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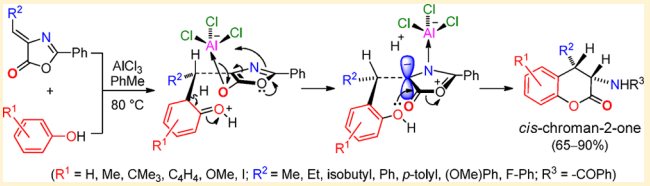
Syntheses of Chroman-2-ones and α-Amino Acids through a Diastereoselective Domino Reaction

D. Balaji Chandrasekhar, Shwu-Chen Tsay, Tapan K. Pradhan, and Jih Ru Hwu*

Department of Chemistry and Frontier Research Center on Fundamental & Applied Sciences of Matters, National Tsing Hua University, Hsinchu 30013, Taiwan

Supporting Information

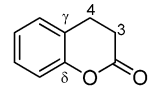
ABSTRACT: Many 3-aminochroman-2-ones and β,β-diarylalanines exhibit significant biological activities. A new method was thus developed for the syntheses of these compounds with high efficiency and diastereoselectivity. First, treatment of various phenols with Erlenmeyer−Plochl (*Z*)-azlactones and $AlCl_3$ in toluene produced the desired *cis*-3-aminochroman-2-ones in 65−90% yields under kinetic control. This coupling reaction involved a domino process of Friedel−Crafts alkylation, 1,4-$AlCl_3$ shift, transesterification, and protodealumination in a "single-flask." The corresponding products, however, were not generated by replacement of $AlCl_3$ with a protonic acid. Second, hydrolysis of the resultant 3-amino-4-arylchroman-2-ones by $NaHCO_3$ in a mixture of THF and water gave α-(*N*-benzoyl)amino acids. Further deprotection of these isolated compounds by use of hydrochloric acid (12 N) in methanol afforded the desired free amino acids in 80−88% yields. Under these optimized conditions, epimerization did not occur at the α carbons of α-(*N*-benzoyl)- and free α-amino acids. These new findings provide a convenient way to generate 3,4-disubtituted chroman-2-ones and β,β-diarylalanine derivatives with very high stereoselectivity.



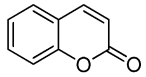
INTRODUCTION

Chroman-2-one (**1**) is a heterobicyclic compound, which possesses a benzene ring fused at the C_γ−C_δ bond of a δ-valerolactone. It is also referred to as dihydrocoumarin (cf. the structure of coumarin (**2**)). Many synthetic and some natural chroman-2-one derivatives with substituents at the C-3 or the C-4 position or both exhibit a broad range of biological activities or display pharmacological properties.[1] They include antiherpetic,[2] anti-inflammatory[3] antileishmanial,[4] antioxidative,[5] estrogenic,[6] pro-apoptotic, and cyto-differentiating[7] activities. Some chroman-2-one derivatives are found effective for anticolon/rectal cancer,[8] disruption of epigenetic process,[9] and increment of p53 tumor suppressor protein acetylation.[9] Certain compounds in this family function as inhibitors of bovine lens aldose reductase,[10] human Sir2 family deactylase (SIRT1 and SIRT2),[9] and protein transacetylase.[11]

More examples that are appealing are C-3 amino-substituted chroman-2-ones, which exhibit intriguing biological activities. They include antihypertensive activity reported by Reinhold,[12] inhibitor of Temoneria β-lactamase reported by Wakselman[13] and inhibitor of platelet aggregation reported by Rico,[14] Bovy,[15] and their co-workers.



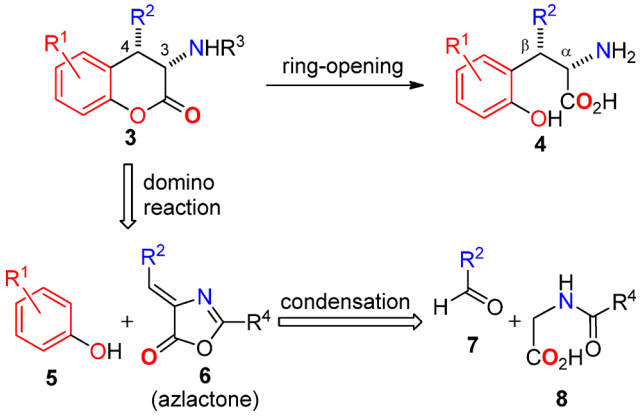
1 (chroman-2-one)



2 (coumarin)

Chroman-2-one derivatives are of great popularity in flavor industry and manufactured for used as fragrance.[1] They exist in baked substance, beverages, candies, chewing gum, cosmetics, frozen dairy foods, gelatins, lotions, perfumes, puddings, soaps, etc.[1] Chroman-2-ones are also important synthetic intermediates for pharmaceutical compounds of various types.[16] Furthermore, they were applied as building blocks for the synthesis of other biologically active compounds.[17] One of the prominent possibilities is the hydrolysis of 3-aminosubstituted chroman-2-ones **3** to generate α-amino acids **4** through the lactone ring opening as shown in Scheme 1.

Scheme 1. Retrosynthetic Analysis of the Targets 3-Aminochroman-2-ones 3 and α-Amino Acids 4



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Amino acids are the structural units that make up proteins and can also be used as a source of energy by the body.[18] Among about 500 known species,[19] their structures are classified as α-, β-, γ-, δ-amino acids, etc. Twenty proteinogenic amino acids are incorporated into polypeptides and conceded by the universal genetic code.[20] Many other nonproteinogenic amino acids are not produced directly.[21] They may be formed by post-translational modification during protein synthesis. Because of their biological activities, some amino acids have been commonly used in nutritional supplements,[22] fertilizers,[23] and food technology.[24] Other industrial uses include the production of drugs,[25] biodegradable plastics,[26] chiral catalysts,[27] etc.

An important pharmacophore in the family of amino acids is β,β-disubstituted arylalanines. These valuable chemical agents have been utilized to target various diseases including atherosclerosis reported by Doi and co-workers,[28] cancer by Hashimoto et al.,[29] diabetes insipidus by Kwiatkowska and co-workers,[30] diabetes mellitus type 2 by Patterson and co-workers,[31] and thrombosis by Nilsson,[32] Klebe,[33] Cheng et al.[34] Extensive studies related to human immunodeficiency virus are performed by McCauley,[35] Boyd,[36] Rajapakse,[37] Jones,[38] Stranix,[39] and their co-workers independently.

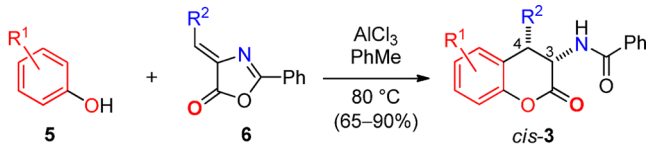
A main challenge to synthesize alanine derivatives bearing two different (especially β,β-diaryl) groups residing at the same β position is to generate two vicinal stereogenic centers at the α and β positions of an amino acid. Different approaches have been established to reach this objective. Representative examples include Armstrong's[40] ring opening of aziridines, Bach's[41] diastereoselective S_N1 reactions on phenylalanine derivatives, Chen,[42] Yu,[43] Daugulis,[44] and Corey's[45] palladium-catalyzed C−H functionalization of alanine derivatives, Liu[46] and Hruby's[47] alkylations with a chiral auxiliary, Leighton's[48] aza-Darzens/ring opening reactions, Molinaro's[49] hydrogenation of tetrasubstituted olefin, Chen's[50] chiral catalyst applied to nitroacrylates, Hou's[51] alkylation of glycine derivatives, etc. These methods may require directing ligands, expensive chiral auxiliaries, metallic catalysts, or protecting groups. Some of these methods are limited to specific types of substrates.

It was our plan to develop a new and efficient domino method[52] for the synthesis of amino-containing 3,4-disubstituted chroman-2-ones **3**. It involved the reaction of phenols **5** with the Erlenmeyer−Plochl azlactones[53] **6** as shown in Scheme 1. This new method went through a highly stereoselective and catalytic process to produce the targets **3** in good yields under mild conditions. Furthermore, the resultant 3-aminochroman-2-ones **3** were converted to the corresponding α-amino acids **4** (especially β,β-diarylalanines) in excellent yields.

The design and conditions employed in our process differed from the established reactions. Their approaches include the use of the Baeyer−Villiger oxidation, the Diels−Alder reaction, electrochemical reduction, enzymic reduction, the Friedel−Crafts alkylation, hydrogenation, lactonization, metal-catalyzed cyclization, the Michael addition, the Michael−Aldol reaction, oxidative cyclization, sequential Ugi and intramolecular Michael reaction, etc. Recently, Tilve et al.[1] have provided many working examples in their review article.

It was conceivable that an acid-catalyzed coupling of phenols **5** with Erlenmeyer−Plochl azlactones **6** would lead to a C−C bond formation, lactonization, and azlactone ring-opening in situ. Meanwhile, two stereogenetic centers could be generated with stereoselectivity in 3,4-disubstituted chroman-2-ones **3** as the final products. Nevertheless, Mohammadpoor-Baltork et al.[54] reported that the reaction of various azlactones with napthols in the presence of *p*-toluenesulfonic acid at 120 °C gives five-membered naphtho[2,1-*b*]furan-2(1*H*)-ones as the major products. They proposed a process that involves a transesterification reaction as the first step and then followed by tautomerization and a pseudo-Friedel−Crafts reaction. Consequently γ-butyrolactone, instead of δ-valerolactone, derivatives are generated. On the other hand, Halimehjani and Khoshdoun[55] used *p*-toluenesulfonic acid to catalyze the coupling of phenols with sulfur-containing starting materials 2-(alkylthio)thioazlactones. *cis*-3-(4-Arylchroman-2-onyl)-carbamodithioates can be generated at 120 °C under the solvent-free conditions. Its initial step is similar to that mentioned above, which involves proton activation of the thiozalactone ring to lead to ring opening. Here we report our disparate findings by using $AlCl_3$ to catalyze the coupling of phenols **5** with (*Z*)-azlactones **6**. The desired 3,4-disubstituted *cis*-chroman-2-ones **3** were generated in success under kinetic control as shown in Scheme 2.

Scheme 2. Reaction of Phenol 5 and (*Z*)-Azlactons 6 in the Presence of $AlCl_3$ To Produce *cis*-Aminochroman-2-ones 3



RESULTS

Synthesis of 3,4-Disubstituted *cis*-Chroman-2-ones 3.

To develop an efficient and stereoselective way to synthesize 3,4-disubstituted *cis*-chroman-2-ones **3**, we chose azlactone **6a** holding a *Z* configuration as the starting material. This azlactone can be prepared easily by the condensation of benzaldehyde (**7**, R^2 = Ph) with *N*-benzoyl glycine (**8**, R^4 = Ph) according to the method reported by Sampedro et al.[56] Thus, (*Z*)-azlactone **6a** was treated with *p*-methoxyphenol (**5f**) in the presence of a protonic acid as shown in Table 1. Among the five protonic acids used as listed in entries 1−5, their acidic strength is in the order of $CH_3C_6H_4SO_3H$ < camphorsulfonic acid < CF_3COOH < polyphoshoric acid < CF_3SO_3H.[57] The solvents utilized included toluene and 1,2-dichloroethane, the temperature was kept at 70−80 °C; and reaction time lasted from 3.0−5.0 h. Under these conditions, none of protonic acids was able to catalyze the reactions to generate a significant amount of the desired chroman-2-one **3f**. Nevertheless, these results obtained by us are indeed consistent with those reported previously by Mohammadpoor-Baltork et al.[54]

For the accomplishment of our goal to obtain chroman-2-one derivatives, an alternative method was explored by use of Lewis acids[58] to initiate the Friedel−Crafts alkylation between *p*-methoxyphenol (**5f**) and azlactone **6a**. These Lewis acids included AgOTf, $BF_3{\cdot}Et_2O$, $CeCl_3{\cdot}7\ H_2O$, $CuBr_2$, $Cu(OAc)_2$, $Cu(OTf)_2$, $FeCl_3$, $InCl_3$, $Sc(OTf)_3$, $SnCl_4$, $TiCl_4$, and $Zn(OTf)_2$ as shown in entries 6−17 of Table 1. Within 4.0 h at 40−70 °C, chroman-2-one **3f** was generated ≤10% yields in some of these

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Table 1. Optimization of the Yield for the Coupling of *p*-Methoxyphenol (5f) with (*Z*)-Azlactone 6a to Give Disubstituted Chroman-2-one 3f

entry	catalyst	equiv.	solvent	temp. (°C)	time (h)	yield[a] (%)
1	$CH_3C_6H_4SO_3H$[b]	1.1	toluene	80	5.0	0
2	camphorsulfonic acid	1.0	toluene	80	3.0	trace
3	CF_3COOH	1.2	$ClCH_2CH_2Cl$	70	3.0	0
4	polyphoshoric acid	1.3	$ClCH_2CH_2Cl$	70	3.0	0
5	CF_3SO_3H	0.50	$ClCH_2CH_2Cl$	70	3.0	0[c]
6	AgOTf	1.1	$ClCH_2CH_2Cl$	70	4.0	trace
7	$BF_3{\cdot}Et_2O$	2.0	$ClCH_2CH_2Cl$	70	4.0	<10
8	$CeCl_3{\cdot}7H_2O$	1.1	CH_2Cl_2	40	4.0	<10
9	$CuBr_2$	1.5	CH_2Cl_2	40	4.0	<10
10	$Cu(OAc)_2$	1.5	CH_2Cl_2	40	4.0	trace
11	$Cu(OTf)_2$	1.1	CH_2Cl_2	40	4.0	5
12	$FeCl_3$	1.5	CH_2Cl_2	40	4.0	trace
13	$InCl_3$	1.0	$ClCH_2CH_2Cl$	70	4.0	10
14	$Sc(OTf)_3$	0.50	$ClCH_2CH_2Cl$	70	4.0	trace
15	$SnCl_4$	0.50	$ClCH_2CH_2Cl$	70	4.0	0[c]
16	$TiCl_4$	0.50	$ClCH_2CH_2Cl$	70	4.0	0[c]
17	$Zn(OTf)_2$	1.1	CH_2Cl_2	40	4.0	<10
18	$AlCl_3$	2.5	$ClCH_2CH_2Cl$	24	12	30
19	$AlCl_3$	2.5	$ClCH_2CH_2Cl$	70	3.0	88
20	$AlCl_3$	2.0	toluene	0	3.0	15
21	$AlCl_3$	1.2	toluene	24	12	28
22	$AlCl_3$	0.50	toluene	70	3.0	trace
23	$AlCl_3$	1.1	toluene	70	3.0	23
24	$AlCl_3$	2.1	toluene	80	3.0	85
25	**$AlCl_3$**	**2.5**	**toluene**	**80**	**4.0**	**90**
26	$AlCl_3$	3.2	toluene	80	3.0	90
27	$AlEtCl_2$	2.5	toluene	24	12	<5
28	$AlEt_2Cl$	2.5	toluene	24	12	<4
29	Al(salen)Cl	0.50	toluene	24	12	trace
30	$Al(O\text{-}i\text{-}Pr)_3$	2.5	toluene	80	5.0	5

[a]Isolated yield. [b]Ref 54. [c]Azlactone decomposed.

reactions. Apparently, employment of Lewis acids as the catalysts was able to lead the coupling reaction to the desired δ-valerolactone derivative though the yield was low.[58]

Aluminum trichloride is among the most popular reagents applied to catalyze the Friedel–Crafts alkylation.[59] Under various conditions as shown in entries 18–26 of Table 1, the use of 2.5 equiv of $AlCl_3$ was able to produce the desired chroman-2-one **3f** with yields reaching as high as 90% (entry 25) from the starting materials *p*-methoxyphenol (**5f**) and (*Z*)-azlactone **6a**. It is known that the aluminum chloride is often required in full stoichiometric quantities for catalysis of the Friedel–Crafts reaction. This is due to its strong complexation with the product,[60] especially chroman-2-one **3f** possessing several binding sites such as oxygen and nitrogen atoms as well as phenyl rings.[61] The related but less chlorinated aluminum Lewis acids like $AlEtCl_2$, $AlEt_2Cl$, Al(salen)Cl,[62] and Al(O-*i*-Pr)3 were also applied. Nevertheless, the desired chroman-2-one **3f** was generated in very low yields (5% or less, see entries 27–30).

After the optimum conditions were obtained, the general scope and applicability were explored for this newly established reaction shown in Scheme 2. Consequently, nine phenols **5a–i** (1.0 equiv) with Me-, *tert*-butyl-, MeO-, dioxolane, I-, and benzofused substituents at different positions were used as the starting materials. Meanwhile, ten different (*Z*)-azlactones **6a–j** (1.5 equiv) with Ph-, *p*-tolyl-, (MeO)Ph-, F-Ph-, Me-, Et-, and isobutyl- substituents were also used. The coupling reactions were catalyzed by addition of 2.5 equiv of $AlCl_3$ in toluene at 80 °C for 3.0–4.0 h. Eighteen 3,4-disubstituted *cis*-chroman-2-ones (i.e., **3a–r**) were generated in 65–90% yields. All of these reactions led to the cis isomers exclusively except the product **3m** (cis/trans = 10:1). The details on the starting materials, products, and yields are listed in Table 2.

The structures of all new compounds were fully characterized by spectroscopic methods. For example, the exact mass of *cis*-3-(*N*-benzoyalamino)chroman-2-one **3d** was measured as 371.1520, which is very close to its theoretical value of 371.1521 $(C_{24}H_{21}NO_3)^+$. Its ^1H NMR spectrum included a doublet of doublet with J = 6.6 and 6.6 Hz at δ 5.30 ppm for the $NCHCO_2$ proton and a doublet with J = 6.6 Hz at δ 4.86 ppm for the ArCHPh proton. The coupling constants J^3 for the protons at the C-3 and C-4 positions of disubstituented chromane-2-ones are ∼6.8 and ∼9.4 Hz for cis[55] and trans[63] isomers, respectively. Thus, the product **3d** was assigned to be the cis isomer. Two singlets appeared at δ 2.34 and 2.13 ppm for the two methyl groups in the same benzene ring. In the downfield region, two very close singlets resonated at δ 6.86 and 6.85 ppm. They were assigned to the aromatic protons in the chroman-2-one nucleus. The ^{13}C NMR spectrum of **3d** exhibited two peaks in the downfield region at δ 167.54 and 167.24 ppm, which corresponded with the two C═O carbons. Moreover, 14 peaks were clearly observed between δ 150.73–115.10 ppm, which were associated with the carbons in three different benzene rings. Its IR spectrum exhibited two strong absorption bands at 1770 and 1661 cm^{-1}, which were related to the stretching vibrations of C═O in the ester and amido groups, respectively.

For verification of the configuration conclusively, the molecular framework of compound **3d** was obtained by single crystal X-ray diffraction analysis (Figure 1). Its monoclinic crystals (mp 194.4–195.8 °C, methanol) possessed the space group $P2_1/n$ with a = 13.1943(13) Å, b = 8.1217(8) Å, c = 18.6026(18) Å, α = 90°, β = 107.453(3)°, and γ = 90°. Its X-ray data revealed that the two substituents at the C-3 benzoylamino group and the C-4 phenyl group indeed held a cis configuration.

Synthesis of β,β-Disubstituted Arylalanines and *N*-Protected Derivatives. 3,4-Disubstituted chroman-2-ones **3** exist as a masked form of β,β-disubstituted arylalanines.

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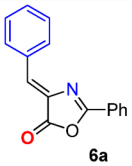
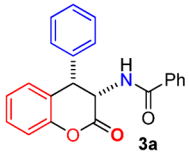
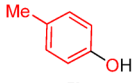
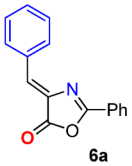
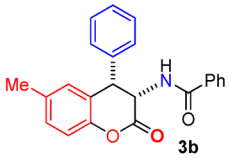
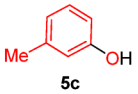
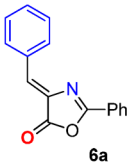
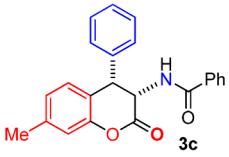
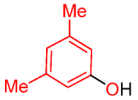
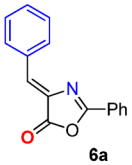
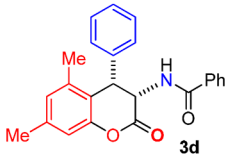
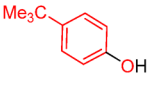
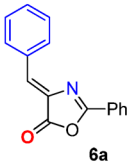
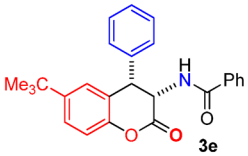
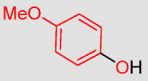
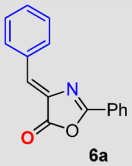
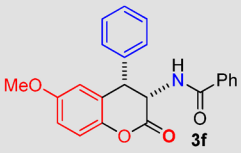
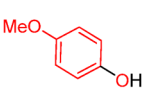
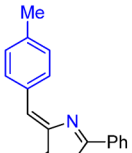
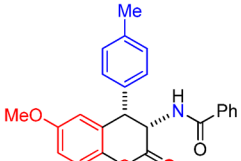
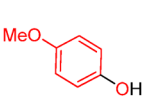
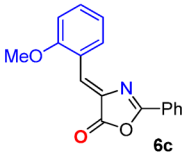
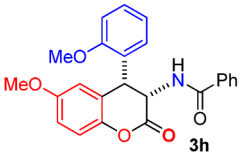
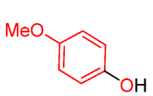
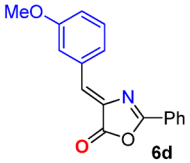
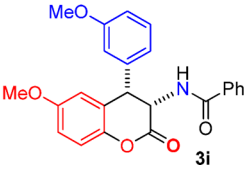
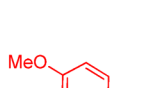
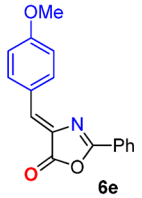
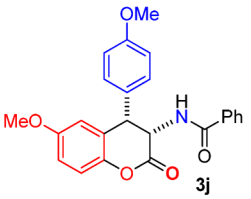
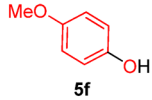
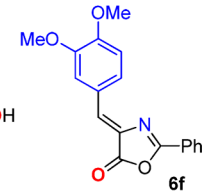
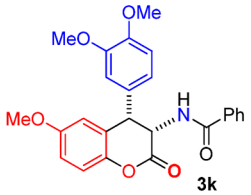
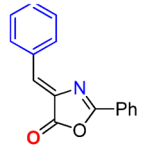
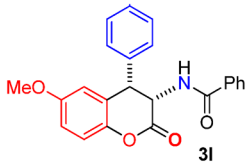
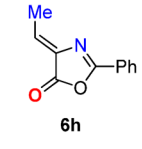
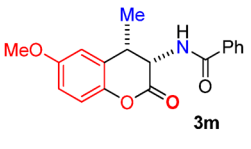
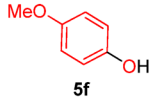
Table 2. Starting Materials, Products, and Yields in the Synthesis of *cis*-Chroman-2-ones from Phenols and Azlactones by Use of 2.5 equiv of $AlCl_3$ in Toluene at 80 °C

phenols **5**	+	azlactones **6**	disubstituted *cis*-chromane-2-ones **3**	yield (%)
 **5a**		 **6a**	 **3a**	86
 **5b**		 **6a**	 **3b**	90
 **5c**		 **6a**	 **3c**	88
 **5d**		 **6a**	 **3d**	86
 **5e**		 **6a**	 **3e**	85
 **5f**		 **6a**	 **3f**	90
 **5f**		 **6b**	 **3g**	77
 **5f**		 **6c**	 **3h**	73
 **5f**		 **6d**	 **3i**	75
 **5f**		 **6e**	 **3j**	81
 **5f**		 **6f**	 **3k**	78
 **5f**		 **6g**	 **3l**	71
 **5f**		 **6h**	 **3m**	73[a]
 **5f**		**6i**	**3n**	75
5f		**6j**	**3o**	80
5g		**6a**	**3p**	86
5h		**6a**	**3q**	65
5i		**6a**	**3r**	83

[a]This was the only example that a mixture of *cis*- and *trans*-isomer (10:1) was generated.

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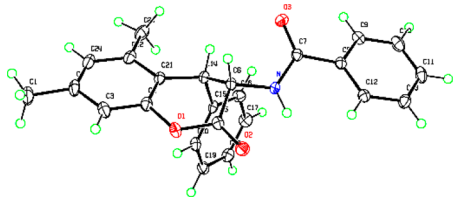
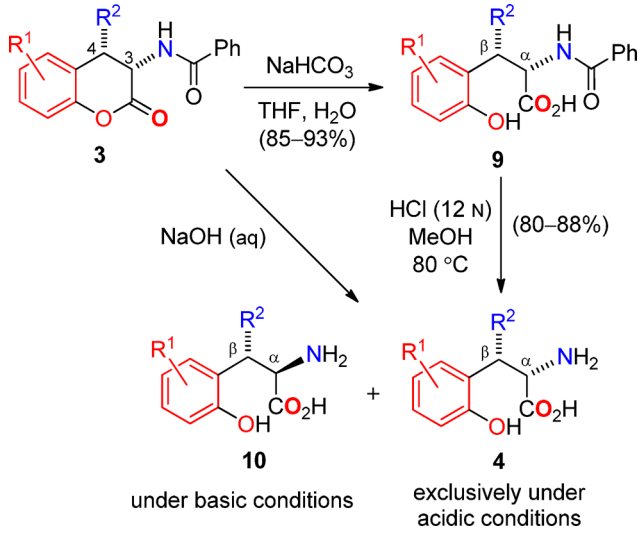


Figure 1. ORTEP diagram of compound **3d** as determined by X-ray analysis (ellipsoid contour probability 50%).

Hydrolysis under controlled conditions to cause only the selective ring opening of the lactone moiety therein would lead to the corresponding *N*-protected α-amino acids **9** as shown in Scheme 3. On the other hand, hydrolysis occurring to both of

Scheme 3. Hydrolyses of *cis*-Chroman-2-ones 3 to give *N*-Protected α-Amino Acids 9 and Then α-Amino Acids 4



the lactone moiety and the C-3 benzoylamino groups in compounds **3** would lead to free α-amino acids **4**. A challenge to these hydrolysis reactions was how to prevent the undesired epimerization from occurring at the α carbon center to give the diastereomeric byproducts **10**.

The conversion of 3,4-disubstituted *cis*-chroman-2-ones **3** to free α-amino acids **4** was initially accomplished by use of compound **3f** in an aqueous NaOH solution at 100 °C within 1.0 h. Nevertheless, annoying epimerization indeed took place at the α carbon center. It led to a 1:1 mixture of α-amino acids **4** (R^1 = OMe, R^2 = Ph) and **10** (R^1 = OMe, R^2 = Ph) in 78% overall yield.

The *N*-protected α-amino acids **9** as shown in Scheme 3 are in a class of valuable compounds in proteomic and synthetic chemistry. The free hydroxyl and carboxyl groups therein allow them to be coupled with nucleic acids, various drugs, and other amino acids. Afterward, the *N*-protected group can be removed to give free amines. On the basis of this advantage, it encouraged us to find mild conditions for the generation of *N*-protected α-amino acids from chroman-2-ones **3**.

Among various reagents, solvents, and temperatures shown in Table 3, sodium bicarbonate in a mixture of THF and water (3:1) was found to serve the purpose of selective hydrolysis well for chroman-2-one **3f** in 12 h. Application of the optimum conditions listed in entry 11 allowed the desired α-(*N*-benzoyl)amino acid **9b** isolated in 90% yield without

Table 3. Conditions and Yields for the Hydrolysis of *cis*-Chroman-2-one 3f to Give Amino Acid 9b

entry	base	equiv	solvent	temp (°C)	time (h)	yield[a] (%)
1	LiOH	2.0	THF:H_2O (= 3:1)	25	1.0	40
2	LiOH	1.5	THF:MeOH:H_2O (= 3:1:1)	25	2.0	0[b]
3	NaOH	1.5	MeOH	25	1.0	0[b]
4	NaOMe	1.1	MeOH	25	1.0	0[b]
5	K_2CO_3	1.5	MeOH	25	3.0	0[b]
6	Na_2CO_3	2.0	THF:H_2O (= 3:1)	60	2.0	50
7	$NaHCO_3$	3.0	acetonitrile:H_2O (= 3:1)	25	3.0	70
8	$NaHCO_3$	3.0	acetonitrile:H_2O (= 3:1)	60	4.0	75
9	$NaHCO_3$	2.0	THF:H_2O (= 3:1)	25	5.0	60
10	$NaHCO_3$	5.0	THF:H_2O (= 3:1)	25	12	65
11	$NaHCO_3$	10	THF:H_2O (= 3:1)	25	12	90
12	$NaHCO_3$	20	THF:H_2O (= 3:1)	25	12	72

[a]Isolated yield on the basis of *cis*-chromane-2-one **3f** used with 1.0 equiv. [b]The methyl ester of acid **9b** was isolated along with its α-epimer in 90–95% yields.

epimerization at the α carbon. Further hydrolysis at the amido functionality therein did not occur in situ. When methanol was present in the reaction solution, the methyl ester of **9b** along with its α epimer was generated together in 90–95% yields regardless the base employed was LiOH, NaOH, NaOMe, or K_2CO_3 (entries 2–5 of Table 3). Accordingly, the optimum conditions were applied to six representative *cis*-chroman-2-ones as shown in Table 4 to give nonepimeric α-(*N*-benzoyl)amino acids **9a–f** in 85–93% yields.

Furthermore, various conditions were tested to convert α-(*N*-benzoyl)amino acids **9** to the corresponding free α-amino acids **4** as the exclusive products. Use of either NaOH or KOH, which is stronger than sodium bicarbonate, led benzoylamino acid **9b** to a mixture containing α-amino acid **4b** and its α epimer (see entries 1 and 2 of Table 5). The substrate **9b**, however, remained intact in an ethanolic solution containing a mild base hydrazine (entry 3). Finally, use of the methanolic solution containing hydrochloric acid[64] (aqueous 12 N HCl/MeOH = 1:2.3) at 80 °C allowed us to achieve our aim of deprotection of the benzoyl group in **9b**. As shown in entry 8 of Table 5, the desired free α-amino acid **4b** was obtained in 81% yield. Tourwé et al.[65] performed detailed studies on the deprotection of α-(*N*-benzoyl)amino acids with strong mineral acids. They confirmed that epimerization does not occur at the α position of the resultant α-amino acid products.

As a result, the optimum conditions shown in entry 8 of Table 5 were applied to deprotect benzoates **9a–f**. The corresponding hydrolyzed free amino acids **4a–f** were obtained as the exclusive epimers in 80–88% yields as shown in Table 4.

DISCUSSION

A cogent mechanism is depicted in Scheme 4 for the newly developed domino process in the synthesis of 3,4-disubstituted *cis*-chroman-2-ones **3** by use of $AlCl_3$ as the catalyst. It illustrates our design on how to obtain the diastereoselectivity with phenol **5a** and (*Z*)-azlactone **11** as a representative example. First, coordination of the Lewis acid $AlCl_3$ at the carbonyl group of the enone moiety of azlactone **11** generates a carbocationic intermediate **12**, which contains a benzylic cation. Sampedro[56] reported that the phenyl group (in blue) of the

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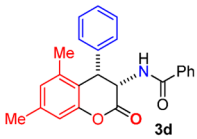
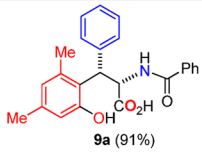
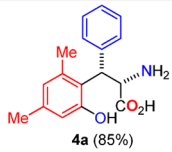
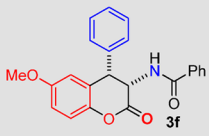
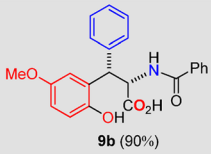
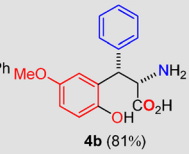
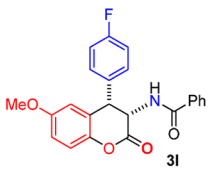
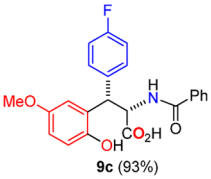
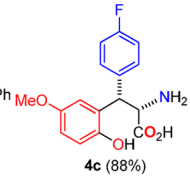
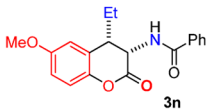
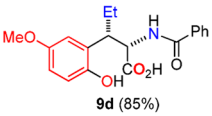
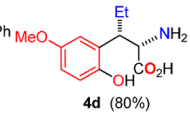
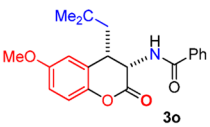
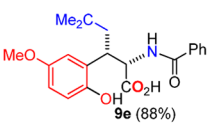
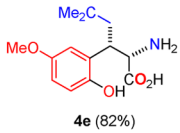
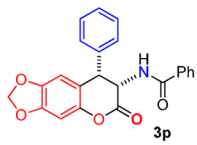
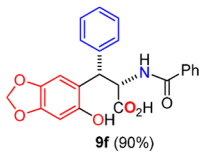
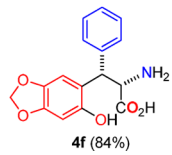
Table 4. Products and Yields in the Hydrolysis of *cis*-Chroman-2-ones to Give Amino Acids 9a–f, and the Following Debenzoylation to α-Amino Acids 4a–f, Respectively

entry	*cis*-chroman -2-one **3**	α-(*N*-benzoyl)amino acid[a] **9** (yield)	α-amino acid[b] **4** (yield)
1	 **3d**	 **9a** (91%)	 **4a** (85%)
2	 **3f**	 **9b** (90%)	 **4b** (81%)
3	 **3l**	 **9c** (93%)	 **4c** (88%)
4	 **3n**	 **9d** (85%)	 **4d** (80%)
5	 **3o**	 **9e** (88%)	 **4e** (82%)
6	 **3p**	 **9f** (90%)	 **4f** (84%)

[a]α-(*N*-Benzoyl)amino acids were obtained by hydrolysis of *cis*-chroman-2-ones with 10 equiv of sodium bicarbonate in a mixture of THF and water (= 3:1) at room temperature for 12 h. [b]Free a-amino acids were obtained by debenzoylation of α-(*N*-benzoyl)amino acids with a mixture of 12 N hydrochloric acid and methanol (1:2.3) at 80 °C for 12 h.

azlactone holds a *Z* geometry relative to the nitrogen atom. This geometry plays a crucial role in the determination of the stereoseletivity in the following addition steps. When the Friedel–Crafts reaction proceeds, the starting material phenol **5a** would first attach to the carbocationic intermediate **12**. It proceeds preferentially at the site opposite to where the tetrahedral aluminum group[66] resides. The resultant aluminate **13** holds a configuration with the benzylic hydrogen at the same site of the aluminate group. It leaves two six-membered rings (in green and sorrel) away from the aluminum group to avoid steric congestion.

Second, transposition of the $AlCl_3$ group from an enolate oxygen to the imine nitrogen atom in the oxazole intermediate **13** takes place. It is initiated by the donation of an unshared electron pair from its ethereal oxygen atom to the imine moiety. After the $AlCl_3$ group is coordinated at the nitrogen

Table 5. Optimization for the Hydrolysis of α-(*N*-Benzoyl)amino Acid 9b to Give Free α-Amino Acid 4b with Minimal Epimerization

entry	base	equiv	solvent	temp (°C)	time (h)	yield[a] (%)
1	NaOH	2.0	H_2O	90	5.0	55[b]
2	KOH	2.0	H_2O	90	5.0	65[b]
3	$H_2N–NH_2$	5.0	EtOH	90	12	0
4	HCl	20	H_2O	90	8.0	10
5	HCl[c]	20	AcOH	120	8.0	20
6	HCl[d]	15	MeOH	80	12	65
7	HCl[d]	20	MeOH	80	12	75
8	HCl[d]	26	MeOH	80	12	81
9	HCl[d]	35	MeOH	80	12	75
10	HBr	20	H_2O	90	5.0	25
11	HBr[e]	20	AcOH	120	2.0	80

[a]Isolated yield on the basis of α-(*N*-benzoyl)amino acid **9b** used with 1.0 equiv. [b]The α-epimeric mixture of acid **4b** was obtained. [c]Aqueous HCl (12 N)/acetic acid (= 1:4). [d]Aqueous HCl (12 N)/methanol (= 1:2.3). [e]Aqueous HBr (48%)/acetic acid (= 1:4).

atom through a 1,4-shift, a carbanionic center is generated in intermediates **14** and **15**. Computational results obtained by use of the DMol3 in Material Studio 5.5 program for geometry optimization show that the distance between the center of aluminate and the center of the phenyl ring (originally from azlactone) in **14** was 5.87 Å. It was longer than 4.95 Å that was the distance between the center of aluminate and the center of the phenol ring in **15**. The energy difference (i.e., Δ*E*) was calculated as 9.31 kcal/mol, which favored the formation of intermediates **14**.

Meanwhile, the Friedel–Crafts alkylation is completed and liberates a proton from the cyclohexadiene ring in **13**. The H^+ prefers to "float" at the electron-rich site of RR′N → Al^-Cl_3 as shown in the carbanion **14** instead of the carbanion **15** due to the electronic effect. At the same time, the phenyl group containing delocalized π-electrons above and below the six-membered ring repulses the electron-rich moiety of RR′N → Al^-Cl_3 to a different site. As a result, the carbanion center traps an H^+ from the oppositesite of the phenyl group. Concurrently, a new lactone ring was formed and opening of the azlactone ring in **14** occurred to produce the amide intermediate **16** through a kinetic process.

Third, the aluminum group in the protonated lactone **16** is replaced by a proton to give the target *cis*-chorman-2-one **18** exclusively through the RR′N → Al^-Cl_3 species **17**. The two factors that involve the use of $AlCl_3$ as the catalyst and the phenyl group holding a *Z* configuration play essential roles in control of stereoselectivity. When this phenyl group is replaced by a methyl group in the starting material (i.e., azlactone **6h**), the *cis*-chorman-2-one **3m** was generated along with its trans isomer in a ratio of 10:1.

The mechanism shown in Scheme 4 illustrates the steric and electronic effects associated with $AlCl_3$. These effects cannot be reached by use of a proton as the acid catalyst, which is regarded as the smallest element of Lewis acid.[67] Mohammadpoor-Baltork et al.[54] activated azlactones with a Brønsted acid (*p*-TsOH) at the carbonyl group to allow an attack by an alcohol at the carbonyl carbon. They believe that their reaction proceeds through a tandem esterification/intramolecular 1,4-addition-type Friedel–Crafts alkylation reaction. The stereochemical outcome is dictated under thermodynamic control by the last tautomerization step at high temperature. We also

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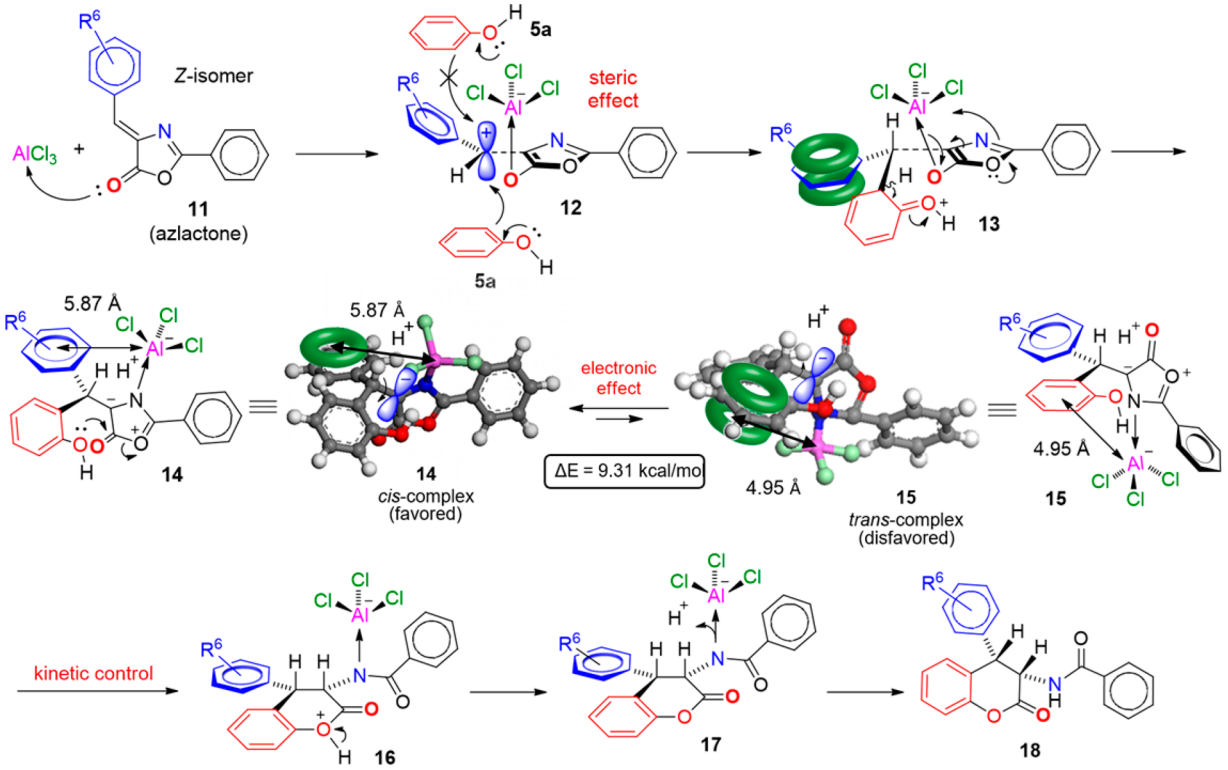
Scheme 4. Plausible Mechanistic Pathway Including Four Domino Steps



confirmed the feasibility of their pathway by use of our starting materials to give [2,1-*b*]furan-2(1*H*)-ones.

In contrast, replacement of the proton of a Brønsted acid by the "bulkier" Lewis acid $AlCl_3$ as the catalyst would lead the nucleophilic alcohols to attack the activated intermediate **12** at the farther carbon. As a result, the entire domino process shown in Scheme 4 includes a Friedel–Crafts alkylation, 1,4-$AlCl_3$ shift, lactone formation, azlactone ring opening, and protodealumination in sequence.

The new reaction as shown in Scheme 2 for synthesis of 3,4-disubstituted chroman-2-ones possesses four advantages: (1) The starting materials, phenols and Erlenmeyer–Plochl (*Z*)-azlactones with various substituents, are readily available. (2) The chroman-2-one targets are generated in a highly stereoselective manner with a cis configuration. (3) The reaction leads to the desired products in good to excellent yields (65–90%) under mild conditions (80 °C). (4) The entire process is a "single-flask" reaction in nature. It can be conducted with easy and establishes an ecologically and economically favorable way to produce chroman-2-one derivatives.

CONCLUSIONS

A new and efficient method was developed for the synthesis of 3,4-disubstituted *cis*-chroman-2-ones **3** from one equivalent of phenols **5** and 1.5 equiv of (*Z*)-azlactones **6** in the presence of 2.5 equiv of $AlCl_3$ as the catalyst. It involves a cationic hetero domino process of Friedel–Crafts alkylation/1,4-$AlCl_3$ shift/transesterification/protodealumination. The new findings are with the benefit of atom economy, reduction of waste generated by alternative methods with multiple chemical steps, as well as downsize of time and work required.

Furthermore, the conversions of chroman-2-ones **3** to *N*-protected α-amino acids and then to free α-amino acids were accomplished in success by stepwise hydrolysis under optimum alkaline and acidic conditions, respectively. Consequently, the target molecules were generated without undesired epimerization at the α-carbon centers. Continuous works in quest of chiral catalysts and ligands to induce asymmetric syntheses of 3,4-disubstituted chorman-2-ones and α-amino acids are underway. The results will be reported in due course.

EXPERIMENTAL SECTION

General Procedure. All reactions were carried out in oven-dried glassware (120 °C) under an atmosphere of nitrogen unless as indicated otherwise. Dichloroethane, dichloromethane, and methanol were purchased from Mallinckrodt Chemical Co. THF from Mallinckrodt Chemicals Co. was dried by distillation from sodium and benzophenone under an atmosphere of nitrogen. Ethyl acetate and hexanes from Mallinckrodt Chemical Co. were dried and distilled from CaH_2. Aluminum trichloride ($AlCl_3$), 3-methylphenol, and 4-methylphenol were purchased from Merck. 4-Methoxyphenol, 3,4-(methylenedioxy)phenol, and 2-naphthol were purchased from Alfa Aesar Chemical Co. 3,5-Dimethylphenol, 4-iodophenol, phenol, and 4-*tert*-butylphenol were purchased from TCI. Azlactones **6a–j** were synthesized according to the reported procedures.[68−74]

Analytical thin layer chromatography (TLC) was performed on precoated plates (silica gel 60 F-254). Purification by gravity column chromatography was carried out by use of Silicycle ultra-pure silica gel (particle size 40–63 μM, 230–400 mesh). Melting points were obtained with a melting point apparatus. HPLC analysis was performed on high performance liquid chromatography, UV detection monitored at 254 nm, using a Thermo 5 μm Hypersil ODS (250 mm 4.6 mm i.d.) column with acetonitrile and water as the eluent.

Infrared spectra (IR) were measured on a Fourier transform infrared spectrometer (FT-IR). Absorption intensities are recorded by the following abbreviations: s, strong; m, medium; and w, weak. Proton NMR spectra were obtained on 400 MHz spectrometers by use of chloroform-*d* ($CDCl_3$), dimethyl sulfoxide-d_6 (DMSO-d_6), and methanol-d_3 (CD_3OD) as the solvents. Proton NMR chemical shifts were referenced to residual protonated solvent (δ 7.24 ppm for

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chloroform, 2.49 ppm for dimethyl sulfoxide, and 3.31 ppm for methanol). Carbon-13 NMR spectra were obtained 100 MHz spectrometers by use of chloroform-*d* ($CDCl_3$), dimethyl sulfoxide-d_6 (DMSO-d_6), and methanol-d_3 (CD_3OD) as the solvents. Carbon-13 chemical shifts were referenced to the center of the $CDCl_3$ triplet (δ 77.0 ppm), DMSO-d_6 septet (δ 39.5 ppm), or CD_3OD septet (δ 49.0 ppm). Multiplicities are recorded by the following abbreviations: s, singlet; d, doublet; dd, doublet of doublet; ddd, doublet of doublet of doublet; t, triplet; q, quartet; m, multiplet; and *J*, coupling constant (hertz). High-resolution mass spectra (HRMS) were measured on an instrument using a time-of-flight mass analyzer (TOF) with electrospray ionization (ESI).

Standard Procedure 1 for the Syntheses of Chroman-2-one Derivatives 3a–r. To a stirred solution of azlactone **6** (1.5 equiv) in dry toluene at room temperature was added substituted phenol **5** (1.0 equiv) and $AlCl_3$ (2.5 equiv). After the reaction mixture was stirred at 80 °C for 3.0–4.0 h, it was cooled down to room temperature. The reaction was quenched with saturated sodium bicarbonate aqueous solution, which was extracted with EtOAc (3 × 15 mL). The combined organic layers were dried over $MgSO_4$ (s), filtered, and concentrated under reduced pressure to afford the residue. It was then purified by use of column chromatography on silica gel with EtOAc in hexanes as the eluent to give the desired chroman-2-one.

***cis*-3-(*N*-Benzoylamino)-4-phenylchroman-2-one (3a).** The Standard Procedure 1 was followed by use of oxazol-5(4*H*)-one **6a**[68] (53.4 mg, 0.214 mmol, 1.5 equiv), phenol **5a** (13.5 mg, 0.142 mmol, 1.0 equiv), and $AlCl_3$ (47.3 mg, 0.355 mmol, 2.5 equiv) in toluene (2.0 mL). After the reaction mixture was stirred for 4.0 h and worked up, the residue was purified by use of column chromatography (2.0% EtOAc in hexanes as the eluent) to give chroman-2-one **3a** (42.1 mg, 0.122 mmol) in 86% yield as white solids: mp (recrystallized from MeOH) 156.8–157.6 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.70 (d, *J* = 7.2 Hz, 2 H, 2 × ArH), 7.51 (t, *J* = 7.2 Hz, 2 H, 2 × ArH), 7.43–7.35 (m, 3 H, 3 × ArH), 7.25–7.16 (m, 5 H, 5 × ArH), 7.00–6.97 (m, 2 H, 2 × ArH), 6.65 (d, *J* = 6.4 Hz, 1 H, NH), 5.37 (dd, *J* = 6.4, 6.4 Hz, 1 H, CHN), 4.88 (d, *J* = 6.4 Hz, 1 H, CHPh); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.3 (C═O), 167.3 (C═O), 150.6, 136.5, 133.4, 132.1, 129.6, 129.5, 129.0, 128.7, 128.3, 128.1, 127.1, 125.6, 124.5, 117.1, 53.7 (CHN), 45.0 (CPh); IR (neat) 3375–3360 (m, NH), 1768 (s, C═O), 1657 (s, C═O), 1486 (w), 1165 (m) 780 cm^{-1}; HRMS (ESI-TOF) *m*/*z* [M]$^+$ Calcd for $C_{22}H_{17}NO_3$ 343.1208; Found 343.1209.

***cis*-3-(*N*-Benzoylamino)-6-methyl-4-phenylchroman-2-one (3b).** The Standard Procedure 1 was followed by use of oxazol-5(4*H*)-one **6a**[68] (52.4 mg, 0.211 mmol, 1.5 equiv), 4-methylphenol **5b** (15.4 mg, 0.141 mmol, 1.0 equiv), and $AlCl_3$ (47.3 mg, 0.352 mmol, 2.5 equiv) in toluene (3.5 mL). After the reaction mixture was stirred for 4.0 h and worked up, the residue was purified by use of column chromatography (2.0% EtOAc in hexanes as the eluent) to give chroman-2-one **3b** (45.3 mg, 0.126 mmol) in 90% yield as white solids: mp (recrystallized from MeOH) 136.2–137.5 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.71–7.69 (d, *J* = 7.6 Hz, 2 H, 2 × ArH), 7.51 (tt, *J* = 7.6, 1.2 Hz, 1 H, ArH), 7.43–7.39 (m, 2 H, 2 × ArH), 7.26–7.22 (m, 3 H, 3 × ArH), 7.17 (dd, *J* = 8.4, 2.0 Hz, 1 H, ArH), 7.10 (d, *J* = 8.4 Hz, 1 H, ArH), 7.04 (brs, 1 H, ArH), 7.01–6.99 (m, 2 H, 2 × ArH), 6.65 (d, *J* = 6.2 Hz, 1 H, NH), 5.33 (dd, *J* = 6.2, 6.2 Hz, 1 H, CHN), 4.83 (d, *J* = 6.2 Hz, 1 H, CHPh), 2.29 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.5 (C═O), 167.2 (C═O), 148.5, 136.6, 135.3, 133.4, 132.0, 130.0, 129.8, 128.9, 128.6, 128.2, 128.0, 127.0, 124.1, 116.8, 53.7 (CHN), 45.0 (CPh), 20.7 (CH_3); IR (neat) 3401–3396 (m, NH), 1766 (s, C═O), 1651 (s, C═O), 1488 (s), 1356 (m), 1173 (s), 1149 (s), 723 (s) cm^{-1}; HRMS (ESI-TOF) *m*/*z* [M + Na]$^+$ Calcd for $C_{23}H_{19}NO_3Na$ 380.1263; Found 380.1264.

***cis*-3-(*N*-Benzoylamino)-7-methyl-4-phenylchroman-2-one (3c).** The Standard Procedure 1 was followed by use of oxazol-5(4*H*)-one **6a**[68] (51.4 mg, 0.211 mmol, 1.5 equiv), 3-methylphenol **5c** (15.4 mg, 0.141 mmol, 1.0 equiv), and $AlCl_3$ (46.6 mg, 0.351 mmol, 2.5 equiv) in toulene (3.5 mL). After the reaction mixture was stirred for 4.0 h and worked up, the residue was purified by use of column chromatography (2.0% EtOAc in hexanes as the eluent) to give chroman-2-one **3c** (44.3 mg, 0.123 mmol) in 88% yield as white solids: mp (recrystallized from EtOH) 143.5–144.4 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.71–7.68 (m, 2 H, 2 × ArH), 7.51 (tt, *J* = 7.6, 2.0 Hz, 1 H, ArH), 7.43–7.39 (m, 2 H, 2 × ArH), 7.25–7.21 (m, 3 H, 3 × ArH), 7.11 (d, *J* = 7.6 Hz, 1 H, ArH), 7.03–6.97 (m, 4 H, 4 × ArH), 6.65 (d, *J* = 6.4 Hz, 1 H, NH), 5.34 (dd, *J* = 6.4, 6.4 Hz, 1 H, CHN), 4.83 (d, *J* = 6.4 Hz, 1 H, CHPh), 2.39 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.5 (C═O), 167.2 (C═O), 150.4, 139.9, 136.8, 133.4, 132.0, 129.2, 128.9, 128.7, 128.2, 127.9, 127.1, 126.4, 121.3, 117.4, 53.8 (CHN), 44.7 (CPh), 21.19 (CH_3); IR (neat) 3400–3390 (m, NH), 1762 (s, C═O), 1655 (s, C═O), 1482 (s), 1346 (m), 1163 (s), 1034 (m), 723 (s) cm^{-1}; HRMS (ESI-TOF) *m*/*z* [M]$^+$ Calcd for $C_{23}H_{19}NO_3$ 357.1365; Found 357.1364.

***cis*-3-(*N*-Benzoylamino)-5,7-dimethyl-4-phenylchroman-2-one (3d).** The Standard Procedure 1 was followed by use of oxazol-5(4*H*)-one **6a**[68] (54.1 mg, 0.217 mmol, 1.5 equiv), 3,5-dimethylphenol **5d** (17.7 mg, 0.144 mmol, 1.0 equiv), and $AlCl_3$ (48.2 mg, 0.361 mmol, 2.5 equiv) in toluene (3.0 mL). After the reaction mixture was stirred for 4.0 h and worked up, the residue was purified by use of column chromatography (2.0% EtOAc in hexanes as the eluent) to give chroman-2-one **3d** (46.3 mg, 0.128 mmol) in 86% yield as white solids: mp (recrystallized from MeOH) 194.4–195.8 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.70–7.69 (m, 2 H, 2 × ArH), 7.50 (t, *J* = 7.4 Hz, 1 H, ArH), 7.43–7.39 (m, 2 H, 2 × ArH), 7.24–7.22 (m, 3 H, 3 × ArH), 7.02–6.99 (m, 2 H, 2 × ArH), 6.86 (s, 1 H, ArH), 6.85 (s, 1 H, ArH), 6.62 (d, *J* = 6.6 Hz, 1 H, NH), 5.30 (dd, *J* = 6.6, 6.6 Hz, 1 H, CHN), 4.86 (d, *J* = 6.6 Hz, 1 H, CHPh), 2.34 (s, 3 H, CH_3), 2.13 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.5 (C═O), 167.2 (C═O), 150.7, 139.3, 137.3, 135.7, 133.4, 132.0, 128.9, 128.7, 128.5, 128.0, 128.0, 127.1, 120.1, 115.1, 53.7 (CHN), 42.3 (CPh), 21.1 (CH_3), 18.6 (CH_3); IR (neat) 3435–3429 (m, NH), 1770 (s, C═O), 1661 (s, C═O), 1515 (m), 1485 (m), 1358 (m), 1176 (m) cm^{-1}; HRMS (ESI-TOF) *m*/*z* [M]$^+$ Calcd for $C_{24}H_{21}NO_3$ 371.1521; Found 371.1520.

***cis*-3-(*N*-Benzoylamino)-6-*tert*-butyl-4-phenylchroman-2-one (3e).** The Standard Procedure 1 was followed by use of oxazol-5(4*H*)-one **6a**[68] (51.6 mg, 0.207 mmol, 1.5 equiv), 4-*tert*-butylphenol **5e** (20.8 mg, 0.138 mmol, 1.0 equiv), and $AlCl_3$ (46.2 mg, 0.345 mmol, 2.5 equiv) in toluene (2.0 mL). After the reaction mixture was stirred for 4.0 h and worked up, the residue was purified by use of column chromatography (2.0% EtOAc in hexanes as the eluent) to give chroman-2-one **3e** (47.2 mg, 0.118 mmol) in 85% yield as white solids: mp (recrystallized from MeOH) 136.3–137.1 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.72–7.70 (m, 2 H, 2 × ArH), 7.51 (t, *J* = 7.3 Hz, 1 H, ArH), 7.42–7.37 (m, 3 H, 3 × ArH), 7.26–7.23 (m, 4 H, 4 × ArH), 7.14 (d, *J* = 8.6 Hz, 1 H, ArH), 7.01–6.99 (m, 2 H, 2 × ArH), 6.65 (d, *J* = 6.0 Hz, 1 H, NH), 5.33 (dd, *J* = 6.0, 6.0 Hz, 1 H, CHN), 4.86 (d, *J* = 6.0 Hz, 1 H, CHPh), 1.27 (s, 9 H, 3 × CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.7 (C═O), 167.2 (C═O), 148.8, 148.4, 136.7, 133.5, 132.1, 129.0, 128.7, 128.4, 128.0, 127.1, 126.6, 126.3, 123.7, 116.5, 54.0 (CHN), 45.3 (CPh), 34.5 (CMe_3), 31.3 (3 × CH_3); IR (neat) 3433–3423 (m, NH), 1771 (s, C═O), 1662 (s, C═O), 1496 (m), 1356 (m), 1164 (m), 705 (w) cm^{-1}; HRMS (ESI-TOF) *m*/*z* [M + H]$^+$ Calcd for $C_{26}H_{25}NO_3H$ 400.1913; Found 400.1907.

***cis*-3-(*N*-Benzoylamino)-6-methoxy-4-phenylchroman-2-one (3f).** The Standard Procedure 1 was followed by use of oxazol-5(4*H*)-one **6a**[68] (53.4 mg, 0.214 mmol, 1.5 equiv), 4-methoxyphenol **5f** (18.5 mg, 0.142 mmol, 1.0 equiv), and $AlCl_3$ (47.5 mg, 0.355 mmol, 2.5 equiv) in toluene (3.0 mL). After the reaction mixture was stirred for 4.0 h and worked up, the residue was purified by use of column chromatography (2.0% EtOAc in hexanes as the eluent) to give chroman-2-one **3f** (47.8 mg, 0.127 mmol) in 90% yield as white solids: mp (recrystallized from MeOH) 111.5–112.4 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.70–7.68 (m, 2 H, 2 × ArH), 7.50 (t, *J* = 7.4 Hz, 1 H, ArH), 7.42–7.39 (m, 2 H, 2 × ArH), 7.25–7.22 (m, 3 H, 3 × ArH), 7.14 (d, *J* = 8.9 Hz, 1 H, ArH), 7.00–6.97 (m, 2 H, 2 × ArH), 6.89 (dd, *J* = 8.9, 2.9 Hz, 1 H, ArH), 6.73 (d, *J* = 2.9 Hz, 1 H, ArH), 6.68 (d, *J* = 6.4 Hz, 1 H, NH), 5.32 (dd, *J* = 6.4, 6.4 Hz, 1 H, CHN), 4.83 (d, *J* = 6.4 Hz, 1 H, CHPh), 3.74 (s, 3 H, OCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.4 (C═O), 167.3 (C═O), 156.9, 144.41, 136.3, 133.3, 132.1, 129.0, 128.7, 128.3, 128.1, 127.1, 125.3, 118.0, 115.34, 113.6,

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55.6 (OCH_3), 53.7 (CHNH), 45.2 (CHPh); IR (neat) 3435−3424 (m, NH), 1765 (s, C═O), 1661 (s, C═O), 1515 (s), 1357 (m), 1199 (s), 710 (s) cm^{-1}; HRMS (ESI-TOF) m/z $[M]^+$ Calcd for $C_{23}H_{19}NO_4$ 373.1314; Found 373.1317.

***cis*-3-(*N*-Benzoylamino)-6-methoxy-4-(4′-methyl-phenyl)-chroman-2-one (3g).** The Standard Procedure 1 was followed by use of oxazol-5-one **6b**[68] (54.5 mg, 0.207 mmol, 1.5 equiv), 4-methoxyphenol **5f** (17.1 mg, 0.138 mmol, 1.0 equiv), and $AlCl_3$ (47.5 mg, 0.345 mmol, 2.5 equiv) in toluene (3.5 mL). After the reaction mixture was stirred for 4.0 h and worked up, the residue was purified by use of column chromatography (5.0% EtOAc in hexanes as the eluent) to give chroman-2-one **3g** (41.6 mg, 0.107 mmol) in 77% yield as white solids: mp (recrystallized from EtOH) 143.4−144.2 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.72−7.70 (m, 2 H, 2 × ArH), 7.49 (tt, J = 7.2, 1.6 Hz, 1 H, ArH), 7.44−7.40 (m, 2 H, 2 × ArH), 7.13 (d, J = 8.8 Hz, 1 H, ArH), 7.05 (d, J = 7.6 Hz, 2 H, 2 × ArH), 6.90−6.87 (m, 3 H, 3 × ArH), 6.72 (d, J = 2.8 Hz, 1 H, ArH), 6.66 (d, J = 6.2 Hz, 1 H, NH), 5.31 (dd, J = 6.2, 6.2 Hz, 1 H, CHN), 4.78 (d, J = 6.2 Hz, 1 H, CHPh), 3.74 (s, 3 H, OCH_3), 2.27 (s, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.5 (C═O), 167.2 (C═O), 156.9, 144.5, 137.9, 133.5, 133.3, 132.1, 129.7, 128.7, 128.1, 127.1, 125.6, 118.0, 115.4, 113.5, 55.7 (OCH_3), 53.7 (CHN), 45.0 (CPh), 21.0 (CH_3); IR (neat) 3435−3428 (m, NH), 1769 (s, C═O), 1661 (s, C═O), 1494 (s), 1356 (m), 1199 (s) cm^{-1}; HRMS (ESI-TOF) m/z $[M]^+$ Calcd for $C_{24}H_{21}NO_4$ 387.1471; Found 387.1472.

***cis*-3-(*N*-Benzoylamino)-6-methoxy-4-(2′-methoxy-phenyl)-chroman-2-one (3h).** The Standard Procedure 1 was followed by use of oxazol-5-one **6c**[69] (55.6 mg, 0.199 mmol, 1.5 equiv), 4-methoxyphenol **5f** (16.5 mg, 0.132 mmol, 1.0 equiv), and $AlCl_3$ (44.2 mg, 0.331 mmol, 2.5 equiv) in toulene (3.5 mL). After the reaction mixture was stirred for 4.0 h and worked up, the residue was purified by use of column chromatography (5.0% EtOAc in hexanes as the eluent) to give chroman-2-one **3h** (38.8 mg, 0.0961 mmol) in 73% yield as white solids: mp (recrystallized from EtOH) 155.4−157.2 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.72−7.07 (m, 2 H, 2 × ArH), 7.46 (tt, J = 7.2, 1.2 Hz, 1 H, ArH), 7.44−7.40 (m, 2 H, 2 × ArH), 7.16 (t, J = 8.0 Hz, 1 H, ArH), 7.13 (d, J = 9.2 Hz, 1 H, ArH), 6.89 (dd, J = 9.2, 3.2 Hz, 1 H, ArH), 6.85−6.77 (m, 1 H, ArH), 6.72 (d, J = 2.4 Hz, 1 H, ArH), 6.68 (d, J = 6.2 Hz, 1 H, NH), 6.57 (d, J = 8.0 Hz, 1 H, ArH), 6.52 (t, J = 2.4 Hz, 1 H, ArH), 5.33 (dd, J = 6.2, 6.2 Hz, 1 H, CHN), 5.22 (d, J = 6.2 Hz, 1 H, CHPh), 3.71 (s, 3 H, OCH_3), 3.53 (s, 3 H, OCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.6 (C═O), 167.2 (C═O), 157.1, 156.6, 144.8, 133.7, 131.8, 129.9, 129.3, 128.5, 127.0, 125.6, 124.8, 121.2, 117.7, 114.9, 113.8, 110.5, 55.6 (OCH_3), 54.7 (OCH_3), 52.3 (CHN), 40.9 (CPh); IR (neat) 3368−3357 (m, NH), 1763 (s, C═O), 1663 (s, C═O), 1492 (s), 1356 (m), 1199 (s), 732 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_{24}H_{21}NO_5H$ 404.1498; Found 404.1493.

***cis*-3-(*N*-Benzoylamino)-6-methoxy-4-(3′-methoxy-phenyl)-chroman-2-one (3i).** The Standard Procedure 1 was followed by use of oxazol-5-one **6d**[69] (53.3 mg, 0.191 mmol, 1.5 equiv), 4-methoxyphenol **5f** (15.8 mg, 0.127 mmol, 1.0 equiv), and $AlCl_3$ (42.5 mg, 0.318 mmol, 2.5 equiv) in toluene (3.0 mL). After the reaction mixture was stirred for 4.0 h and worked up, the residue was purified by use of column chromatography (5.0% EtOAc in hexanes as the eluent) to give chroman-2-one **3i** (37.4 mg, 92.7 μmol) in 75% yield as white solids: mp (recrystallized from EtOH) 117.2−118.3 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.72−7.70 (m, 2 H, 2 × ArH), 7.51 (tt, J = 7.2, 1.2 Hz, 1 H, ArH), 7.44−7.40 (m, 2 H, 2 × ArH), 7.16 (t, J = 8.0 Hz, 1 H, ArH), 7.13 (d, J = 9.2 Hz, 1 H, ArH), 6.89 (dd, J = 9.2, 3.2 Hz, 1 H, ArH), 6.85−6.77 (m, 1 H, ArH), 6.72 (d, J = 2.4 Hz, 1 H, ArH) 6.68 (d, J = 6.2 Hz, 1 H, NH), 6.57 (d, J = 8.0 Hz, 1 H, ArH), 6.52 (t, J = 2.4 Hz, 1 H, ArH), 5.30 (dd, J = 6.2, 6.2 Hz, 1 H, CHN), 4.81 (d, J = 6.2 Hz, 1 H, CHPh), 3.73 (s, 3 H, OCH_3), 3.60 (s, 3 H, OCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.4 (C═O), 167.2 (C═O), 159.9, 156.9, 144.3, 137.7, 133.3, 132.0, 130.0, 128.6, 127.3, 127.0, 125.2, 120.3, 118.0, 115.4, 113.8, 113.5, 55.6 (OCH_3), 55.0 (OCH_3), 53.6 (CHN), 45.2 (CPh); IR (neat) 3366−3357 (m, NH), 1763 (s, C═O), 1663 (s, C═O), 1492 (s), 1356 (m), 1199 (s), 787 cm^{-1}; HRMS (ESI-TOF) m/z $[M]^+$ Calcd for $C_{24}H_{21}NO_5$ 403.1420; Found 403.1419.

***cis*-3-(*N*-Benzoylamino)-6-methoxy-4-(4′-methoxy-phenyl)-chroman-2-one (3j).** The Standard Procedure 1 was followed by use of oxazol-5(4*H*)-one **6e**[68] (55.3 mg, 0.198 mmol, 1.5 equiv), 4-methoxyphenol **5f** (16.4 mg, 0.132 mmol, 1.0 equiv), and $AlCl_3$ (44.6 mg, 0.331 mmol, 2.5 equiv) in toluene (2.0 mL). After the reaction mixture was stirred for 4.0 h and worked up, the residue was purified by use of column chromatography (5.0% EtOAc in hexanes as the eluent) to give chroman-2-one **3j** (43.2 mg, 0.107 mmol) in 81% yield as white solids: mp (recrystallized from MeOH) 141.6−142.5 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.73−7.70 (m, 2 H, 2 × ArH), 7.53 (tt, J = 7.6, 1.6 Hz, 1 H, ArH), 7.44−7.40 (m, 2 H, 2 × ArH), 7.13 (d, J = 9.2 Hz, 1 H, ArH), 6.91−6.87 (m, 3 H, 3 × ArH), 6.78 (t, J = 2.8 Hz, 1 H, ArH), 6.75 (d, J = 5.6 Hz, 1 H, ArH), 6.71 (d, J = 3.2 Hz, 1 H, ArH), 6.68 (d, J = 6.2 Hz, 1 H, NH), 5.28 (dd, J = 6.2 6.2 Hz, 1 H, CHN), 4.77 (d, J = 6.2 Hz, 1 H, CHPh), 3.74 (s, 3 H, OCH_3), 3.72 (s, 3 H, OCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.6 (C═O), 167.3 (C═O), 159.3, 156.9, 144.4, 133.4, 132.1, 129.4, 128.7, 128.2, 127.1, 125.7, 118.0, 115.3, 114.4, 113.5, 55.7 (OCH_3), 55.2 (OCH_3), 53.9 (CHN), 44.5 (CPh); IR (neat) 3370−3357 (m, NH), 1763 (s, C═O), 1663 (s, C═O), 1492 (s), 1356 (m), 1199 (s), 850 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ Calcd for $C_{24}H_{21}NO_5H$ 404.1498; Found 404.1490.

***cis*-3-(*N*-Benzoylamino)-4-(3′,4′-dimethoxyphenyl)-6-methoxychroman-2-one (3k).** The Standard Procedure 1 was followed by use of oxazol-5(4*H*)-one **6f**[70] (53.6 mg, 0.173 mmol, 1.5 equiv), 4-methoxyphenol **5f** (14.3 mg, 0.115 mmol, 1.0 equiv), and $AlCl_3$ (38.3 mg, 0.287 mmol, 2.5 equiv) in toluene (3.5 mL). After the reaction mixture was stirred for 4.0 h and worked up, the residue was purified by use of column chromatography (10% EtOAc in hexanes as the eluent) to give chroman-2-one **3k** (38.8 mg, 0.0895 mmol) in 78% yield as white solids: mp (recrystallized from EtOH) 125.3−126.2 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.77−7.70 (m, 2 H, 2 × ArH), 7.53 (tt, J = 7.2, 1.6 Hz, 1 H, ArH), 7.43−7.39 (m, 2 H, 2 × ArH), 7.13 (d, J = 8.8 Hz, 1 H, ArH), 6.88 (dd, J = 8.8, 2.8 Hz, 1 H, ArH), 6.73−6.70 (m, 3 H, 2 × ArH + 1 × NH), 6.50 (d, J = 2.0 Hz, 1 H, ArH), 6.47 (dd, J = 8.0, 2.0 Hz, 1 H, ArH), 5.26 (dd, J = 6.6, 6.6 Hz, 1 H, CHN), 4.80 (d, J = 6.6 Hz, 1 H, CHPh), 3.78 (s, 3 H, OCH_3), 3.74 (s, 3 H, OCH_3), 3.57 (s, 3 H, OCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.5 (C═O), 167.1 (C═O), 156.9, 149.0, 148.7, 144.3, 133.3, 132.1, 129.2, 128.7, 127.0, 125.4, 119.9, 118.0, 115.3, 113.8, 113.5, 111.5, 55.8 (OCH_3), 55.6 (OCH_3), 55.5 (OCH_3), 53.9 (CHN), 44.7 (CPh); IR (neat) 3376−3357 (m, NH), 1766 (s, C═O), 1655 (s, C═O), 1493 (s), 1138 (m), 1356 (m), 720 (m) cm^{-1}; HRMS (ESI-TOF) m/z $[M]^+$ Calcd for $C_{25}H_{23}NO_6$ 433.1525; Found 433.1528.

***cis*-3-(*N*-Benzoylamino)-6-methoxy-4-(4′-fluoro-phenyl)-chroman-2-one (3l).** The Standard Procedure 1 was followed by use of oxazol-5-one **6g**[68] (51.5 mg, 0.192 mmol, 1.5 equiv), 4-methoxyphenol **5f** (16.1 mg, 0.128 mmol, 1.0 equiv), and $AlCl_3$ (43.2 mg, 0.321 mmol, 2.5 equiv) in toluene (2.0 mL). After the reaction mixture was stirred for 3.5 h and worked up, the residue was purified by use of column chromatography (5.0% EtOAc in hexanes as the eluent) to give chroman-2-one **3l** (35.6 mg, 0.0909 mmol) in 71% yield as white solids: mp (recrystallized from EtOH) 169.3−170.1 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.72−7.70 (m, 2 H, 2 × ArH), 7.51 (tt, J = 7.2, 1.6 Hz, 1 H, ArH), 7.44−7.41 (m, 2 H, 2 × ArH), 7.15 (d, J = 9.2 Hz, 1 H, ArH), 6.94−6.89 (m, 5 H, 5 × ArH), 6.72 (d, J = 2.8 Hz, 1 H, ArH), 6.70 (d, J = 6.4 Hz, 1 H, NH), 5.26 (dd, J = 6.4, 6.4 Hz, 1 H, CHN), 4.86 (d, J = 6.4 Hz, 1 H, CHPh), 3.74 (s, 3 H, OCH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.3 (C═O), 167.3 (C═O), 162.2 (d, J_{C-F} = 246 Hz), 157.0, 144.3, 133.2, 132.2, 132.1, 129.9 (d, J_{C-F} = 8.0 Hz), 128.7, 127.0, 125.1, 118.1, 115.9 (d, J_{C-F} = 22 Hz), 115.5, 113.6, 55.7 (OCH_3), 53.8 (CHN), 44.3 (CPh); IR (neat) 3369−3358 (m, NH), 2918 (s), 1764 (s, C═O), 1657 (s, C═O), 1492 (s), 1356 (m), 1031 (w) cm^{-1}; HRMS (ESI-TOF) m/z $[M]^+$ Calcd for $C_{23}H_{18}FNO_4$ 391.1220; Found 391.1219.

***cis*-3-(*N*-Benzoylamino)-6-methoxy-4-methyl-chroman-2-one (3m).** The Standard Procedure 1 was followed by use of oxazol-5(4*H*)-one **6i**[71] (54.5 mg, 0.279 mmol, 1.5 equiv), 4-methoxyphenol

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5f (23.1 mg, 0.186 mmol, 1.0 equiv), and $AlCl_3$ (62.2 mg, 0.465 mmol, 2.5 equiv) in toluene (2.0 mL). After the reaction mixture was stirred for 4.0 h and worked up, the residue was purified by use of column chromatography (5.0% EtOAc in hexanes as the eluent) to give chroman-2-one **3m** (42.3 mg, 0.135 mmol) in 73% yield as white solids: mp (recrystallized from EtOH) 154.3−156.7 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.85 (d, J = 7.4 Hz, 2 H, 2 × ArH), 7.52 (tt, J = 7.4, 1.1 Hz, 1 H, ArH), 7.48−7.44 (m, 2 H, 2 × ArH), 7.14 (d, J = 5.2 Hz, 1 H, NH), 7.00 (d, J = 8.8 Hz, 1 H, ArH), 6.80 (dd, J = 8.8, 2.8 Hz, 1 H, ArH), 6.74 (d, J = 2.8 Hz, 1 H, ArH), 5.02 (dd, J = 5.2, 5.2 Hz, 1 H, CHN), 3.79 (s, 3 H, OCH_3), 3.74−3.67 (m, 1 H, CHMe), 1.15 (d, J = 7.2 Hz, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.5 (C═O), 167.2 (C═O), 156.8, 143.5, 133.3, 132.2, 128.7, 128.4, 127.1, 117.9, 114.1, 113.1, 55.7 (OCH_3), 53.5 (CHN), 34.6 (CMe), 15.5 (CH_3); IR (neat) 3376−3361 (m, NH), 1768 (s, C═O), 1655 (s, C═O), 1496 (s), 1358 (m), 1199 (s), 720 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ Calcd for $C_{18}H_{17}NO_4H$ 312.1236; Found 312.1231.

***cis*-3-(*N*-Benzoylamino)-4-ethyl-6-methoxy-chroman-2-one (3n).** The Standard Procedure 1 was followed by use of oxazol-5(4*H*)-one **6i**[72] (52.5 mg, 0.261 mmol, 1.5 equiv), 4-methoxyphenol **5f** (21.6 mg, 0.174 mmol, 1.0 equiv), and $AlCl_3$ (58.6 mg, 0.435 mmol, 2.5 equiv) in toluene (2.0 mL). After the reaction mixture was stirred for 4.0 h and worked up, the residue was purified by use of column chromatography (5.0% EtOAc in hexanes as the eluent) to give chroman-2-one **3n** (42.3 mg, 0.131 mmol) in 75% yield as white solids: mp (recrystallized from EtOH) 151.2−152.3 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.87−7.84 (m, 2 H, 2 × ArH), 7.54 (tt, J = 7.2, 1.2 Hz, 1 H, ArH), 7.48−7.44 (m, 2 H, ArH), 7.16 (d, J = 5.2 Hz, 1 H, NH), 7.02 (d, J = 8.8 Hz, 1 H, ArH), 6.82 (dd, J = 8.8, 2.8 Hz, 1 H, ArH), 6.71 (d, J = 2.8 Hz, 1 H, ArH), 5.03 (dd, J = 5.2, 5.2 Hz, 1 H, CHN), 3.79 (s, 3 H, OCH_3), 3.44 (ddd, J = 10.8, 5.2, 3.6 Hz, 1 H, CHEt), 1.81−1.74 (m, 1 H, C*H*HMe), 1.29−1.21 (m, 1 H, CH*H*Me), 0.88 (t, J = 7.2 Hz, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.9 (C═O), 167.1 (C═O), 156.4, 143.8, 133.4, 132.2, 128.7, 127.2, 126.6, 117.8, 114.7, 114.0, 55.7 (OCH_3), 53.2 (CHN), 41.2 (CHEt), 21.9 (CH_2Me), 11.1 (CH_3); IR (neat) 3380−3361 (m, NH), 1767 (s, C═O), 1651 (s, C═O), 1489 (s), 1359 (m), 1199 (s), 760 cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ Calcd for $C_{19}H_{19}NO_4H$ 326.1392; Found 326.1384.

***cis*-3-(*N*-Benzoylamino)-4-isobutyl-6-methoxy-chroman-2-one (3o).** The Standard Procedure 1 was followed by use of oxazol-5(4*H*)-one **6j**[73] (53.3 mg, 0.232 mmol, 1.5 equiv), 4-methoxyphenol **5f** (19.5 mg, 0.154 mmol, 1.0 equiv), and $AlCl_3$ (51.3 mg, 0.385 mmol, 2.5 equiv) in toluene (2.0 mL). After the reaction mixture was stirred for 3.5 h and worked up, the residue was purified by use of column chromatography (5.0% EtOAc in hexanes as the eluent) to give chroman-2-one **3o** (43.6 mg, 0.123 mmol) in 80% yield as white solids; mp (recrystallized from EtOH) 158.3−160.2 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.86−7.84 (m, 2 H, 2 × ArH), 7.52 (tt, J = 7.2, 1.2 Hz, 1 H, ArH), 7.48−7.44 (m, 2 H, 2 × ArH), 7.13 (d, J = 5.2 Hz, 1 H, NH), 7.01 (d, J = 8.8 Hz, 1 H, ArH), 6.80 (dd, J = 8.8, 2.8 Hz, 1 H, ArH), 6.72 (d, J = 3.2 Hz, 1 H, ArH), 5.02 (dd, J = 5.2, 5.2 Hz, 1 H, CHN), 3.78 (s, 3 H, OCH_3), 3.60 (ddd, J = 11.6, 5.2, 3.6 Hz, 1 H, CHBu^i), 1.58−1.52 (m, 1 H, $CHMe_2$), 1.38 (ddd, J = 13.2, 10.4, 3.6 Hz, 1 H, C*H*HCH), 1.24−1.18 (m, 1 H, CH*H*CH), 0.96 (d, J = 6.4 Hz, 3 H, CH_3), 0.92 (d, J = 6.4 Hz, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.8 (C═O), 167.1 (C═O), 156.3, 143.6, 133.4, 132.1, 128.7, 127.5, 127.1, 117.89, 114.2, 113.6, 55.7 (OCH_3), 53.2 (CHN), 38.0, 37.5, 24.8, 23.8 (CH_3), 21.3 (CH_3); IR (neat) 3410−3400 (m, NH), 1766 (s, C═O), 1657 (s, C═O), 1489 (s), 1358 (m), 1199 (s) cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ Calcd for $C_{21}H_{23}NO_4H$ 354.1705; Found 354.1697.

***cis*-3-(*N*-Benzoylamino)-6,7-methylenedioxy-4-phenylchroman-2-one (3p).** The Standard Procedure 1 was followed by use of oxazol-5(4*H*)-one **6a**[68] (52.6 mg, 0.211 mmol, 1.5 equiv), 3,4-(Methylenedioxy)phenol **5g** (19.4 mg, 0.141 mmol, 1.0 equiv), and $AlCl_3$ (47.1 mg, 0.352 mmol, 2.5 equiv) in toluene (2.0 mL). After the reaction mixture was stirred for 4.0 h and worked up, the residue was purified by use of column chromatography (7.0% EtOAc in hexanes as the eluent) to give chroman-2-one **3p** (47.2 mg, 0.121 mmol) in 86% yield as white solids: mp (recrystallized from EtOH) 148.6−149.5 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.68 (d, J = 7.2 Hz, 2 H, 2 × ArH), 7.51 (t, J = 7.0 Hz, 1 H, ArH), 7.41 (t, J = 7.7 Hz, 2 H, 2 × ArH), 7.25−7.24 (m, 3 H, 3 × ArH), 6.99−6.96 (m, 2 H, 2 × ArH), 6.65 (s, 1 H, ArH), 6.62−6.59 (m, 2 H, 1 × ArH + 1 × NH), 5.99 (d, J = 12.0 Hz, 2 H, OCH_2O), 5.33 (dd, J = 6.6, 6.6 Hz, 1 H, CHN), 4.73 (d, J = 6.6 Hz, 1 H, CHPh); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.3 (C═O), 167.2 (C═O), 148.2, 145.2, 145.1, 136.5, 133.4, 132.1, 129.0, 128.7, 128.2, 128.1, 127.1, 116.7, 108.1, 102.0, 99.0 (OCH_2O), 53.6 (CHN), 45.0 (CPh); IR (neat) 3366−3357 (m, NH), 1769 (s, C═O), 1663 (s, C═O), 1481 (s), 1241 (m), 1170 (s), 703 (m) cm^{-1}; HRMS (ESI-TOF) m/z [M]$^+$ Calcd for $C_{23}H_{17}NO_5$ 387.1107; Found 387.1108.

***cis*-3-(*N*-Benzoylamino)-6-iodo-4-phenylchroman-2-one (3q).** The Standard Procedure 1 was followed by use of oxazol-5(4*H*)-one **6a**[68] (55.3 mg, 0.222 mmol, 1.5 equiv), 4-iodophenol **5h** (32.6 mg, 0.148 mmol, 1.0 equiv), and $AlCl_3$ (49.6 mg, 0.371 mmol, 2.5 equiv) in toluene (2.0 mL). After the reaction mixture was stirred 3.5 h and worked up, the residue was purified by use of column chromatography (2.0% EtOAc in hexanes as the eluent) to give chroman-2-one **3q** (45.1 mg, 0.0962 mmol) in 65% yield as white solids: mp (recrystallized from MeOH) 153.4−155.2 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.73−7.71 (m, 2 H, 2 × ArH), 7.50 (tt, J = 7.6, 1.6 Hz, 1 H, ArH), 7.46−7.37 (m, 3 H, 3 × ArH), 7.28−7.24 (m, 4 H, 4 × ArH), 7.21 (dd, J = 7.2, 1.2 Hz, 1 H, ArH), 7.20−6.99 (m, 2 H, 2 × ArH), 6.64 (d, J = 6.4 Hz, 1 H, NH), 5.37 (dd, J = 6.4, 6.4 Hz, 1 H, CHN), 4.88 (d, J = 6.4 Hz, 1 H, CHPh); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.4 (C═O), 167.3 (C═O), 150.6, 136.5, 133.4, 132.1, 129.6, 129.5, 129.0, 128.7, 128.3, 128.1, 127.1, 125.6, 124.5, 117.1, 53.7 (CHN), 45.1 (CPh); IR (neat) 3537−3525 (m, NH), 1769 (s, C═O), 1660 (s, C═O), 1514 (s), 1485 (s), 1165 (s), 753 cm^{-1}; HRMS (ESI-TOF) m/z [M]$^+$ Calcd for $C_{22}H_{16}INO_3$ 469.0175; Found 469.0174.

***cis*-2-(*N*-Benzoylamino)-1-phenyl-3*H*-benzo[*f*]-chroman-3-one (3r).** The Standard Procedure 1 was followed by use of oxazol-5(4*H*)-one **6a**[68] (50.4 mg, 0.202 mmol, 1.5 equiv), 2-naphthol **5i** (19.4 mg, 0.134 mmol, 1.0 equiv), and $AlCl_3$ (44.8 mg, 0.335 mmol, 2.5 equiv) in toluene (2.0 mL). After the reaction mixture was stirred for 4.0 h and worked up, the residue was purified by use of column chromatography (5.0% EtOAc in hexanes as the eluent) to give chroman-2-one **3r** (43.8 mg, 0.111 mmol) in 83% yield as white solids: mp (recrystallized from MeOH) 238.5−240.2 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.89 (d, J = 9.2 Hz, 1 H, ArH), 7.84 (d, J = 7.6 Hz, 1 H, ArH), 7.80 (d, J = 7.6 Hz, 1 H, ArH), 7.72 (d, J = 8.0 Hz, 2 H, 2 × ArH), 7.53 (t, J = 7.2 Hz, 1 H, ArH), 7.47−7.41 (m, 4 H, 4 × ArH), 7.38 (d, J = 8.8 Hz, 1 H, ArH), 7.26−7.22 (m, 3 H, 3 × ArH), 7.13−7.10 (m, 2 H, 2 × ArH), 6.67 (d, J = 5.2 Hz, 1 H, NH), 5.53−5.46 (m, 2 H, CHN + CHPh); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 167.3 (C═O), 167.2 (C═O), 148.4, 135.8, 133.3, 132.1, 131.3, 130.9, 130.5, 129.1, 128.7, 128.6, 128.3, 128.2, 127.6, 127.1, 125.6, 123.3, 117.7, 116.8, 53.5 (CHN), 42.0 (CPh); IR (neat) 3368−3359 (m, NH), 1770 (s, C═O), 1660 (s, C═O), 1515 (s), 1486 (m), 1360 (m), 1222 (m) cm^{-1}; HRMS (ESI-TOF) m/z [M]$^+$ Calcd for $C_{26}H_{19}NO_3$ 393.1365; Found 393.1366.

Standard Procedure 2 for the Preparation of *N*-Protected Amino Acids. To a stirred solution of chroman-2-one (1.0 equiv) in THF/H_2O (3:1, 3.0 mL) was added $NaHCO_3$ (s, 10 equiv) and the reaction mixture was stirred at room temperature for 12 h. After consumption of the starting material, the reaction mixture was cooled to 0 °C and the pH value of reaction was adjusted carefully to ∼2 with aqueous HCl (2.0 N) during which time a lot of bubbles came out. The product was extracted with EtOAc (3 × 15 mL), combined organic layers were washed with water (5.0 mL), saturated NaCl solution (5.0 mL), dried over $MgSO_4$ (s), filtered, and concentrated under reduced pressure to afford the residue. The residue was crystallized form aqueous EtOH and dried under reduced pressure over P_2O_5 to give the desired *N*-protected amino acids.

(2*SR*,3*SR*)-2-(*N*-Benzoylamino)-3-(2-hydroxy-3,5-dimethylphenyl)-3-phenylpropionic Acid (9a). The Standard Procedure 2 was followed by use of chroman-2-one **3d** (50.5 mg, 0.136 mmol, 1.0

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equiv) and $NaHCO_3$ (s, 144 mg, 0.136 mmol, 10 equiv) in THF/H_2O (3:1, 3.0 mL). After the reaction mixture was stirred and worked up, the solids were purified by crystallization (70% EtOH in water) to give the *N*-protected amino acid **9a** (51.6 mg, 0.134 mmol) in 91% yield as white solids: TLC R_f 0.15 (EtOAc as the eluent); mp (recrystallized from aqueous EtOH) 184.2−186.1 °C; ^{1}H NMR (CD_3OD, 400 MHz) δ 7.78−7.75 (m, 2 H, 2 × ArH), 7.46 (tt, J = 7.6, 0.81 Hz, 1 H, ArH), 7.47−7.43 (m, 2 H, 2 × ArH), 7.30−7.26 (m, 3 H, 3 × ArH), 7.03−7.01 (m, 2 H, 2 × ArH), 6.93 (d, J = 2.8 Hz, 2 H, 2 × ArH), 5.43 (d, J = 6.8 Hz, 1 H, CHN), 4.83 (d, J = 6.8 Hz, 1 H, CHPh), 2.36 (s, 3 H, CH_3), 2.13 (s, 3 H, CH_3); ^{13}C NMR (CD_3OD, 100 MHz) δ 170.2 (COO), 168.2 (C═O), 152.3, 140.8, 138.5, 137.7, 134.9, 133.2, 130.1, 129.8, 129.7, 129.1, 128.9, 128.6, 121.7, 116.0, 55.0 (CHN), 43.8 (CPh), 21.1(CH_3), 18.6 (CH_3); IR (KBr) 3500−3410 (s, NH + OH), 2926 (m), 1718 (s, C═O), 1645 (s, C═O), 1178 (w), 1071 (s), 709 (m) cm^{-1}; HRMS (ESI-TOF) m/z [M − H]$^-$ Calcd for $C_{24}H_{23}NO_4H$ 388.1549; Found 388.1550.

(2*SR*,3*SR*)-2-(*N*-Benzoylamino)-3-(2-hydroxy-5-methoxyphenyl)-3-phenylpropionic Acid (9b). The Standard Procedure 2 was followed by use of chroman-2-one **3f** (35.5 mg, 95.1 μmol, 1.0 equiv) and $NaHCO_3$ (s, 80.5 mg, 0.951 mmol, 10 equiv) in THF/H_2O (3:1, 3.0 mL). After the reaction mixture was stirred and worked up, the solids were purified by crystallization (70% EtOH in water) to give the *N*-protected amino acid **9b** (34.6 mg, 88.4 μmol) in 90% yield as white solids: TLC R_f 0.12 (EtOAc as the eluent); mp (recrystallized from aqueous EtOH) 203.3−205.2 °C; ^{1}H NMR (CD_3OD, 400 MHz) δ 7.58−7.54 (m, 2 H, 2 × ArH), 7.47 (tt, J = 7.6, 1.2 Hz, 1 H, ArH), 7.40−7.36 (m, 4 H, 4 × ArH), 7.35−7.31 (m, 4 H, 4 × ArH), 7.09 (d, J = 9.2 Hz, 1 H, 1 × ArH), 6.88 (m, 1 H, 1 × ArH), 5.29 (d, J = 13.6 Hz, 1 H, CHN), 4.67 (d, J = 13.6 Hz, 1 H, CHPh), 3.61 (s, 3 H, OCH_3); ^{13}C NMR (CD_3OD, 100 MHz) δ 172.1 (COO), 168.8 (C═O), 152.9, 148.7, 144.5, 140.7, 133.9, 131.3, 129.1, 128.3, 128.0, 127.0, 126.2, 115.5, 114.4, 112.7. 55.5 (OCH_3), 54.8 (CHN), 46.3 (CPh); IR (KBr) 3500−3330 (s, NH), 3330−3310 (s, OH), 2807 (m), 1717 (s, C═O), 1661 (s, C═O), 1308 (m), 1206 (w), 792 (m) cm^{-1}; HRMS (ESI-TOF) m/z [M − H]$^-$ Calcd for $C_{23}H_{21}NO_5H$ 390.1341; Found 390.1344.

(2*SR*,3*SR*)-2-(*N*-Benzoylamino)-3-(4-fluorophenyl)-3-(2-hydroxy-5-methoxyphenyl)propionic Acid (9c). The Standard Procedure 2 was followed by use of chroman-2-one **3l** (33.6 mg, 85.9 μmol, 1.0 equiv) and $NaHCO_3$ (s, 72.4 mg, 0.859 mmol, 10 equiv) in THF/H_2O (3:1, 3.0 mL). After the reaction mixture was stirred and worked up, the solids were purified by crystallization (70% EtOH in water) to give the *N*-protected amino acid **9c** (32.1 mg, 78.4 μmol) in 93% yield as white solids: TLC R_f 0.21 (EtOAc as the eluent); mp (recrystallized from aqueous EtOH) 193.7−195.6 °C; ^{1}H NMR (CD_3OD, 400 MHz) δ 7.64−7.61 (m, 2 H, 2 × ArH), 7.48 (m, 1 H, ArH), 7.41−7.36 (m, 4 H, 4 × ArH), 7.02−6.96 (m, 2 H, 2 × ArH), 6.84 (d, J = 3.0 Hz, 1 H, ArH), 6.72 (d, J = 8.0 Hz, 1 H, ArH), 6.65 (dd, J = 8.0, 3.0 Hz, 1 H, ArH), 5.44 (d, J = 10.8 Hz, 1 H, CHN), 4.94 (d, J = 10.8 Hz, 1 H, CHPh), 3.67 (s, 3 H, CH_3); ^{13}C NMR (CD_3OD, 100 MHz) δ 174.5 (COO), 170.0 (C═O), 163.1 (d, J_{C-F} = 241 Hz), 154.6, 149.9, 137.4 (d, J_{C-F} = 8.4 Hz), 135.3, 132.8, 131.4, 131.3, 129.5, 128.6, 117.3, 116.2, 115.8 (d, J_{C-F} = 21 Hz), 114.6, 57.8 (OCH_3), 56.2 (CHN), 48.0 (CPh); IR (KBr) 3400−3100 (m, NH + OH), 2917 (m), 1701 (s, C═O), 1626 (s, C═O), 1482 (m), 1236 (s), 737 (s) cm^{-1}; HRMS (ESI-TOF) m/z [M − H]$^-$ Calcd for $C_{23}H_{20}FNO_5H$ 408.1247; Found 408.1251.

(2*SR*,3*SR*)-2-(*N*-Benzoylamino)-3-(2-hydroxy-5-methoxyphenyl)pentanoic Acid (9d). The Standard Procedure 2 was followed by use of chroman-2-one **3n** (40.6 mg, 0.125 mmol, 1.0 equiv) and $NaHCO_3$ (s, 0.105 g, 1.25 mmol, 10 equiv) in THF/H_2O (3:1, 3.0 mL). After the reaction mixture was stirred and worked up, the solids were purified by crystallization (90% EtOH in water) to give the *N*-protected amino acid **9d** (39.3 mg, 0.114 mmol) in 85% yield as white solids: TLC R_f 0.26 (EtOAc as the eluent); mp (recrystallized from aqueous EtOH) 174.8−176.5 °C; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.69 (d, J = 7.4 Hz, 2 H, 2 × ArH), 7.40 (t, J = 7.4 Hz, 2 H, ArH), 7.31−7.28 (m, 2 H, 1 × ArH + 1 × NH), 6.75 (d, J = 8.8 Hz, 1 H, 1 × ArH), 6.64 (d, J = 2.4 Hz, 1 H, ArH), 6.57 (dd, J = 8.8, 2.4 Hz, 1 H, 1 × ArH), 4.80 (dd, J = 6.0, 6.0 Hz, 1 H, CHN), 3.65 (s, 3 H, OCH_3), 3.47−3.38 (m, 1 H, CHEt), 1.90−1.78 (m, 2 H, CH_2CH_3), 0.81 (t, J = 6.8 Hz, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 175.1 (COO), 168.5 (C═O), 153.1, 148.8, 133.0, 132.0, 128.6, 127.2, 126.1, 116.8, 115.4, 113.2, 57.3 (OCH_3), 55.7 (CHN), 43.8 (CPh), 23.1 (CH_2), 12.2 (CH_3); IR (KBr) 3500−3310 (m, NH + OH), 3065 (m), 1694 (s, C═O), 1665 (s, C═O), 1416 (s), 1233 (s), 1007 (m) cm^{-1}; HRMS (ESI-TOF) m/z [M − H]$^-$ Calcd for $C_{19}H_{21}NO_5H$ 342.1341; Found 342.1343.

(2*SR*,3*SR*)-2-(*N*-Benzoylamino)-3-(2-hydroxy-5-methoxyphenyl)-5-methylhexanoic Acid (9e). The Standard Procedure 2 was followed by use of chroman-2-one **3o** (35.3 mg, 0.101 mmol, 1.0 equiv) and $NaHCO_3$ (s, 85.4 mg, 1.01 mmol, 10 equiv) in THF/H_2O (3:1, 3.0 mL). After the reaction mixture was stirred and worked up, the solids were purified by crystallization (90% EtOH in water) to give the *N*-protected amino acid **9e** (33.5 mg, 90.5 μmol) in 88% yield as white solids: TLC R_f 0.22 (EtOAc as the eluent); mp (recrystallized from aqueous EtOH) 168.3−170.1 °C; ^{1}H NMR (CD_3OD, 400 MHz) δ 7.73−7.71 (m, 2 H, 2 × ArH), 7.40 (t, J = 7.6 Hz, 1 H, ArH), 7.45−7.41 (m, 2 H, 2 × ArH), 6.76 (d, J = 8.8 Hz, 1 H, 1 × ArH), 6.70 (d, J = 2.8 Hz, 1 H, ArH), 6.66 (dd, J = 8.8, 2.8 Hz, 1 H, 1 × ArH), 4.70 (d, J = 7.6 Hz, 1 H, CHN), 3.69 (s, 3 H, OCH_3), 3.63−3.56 (m, 1 H, CHBu^i), 2.12−2.05 (m, 1 H, C*H*HCH), 1.56−1.49 (m, 1 H, CH*H*CH), 1.48−1.38 (m, 1 H, $CHMe_2$), 0.89 (d, J = 6.4 Hz, 3 H, CH_3), 0.87 (d, J = 6.4 Hz, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 174.9 (COO), 169.7 (C═O), 154.6, 150.2, 135.1, 132.9, 129.6, 128.1, 117.5, 117.2, 114.2, 60.0, 56.1 (OCH_3), 42.9 (CHN), 40.6 (C Bu^i), 26.8 (CH_2), 23.9 (CH_3), 21.9 (CH_3); IR (KBr) 3500−3200 (m, NH + OH), 2932 (m), 1692 (s, C═O), 1656 (s, C═O), 1484 (m), 1397 (m), 1111 (m) cm^{-1}; HRMS (ESI-TOF) m/z [M − H]$^-$ Calcd for $C_{21}H_{25}NO_5H$ 370.1654; Found 370.1653.

(2*SR*,3*SR*)-2-(*N*-Benzoylamino)-3-(2-hydroxy-4,5-methylenedioxyphenyl)-3-phenylpropionic Acid (9f). The Standard Procedure 2 was followed by use of chroman-2-one **3p** (42.3 mg, 0.109 mmol, 1.0 equiv) and $NaHCO_3$ (s, 92.4 mg, 1.09 mmol, 10 equiv) in THF/H_2O (3:1, 3.0 mL). After the reaction mixture was and worked up, the solids were purified by crystallization (70% EtOH in water) to give the *N*-protected amino acid **9f** (42.6 mg, 0.105 mmol) in 90% yield as white solids: TLC R_f 0.12 (EtOAc as the eluent); mp (recrystallized from aqueous EtOH) 195.4−197.1 °C; ^{1}H NMR (CD_3SOCD_3, 400 MHz) δ 8.87 (d, J = 8.4 Hz, 1 H, NH), 7.64 (d, J = 8.0 Hz, 2 H, 2 × ArH), 7.46 (t, J = 6.8 Hz, 1 H, ArH), 7.47−7.30 (m, 5 H, 5 × ArH), 7.27 (d, J = 6.4 Hz, 2 H, 2 × ArH), 6.91 (s, 1 H, ArH), 6.01−6.00 (m, 2 H, OCH_2O), 5.89 (s, 1 H, ArH),[74] 5.24 (dd, J = 12.8, 8.4, Hz, 1 H, CHN), 4.65 (d, J = 12.8 Hz, 1 H, CHPh); ^{13}C NMR (CD_3OD, 100 MHz) δ 167.0 (COO), 166.2 (C═O), 147.1, 144.6, 143.8, 138.2, 133.6, 131.5, 129.1, 128.7, 128.3, 127.6, 127.1, 118.3, 106.8, 101.8, 98.7 (OCH_2O), 52.4 (CHN), 44.5 (CPh); IR (KBr) 3500−3250 (m, NH + OH), 2926 (w), 1718 (s, C═O), 1635 (s, C═O), 1314 (w), 1026 (m), 732 (w) cm^{-1}; HRMS (ESI-TOF) m/z [M − H]$^-$ Calcd for $C_{23}H_{19}NO_6H$ 404.1134; Found 404.1137.

Standard Procedure 3 for the Preparation of α-Amino Acids. To a solution of *N*-protected amino acid (1.0 equiv) in a mixture of aqueous HCl (12 N, 26 equiv) and methanol (= 1:2.3) was heated to 80 °C for 12 h. The reaction mixture was diluted with water (5.0 mL) and the pH value of solution was adjusted to ∼6 with saturated aqueous NH_4OH. The amino acid precipitated was filtered, washed with diethyl ether, and dried under reduced pressure over P_2O_5. The free α-amino acid was further purified by crystallization from aqueous EtOH (70%).

(2*SR*,3*SR*)-2-Amino-3-(2-hydroxy-3,5-dimethyl-phenyl)-3-phenylpropionic Acid (4a). The Standard Procedure 3 was followed by use of *N*-protected amino acid **9a** (30.2 mg, 77.6 μmol, 1.0 equiv) in methanol (0.20 mL) and aqueous HCl (12 N, 2.01 mmol, 75.0 μL, 26 equiv). After the reaction mixture was stirred and worked up, the solids were purified by crystallization to give the α-amino acid **4a** (18.6 mg, 65.2 μmol) in 85% yield as a brown gummy solids: ^{1}H NMR (CD_3OD, 400 MHz) δ 7.40−7.38 (m, 3 H, 3 × ArH), 7.19−7.17 (m, 2 H, 2 × ArH), 6.95 (d, J = 10 Hz, 2 H, 2 × ArH), 4.97 (d, J = 6.8 Hz, 1 H, CHN), 4.69 (d, J = 6.8 Hz, 1 H, CHPh), 2.35 (s, 3 H, CH_3), 2.15

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(s, 3 H, CH_3); ^{13}C NMR (CD_3OD, 100 MHz) δ 166.0 (COO), 151.8, 141.5, 138.3, 135.1, 130.9, 130.2, 129.8, 129.4, 120.6, 116.3, 53.9 (CHN), 43.4 (CPh), 21.1 (CH_3), 18.6 (CH_3); IR (KBr) 3500−3100 (m, NH_2 + OH), 2926, 1728 (s, C═O), 1595, 1379, 1287, 721 cm^{-1}; HRMS (ESI-TOF) m/z [M − H]$^-$ Calcd for $C_{17}H_{19}NO_3H$ 284.1287; Found 284.1285.

(2*SR*,3*SR*)-2-Amino-3-(2-hydroxy-5-methoxy-phenyl)-3-phenylpropionic Acid (4b). The Standard Procedure 3 was followed by use of *N*-protected amino acid **9b** (30.2 mg, 77.2 μmol, 1.0 equiv) in methanol (0.20 mL) and aqueous HCl (12 N, 2.01 mmol, 75.0 μL, 26 equiv). After the reaction mixture was stirred and worked up, the solids were purified by crystallization to give the α-amino acid **4b** (17.8 mg, 62.3 μmol) in 81% yield as white solids; mp (recrystallized from aqueous EtOH) 218.1−220.2 °C; ^{1}H NMR (CD_3OD, 400 MHz) δ 7.39−7.36 (m, 3 H, 3 × ArH), 7.21−7.16 (m, 3 H, 3 × ArH), 6.98 (dd, J = 12, 2.8 Hz, 1 H, 1 × ArH), 6.84 (d, J = 2.8 Hz, 1 H, 1 × ArH), 4.99 (d, J = 6.8 Hz, 1 H, CHN), 4.63 (d, J = 6.8 Hz, 1 H, CHPh), 3.74 (s, 3 H, OCH_3); ^{13}C NMR (CD_3OD, 100 MHz) δ 167.3 (COO), 160.1, 146.6, 137.5, 132.1, 131.4, 130.6, 127.2, 120.6, 118.0, 115.6, 57.4 (OCH_3), 54.8 (CHN), 47.6 (CPh); IR (KBr) 3500−3150 (m, NH_2 + OH), 2978 (m), 1725 (s, C═O), 1451 (s), 1253 (m), 1157 (m), 773 (w) cm^{-1}; HRMS (ESI-TOF) m/z [M − H]$^-$ Calcd for $C_{16}H_{17}NO_4H$ 286.1079; Found 286.1075.

(2*SR*,3*SR*)-2-Amino-3-(2-hydroxy-5-methoxy-phenyl)-3-(4-fluorophenyl)propionic Acid (4c). The Standard Procedure 3 was followed by use of *N*-protected amino acid **9c** (25.2 mg, 61.5 μmol, 1.0 equiv) in methanol (0.15 mL) and aqueous HCl (12 N, 1.61 mmol, 60.0 μL, 26 equiv). After the reaction mixture was stirred and worked up, the solids were purified by crystallization to give the α-amino acid **4c** (16.5 mg, 54.1 μmol) in 88% yield as white solids; mp (recrystallized from aqueous EtOH) 189.8−191.4 °C; ^{1}H NMR (CD_3OD, 400 MHz) δ 7.23−7.19 (m, 3 H, 3 × ArH), 7.14−7.10 (m, 2 H, 2 × ArH), 6.99 (dd, J = 9.2, 2.8 Hz, 1 H, ArH), 6.86 (d, J = 2.8 Hz, 1 H, ArH), 4.99 (d, J = 6.4 Hz, 1 H, CHN), 4.70 (d, J = 6.4 Hz, 1 H, CHPh), 3.75 (s, 3 H, OCH_3); ^{13}C NMR (CD_3OD, 100 MHz) δ 166.1 (COO), 164.4 (d, J_{C-F} = 245 Hz), 158.9, 145.3, 132.3, 131.6 (d, J_{C-F} = 8.0 Hz), 125.9, 119.4, 117.7 (d, J_{C-F} = 22 Hz), 116.9, 114.4, 56.3 (OCH_3), 53.8 (CHN), 45.4 (CPh); IR (KBr) 3500−3100 (s, NH_2 + OH), 2922 (m), 1714 (s, C═O), 1567 (m), 1186 (w), 1074 (m), 785 (w) cm^{-1}; HRMS (ESI-TOF) m/z [M − H]$^-$ Calcd for $C_{16}H_{16}FNO_4H$ 304.0985; Found 304.0986.

(2*SR*,3*SR*)-2-Amino-3-(2-hydroxy-5-methoxy-phenyl)-pentanoic Acid (4d). The Standard Procedure 3 was followed by use of *N*-protected amino acid **9d** (32.2 mg, 93.8 μmol, 1.0 equiv) in methanol (0.21 mL) and aqueous HCl (12 N, 2.43 mmol, 90 μL, 26 equiv). After the reaction mixture was stirred and worked up, the solids were purified by crystallization to give the α-amino acid **4d** (17.7 mg, 74.1 μmol) in 80% yield as white solids; mp (recrystallized from aqueous EtOH) 195.4−197.1 °C; ^{1}H NMR (CD_3OD, 400 MHz) δ 7.08 (d, J = 9.2 Hz, 1 H, ArH), 6.94 (dd, J = 9.2, 2.8 Hz, 1 H, ArH), 6.84 (d, J = 2.8 Hz, 1 H, ArH), 4.64 (d, J = 5.6 Hz, 1 H, CHN), 3.80 (s, 3 H, OCH_3), 3.21−3.15 (m, 1 H, CHEt), 1.85−1.79 (m, 1 H, C*H*HMe), 1.33−1.16 (m, 1 H, CH*H*Me), 0.92 (t, J = 7.2 Hz, 3 H, CH_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 168.2 (COO), 158.2, 145.1, 125.9, 119.1, 115.7, 115.7, 56.3 (OCH_3), 53.3 (CHN), 41.7 (CEt), 22.8 (CH_2), 10.9 (CH_3); IR (KBr) 3450−3100 (m, NH_2 + OH), 2937 (m), 1712 (s, C═O), 1527 (m), 1263 (m), 1026 (m), 804 (w) cm^{-1}; HRMS (ESI-TOF) m/z [M − H]$^-$ Calcd for $C_{12}H_{17}NO_4H$ 238.1079; Found 238.1079.

(2*SR*,3*SR*)-2-Amino-3-(2-hydroxy-5-methoxy-phenyl)-5-methylhexanoic Acid (4e). The Standard Procedure 3 was followed by use of *N*-protected amino acid **9e** (30.2 mg, 81.5 μmol, 1.0 equiv) in methanol (0.20 mL) and aqueous HCl (12 N, 2.12 mmol, 80.0 μL, 26 equiv). After the reaction mixture was stirred and worked up, the solids were purified by crystallization to give the α-amino acid **4e** (17.8 mg, 66.8 μmol) in 82% yield as white solids; mp (recrystallized from aqueous EtOH) 180.3−182.5 °C; ^{1}H NMR (CD_3OD, 400 MHz) δ 7.08 (d, J = 8.8 Hz, 1 H, ArH), 6.94 (dd, J = 8.8, 2.8 Hz, 1 H, 1 × ArH), 6.82 (d, J = 2.8 Hz, 1 H, ArH), 4.60 (d, J = 5.2 Hz, 1 H, CHN), 3.80 (s, 3 H, OCH_3), 3.69−3.54 (m, 1 H, CHBu^i), 1.56−1.53 (m, 1 H, $CHMe_2$), 1.47−1.41 (m, 1 H, CHC*H*H), 1.23−1.15 (m, 1 H, CHCH*H*), 1.06 (d, J = 6.4 Hz, 3 H, CH_3), 0.85 (d, J = 6.4 Hz, 3 H, CH_3); ^{13}C NMR (CD_3OD, 100 MHz) δ 167.0 (COO), 158.2, 144.9, 126.8, 119.3, 115.4, 115.3, 56.3 (OCH_3), 53.6 (CHN), 38.4 (CHBu^i), 38.3 ($CHCH_2Me_2$), 25.8 ($CHMe_2$), 24.2 (CH_3), 21.5 (CH_3); IR (KBr) 3500−3250 (m, NH_2), 3250−3100 (m, OH), 2961 (m), 1720 (s, C═O), 1462 (m), 1263 (m), 1020 (m), 757 (w) cm^{-1}; HRMS (ESI-TOF) m/z [M + H]$^+$ Calcd for ($C_{14}H_{21}NO_4H$ 268.1549; Found 268.1543.

(2*SR*,3*SR*)-2-Amino-3-(2-hydroxy-4,5-methylene-dioxyphenyl)-3-phenylpropionic Acid (4f). The Standard Procedure 3 was followed by use of *N*-protected amino acid **9f** (32.2 mg, 79.4 μmol, 1.0 equiv) in methanol (0.20 mL) and aqueous HCl (12 N, 2.06 mmol, 75.0 μL, 26 equiv). After the reaction mixture was stirred and worked up, the solids were purified by crystallization to give the α-amino acid **4f** (20.1 mg, 66.7 μmol) in 84% yield as white solids; mp (recrystallized from aqueous EtOH) 199.6−201.5 °C; ^{1}H NMR (CD_3OD, 400 MHz) δ 7.40−7.35 (m, 3 H, 3 × ArH), 7.18−7.15 (m, 2 H, 2 × ArH), 6.81 (s, 1 H, ArH), 6.73 (s, 1 H, ArH), 6.01−5.97 (m, 2 H, OCH_2O), 4.99 (d, J = 6.8 Hz, 1 H, CHN), 4.54 (d, J = 6.8 Hz, 1 H, CHPh); ^{13}C NMR (CD_3SOCD_3, 100 MHz) δ 165.8 (COO), 150.1, 147.0, 146.1, 136.3, 130.9, 130.1, 129.4, 117.3, 108.5, 103.7, 99.9 (OCH_2O), 53.6 (CHN), 45.9 (CPh); IR (KBr) 3450−3100 (m, NH_2 + OH), 2924 (m), 1708 (s, C═O), 1579 (w), 1273 (m), 1107 (m), 782 (w) cm^{-1}; HRMS (ESI-TOF) m/z [M − H]$^-$ Calcd for $C_{16}H_{15}NO_5H$ 300.0872; Found 300.0877.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00260.

Spectra of all new compounds; the heteronuclear single-quantum correlation experiment for compound **3d** (PDF)

X-ray crystallographic data for **3d** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: jrhwu@mx.nthu.edu.tw.

ORCID

Jih Ru Hwu: 0000-0002-9225-8484

Notes

The authors declare no competing financial interest.

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