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Enantioselective Synthesis of Iclaprim Enantiomers—A Versatile Approach to 2-Substituted Chiral Chromenes

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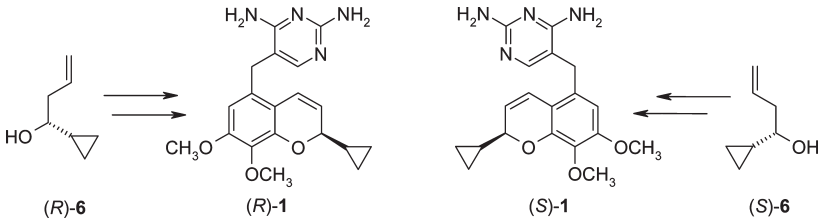

Both enantiomers of the DHFR inhibitor iclaprim (*R*)-**1** and (*S*)-**1** were synthesized from the cyclopropyl homoallyl alcohols (*R*)-**6** and (*S*)-**6**, respectively. As key steps these transformations include a Mitsunobu reaction and the formation of the diaminopyrimidine unit prior to a novel cyclization procedure to obtain the desired chromene heterocycle. The moderate enantioselectivity of the products (*R*)-**1** and (*S*)-**1** is related to the Mitsunobu reaction, which unfortunately did not proceed with complete inversion of configuration.

Introduction

Iclaprim and trimethoprim are diaminopyrimidine derivatives which are active against a broad panel of bacteria.[1] Trimethoprim (TMP) is successfully used in combination with sulfamethoxazole in the sequential blockade of the de novo synthesis of tetrahydrofolic acid to treat bacterial infections. Since the discovery of trimethoprim in 1965 many companies have initiated programs to synthesize derivatives within the benzyldiaminopyrimidine series to improve physicochemical and pharmacological profiles.[1,2] As a result of these activities several new inhibitors of dihydrofolate reductase (DHFR) have recently progressed into clinical development due to their potent anticancer or antibiotic properties.[1,3]

ARPIDA AG developed iclaprim **1** (Figure 1) as a racemate for complicated skin and skin structure infections (cSSSI) caused by Gram-positive organisms, especially methicillin-resistant (MRSA) and TMP-resistant *Staphylococcus aureus*. This chromene-benzyldiaminopyrimidine shows submicromolar activities against pathogenic microorganisms such as *Staphylococci*, *Enterobacter*, *Neisseria*, *Pneumocystis carinii*, *Streptococcus pneumoniae*, and *Haemophilus influenza*. Both enantiomers of iclaprim exhibit similar activity against the DHFR enzymes of S. *aureus* and a similar antimicrobial profile against a broad range of bacteria.[4]

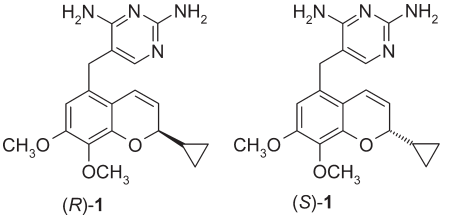

FIGURE 1. Enantiomers of iclaprim.

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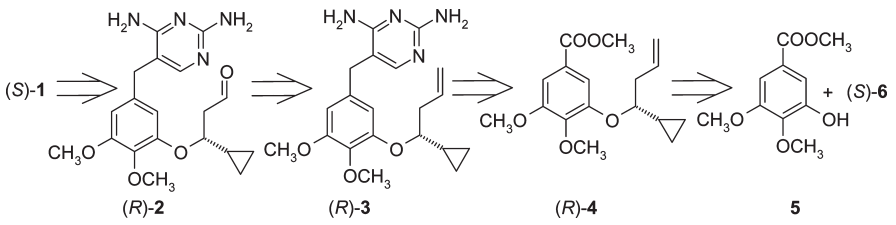
SCHEME 1. Retrosynthesis Leading to Iclaprim Enantiomer (*S*)-1



Chromenes (2*H*-1benzopyran derivatives) have been widely identified as important core-structures in many natural products and in many bioactive compounds.[5−7] Wipf et al.[7] have developed a seven step synthesis of a 2-cyclopropylchromene with a 59% enantiomeric excess (ee), which could serve as an intermediate for the preparation of (*S*)-**1**. However, the synthesis was not completed to obtain iclaprim enantiomer (*S*)-**1** because the elevated reaction conditions to generate the diaminopyrimidine moiety would have racemized the product. Indeed, racemization of chiral chromenes is known to be induced by light[7,8] or by heat.[9] Chromenes have been obtained by ring-closing olefin metathesis[7,10] or through chroman-4-ones and subsequent reduction of the ketone and elimination of water.[11,12]

Herein, we wish to report various approaches to chiral cyclopropyl allyl methanols as intermediates for the synthesis of both iclaprim enantiomers, (*R*)-**1** and (*S*)-**1**.

Results and Discussion

Our strategy is outlined in Scheme 1 using the cyclization of the chiral intermediate (*R*)-**2** to obtain the desired chiral iclaprim enantiomer (*S*)-**1**. To prevent racemization, the diaminopyrimidine moiety had to be generated before this cyclization in three steps starting from chiral ether (*R*)-**4**, which could be obtained by a Mitsunobu reaction between phenol **5** and the chiral homoallylic alcohol (*S*)-**6**.

To prepare both enantiomers of iclaprim an efficient synthesis of the homoallylic alcohols (*S*)-**6** and (*R*)-**6** was required. For the purpose we pursued an enzymatic resolution of racemic **6**, which was easily available from aldehyde **7** (Scheme 2).[13]

Several lipases[14] were investigated for their efficiency in the presence of vinyl acetate: Amano Lipase PS from *Pseudomonas cepacia*, Amano Lipase from *Pseudomonas fluorescens*, lipase from *Candida cylindracea*, Amano Lipase M from *Mucor javanicus*, Amano Lipase A from *Aspergillus niger*, and Amano Lipase G from *Penicillium camemberti*. Among these enzymes, only the lipases from *Pseudomonas cepacia* and from *Candida cylindracea* displayed an enzymatic resolution (Table 1). The best enantioselectivity was accomplished by using the Amano lipase PS from *Pseudomonas cepacia*. The homoallylic alcohol (*S*)-**6** was obtained in 91% ee and the (*R*)-**6** in 58% ee after hydrolysis of the acetate (*R*)-**6-Ac** (Table 1). Several attempts to improve the ee values for both enantiomers by changing the ratio of substrate/enzyme proved to be unsuccessful (Table 2).

Accordingly, the lipase-catalyzed resolution of **6** at a strictly defined substrate/enzyme ratio gave (*S*)-**6** with a high

SCHEME 2. Enzymatic Resolution of Racemic 6

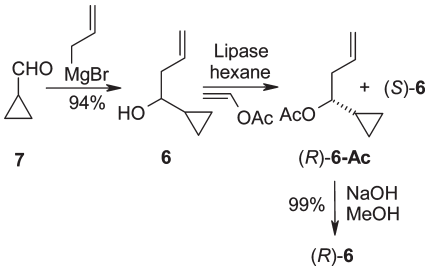


TABLE 1. Lipase-Catalyzed Resolution of 6

lipase[a] from	product	yield (%)	enantiomeric excess (ee)
Candida cylindracea	(*R*)-**6**	35	43%
	(*S*)-**6**	60	12%
Pseudomonas cepacia	(*R*)-**6**	50	58%
	(*S*)-**6**	47	91%

[a]50 mg lipase/mmol of **6**.

TABLE 2. Enantiomeric Excess of Products at Various Ratios of Substrate 6 to Lipase from *Pseudomonas cepacia*

entry	mg of lipase per mmol 6	products	enantiomeric excess (ee)
1	35	(*R*)-**6**	48%
	35	(*S*)-**6**	90%
2	50	(*R*)-**6**	58%
	50	(*S*)-**6**	91%
3	100	(*R*)-**6**	72%
	100	(*S*)-**6**	64%
4	250	(*R*)-**6**	78%
	250	(*S*)-**6**	39%

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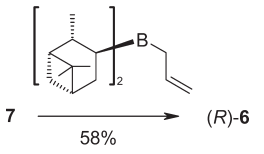
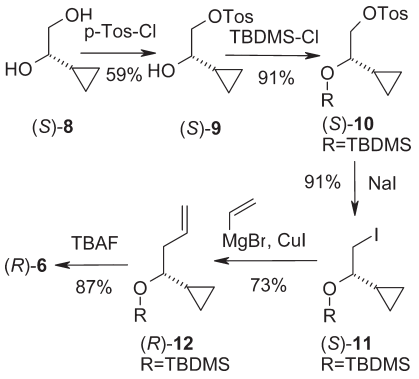
SCHEME 3. Asymmetric Allylboration of 7



SCHEME 4. Synthesis of (*R*)-6 from Commercially Available Diol (*S*)-8

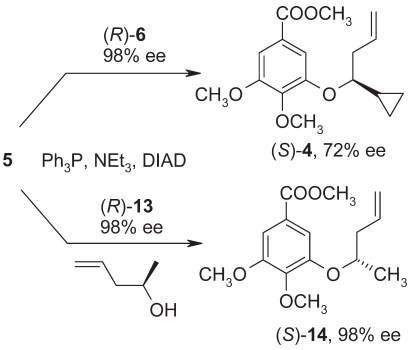


91% ee value; however, the value for (*R*)-**6** remained at modest 58% ee (Table 2, entry 2). We therefore tried the enantioselective allylation of **7** by means of *B*-allyldiisopinocampheylborane ((+)-Ipc_2B-allyl),[15] but also under these conditions the homoallylic alcohol (*R*)-**6** was obtained in only 76% ee (Scheme 3).

Alternatively to the enzymatic resolution of **6** and the direct allylation of **7**, which gave (*R*)-**6** with only modest ee values, we developed a synthesis of (*R*)-**6** starting from the commercially available chiral diol (*S*)-**8** (98% ee). Compound (*S*)-**8** could be made following the enzymatic reduction of cyclopropyl-oxo-acetic acid.[16] Selective protection gave the monotosylate (*S*)-**9**, which was subsequently silylated to furnish (*S*)-**10** in 54% yield over two steps. Exchange of the tosyl group for iodide gave (*S*)-**11**, which was converted to the protected homoallyl alcohol (*R*)-**12** in 73% yield.[17] Finally the TBDMS protecting group was removed to yield (*R*)-**6** in 31% yield over five steps. The absolute configuration at C1 of (*R*)-**6** was confirmed according to Mosher's method[18] and the enantiomeric excess was determined by GC of the alcohol (*R*)-**6** being 98% ee in agreement with the value of the starting material (*S*)-**8**.

As predicted, the synthesis of the iclaprim enantiomer (*R*)-**1** was continued with (*R*)-**6** (98% ee, prepared as shown in Scheme 4). The Mitsunobu coupling of (*R*)-**6** with phenol **5** gave the desired ether (*S*)-**4** in 73% yield, however, with only 72% ee. Loss of enantiopurity during this reaction was also

SCHEME 5. Mitsunobu Reactions of 5 with Homoallyl Alcohols



observed with (*S*)-**6**, resulting in ether (*R*)-**4**. The stabilization properties of a cyclopropyl ring,[19] which causes the Mitsunobu's phosphonium salt intermediate to have significant carbocation character, triggers a mixed S_N2/S_N1 reaction leading to partially racemized products. Several solvents like toluene, THF, or dichloromethane were examined in this reaction of which THF was found to be superior.

In contrast, a control reaction under the same conditions with the homoallyl alcohol (*R*)-**13** and **5** gave (*S*)-**14** with complete inversion of configuration (Scheme 5). Several attempts to improve the Mitsunobu coupling[20] conditions for enantiomers (*R*)-**6** and (*S*)-**6** with **5** failed; hence we had to accept the loss of ee during this transformation.

The synthesis was then continued for both enantiomers (*R*)-**4** and (*S*)-**4**; the transformations of (*S*)-**4** are shown in Scheme 6. Reduction of the methyl ester (*S*)-**4** led to the aldehyde (*S*)-**15** in 91% yield. Constructing the diaminopyrimidine heterocycle was done in two steps[2] leading to (*S*)-**3**. As oxidation of the double bond at this stage led to complete decomposition, the amino groups at the diaminopyrimidine were protected to yield (*S*)-**16** in 70% over three steps.

Subsequently the terminal double bond of (*S*)-**16** was oxidized with potassium osmate and sodium periodate. Since purification of the resulting aldehyde (*S*)-**17** induced a retro 1,4-addition the oxidation product was directly cyclized to the chromene system (*R*)-**18** in the presence of TFA anhydride/TFA in 65% yield. In our hands this new method proved to be superior over the cyclization to 4-hydroxychromanes mediated by $ZnCl_2$.[21]

The final deprotection of the diaminopyrimidine moiety was pursued under the mildest conditions available in order to prevent racemization of the chiral center. Throughout this synthesis, the ee of intermediates remained constant within experimental error and iclaprim enantiomer (*R*)-**1** was obtained in 70% ee and 27% overall yield starting from **5**. The corresponding reactions with (*R*)-**4** (55% ee) led to iclaprim enantiomer (*S*)-**1** (50% ee).

Conclusions

In conclusion, this synthesis of the iclaprim enantiomers (*R*)-**1** and (*S*)-**1** includes three methods to obtain the key intermediates (*R*)-**6** and (*S*)-**6** in good to excellent enantiomeric excess and a new approach to chromenes through an intramolecular, acid-catalyzed cyclization of an aldehyde

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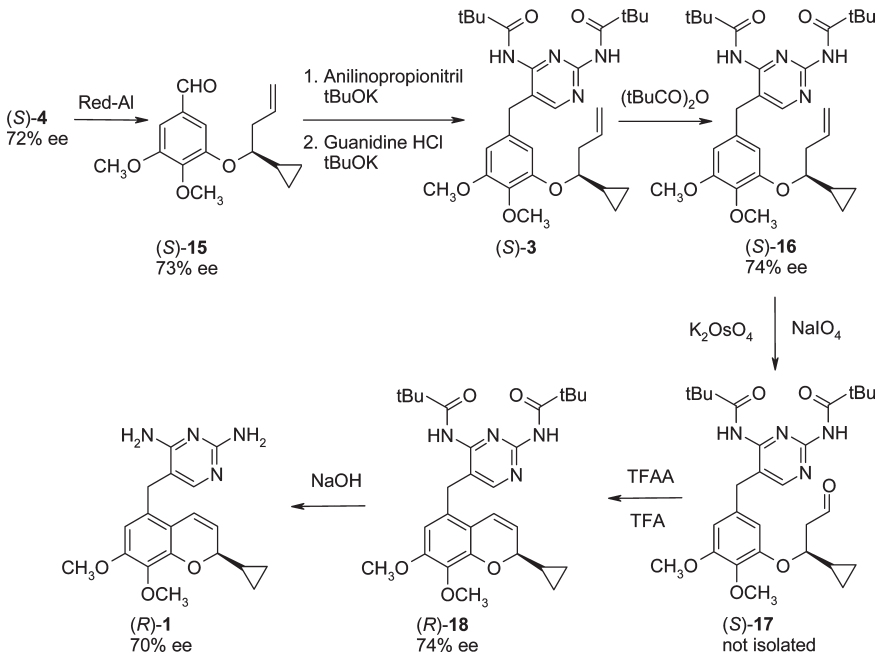
SCHEME 6. Completing the Synthesis of Iclaprim Enantiomer (*R*)-1



with an electron-rich aromatic ring. Unfortunately, the Mitsunobu reaction between the phenol **5** and the cyclopropyl homoallyl alcohols (*R*)-**6** and (*S*)-**6** led to moderate racemized products; nevertheless iclaprim enantiomers (*R*)-**1** and (*S*)-**1** were obtained in 70% ee and 50% ee, respectively.

Experimental Section

General Procedure for Enzymatic Resolution. To a solution of **6 rac** (1 g, 8.91 mmol) in hexane (100 mL) were added vinylacetate (2.47 mL, 26.745 mmol, 3 equiv) and the corresponding enzyme (ratio of enzyme and alcohol are outlined in Tables 1 and 2). The mixture was stirred 24 h at room temperature. The slurry was filtered off and the enzymatic residue was washed with 20 mL of hexane. This mixture was then poured directly onto a silica gel column and eluted with pentane 100%, pentane/diethyl ether 4:1, pentane/diethyl ether 1:1, then diethyl ether 100% to separate the acylated product (*R*)-**6-Ac** (first eluted) from the nonacetylated (*S*)-**6** (second eluted). R_f (AcOEt/cHex 1:9) = 0.47 for (*R*)-**6-Ac** and 0.13 for the alcohol (*S*)-**6**. Yields and enantiomeric purity are summarized in Tables 1 and 2 (for further details see the Supporting Information).

3-((*S*)-1-Cyclopropylbut-3-enyloxy)-4,5-dimethoxybenzoic Acid Methyl Ester, (*S*)-4. Under N_2, the benzoic methyl ester **5** (1 g, 4.71 mmol, 1 equiv) was dissolved in THF (13 mL). The homoallylic alcohol (*R*)-**6** (0.528 g, 4.71 mmol, 1 equiv), PPh_3 (1.234 g, 4.71 mmol, 1 equiv), and NEt_3 (0.1 mL, 0.707 mmol, 0.15 equiv) were added. The mixture was cooled to 0 °C, then DIAD (0.931 mL, 4.71 mmol, 1 equiv) in 2 mL of THF was added dropwise. The reaction mixture was allowed to stir at room temperature for 2 h, the reaction mixture was checked by LCMS and TLC, and the same amounts of homoallylic alcohol, PPh_3, and DIAD were added to complete the reaction. TLC (AcOEt/cHex 1:9, R_f 0.21, stained with vanillin). The reaction mixture was evaporated to dryness, and then purified by FC (AcOEt/cHex 1:9) to give (*S*)-**4** as a colorless oil. Yield: 1.05 g, 73%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.25 (d, J = 1.6 Hz, 1 H), 7.22 (d, J = 1.6 Hz,1 H), 5.86−5.96 (m, 1H), 5.00−5.1 (m, 2 H), 3.84 (s, 3 H), 3.83 (s, 3 H), 3.82 (s, 3H), 3.67−3.72 (m, 1 H), 2.49−2.51 (t, J = 6.25 Hz, 2 H), 1.03−1.12 (m, 1 H), 0.40−0.50 (m, 2 H), 0.15−0.28 (m, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 166.6, 153.2, 151.6, 144.1, 134.2, 124.8, 117.2, 112.2, 106.8, 83.6, 60.8, 56.1, 52.1, 39.4, 14.9, 3.6, 2.1. LCMS ESI$^+$ (method A) not ionizing. Retention time (Rt): 2.70 min. UV: 233, 265 nm. Chiral HPLC: method 1, 72% ee. HRMS: $[M + Na]^+$ calcd for $C_{17}H_{22}O_5$ 329.1359, obsd 329.1352.

3-((*S*)-1-Cyclopropylbut-3-enyloxy)-4,5-dimethoxybenzaldehyde, (*S*)-15. Red-Al (70% in toluene, 1 mL, 3.52 mmol, 3 equiv) in toluene (5 mL) was cooled to 0 °C under N_2. Morpholine (0.194 mL, 2.23 mmol, 1.9 equiv) was added dropwise and the mixture was stirred for 30 min at 0 °C. Compound (*S*)-**4** (360 mg, 1.175 mmol, 1 equiv) in 5 mL of toluene was cooled to −35 °C. The Red-Al/morpholine mixture was slowly added to the (*S*)-**4** solution. The reaction mixture was stirred and slowly warmed to −20 °C. After 1 h, the reaction was complete and 1.5 mL of 4 N NaOH was added at −20 °C, and then allowed to warm to room temperature during 1 h. The reaction mixture was extracted twice with AcOEt. The combined organic layers were washed with H_2O and brine, dried over $MgSO_4$, filtered, and evaporated to dryness. The aldehyde (*S*)-**15** was isolated as a colorless oil. Yield: 296 mg, 91%. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 9.83 (s, 1 H), 7.12 (s, 1 H), 7.11 (s, 1 H), 5.90−6.01 (m, 1 H), 5.08−5.16 (m, 2 H), 3.93 (s, 3 H), 3.92 (s, 3 H), 3.75−3.80 (m, 1 H), 2.55−2.58 (t, J = 5.8 Hz, 2 H), 1.12−1.17 (m, 1 H), 0.49−0.56 (m, 2 H), 0.22−0.30 (m, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 191.5, 154.5, 152.8, 134.5, 131.9, 117.9, 113.3, 106.5, 84.3, 61.4, 56.6, 52.6, 39.8, 30.1, 26.0, 15.4, 4.0, 2.7. LCMS ESI$^+$: method A, not ionizing. Rt: 2.55 min. UV: 230, 285 nm. Chiral HPLC: method 1, 73% ee. HRMS: $[M + Na]^+$ calcd for $C_{16}H_{20}O_4$ 299.1254, obsd 299.1249.

N-[5-[3-((*S*)-1-Cyclopropylbut-3-enyloxy)-4,5-dimethoxybenzyl]-4-(2,2-dimethylpropionylamino)pyrimidin-2-yl]-2,2-dimethylpropionamide, (*S*)-16. To a solution of the aldehyde (*S*)-**15** (465 mg, 1.68 mmol, 1 equiv) in DMSO (5 mL) under N_2 was added anilinopropionitrile (271 mg, 1.85 mmol, 1.1 equiv). *t*BuOK (217 mg, 1.93 mmol, 1.15 equiv) was then added and the mixture was stirred for 1 h at room temperature. The reaction mixture was checked by LCMS then worked up with a mixture of AcOEt and H_2O. The layers were separated and the aqueous layers were reextracted with AcOEt. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and evaporated to dryness. The resulting crude material was used for the next step without further

purification. Guanidine·HCl (484 mg, 5.04 mmol, 3 equiv) was dissolved in dry EtOH (5 mL) before adding *t*BuOK (566 mg, 5.04 mmol, 3 equiv). The mixture was stirred for 30 min at room temperature, then the white precipitate was filtered off and washed with 5 mL of EtOH. The ethanolic guanidine solution was added to the anilinopropionitrile adduct and the mixture was heated for 12 h at 90 °C. The solvent was evaporated and the residue was dissolved in AcOEt and H_2O. The layers were separated, and the organic layer was washed with brine, dried over $MgSO_4$, filtered, and evaporated to dryness to give product (*S*)-**3** as a brown solid. The brown solid was dissolved in pivalic anhydride (0.85 mL, 4.2 mmol, 2.5 equiv) and the mixture was heated at 150 °C for 1 h. AcOEt was added and the mixture was washed with 10 mL of H_2O/NH_4OH 24% 1:1. The mixture was extracted twice with AcOEt; the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and evaporated to dryness. FC (AcOEt/cHex 1:4 then 2:3 then 4:1) gave (*S*)-**16** as a white solid in 70% yield (633 mg). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.31 (br s, 1 H), 8.10 (br s, 1 H), 6.35 (s, 1 H), 6.31 (s, 1 H), 5.85−5.96 (m, 1 H), 5.03−5.11 (m, 2 H), 3.85 (s, 2 H), 3.79 (s, 3 H), 3.78 (s, 3 H), 3.63−3.65 (m, 1 H), 2.47−2.50 (t, J = 6 Hz, 2 H), 1.34 (s, 9 H), 1.14 (s, 9 H), 1.05−1.13 (m, 1 H), 0.45−0.70 (m, 2 H), 0.18−0.26 (m, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.7, 160.6, 157.6, 156.6, 154.5, 152.9, 139.6, 134.7, 133.0, 119.3, 117.6, 111.6, 106.4, 84.0, 61.2, 56.6, 40.7, 40.4, 39.9, 35.7, 30.1, 27.8, 27.6, 15.4, 3.9, 2.6. LCMS ESI$^+$: method A, m/z 539.3 $[M + H]^+$. Rt: 2.57 min. UV: 245, 275 nm. Chiral HPLC: method 2, 74% ee. HRMS: $[M + Na]^+$ calcd for $C_{30}H_{42}N_4O_5$ 561.3047, obsd 561.3037.

N-[5-((*R*)-2-Cyclopropyl-7,8-dimethoxy-2*H*-chromen-5-ylmethyl)-4-(2,2-dimethylpropionylamino)pyrimidin-2-yl]-2,2-dimethylpropionamide, (*R*)-18. To a solution of (*S*)-**16** (200 mg, 0.37 mmol, 1 equiv) in THF (2 mL) was added $NaIO_4$ (0.2 g, 0.93 mmol, 2.5 equiv), $K_2OsO_4 \cdot 2H_2O$ (6.8 mg, 0.018 mmol, 0.05 equiv), and 0.5 mL of H_2O at room temperature. The oxidation was complete after 1 h. AcOEt, H_2O, and a saturated solution of $Na_2S_2O_3$ were added. The aqueous phase was extracted twice with AcOEt. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and evaporated to dryness. Any attempt to purify the aldehyde (*S*)-**17** by FC decomposed the product; therefore the crude material was used without further purification. The crude aldehyde (*S*)-**17** was dissolved in CH_2Cl_2 (2 mL), then cooled to 0 °C. TFA (0.45 mL, 5.92 mmol, 16 equiv) and TFAA (413 μL, 2.96 mmol, 8 equiv) were added at 0 °C. The reaction mixture was stirred at room temperature for 150 min. The reaction mixture was then poured into a saturated solution of $NaHCO_3$ and extracted twice with AcOEt. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and evaporated to dryness. FC with AcOEt/cHex 1:1 gave 126 mg of (*R*)-**18** (65%) as a white solid. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.19 (s, 1 H), 8.12 (s, 1 H), 8.00 (s, 1 H), 6.38 (d, J = 10 Hz, 1 H), 6.16 (s, 1 H), 5.67 (dd, J_1 = 10.2 Hz, J_2 = 3.4 Hz, 1 H), 4.19 (dd, J_1 = 8.4 Hz, J_2 = 3.4 Hz, 1 H), 3.87 (s, 2 H), 3.80 (s, 2 H), 3.75 (s, 3 H), 1.30 (s, 9 H), 1.21 (s, 9 H), 0.43−0.61 (m, 3 H), 0.26−0.34 (m, 2 H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 176.8, 176.1, 159.9, 156.9, 155.7, 153.2, 147.6, 136.6, 127.8, 123.2, 120.7, 120.4, 115.4, 105.6, 78.8, 61.0, 56.0, 49.4, 40.2, 39.9, 31.5, 27.3, 27.1, 26.9, 15.2, 2.8, 1.5. LCMS ESI$^+$: method A m/z 523.3 $[M + H]^+$. Rt: 2.43 min. UV: 245 (280) nm. Chiral HPLC: method 3, 74% ee.

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Supporting Information Available: Experimental details and characterizations for **1**, **4**, **6**, **9**, **10**, **11**, **12**, **14**, **15**, **16**, **18**, and Mosher's esters of (*R*)-**6**; ^{1}H and ^{13}C for all compounds; chiral GC spectra for **6 rac**, (*R*)-**6**, and (*S*)-**6**; and chiral HPLC for **1**, **4**, **14**, **15**, **16**, and **18**. This material is available free of charge via the Internet at http://pubs.acs.org.