3, 180.4, 184.8 ppm; HRMS: *m/z*: calcd for $[C_{29}H_{26}O_6+H]^+$: 471.1802; found: 471.1808.

(*S*)-7,9-Dihydroxy-3-methyl-3,4-dihydro-1*H*-benzo[*g*]isochromene-5,10-dione (26): To a solution of **25** (20.0 mg, 0.042 mmol) in EtOAc (5 mL) was added Pd/C (10%, 5 mg). The resulting reaction mixture was stirred at room temperature under an H_2 atmosphere (balloon pressure) for 3 h. Then EtOAc was removed under reduced pressure and the residue was purified by silica gel column chromatography using CH_2Cl_2/EtOAc (4:1) as eluent to afford **26** (8.7 mg, 79%) as an orange solid; m.p. 174–176 °C; $[\alpha]_D^{25} = +154.5$ ($c = 0.3$, MeOH); lit.[5b] $[\alpha]_D = +160$ ($c = 0.28$, MeOH); IR ($CHCl_3$): $\tilde{\nu} =$ 3418, 2930, 2853, 1641, 1614, 1318, 1243, 1154, 1090, 1037, 976,

775 cm^{-1}; ^1H NMR (400 MHz, [D_6]acetone): $\delta = 1.30$ (d, $J = 6.2$ Hz, 3H), 2.22 (ddd, $J = 19.1$, 11.2, 0.7 Hz, 1H), 2.67 (dt, $J = 18.8$, 2.8 Hz, 1H), 3.65–3.73 (m, 1H), 4.44 (dt, $J = 14.9$, 3.7 Hz, 1H), 4.72 (dd, $J = 18.6$, 2.2 Hz, 1H), 6.57 (d, $J = 2.1$ Hz, 1H), 7.04 (d, $J = 2.1$ Hz, 1H), 12.08 ppm (s, 1H); ^{13}C NMR (100 MHz, [D_6]acetone): $\delta = 21.5$, 30.1, 63.4, 70.1, 108.1, 109.1, 109.4, 135.0, 143.0, 143.6, 165.0, 165.3, 183.5, 187.8 ppm; HRMS: *m/z*: calcd for $[C_{14}H_{12}O_5+H]^+$: 261.0763; found: 261.0768.

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FULL PAPER

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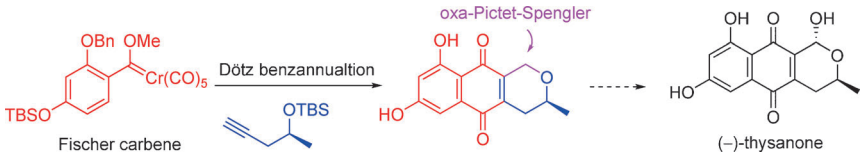
■■ – ■■

Formal Synthesis of the Human Rhinovirus 3C Protease Inhibitor (−)-Thysanone



Join the Dötz: A concise formal synthesis of the human rhinovirus 3C protease inhibitor (−)-thysanone employing the Dötz benzannulation and oxa-Pictet–Spengler reactions as key steps is reported.