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ARTICLE TYPE

Total Synthesis of Gonytolides C and G, Lachnone C, and Formal Synthesis of Blennolide C and Diversonol

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The first stereoselective total synthesis of gonytolide C, which is a monomeric unit of an innate immune promoter gonytolide A, has been accomplished from the aldol reaction between acetophenone derived from orcinol and butyrolactone containing α-keto ester followed by the excellent diastereoselective intramolecular cyclization. The first total synthesis of gonytolide G has been achieved by the oxidation of benzylic methyl in gonytolide C. Additionally, total synthesis of lachnone C and a formal synthesis of blennolide C and diversonol have been achieved from this synthetic method.

Introduction

Chromanones substituted with the γ-lactone moiety is, as a subunit, monomeric and dimeric units (symmetrical and unsymmetrical, homo and hetero) encountered in a vast array of synthetically challenging and biologically significant natural products. It is found as a subunit in ergoxanthin,[1] xanthoquinodin A3,[2] and B3,[3] chaetomanone,[4] blennolide G;[5] an unsymmetrical hetero dimer in noduliprevenone,[6] monodictyochrome A and B;[7] as a homo dimer in paecilin A,[8] phomopsis-H76 A.[9] Recently, Kikuchi et. al., reported the isolation of gonytolides A-G bearing both monomeric and dimeric chromanones substituted with the γ-lactone moiety (symmetrical, unsymmetrical and as a subunit) from the fungus *Gonytrichum sp*. during a screen for innate immune regulators from natural sources.[10] Gonytolide A (**1**) and its derivatives have been identified as innate immune promoters. This axially chiral dimeric chromanone **1**, which also increased TNF-α-stimulated production of IL-8 in human umbilical vein endothelial cells, is composed with two monomeric units of gonytolide C (**2**). Gonytolide B[10a] is an unsymmetrical dimer while gonytolides D-F are unsymmetrical hetero dimers.[10b] Gonytolide G (**3**) differs from that of gonytolide C by one oxygen atom (benzylic methyl group is replaced by a hydroxymethyl group) (Figure 1). Apart from gonytolides, chromanones substituted with the γ-lactone moiety as a monomeric unit was found earlier in several other natural products such as lachnones C-E (**4-6**),[11] microdiplodiasone (**7**),[12] paecilin B (**8**),[8] and blennolides D-F (**9-11**)[5] (Figure 1).

Synthetic approaches towards this biologically important and synthetically challenging framework are very limited, and only two syntheses are available. The first one, en route to the synthesis of blennolide C by Porco et. al.,[13] reported the mixture of (±)-gonytolide C and (±)-*epi*-gonytolide C in racemic form before the isolation of gonytolides. The second approach for this framework has been reported by Bräse et. al., for the synthesis of lachnone C.[14] Herein, we disclose the total synthesis of gonytolides C (**2**), [12] G (**3**), lachnone C (**4**) and formal synthesis of blennolide C and diversonol by developing a short and efficient novel synthetic strategy.

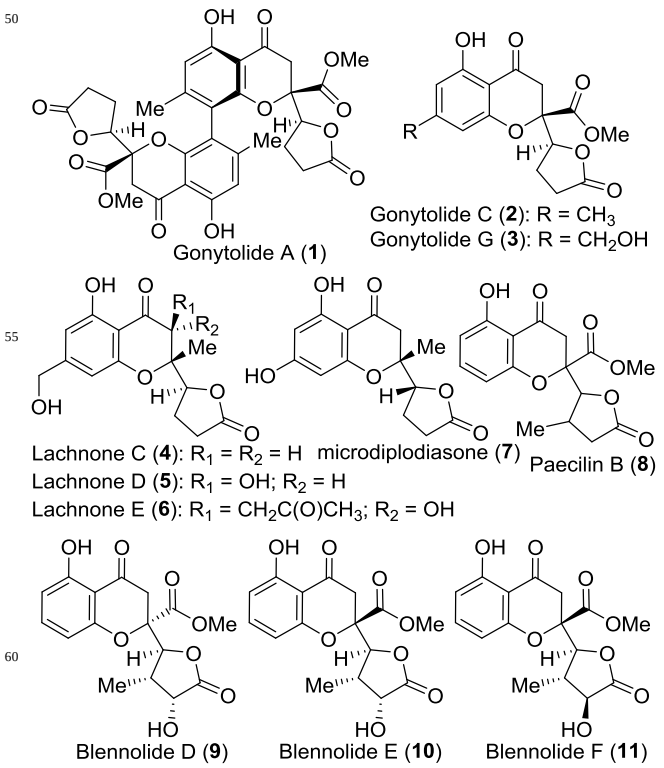


Figure 1. Gonytolides A (1), C (2), G (3), Lachnones C-E (4-6), Microdiplodiasone (7), Paecilin B (8), and Blennolides D-F (9-11).

Results and Discussion

We envisioned that developing a synthetic strategy for monomeric chromanone substituted with the γ-lactone framework would not only allow the synthesis of gonytolide C and G etc., but also the synthesis of dimeric chromanones of this class from

late-stage biaryl coupling of appropriately halogenated monomeric units. Additionally, it can also be utilized in the synthesis of biogenetically related tetrahydroxanthones, which are a larger class of mycotoxins with interesting biological activities,[15] from "retrobiomimetic" synthesis.[13]

Our plan for the synthesis of monomeric gonytolide C focused on the oxa-Michael addition of enone **12** (Figure 2) by activation with acid or base. Enone **12** was expected to derive from cross-metathesis reaction of crotonophenone **13** and methylene γ-butyrolactone **14**, and/or alternatively from aldol condensation between acetophenone **15**[13] and α-keto ester **16**. While **13** and **15** can, in turn, be synthesized from orcinol by Friedel-Crafts acylation reaction, whereas α-keto ester **16** can be synthesized from γ-butyrolactone **14** by ozonolysis.

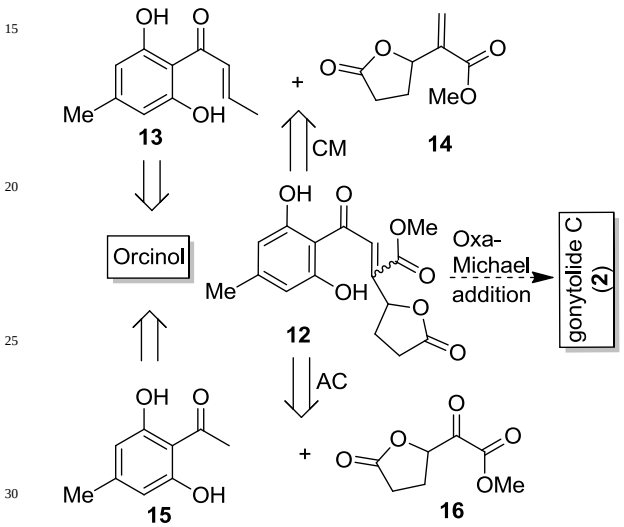
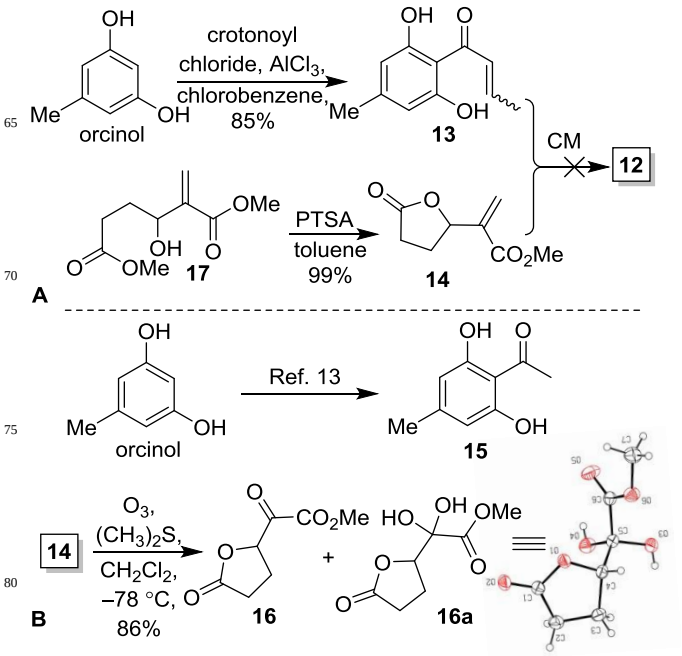


Figure 2. Synthetic plan for gonytolide C (**2**) and Retrosynthetic analysis for **12**.

Substrates **13** and **14** required for cross-metathesis reaction were prepared as shown in Scheme 1A. The synthesis of **13** was easily achieved in 85% yield from Friedel-Crafts acylation reaction between orcinol and crotonoyl chloride. Methylene γ-butyrolactone **14**[16] was derived from **17** which was synthesized from methyl 4-oxobutanoate.[16] With both fragments in hand, however, all attempts to effect cross-metathesis reaction between **13** and **14** under various conditions (Grubbs I, II and Grubbs-Hoveyda I, II (0.05 equiv to 0.3 equiv) in CH_2Cl_2, toluene, and xylene at rt and reflux) failed, and no reaction was observed. Starting materials were recovered quantitatively, but ester **14** was decomposed at higher temperatures.

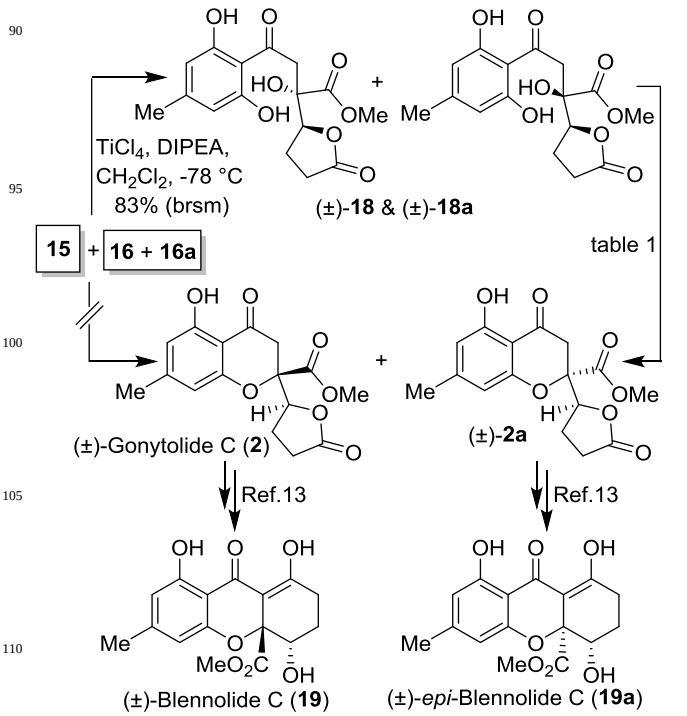
We then decided to adopt the synthesis of **12** from an alternate approach (Figure 2), aldol condensation of acetophenone **15** and α-keto-ester **16**. Accordingly, **15** was synthesized in a single step from orcinol by using Friedel-Crafts acylation reaction reported in the literature.[13] While **16** in 86% yield was derived from **14** under the ozonolysis condition (Scheme 1B). The ^1H & ^{13}C NMR spectra of **16** has shown two set of peaks : a mixture of ketone **16** and its dihydroxy derivative **16a** in the ratio 1:1, and the structure of **16a** was confirmed by the X-ray crystallographic analysis.[17]

With access to both **15** and **16**/**16a**, it was expected that the synthesis of **12** from **15** and **16**/**16a** by aldol condensation may also effect the *in situ* intramolecular oxa-Michael addition to give the target molecule (**2** and/or **2a**), directly, in one-pot. Unfortunately, attempts to a one-pot tandem aldol condensation/oxa-Michael addition reaction failed under several reaction conditions and only the decomposition of the ketone **16**



Scheme 1. A: Synthesis of **13** and **14** and attempts to synthesize **12** from cross-metathesis reaction; **B**: Synthesis of **15** and **16** & **16a**.

was observed in forced conditions such as pyrrolidine as a base in different solvents: CH_3CN, toluene, MeOH, EtOH and at various temp: rt to reflux.[18] However, much to our satisfaction, the stepwise synthesis such as aldol reaction followed by the intramolecular cyclization produced the desired product (Scheme



Scheme 2. Synthesis of (±)-Gonytolide C (**2**) and (±)-*epi*-Gonytolide C (**2a**) and formal synthesis of (±)-Blennolide C and (±)-*epi*-Blennolide C.

2). Interestingly, we found tunable diastereoselectivity at cyclization step (Table 1). After several experimentations, aldol reaction between acetophenone **15** and ketone **16**/**16a** was achieved using $TiCl_4$, DIPEA in CH_2Cl_2 at –78 °C (Scheme 2)[19] to afford column chromatographically separable diastereomers **18** and **18a** (dr 2.5:1) in 49% combined yield (83%, brsm).

With the aldol products **18** & **18a** in hand, the next task was to achieve intramolecular cyclization to get the target molecule **2**. Initially, no expected cyclization effected under a variety of conditions such as 1) PTSA in toluene/benzene at rt and reflux,[20] 2) DIAD, TPP, Et_3N in THF,[21] and 3) TFA neat as well as in benzene. Only isomerization (major aldol product to minor) was observed with $SOCl_2$, Et_3N in CH_2Cl_2 at rt for 36 h.[22] Gratifyingly, reaction with $SOCl_2$, Py in toluene at 65 °C[23] provided the desired **2** along with **2a**, which were easily separated by using column chromatography. Thus, total synthesis of the (±)-gonytolide C and (±)-*epi*-gonytolide C also became the formal synthesis of (±)-blennolide C and (±)-*epi*-blennolide C, respectively,[13] Interestingly, the diastereoselectivity and yields at cyclization stage are manoeuvred by the time and temp as shown in table 1. Importantly, **18** and **18a** either individually or together, provided the same mixture of **2** and **2a** with respect to the dr and yield. Reaction at rt for 2 h resulted **2** and **2a** in the ratio of 1.3:1 in 47% combined yield (Table 1, entry 1). Increasing the temp up to 65 °C decreased the reaction time (1 h) and increased the yield (66%) as well as dr (1.7:1) (entry 2). Increasing the temp further decreased the reaction time considerably (10 min) with no significant change in yield (67%) and dr (1.6:1) (entry 3). Running the reaction for a long time also greatly improved the diastereoselectivity towards the desired product **2**. At rt for 24 h, **2** and **2a** were obtained in the ratio of 8:1 with 40% yield (entry 4). Within 3 h at 65 °C, **2** and **2a** were obtained in 66% yield and with a dr of 6:1 (entry 5). However, the maximum distereoselectivity (**2** & **2a**, dr 18:1) was achieved despite with a moderate yield (51%) when the reaction heated to 110 °C for 3 h (entry 6). No reaction was observed at lower temp –78 °C and the reaction at 0 °C gave some unidentified compounds (entries 7-8).

Table 1. Screening of reaction conditions: temp and time to give (±)-**2** & (±)-**2a** from (±)-**18** and/or (±)-**18a**.

(±)-**18** and/or (±)-**18a** $\xrightarrow[\text{toluene}]{SOCl_2,\ Py}$ (±)-**2** + (±)-**2a**

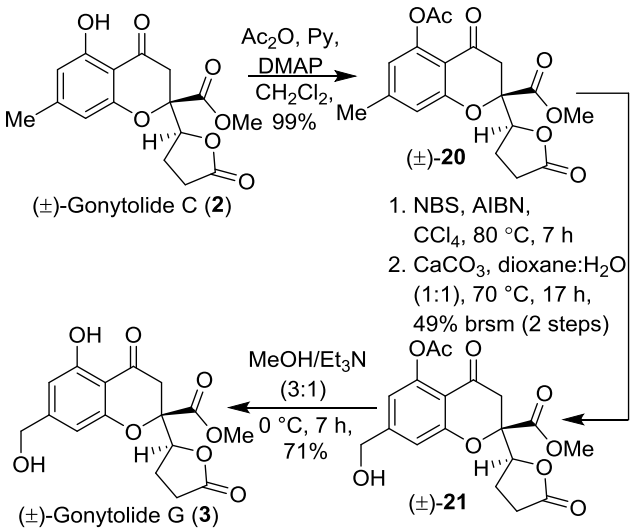
Entry	Temp	Time	**2** & **2a** (dr)[a]	Yield[b]
1	rt	2 h	1.3:1	47%
2	65 °C	1 h	1.7:1	66%
3	110 °C	10 min	1.6:1	67%
4	rt	24 h	8:1	40%
5	65 °C	3 h	6:1	66%
6	110 °C	3 h	18:1	51%
7	–78 °C	24 h		nr[c]
8	0 °C	24 h		uc[d]

[a]Diastereomeric ratio of **2** and **2a** is based on the ^{1}H NMR; [b]Isolated yields of combined **2** and **2a**, [c]No reaction. [d]Unidentified compounds

It is noteworthy that monitoring the reaction at different intervals,[24] formation of **2** and **2a** are equal or **2a** is major at the beginning of the reaction (immediately after the addition of thionyl chloride to a solution of **18** and/or **18a**, and Py in toluene) but with the time in progress, a formation of **2** predominates. Further, we ascertained[25] that the initially formed kinetic product **2a** is converted to thermodynamic product **2** and the conversion rate is faster at higher temperature with time. The diastereoselectivity of **2** over **2a** and epimerization of **2a** to **2** at higher temperatures with time is in line with the vinylogous addition of siloxyfurans to benzopyryliums reported by Porco and co-workers.[13] In the same report, the diastereoselectivity was assessed by employing the density functional theory method and the epimerization at higher temperature was proposed based on butenolide enolization.[13]

Mechanistically in our protocol, aldol product **18** and/or **18a** with dehydrating agent (thionyl chloride and Py) may give **12** which would affect the oxa-Michael addition to give **2** and **2a**, wherein the diastereoselectivity is governed by the asymmetric center present in γ-butyrolactone. Unlike epimerization by butenolide enolization proposed in Porco's protocol, here the epimerization of kinetic product **2a** to thermodynamic product **2** is presumably *via* **12** by retro-oxa-Michael addition and followed by oxa-Michael addition. As no loss of chirality in butyrolactone of this method, it is advantageous and can be valuable in constructing the stereoselective synthesis of gonytolide C by taking enantiomerically pure butyrolactone **16**/**16a**.

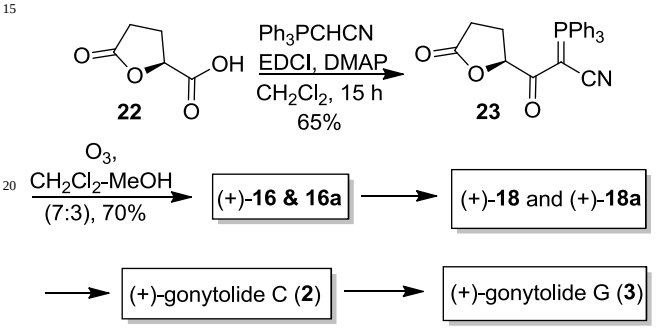
Having developed a diastereoselctive synthesis of (±)-gonytolide C, gonytolide G (**3**) could be synthesized by applying this protocol: taking the hydroxymethyl derivative of **15** and **16**/**16a** as starting materials. However, we envisaged that the oxidation of benzylic methyl in (±)-gonytolide C (**2**) would also provide the (±)-gonytolide G (**3**).[26] Towards this end, acetylation of the phenolic group in **2**[27] afforded **20** in nearly quantitative yield. Subsequent two-step transformation: oxidation-hydrolysis[28] afforded acetyl derivative of gonytolide G **21** in 49% yield based on recovery of **20**. Selective hydrolysis of acetyl group of **21** under mild condition[29] accomplished the first total synthesis of (±)-gonytolide G (**3**) in 71% yield and with 35% overall yield in four steps from **2** (Scheme 3).



Scheme 3. Synthesis of (±)-gonytolide G (**3**) from (±)-gonytolide C (**2**).

Having achieved diastereoselective synthesis of (±)-gonytolide C and (±)-gonytolide G, we considered synthesis of **16** and **16a** in enantiomerically pure form can provide an access to the first stereoselective total synthesis of gonytolide C and gonytolide G. Then it was commenced from the activation of (*S*)-(+)-5-oxo-2-tetrahydrofurancarboxylic acid (**22**)[30] with EDCI

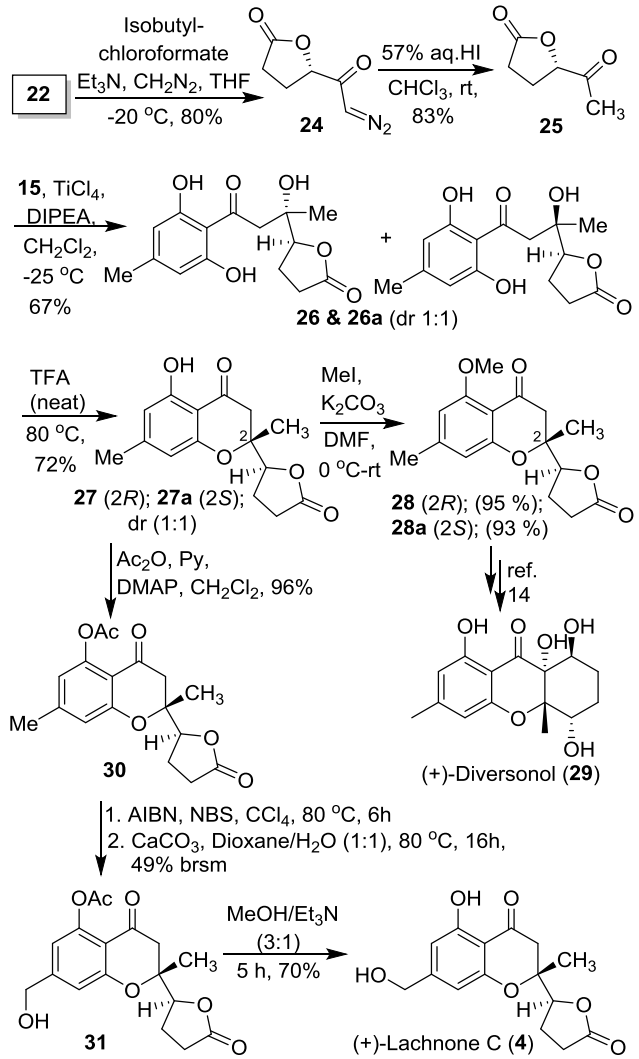
followed by coupling with (cyanomethylene)triphenylphosphorane gave β-keto cyanophosphorane **23** which upon under ozonolysis in MeOH/CH_2Cl_2 (3:7) provided (+)-**16**/**16a** in 1:1 ratio with 45% yield over two steps[31] (Scheme 4). Conversion of (+)-**16**/**16a** to (+)-gonytolide C (**2**) and G (**3**) was achieved from the steps developed for their racemic synthesis. The spectroscopic data of synthesized gonytolide C (**2**), *epi*-gonytolide C (**2a)** and gonytolide G (**3**) are in full agreement with those of reported compounds.[10,13] The specific rotations of gonytolide C (**2**): $[\alpha]^{23}_D$ = +23.1 (c 0.39, $CHCl_3$) (synthetic) and $[\alpha]_D$ = +25.1 (c 0.184, $CHCl_3$) (natural);[10a] and gonytolide G (**3**): $[\alpha]^{23}_D$ = +18.0 (c 0.19, $CHCl_3$) (synthetic) and: $[\alpha]_D$ = +19.7 (c 0.315, $CHCl_3$) (natural),[10b] are also well matched.



Scheme 4. Stereoselective synthesis of (+)-gonytolide C (**2**) and (+) gonytolide G (**3**).

Having achieved stereoselective synthesis of gonytolide C and G from lactone **22**, we expected that the same starting material can be used in the synthesis of lachnone C. Accordingly, conversion of acid **22** to the diazoketone **24** was achieved by using isobutylchloroformate, diazomethane and Et_3N in THF in 80% yield. Methyl ketone **25**[32] in 83% yield was obtained by the reduction of **24** with hydroiodic acid. The reaction of **25** with **15** under aldol reaction conditions developed for gonytolide C, ($TiCl_4$, DIPEA in CH_2Cl_2), except at higher temperature (−25 °C) in this case furnished inseparable mixture of **26 & 26a** (dr 1:1, based on the ^{1}H NMR) in 67% yield. Intramolecular cyclization of **26** & **26a** to give **27 & 27a** was achieved only after the use of neat triflouroacetic acid at 80 °C. Albeit, column chromatographically separable **27 & 27a** in 72% yield was obtained but with no diastereoselectivity in this case.

To know the absolute stereochemistry of cyclized products, **27 & 27a** were individually converted to corresponding methyl ethers **28** (95%) **& 28a** (93%), respectively, by using MeI, potassium carbonate in DMF.[14] Comparison of spectral data and specific rotation with the data reported,[14] clears that **27** is the required diastereomer for achieving lachnone C and also it accomplishes the formal synthesis of (+)-Diversonol **(29)**. Therefore, compound **27** was subjected to acetylation using Ac_2O, Pyridine in CH_2Cl_2 to afford **30**. Benzylic bromination of the methyl group with NBS and AIBN in CCl_4 under heating at 80 °C gave benzylic bromide. Hydrolysis of the benzylic bromide with $CaCO_3$ in aqueous dioxane at 80 °C furnished acetyl derivative of lachnone C **31**.[28] Deacetylation[29] of **31** in MeOH/ Et_3N provided lachnone C **(4)** in 70% yield. Comparison of spectral data, including specific rotation (synthetic: $[\alpha]^{28}_D$ = +39.0 (*c* 0.065, MeOH); natural: $[\alpha]^{29}_D$ = +43.4 (*c* 0.13, MeOH)) is in full agreement with literature.[11,33]



Scheme 5. Synthesis of (+)- Lachnone C (**4**)

Conclusions

In conclusion, a concise, protecting group free, and stereoselective synthetic strategy was developed for the synthesis of gonytolide C. Oxidation of the benzylic methyl group in gonytolide C provided the first total synthesis of gonytolide G. Total synthesis of lachnone C, formal synthesis of blennolide C and diversonol were also accomplished from this synthetic method. Application of this method in the synthesis of further monomeric and dimeric chromanones of this class of molecules as well as biogenetically related tetrahydroxanthones is in progress in our lab and will be reported in due course.

Experimental Section

(*E*)-1-(2,6-dihydroxy-4-methylphenyl)but-2-en-1-one (13): To a mixture of anhydrous aluminium chloride (9.67 g, 72.58 mmol) and orcinol (3 g, 24.19 mmol), chlorobenzene (20 mL) was added at rt. Upon heating to 40 °C, crotonoyl chloride (3.27 mL, 33.87 mmol) was added carefully. The reaction mixture was stirred at 70 °C for 2 h. After cooling to rt, the reaction mixture was poured

into ice and stirred for 30 min. The aq phase was extracted twice with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated to give the crude product which was purified by column chromatography to give **13** (3.97 g, 85%) as a yellow oil. R_f = 0.5 (15% EtOAc /hexane); IR (Neat): ν_{max} 3457, 2919, 1740, 1655, 1441, 1287, 1235, 1153, 1098, 973, 837, 769 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.14 (m, 1H), 6.79 (d, J = 2.0 Hz, 1.4H) 6.73 (d, J = 2.0 Hz, 0.4H), 6.0 (m, 1H), 2.38 (s, 3H), 1.98 (d, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.8, 151.3, 147.5, 140.5, 122.2, 120.0, 112.9, 21.7, 18.5; HRMS (ESI): calcd for $C_{11}H_{13}O_3$ $[M+H]^+$ 193.0859; found 193.0856

Methyl 2-(5-oxotetrahydrofuran-2-yl)acrylate ((±)-14): To a stirred solution of hydroxyl ester **17**[16] (12.46 g, 61.68 mmol) in toluene (120 mL) at rt, was added *p*-toluenesulfonic acid (3.51 g, 18.50 mmol) and allowed the reaction mixture to stir at rt for 3 h. The reaction mixture was quenched by addition of H_2O and extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography to furnish lactone **(±)-14** (10.43 g, 99.5%) as a colorless liquid. R_f = 0.5 (30% EtOAc /hexane); IR (Neat): ν_{max} 2956, 2924, 1779, 1721, 1441, 1276, 1185, 1146, 1044 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 6.33 (s, 1H), 5.93 (d, J = 1.5 Hz, 1H), 5.29 (t, J = 7.1 Hz, 1H), 3.79 (s, 3H), 2.72 -2.52 (m, 3H), 2.03 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.6, 165.0, 138.4, 125.1, 77.6, 52.0, 28.2, 27.7; HRMS (ESI): calcd. for $C_8H_{10}O_4Na$ $[M+Na]^+$ 193.0471; found 193.0476.

Synthesis of (±)-16/16a: The solution of lactone **(±)-14** (4 g, 23.52 mmol) in CH_2Cl_2 was cooled to −78 °C and O_3 gas was bubbled through the solution until a blue color had been persisted, followed by oxygen gas to remove the excess of O_3. Dimethyl sulfide was added to the reaction mixture and the solution was warmed to rt and stirred for additional 1.5 h. The reaction mixture was taken up in EtOAc and it was washed with water and brine, dried over Na_2SO_4, filtered, and concentrated. The residue was purified by flash column chromatography to give **(±)-16/16a** as a white solid (3.5 g, 86 %). R_f = 0.25 (50% EtOAc /hexane); mp 90-93 °C; IR (Neat): ν_{max} 3357, 2972, 1756, 1737, 1353, 1209, 1107, 1013 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 5.49 (dd, J = 9.0, 5.0 Hz, 0.5H), 4.84 (dd, J = 8.0, 5.0 Hz, 0.5H), 3.93 (s, 1.5H), 3.90 (s, 1.5H), 2.68 (m, 1H), 2.58 (m, 1H), 2.46 (m, 0.5H), 2.41-2.28 (m, 1.5H), 1.78 (br, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 188.6, 177.6, 175.7, 171.0, 162.8, 93.4, 80.1, 78.9, 53.5, 53.3, 27.6, 26.2, 24.2, 21.0; HRMS (ESI): calcd for $C_7H_9O_5$ $[M+H]^+$ 173.0444; found 173.0442.

Synthesis of (±)-18 & (±)-18a: $TiCl_4$ (1 M in CH_2Cl_2, 34.88 mL, 34.88 mmol) and diisopropylethyl amine (7.08 mL, 40.69 mmol) were successively added to a stirred solution of **15**[13] (1.60 g, 9.68 mmol) in CH_2Cl_2 (143 mL) at −78 °C under an argon atmosphere. After 30 min α-ketoester (±)-**16/16a** (2 g, 11.6279 mmol) in CH_2Cl_2 (230 mL) was added to the reaction mixture, which was stirred at −78 °C for 3 h. The reaction mixture was quenched with water at −78 °C and extracted twice with EtOAc. The organic phase was washed with water, brine, dried over Na_2SO_4, filtered, and concentrated. The obtained crude oil was purified by silica gel column chromatography to give separable aldol products **(±)-18 & (±)-18a** in a dr of 2.5:1 (1.63 g, 49%) (83% brsm, 650 mg of **15** was recovered).

Minor: as a brown solid; R_f = 0.35 (50% EtOAc /hexane); mp 178-182 °C; IR (Neat): ν_{max} 3482, 3249, 2923, 2854, 1748, 1644, 1603, 1418, 1376, 1207, 1176, 1081, 1012, 821, 792 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.90 (brs, 1H), 6.19 (s, 2H), 4.72 (dd, J = 8.1, 4.1 Hz, 1H), 4.03 (d, J = 18.8 Hz, 1H), 3.98 (brs, 1H), 3.82 (s, 3H), 3.73 (d, J = 18.8 Hz, 1H), 2.78 (m, 1H), 2.49 (m, 1H), 2.31 (m, 1H), 2.21 (s, 3H), 2.15 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 202.9, 178.7, 173.5, 161.5, 149.0, 108.8, 107.8, 82.7, 77.3, 53.3, 50.0, 28.2, 21.9, 21.7; HRMS (ESI): calcd for $C_{16}H_{18}O_8Na$ $[M+Na]^+$ 361.0893; found 361.0888.

Major: as a liquid; R_f = 0.25 (50% EtOAc /hexane); IR (Neat): ν_{max} 3446, 2925, 2855, 1746, 1635, 1426, 1379, 1208, 1080, 1041, 828, 764 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 9.88 (brs, 1H), 6.20 (s, 2H), 4.71 (dd, J = 7.5, 5.2 Hz, 1H), 3.99 (brs, 1H), 3.84 (s, 3H), 3.68 (d, J = 17.9 Hz, 1H), 3.54 (d, J = 17.9 Hz, 1H), 2.65 (m, 1H), 2.54 (m, 1H), 2.49-2.29 (m, 2H), 2.21 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 201.4, 177.3, 173.8, 161.2, 149.0, 109.1, 108.1, 82.6, 76.3, 53.5, 48.4, 28.0, 21.9, 21.8; HRMS (ESI): calcd for $C_{16}H_{18}O_8Na$ $[M+Na]^+$ 361.0893; found 361.0902.

Synthesis of gonytolide (±)-(2) and (±)-*epi*-gonytolide (2a): To a solution of **(±)-18** and/or **(±)-18a** (210 mg, 0.62 mmol) in dry toluene (6 mL) and py (0.2 mL, 2.60 mmol), thionyl chloride (0.09 mL, 1.30 mmol) in dry toluene (2 mL) was cannulated drop wise under N_2 at 65 °C. The reaction was stirred for 3 h at 65 °C, allowed to come to rt then poured into crushed ice and extracted with EtOAc. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated under vacuum. The residue was purified by column chromatography to give **(±)-2** as a white solid & **(±)-2a** as white solid (131 mg, 66%) in the combined yield in the ratio (6:1) respectively.

(±)-Gonytolide C (2): R_f = 0.45 (1% EtOAc /CH_2Cl_2); mp 136-138 °C; IR (Neat): ν_{max} 2924, 2854, 1786, 1743, 1645, 1570, 1455, 1368, 1201, 1138, 835, 751 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 11.38 (s, 1H), 6.40 (s, 1H), 6.37 (s, 1H), 4.86 (dd, J = 7.9, 6.0 Hz, 1H), 3.74 (s, 3H), 3.11 (d, J = 16.9 Hz, 1H), 2.95 (d, J = 16.9 Hz, 1H), 2.70 (ddd, J = 18.0, 10.1, 7.1 Hz, 1H), 2.59 (ddd, J = 18.0, 10.1, 6.7 Hz, 1H), 2.50-2.36 (m, 2H), 2.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 193.0, 175.5, 168.9, 161.7, 159.0, 151.6, 111.0, 108.4, 105.6, 84.0, 80.9, 53.6, 39.4, 27.6, 22.6, 22.0; HRMS (ESI): calcd for $C_{16}H_{17}O_7$ $[M+H]^+$ 321.0968; found 321.0967.

(±)-*epi*-Gonytolide (2a): R_f = 0.5 (1% EtOAc /CH_2Cl_2); mp 174-178 °C; IR (Neat): ν_{max} 2924, 1787, 1752, 1646, 1571, 1456, 1367, 1202, 1163, 836, 747 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 11.41 (s, 1H), 6.37 (s, 1H), 6.36 (s, 1H), 4.77 (dd, J = 8.2, 4.1 Hz, 1H), 3.74 (s, 3H), 3.45 (d, J = 17.3 Hz, 1H), 3.06 (d, J = 17.3 Hz, 1H), 2.81 (ddd, J = 18.0, 10.5, 8.3 Hz, 1H), 2.57 (ddd, J = 18.0, 10.5, 5.3 Hz, 1H), 2.49 (m, 1H), 2.34 (m, 1H), 2.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 194.0, 175.9, 169.1, 161.7, 158.9, 151.2, 111.0, 108.3, 105.5, 84.6, 79.7, 53.6, 40.3, 27.7, 22.6, 21.7; HRMS (ESI): calcd. for $C_{16}H_{17}O_7$ $[M+H]^+$ 321.0968; found 321.0966.

Methyl 5-acetoxy-7-methyl-4-oxo-2-(5-oxotetrahydrofuran-2-yl)chroman-2-carboxylate (20): To a solution of (±)-gonytolide C (**2**) (50 mg, 0.15 mmol) in dry CH_2Cl_2 (1 mL) were added Ac_2O (0.045 mL, 0.47 mmol), py (0.075 mL, 0.94 mmol) and DMAP (3.8 mg, 0.03 mmol) and the resulting solution was stirred

at rt for 4 h. Water was added to the reaction, and stirred for another 30 min. The reaction mixture was then extracted with CH_2Cl_2, washed with 1N HCl, saturated aq $NaHCO_3$, brine, dried over Na_2SO_4, and filtered. The organic layer was concentrated on a rotary evaporator to give the crude product which was purified by silica gel column chromatography to give the compound (±)-**20** (54 mg, 99%) as a white solid. R_f = 0.45 (50%, EtOAc/hexane); mp 135-138 °C; IR (Neat): ν_{max} 2924, 2853, 1775, 1736, 1687, 1624, 1422, 1326, 1199, 1153, 1072, 1017 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.84 (d, J = 1.5 Hz, 1H), 6.54 (d, J = 1.5 Hz, 1H), 4.86 (dd, J = 8.0, 5.8 Hz, 1H), 3.72 (s, 3H), 2.98 (d, J = 16.6 Hz, 1H), 2.88 (d, J = 16.6 Hz, 1H), 2.71 (ddd, J = 18.0, 9.9, 7.0 Hz, 1H), 2.59 (ddd, J = 18.0, 10.2, 6.5 Hz, 1H), 2.49-2.27 (m, 2H), 2.36 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 185.8, 175.6, 169.4, 168.8, 160.5, 149.6, 148.7, 118.1, 116.3, 111.2, 84.2, 80.9, 53.5, 40.9, 27.6, 22.0, 21.9, 21.0; HRMS (ESI): calcd for $C_{18}H_{19}O_8$ $[M+H]^+$ 363.1079, found 363.1057.

Methyl-5-acetoxy-7-(hydroxymethyl)-4-oxo-2-(5-oxotetrahydrofuran-2-yl)chroman-2-carboxylate (21): A solution of compound **(±)-20** (42 mg, 0.12 mmol) in CCl_4 (1.5 mL) was heated at 80 °C, and then AIBN (3.8 mg, 0.023 mmol) and NBS (23 mg, 0.13 mmol) were added. The reaction mixture was heated to 80 °C for 7 h. The reaction was cooled to rt, H_2O was added and extracted with CH_2Cl_2, washed with 1N HCl and brine, dried over Na_2SO_4, and filtered. Concentration in *vacuum* afforded crude product which was used in the next reaction without further purification. Crude benzyl bromide was taken in 1 mL of 1,4-dioxane/H_2O (1:1). Then $CaCO_3$ (7 mg, 0.07 mmol) was added and heated at the 70 °C for 17 h. The reaction was cooled, added H_2O, extracted with EtOAc, washed with brine, dried over Na_2SO_4, filtered, and concentrated in *vacuo*. The residue was purified by silica gel column chromatography to give the compound **(±)-21** (12 mg, 49% brsm and 18.5 mg of **(±)-20** was recovered) as colorless foam. R_f = 0.2 (50%, EtOAc/hexane); IR (Neat): ν_{max} 2925, 2855, 1774, 1743, 1690, 1625, 1433, 1196, 1048 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.05 (s, 1H), 6.73 (s, 1H), 4.88 (dd, J = 7.9, 5.8 Hz, 1H), 4.73 (s, 2H), 3.72 (s, 3H), 3.01 (d, J = 16.5 Hz, 1H), 2.91 (d, J = 16.5, 1H), 2.72 (ddd, J = 18.0, 9.8, 7.2 Hz, 1H), 2.60 (ddd, J = 18.0, 10.2, 6.7 Hz, 1H), 2.50-2.38 (m, 2H), 2.35 (s, 3H), 1.89 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 185.8, 175.5, 169.4, 168.7, 160.8, 151.0, 150.0, 114.6, 113.2, 112.5, 84.4, 80.9, 63.8, 53.6, 40.9, 27.6, 21.9, 21.0; HRMS (ESI): calcd for $C_{18}H_{18}O_9Na$ $[M+Na]^+$ 401.0843, found 401.0830.

(±)-Synthesis of Gonytolide G (3): Compound **(±)-21** (8 mg, 0.021 mmol) was taken in MeOH:Et_3N (3:1, 0.8 mL) and stirred at rt for 7 h. The reaction mixture was quenched with 1N HCl, extracted with EtOAc, washed with brine. The organic layer was filtered after drying over Na_2SO_4, concentrated in *vacuo* to give a crude product which was purified by silica gel column chromatography to give (±)-gonytolide G (**3**) (4.9 mg, 71%) as a colorless solid. R_f = 0.25 (50%, EtOAc/hexane); mp 120-122 °C; IR (Neat): ν_{max} 2924, 2854, 1781, 1746, 1645, 1440, 1190, 1051 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 11.43 (s, 1H), 6.60 (s, 1H), 6.56 (s, 1H), 4.87 (dd, J = 7.9, 5.9 Hz, 1H), 4.67 (s, 2H), 3.74 (s, 3H), 3.14 (d, J = 17.0, 1H), 2.98 (d, J = 17.0 Hz, 1H), 2.72 (ddd, J = 17.8, 9.7, 7.3 Hz, 1H), 2.60 (ddd, J = 17.8, 10.0, 6.4 Hz, 1H), 2.49-2.39 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 193.3, 175.5, 168.9, 162.1, 159.4, 153.8, 107.7, 106.6, 105.1, 84.2, 80.9, 64.4, 53.7, 39.5, 27.6, 22.0; HRMS (ESI): calcd for $C_{16}H_{15}O_8$ $[M-H]^+$ 335.0761, found 335.0765.

(S)-3-oxo-3-(5-oxotetrahydrofuran-2-yl)-2-(triphenylphosphoranylidene)propane nitrile (23): To a solution of carboxylic acid **22**[30] (5 g, 38.5 mmol) in dry CH_2Cl_2 (200 mL) were added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI) (9.6 g, 50.0 mmol), and DMAP (470 mg, 3.8 mmol) under a nitrogen atmosphere at 0 °C. After 2 min stirring, Ph_3P=CHCN (12.7 g, 42.3 mmol) was added and the reaction mixture was stirred at rt for 15 h. Water (15 mL) was added and the organic layer was separated and washed with sat. aq $NaHCO_3$ solution and brine. The organic layer was dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The residue was purified by column chromatography to give the compound **23** as a colorless solid (10.3 g, 65%). R_f = 0.3 (50%, EtOAc/hexane); mp 245-247 °C; $[\alpha]^{23}_D$ = +26.0 (*c* 0.41, $CHCl_3$); IR (Neat): ν_{max} 2975, 2946, 2175, 1784, 1603, 1436, 1387, 1256, 1157, 1103, 750, 720, 693 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$): δ 7.66-7.61 (m, 3H), 7.60-7.54 (m, 6H), 7.54-7.49 (m, 6H), 5.56 (dd, J = 7.9, 4.5, 1H), 2.59-2.47 (m, 2H), 2.41 (m, 1H), 2.29 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 190.5, 176.8, 133.3, 133.2, 129.1, 129.0, 122.2, 121.4, 120.5, 120.4, 78.4, 78.3, 47.7, 46.7, 27.0, 25.9; HRMS (ESI): calcd. for $C_{25}H_{21}O_3NP$ $[M+H]^+$ 414.1253; found 414.1244.

Synthesis of (+)-16/16a: The compound **23** (10 g, 24.2 mmol) was dissolved in CH_2Cl_2 (168 mL) and methanol (72 mL) and cooled to −78 °C. Ozone was then bubbled through the solution until the reaction mixture was turned to blue. Oxygen was then passed through the solution to remove the excess ozone. The solution was warmed to room temperature and concentrated in *vacuo*. The crude product was purified by column chromatography (60%, EtoAc/hexane), to give compound **(+)-16/16a** (2.9 g, 70%) as a white solid. $[\alpha]^{23}_D$ = +41.4 (*c*, 0.67, $CHCl_3$).

Synthesis of (+)-18 & (+)-18a: Same as its racemic synthesis
Minor: $[\alpha]^{23}_D$ = +8.7 (*c* 0.33, $CHCl_3$); Major: $[\alpha]^{23}_D$ = +33.4 (*c* 0.21, $CHCl_3$);

(+)-Gonytolide C (2) and (–)-*epi*-Gonytolide C (2a): Same as its racemic synthesis

Gonytolide C (2): $[\alpha]^{23}_D$ = +23.1 (*c* 0.39, $CHCl_3$);
***epi*-Gonytolide C (2a):** $[\alpha]^{23}_D$ = −6.4 (*c* 0.4, $CHCl_3$);

Methyl (*R*)-5-acetoxy-7-methyl-4-oxo-2-((*S*)-5-oxotetrahydrofuran-2-yl)chromane-2-carboxylate (20): Same as its racemic synthesis; and specific rotation is $[\alpha]^{23}_D$ = +10.5 (*c* 0.18, $CHCl_3$);

Methyl (*R*)-5-acetoxy-7-(hydroxymethyl)-4-oxo-2-((*S*)-5-oxotetrahydrofuran-2-yl)chromane-2-carboxylate (21): Same as its racemic synthesis; and specific rotation is $[\alpha]^{23}_D$ = +4.2 (*c* 0.2, $CHCl_3$);

(+)- Gonytolide G (3): Same as its racemic synthesis; and specific rotation is $[\alpha]^{23}_D$ = +18.0 (*c* 0.19, $CHCl_3$);

(*S*)-5-(2-diazoacetyl)dihydrofuran-2(3H)-one (24): To a solution of carboxylic acid **22**[30] (5 g, 38.5 mmol) in dry THF (12 mL) were added triethylamine (9 mL, 65.4 mmol) and isobutylchloroformate (7.5 mL, 57.7 mmol) at −20 °C and stirred for 45 min at −20 °C. Excess of Diazomethane was added to the

reaction mixture at −20°C. The reaction mixture was warmed to rt and stirred overnight. Excess of diazomethane was quenched using acetic acid and washed with sat. aq. $NaHCO_3$ solution and extracted with EtOAc. The organic layer was washed with aq. NH_4Cl, and brine solution, dried over Na_2SO_4, filtered and concentrated in *vacuo*. The residue was purified by flash column chromatography to give the compound **24** (4.4 g, 80%) as a yellow oil. R_f = 0.3 (50%, EtOAc/hexane), $[\alpha]^{22}_D$ = –80.0 (*c* 0.2 $CHCl_3$); IR (Neat): ν_{max} 2956, 2116, 1785, 1636, 1379, 1144, 1049 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 5.76 (s, 1H), 4.82 (m, 1H), 2.61-2.48 (m, 3H), 2.36 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.7, 175.7, 80.4, 53.9, 27.1, 25.5; HRMS (ESI): calcd. for $C_6H_6N_2O_3Na$ $[M+Na]^+$ 177.0270; found 177.0260.

(*S*)-5-acetyldihydrofuran-2(3H)-one (25): To a solution of compound **24** (4 g, 25.9 mmol) in chloroform (150 mL) was added hydriodic acid (57%, 6.8 mL, 51.9 mmol) drop wise at room temperature with vigorous stirring. After 10 min, the solution was washed with aqueous 10 % sodium thiosulphate, the organic layer was separated, the aqueous layer was washed with chloroform and the combined organic layers were dried over Na_2SO_4, filtered and concentrated in *vacuo*. The residue was purified by column chromatography to give the compound **25** (2.75 g, 83%) as a yellow oil. R_f = 0.3 (50%, EtOAc/hexane); $[\alpha]^{23}_D$ = +12.6 (*c* 0.46, MeOH); IR (Neat): ν_{max} 2925, 1784, 1726, 1170, 1064 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 4.80 (m, 1H), 2.54-2.43 (m, 3H), 2.23 (s, 3H), 2.22-2.15 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 205.2, 175.9, 81.8, 27.1, 26.0, 24.3; HRMS (ESI): calcd. for $C_6H_9O_3$ $[M+H]^+$ 129.0546 found129.0542.

Synthesis of 26 & 26a: $TiCl_4$ (1 M solution in CH_2Cl_2, 46.8 mL) and diisopropylethyl amine (9.51 mL, 54.6 mmol) were successively added to a stirred solution of **15**[13] (2.1 g, 13.0 mmol) in CH_2Cl_2 (60 mL) at −25 °C under an argon atmosphere. After 30 min. methyl ketone 25 (500 mg, 3.9 mmol) in CH_2Cl_2 (30 mL) was added to the reaction mixture, which was stirred at −25 °C for 3 h. The reaction mixture was quenched with water and was extracted twice with ethyl acetate. The organic phase was washed with water, brine, dried over Na_2SO_4, filtered and concentrated. The obtained crude oil was purified by silica gel column chromatography to give an inseparable mixture of aldol products **26 & 26a** as brown foam in the yield (770 mg, 67%). R_f = 0.35 (50%, EtOAc/hexane); IR (Neat): ν_{max} 3448, 2925, 2855, 1749, 1634, 1417, 1376, 1208, 766 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.23 (s, 2H), 6.20 (s, 2H), 4.60 (t, *J* = 7.4 Hz, 1H), 4.48 (dd, *J* = 7.6, 6.5 Hz, 1H), 3.74 (d, *J* = 15.5 Hz, 1H), 3.57 (d, *J* = 16.0 Hz, 1H), 3.11 (d, *J* = 16.0 Hz, 1H), 3.09 (d, *J* = 15.5 Hz, 1H), 2.68 (m, 1H), 2.61-2.51 (m, 3H), 2.37 (m, 1H), 2.31-2.21 (m, 3H), 2.19-2.17 (m, 6H), 1.35 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 205.2, 205.0, 178.8, 178.1, 161.5, 161.3, 149.0, 148.8, 132.5, 132.5, 132.0, 132.0, 128.8, 128.7, 109.2, 109.1, 85.8, 84.9, 73.7, 73.7, 49.2, 48.7, 28.8, 28.8, 22.4, 22.4, 22.0, 21.9, 21.9, 21.7; HRMS (ESI): calcd. for $C_{15}H_{18}O_6Na$ $[M+Na]^+$ 317.0995; found 317.0982.

Synthesis of 27 & 27a: To the mixture of aldol products **26 & 26a** (310 mg, 1.0 mmol) was added trifluoroacetic acid (8.3 mL, 105.6 mmol) and the reaction mixture was heated to 80 °C. The reaction was monitored by checking thin layer chromatography, after completion of the starting material, quenched with sat aq $NaHCO_3$ solution and extracted with ethyl acetate and washed with water and brine, dried over Na_2SO_4, filtered and concentrated. The obtained products were separated by silica gel column chromatography to give **27** & **27a** as solids (210 mg, 72%) in the combined yield in the ratio (1:1).

(*R*)-5-hydroxy-2,7-dimethyl-2-((*S*)-5-oxotetrahydrofuran-2-yl)chroman-4-one (27): (white solid); R_f = 0.35 (40%, EtOAc/hexane); mp 254-258 °C; $[\alpha]^{22}_D$ = +30.0 (*c* 0.48 $CHCl_3$); IR (Neat): ν_{max} 3449, 2923, 2853, 1775, 1630, 1440, 1250, 1150, 1034 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ 11.51 (s, 1H), 6.34 (s, 1H), 6.23 (s, 1H), 4.56 (t, *J* = 7.3 Hz, 1H), 2.95 (d, *J* = 16.8 Hz, 1H), 2.62 (m, 2H), 2.57 (d, *J* = 16.8 Hz, 1H), 2.37-2.29 (m, 2H), 2.27 (s, 3H), 1.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 195.4, 176.1, 161.6, 158.4, 150.9, 110.1, 108.5, 105.3, 82.5, 80.6, 42.7, 28.1, 22.5, 22.2, 19.1; HRMS (ESI): calcd. for $C_{15}H_{17}O_5$ $[M+H]^+$ 277.1070; found 277.1057.

(*S*)-5-hydroxy-2,7-dimethyl-2-((*S*)-5-oxotetrahydrofuran-2-yl)chroman-4-one (27a): (white solid); R_f = 0.30 (40%, EtOAc/hexane); mp 105-108 °C; $[\alpha]^{23}_D$ = –42.0 (*c* 0.25 $CHCl_3$); IR (Neat): ν_{max} 3423, 2923, 2853, 1769, 1647, 1575, 1460, 1373, 1213, 1172, 1090, 1014, 790; ^1H NMR (500 MHz, $CDCl_3$): δ 11.52 (s, 1H), 6.33 (s, 1H), 6.22 (s, 1H), 4.45 (dd, *J* = 8.0, 5.9 Hz, 1H), 3.30 (d, *J* = 16.9 Hz, 1H), 2.72 (ddd, *J* = 16.9, 10.5, 6.7 Hz, 1H), 2.58 (ddd, *J* = 17.7, 10.3, 7.0 Hz, 1H), 2.49 (d, *J* = 16.9 Hz, 1H), 2.47 (m, 1H), 2.36 (m, 1H), 2.27 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 196.2, 176.1, 161.5, 158.3, 150.6, 110.1, 108.5, 105.2, 82.7, 80.6, 43.1, 28.2, 22.4, 21.5, 19.5; HRMS (ESI): calcd. for $C_{15}H_{15}O_5$ $[M-H]^+$ 275.0914; found 275.0922.

(*R*)-5-methoxy-2,7-dimethyl-2-((*S*)-5-oxotetrahydrofuran-2-yl)chroman-4-one (28): To a solution of compound **27** (10 mg, 0.036 mmol) in dry DMF, at 0 °C were added K_2CO_3 (10 mg, 0.072 mmol) and iodomethane (1M, 0.043 mL, 0.043 mmol). The reaction mixture was stirred for 24 h at room temperature. After completion of the starting material, water was added and the reaction mixture was extracted with ethyl acetate and washed with cold water and brine, dried over Na_2SO_4, filtered and concentrated in *vacuo*. The obtained crude oil was purified by silica gel column chromatography to give the compound **28** (10 mg, 95%) as oil. R_f = 0.3 (50%, EtOAc/hexane); $[\alpha]^{27}_D$ = +38.5 (*c* 0.3, $CHCl_3$); IR (Neat): ν_{max} 2925, 1777, 1677, 1614, 1567, 1465, 1228, 1154, 1112 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.34 (s, 1H), 6.30 (s, 1H), 4.50 (t, *J* = 7.3 Hz, 1H), 3.87 (s, 3H), 2.85 (d, *J* = 16.0 Hz, 1H), 2.67-2.51 (m, 2H), 2.44 (d, *J* = 16.0 Hz, 1H), 2.28 (s, 3H), 2.31-2.25 (m, 2H), 1.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 188.7, 176.3, 160.3, 160.1, 148.0, 110.6, 108.3, 105.0, 83.1, 80.4, 56.0, 44.3, 28.2, 22.3, 22.2, 18.9; HRMS (ESI): calcd. for $C_{16}H_{19}O_5$ $[M+H]^+$ 291.1227; found 291.1225.

(*S*)-5-methoxy-2,7-dimethyl-2-((*S*)-5-oxotetrahydrofuran-2-yl)chroman-4-one (28a): Compound **28a** was prepared from compound **27a** following the same procedure as outlined for the preparation of compound **28**. The residue was purified by silica gel column chromatography to give compound **28a** (9.8 mg, 93%) as oil. R_f = 0.3 (50%, EtOAc/hexane); $[\alpha]^{24}_D$ = –24.0 (*c* 0.3, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): δ 6.34 (s, 1H), 6.31 (s, 1H), 4.45 (dd. *J* = 7.9, 6.2 Hz, 1H), 3.89 (s, 3H), 3.18 (d, *J* = 15.7 Hz, 1H), 2.71 (ddd, *J* = 17.7, 10.0, 6.2 Hz, 1H), 2.57 (ddd, *J* = 17.8, 10.2, 7.1 Hz, 1H), 2.44 (d, 15.7, 1H), 2.48-2.39 (m, 1H), 2.38-2.31 (m, 1H), 2.30 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (75 MHz,

$CDCl_3$): δ 189.5, 176.3, 160.1, 160.1, 147.7, 110.6, 108.3, 105.0, 82.8, 80.4, 56.0, 45.1, 28.3, 22.3, 21.6, 18.7; IR (Neat): ν_{max} 2924, 1774, 1618, 1462, 1164, 1109, 1019, 944 cm^{-1}; HRMS (ESI): calcd. for $C_{16}H_{18}O_5Na$ $[M+Na]^+$ 313.1046; found 313.1043.

(*R*)-2,7-dimethyl-4-oxo-2-((*S*)-5-oxotetrahydrofuran-2-yl)chroman-5-yl acetate (30): To a solution of compound **27** (50 mg, 0.18 mmol) in anhydrous CH_2Cl_2 (1 mL) were added acetic anhydride (0.05 mL, 0.54 mmol), pyridine (0.09 mL, 1.08 mmol) and DMAP (4.4 mg, 0.036 mmol) and the resulting solution was stirred at rt for 4 h. Water was added to the reaction, and the mixture was stirred for another 30 min. The reaction mixture was then extracted with CH_2Cl_2, washed with 1N HCl, saturated aq. $NaHCO_3$ solution, and brine, dried over Na_2SO_4, filtered. The organic layer was concentrated in a rotary evaporator to give crude that was purified by silica gel column chromatography to give the compound **30** (57 mg, 99%) as oil. R_f = 0.4 (50%, EtOAc/hexane); $[\alpha]^{22}_D$ = +21.0 (*c* 0.4 $CHCl_3$); IR (Neat): ν_{max} 2924, 2853, 1776, 1687, 1624, 1564, 1341, 1199, 1151, 1076, 1017, 899 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.68 (s, 1H), 6.49 (s, 1H), 4.52 (t, *J* = 7.3 Hz, 1H), 2.86 (d, *J* = 16.0 Hz, 1H), 2.70-2.54 (m, 2H), 2.46 (d, *J* = 16.0 Hz, 1H), 2.35 (s, 3H), 2.32 (s, 3H), 2.34-2.26 (m, 2H), 1.42 (s , 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 188.3, 176.1, 169.6, 159.7, 149.5, 148.1, 117.1, 116.4, 110.9, 82.7, 80.9, 44.0, 28.2, 22.2, 21.8, 21.0, 18.8; HRMS (ESI): calcd. for $C_{17}H_{18}O_6Na$ $[M+Na]^+$ 341.0995; found 341.0979.

(*R*)-7-(hydroxymethyl)-2-methyl-4-oxo-2-((S)-5-oxotetrahydrofuran-2-yl)chroman-5-yl acetate (31): A solution of compound **30** (80 mg, 0.25 mmol) in CCl_4 (1 mL) was heated at 80 °C, and then AIBN (8.2 mg, 0.05 mmol) and NBS (49 mg, 0.27 mmol) were added. The reaction mixture was heated at the 80 °C for 6 h. The reaction was cooled to rt, water was added and extracted with CH_2Cl_2, washed with 1N HCl and brine, dried over Na_2SO_4 and filtered. Concentration on rotatory evaporator gave crude compound which was used for the next reaction without further purification. Crude benzyl bromide was taken in 1 mL of 1, 4-dioxane/H_2O (1:1) and $CaCO_3$ (15.4 mg, 0.15 mmol) was added and heated at the 80 °C for 16 h. The reaction was cooled, water was added extracted with EtOAc washed with brine, dried over Na_2SO_4, filtered and concentrated in *vacuo*. The residue was purified by silica gel column chromatography to give the compound **31** (15.5 mg, 49% brsm, 50 mg of **30** recovered) as a yellow oil. R_f = 0.3 (50%, EtOAc/hexane); $[\alpha]^{27}_D$ = +37.8 (*c* 0.3, $CHCl_3$); IR (Neat): ν_{max} 3478, 2956, 2924, 1787, 1740, 1639, 1441, 1377, 1264, 1170, 1069 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.88 (t, *J* = 0.76 Hz, 1H), 6.66 (t, *J* = 0.76 Hz, 1H), 4.66 (s, 2H), 4.54 (t, *J* = 7.3 Hz, 1H), 2.88 (d, *J* = 16.1 Hz, 1H), 2.69-2.54 (m, 2H), 2.48 (d, *J* = 16.1 Hz, 1H), 2.35 (s, 3H), 2.34-2.26 (m, 2H), 1.72 (brs, 1H), 1.42 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 188.4, 176.2, 169.7, 159.9, 150.6, 149.8, 113.6, 113.4, 112.0, 82.7, 81.0, 63.7, 43.9, 28.2, 22.2, 21.0, 18.8; HRMS (ESI): calcd. for $C_{17}H_{18}O_7Na$ $[M+Na]^+$ 357.0944; found 357.0947.

(+)-Lachnone C (4): A solution of compound **31** (10 mg, 0.03 mmol) in CH_3OH: Et_3N (3:1, 0.4 mL) was stirred at rt for 5 h. The solution was washed with 1N HCl, extracted with EtOAc, washed with saturated aq. $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated in *vacuo*. The residue was purified by silica gel column chromatography to give lachnone C (**4**) (6 mg, 70%) as a yellow oil. R_f = 0.2 (50%, EtOAc/hexane); $[\alpha]^{28}_D$ = +39.0 (*c* 0.065, MeOH); IR (Neat): ν_{max} 3428, 2924, 2853, 1772, 1642, 1569, 1439, 1375, 1266, 1153, 1087, 1057, 755 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 11.56 (s, 1H), 6.51 (s, 1H), 6.45 (s, 1H), 4.63 (s, 2H), 4.58 (t, *J* = 7.3 Hz, 1H), 2.98 (d, *J* = 17.1 Hz, 1H), 2.61 (d, *J* = 17.1 Hz, 1H), 2.71-2.55 (m, 2H), 2.38-2.27 (m, 2H), 1.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 195.7, 176.1, 161.9, 158.8, 153.1, 106.8, 106.3, 105.2, 82.5, 80.8, 64.4, 42.8, 28.1, 22.3, 19.1, 195.7, 176.1, 161.9, 158.8, 153.1, 106.8, 106.3, 105.2, 82.5, 80.8, 64.4, 42.8, 28.1, 22.3, 19.1; HRMS (ESI): calcd. for $C_{15}H_{16}O_6Na$ $[M+Na]^+$ 315.0839; found 315.0828.

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26 The reverse transformation (reduction of benzylic hydroxymethylene to methyl) was performed by the Kikuchi et. al., to further confirm the structure of gonytolide G by comparison with gonytolide C: See the ref. 10b

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