Pyrimidinone conjugates for the assignment of the absolute configuration of α-chiral carboxylic acids by ^{1}H-NMR

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Abstract

A method is described for the assignment of the absolute configuration of carboxylic acids via the formation of diastereomeric conjugates with known chiral dihydropyrimidinone **1**. Proton NMR $\Delta\delta(R\text{-}S)$ values of conjugates with low molecular weight aromatic and aliphatic carboxylic acids with chiral centers in the alpha position were examined. The signals of primary interest corresponded to the dihydropyrimidinone. Several clearly resolved signals were exhibited at disparate locations of the spectrum with the magnitude and sign of $\Delta\delta$ ($R\text{-}S$) separation dependent upon acid structure.

Keywords: Chiral derivatizing agent, absolute configuration assignment, arylacetic acid, dihydropyrimidinone, chiral carboxylic acid

Introduction

The importance of chiral carboxylic acids in natural products and therapeutic agents spurs the continued development of highly selective methods for their preparation and stereochemical analysis. Though several methods for asymmetric carboxylic acid preparations are highly reliable in effecting predictable stereochemical outcomes, each synthesis requires an independent confirmation of the product configuration and purity. Proton NMR, in particular, has been widely employed to provide dependable assignments for carboxylic acids,[3–7] alcohols,[8,9] and amines[10–14] covalently bound to chiral derivatizing agents (CDAs). In this report we describe the determination of the absolute configuration of chiral acids via proton NMR analysis of their conjugates with known dihydropyrimidinone **1**.[15]

Results and Discussion

We recently reported that novel dihydropyrimidinones **2** and **3** imparted enhanced chirality transfer compared to **1** as chiral auxiliaries in enolate alkylations.[16] Enolate methylations of the phenylacetate analogs of these heterocycles generated diastereomeric products **A** (the major product) and **B**. The proton NMR chemical shifts from each diastereomeric pair produced Δδ (*R-S*) values consistent in sign (Table 1). For example, the C5-*H* yielded negative Δδ (*R-S*) values for all derivatives, as did each of the other non-aryl protons from the diastereomeric products. We recognized that these chemical shift patterns form a potential basis for absolute configuration assignments of carboxylic acids and that the present system incorporated several advantages over other reported chiral derivatizing agents. First, as clearly indicated in Table 1, the proton NMR signals span a wide spectral range permitting assignments from several independent regions. Second, the assignments are facilitated by significant signal separations and splitting simplicities. Third, the *tert*-butyl singlets of analogs of **1**, in particular, enable the examination of highly dilute samples. Here we describe investigations on aspects of the generality of this approach with respect to carboxylic acid structure.

Table 1. Proton NMR shift and Δδ. *R-S*) values of the diastereomeric products in (CDCl$_3$, 300 MHz). Δδ = δA- δ B corresponding to δ 2′*R*,2*R*- δ 2′*S*,2*R*
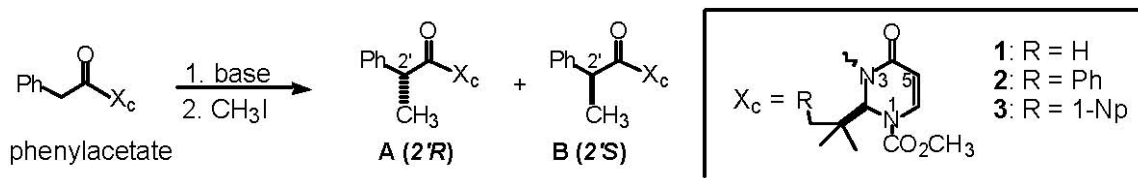
Proton	δ1A/δ1B (Δδ)	δ2A/δ2B (Δδ)	δ3A/δ3B (Δδ)
C(CH$_3$)$_2$CH$_2$-R	0.96/0.80 (+0.16)	0.66/0.82 (+0.16)	0.62/0.83 (+0.21)
C3′H$_3$	1.52/1.45 (+0.07)	1.54/1.48 (+0.06)	1.57/1.51 (+0.06)
CO$_2$CH$_3$	3.83/3.89 (-0.06)	3.86/3.90 (-0.04)	3.88/3.94 (-0.06)
C2′-H	4.97/4.80 (+0.17)	4.99/4.87 (+0.12)	5.03/4.89 (+0.14)
C5-H	5.13/5.33 (-0.20)	5.18/5.39 (-0.21)	5.21/5.42 (-0.21)
C2-H	6.69/6.92 (-0.23)	6.84/7.09 (-0.25)	7.00/7.25 (-0.25)
C6-H	7.46/7.65 (-0.19)	7.53/7.71 (-0.18)	7.55/7.72 (-0.17)

A series of diastereomeric conjugates of **1** were prepared to examine the effect of carboxylic acid structure on the proton NMR shifts patterns (Table 2). The analogs were designed to examine the influence of the size of the alkyl group (**4** and **5**), the presence of a heteroatom attached to the chiral center (**6**), and the size of the aryl group (**7** and **8**) or its absence (**12–14**). In addition, other samples were prepared to investigate combinations of structural influences (**9**) or commercially important applications (**10** and **11**).

Several strategies were employed to generate the targeted samples for these studies. Compounds **4-**, **6-**, **10-** and **12AB** were prepared as diastereomerically enriched samples from the commercially available, chiral carboxylic acids. Typically, coupling of the carboxylic acid to the heterocycle was accomplished by formation of the acid chloride and subsequent exposure to the metallated heterocycle, although it was also found that **1** could be directly attached to the carboxylic acid without epimerization[17] upon exposure to DCC/DMAP. Diastereomeric pairs of several analogs (**5**, **7**, and **9**) required the preparation of the corresponding chiral acids followed by coupling as described. In these samples, the commercially available arylacetic acids were converted to the methyl esters and each enolate was alkylated with iodomethane or 2-iodopropane as appropriate. Subsequent saponification and resolution with (*R*)-α-methylbenzylamine generated optically enriched materials that were appended to **1** as described. Diastereomers **8AB** were prepared via coupling of the commercially available 1-pyreneacetic acid to **1** and the product was alkylated as the enolate. The absolute configurations of the major products of the latter reaction were assigned according to the known chirality transfer property of this system.[15] Conjugate **11B** was prepared via coupling of commercially available (*S*)-Naproxen with **1**. The sample was epimerized under basic conditions to generate the corresponding diastereomer **11A**.

Table 2. Selected ^{1}H NMR (ppm) and Δδ *R-S*) values of **4-14** (300 MHz, acetone-d_6)
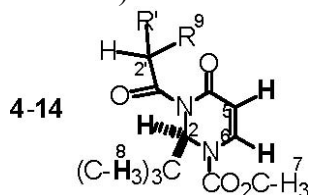
Sample	R	R^1	(C-H$_3$)$_3$	Δδ	C5-H	Δδ	C2-H	Δδ	C6-H	Δδ
4A	Et	Ph	0.97	+0.07	5.15	-0.20	6.74	-0.18	7.58	-0.20
4B	Et	Ph	0.90		5.35		6.92		7.78	
5A	iPr	Ph	0.96	+0.19	5.19	-0.19	6.72	-0.18	7.57	-0.24
5B	iPr	Ph	0.77		5.38		6.90		7.81	
6A	OMe	Ph	0.97	+0.20	5.12	-0.23	6.69	-0.17	7.48	-0.21
6B	OMe	Ph	0.77		5.35		6.86		7.69	
7A	Me	1-naphthyl	0.97	+0.07	4.91	-0.41	6.76	-0.20	7.52	-0.28
7B	Me	1-naphthyl	0.90		5.32		6.96		7.80	
8A	Me	1-pyrenyl	0.98	+0.09	4.71	-0.61	6.80	-0.23	7.35	-0.46
8B	Me	1-pyrenyl	0.89		5.32		7.03		7.81	
9A	iPr	1-naphthyl	0.94	+0.11	4.95	-0.40	6.64	-0.33	8.10	-0.37
9B	iPr	1-naphthyl	0.73		5.35		6.97		8.47	
10A	Me	p-iBu-C$_6$H$_4$	0.94	+0.16	5.11	-0.22	6.67	-0.26	7.55	-0.21
10B	Me	p-iBu-C$_6$H$_4$	0.78		5.33		6.93		7.76	

Table 2. Continued

11A	Me	Arᵃ	0.94	+0.16	5.14	-0.20	nrᵇ	-	7.46	-0.10
11B	Me	Arᵃ	0.78		5.34		nrᵇ		7.56	
12A	Me	Et	0.93	0	5.35	+0.02	6.84	-0.04	7.78	+0.02
12B	Me	Et	0.93		5.33		6.88		7.76	
13A	Me	iPr	0.94	0	5.37	+0.06	6.79	-0.11	7.81	+0.06
13B	Me	iPr	0.94		5.31		6.90		7.75	
14A	Me	C_6H_{11}	0.94	0	5.36	+0.03	6.78	-0.11	7.80	+0.04
14B	Me	C_6H_{11}	0.94		5.33		6.89		7.76	

[a] Ar = 2-(6-methoxynaphthyl); [b] data obscured by overlapping signals.

Preparation of the dialkylacetic acid precursors for diastereomers **13AB** and **14AB** required additional manipulations due to the volatility of the respective methyl esters. The carboxylic acids for **13AB** were prepared by conversion of 3-methylbutyric acid to the corresponding acid chloride followed by coupling to 2-oxazolidinone. Subsequent enolate alkylation, base catalysed hydrolysis, and coupling to **1** generated the diastereomeric products. After chromatographic separation, the relative configurations of these diastereomers were assigned based on spectroscopic identity with the major and minor products obtained for the enolate alkylation of the propionyl analog of **1** with 2-iodopropane. Diastereomers **14AB** were analogously prepared from cyclohexylacetic acid.

The diastereomeric samples prepared as described above were enriched by normal phase chromatography (5–20% ethyl acetate in hexanes). In each case, the more mobile isomer was identified as the 2'R isomer (**A**), though, for **5AB**, three chromatographic cycles were required for adequate sample enrichment. While the consistency of the elution trends may also permit the relative stereochemical assignments for these compounds,[3] no assignments were made on the basis of these phenomena.

Spectroscopic samples were prepared (approximately 0.03 mM in acetone-d_6 or CDCl$_3$) from the enriched samples, and for all diastereomeric pairs, a mixed sample was prepared and examined to confirm the chemical shift differences recorded from the spectra of highly enriched diastereomers (Table 2). The chemical shifts and coupling magnitudes for C2-H, C5-H, and C6-H in CDCl$_3$ for most samples were exhibited as highly broadened singlets that complicated signal assignments. Fortunately, these difficulties were ameliorated in acetone-d_6 (see Figure 1). For example, the C6-H signals for **5A** and **5B** were difficult to identify or correlate to the appropriate proton in CDCl$_3$. However, the signals were exhibited with the expected multiplicities, including w-couplings in most cases, facilitating spectral assignments. Gratifyingly, the use of acetone-d_6 did not modify the relative location or magnitude of Δδ (R-S) for any of the signals described above. Thus, acetone-d_6 is the preferred solvent for these studies, though CDCl$_3$ may be employed in situations where protons other than C2-H, C5-H, and C6-H protons are observed.
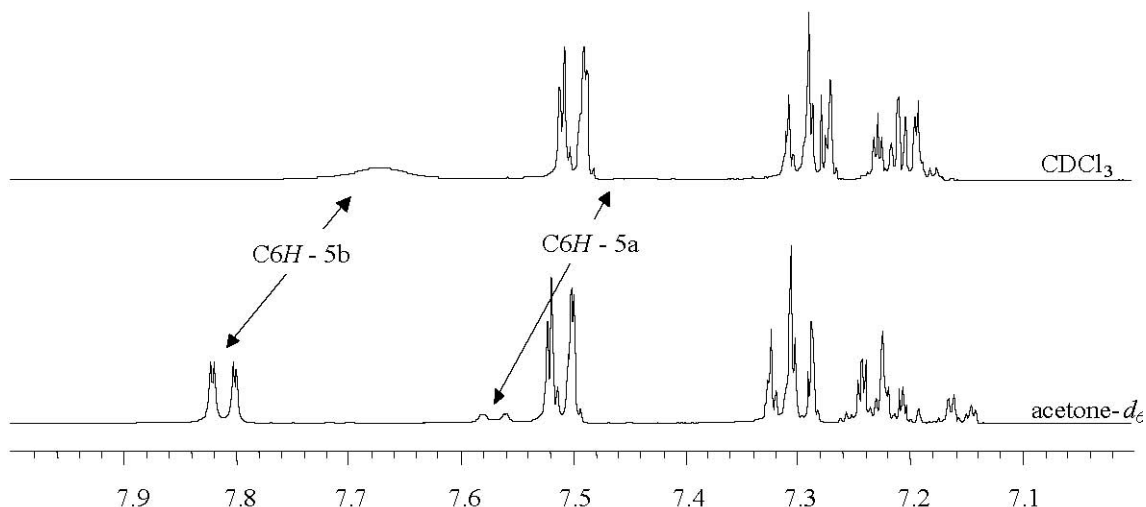
Figure 1. ^{1}H NMR spectra of the C6-*H* and aromatic regions of **5AB** (**5B** is in excess of **5A**) in CDCl$_3$ (top) and in acetone-d_6 (bottom).

Proton NMR analyses of 2′-arylcarboxylic acid analogs **4–10** revealed a pattern of chemical shift differences that were identical to those previously observed for **1–3**. For example, each diastereomer **A** exhibited an upfield shift for C5-*H* and C6-*H* of 0.2 ppm (or larger) relative to **B**. The increased separation of the C5-*H* signals for larger aryl groups (e.g. 0.41 and 0.61 ppm for 1-naphthyl and 1-pyrenyl, respectively) suggests that the differences arise from ring current effects caused by the aryl moiety. Similar patterns of chemical shift differences were also reproduced for the remaining protons (Table 3). In addition, the trends were followed by the conjugates of 2-alkoxy-2-phenylacids **6**, 3-methyl-2-(1-naphthyl)butyric acids **9**,[19] Ibuprofen (**10**), and Naproxen (**11**).

Proton NMR analyses of dialkylacetic acid derivatives **10–12** produced significantly smaller Δδ (*R-S*) separations, and for all but the C2-*H* proton, were opposite in sign compared with derivatives containing an aryl group. The chemical shift differences observed for the latter proton may originate from the nearby C1′-carbonyl anisotropy or other structural difference between the diastereomers. Conversely C5-*H*, C6-*H*, and the *tert*-butyl protons exhibited significantly reduced, or reversed, positioning of the corresponding chemical shifts relative to the 2′-arylcarboxylic acids. For example, the C5-*H* signal of **10A** was *downfield* of the corresponding proton for **10B** (+0.03 ppm). These results provide additional support for the suggestion that the aryl group anisotropy impacts the position of the aforementioned four NMR signals.

Table 3. $\Delta\delta$ (*R-S*) values of **4ab–14ab** recorded in acetone-d_6 (a*d*) and CDCl$_3$ (c*d*) at 300 MHz

Cpd	C2H Ad	cd	C5H ad	cd	C6H ad	cd	7-H ad	cd	8-H ad	cd	C2'H ad	cd	C3'H ad	cd
4ab	-	-	-	-	-	-	-	-	+	+	+	+	+	+
5ab	-	-	-	-	-	-	-	-	+	+	+	+	+	+
6ab	-	-	-	-	-	-	-	-	+	+	+	+		
7ab	-	-	-	-	-	nr	-	-	+	+	+	+	+	+
8ab	-	-	-	-	-	-	-	-	+	+	+	+	+	+
9ab	-	-	-	-	-	nr	-	-	+	+	+	+	+	+
10ab	-	-	-	-	-	-	-	-	+	+	+	+	+	+
11ab	nr	ne	-	ne	-	ne	-	ne	+	ne	+	ne	+	ne
12ab	-	-	+	+	+	0	+	0	0	0	-	-	+	+
13ab	-	-	+	+	+	0	+	0	0	0	-	-	+	+
14ab	-	-	+	+	+	0	+	0	0	0	-	-	+	+

*nr =not resolved, ne=not examined.

An X-ray analysis was performed on **9B**. The requisite acid, (*S*)-3-methyl-2-(1-naphthyl)butyric acid, was prepared via enolate alkylation of the methyl ester of 1-naphthylacetic acid with 2-iodopropane followed by resolution with (*S*)-α-methylbenzylamine. The resolved acid, which was previously prepared and assigned the *S* configuration by Piccolo,[19] was coupled with **1**. Enriched diastereomer **9B** was similarly obtained via coupling of **1** to the acid recovered from the mother liquor of the acid prepared for the synthesis of **9A**. Based on the proton NMR data presented for the arylacetic acid samples (**4–8**, **10**, and **11**), the acid derived from the crystalline salt was assigned the *S* configuration (**9B**), consistent with the reported assignment. The relative configurations of the stereocenters of crystalline **9B** were confirmed by X-ray analysis (see Figure 2), thus enabling an unambiguous assignment of the (*S*)–C2′ configuration based on known **1**.[15] The structure exhibits *anti* imide carbonyls with the naphthyl and *tert*-butyl groups in close proximity suggesting that aryl anisotropy influences the chemical shift of the *tert*-butyl group. The structural origin of the remainder of the chemical shift differences cannot readily be inferred from the X-ray data.

Overall, these data strongly support the generality of proton NMR-derived configurational assignments for pyrimidinone analogs of 2-alkyl-2-aryl- and 2-alkoxy-2-arylcarboxylic acids. In addition, dialkylacetic acid derivatives may be determined based on the sign of the C2-*H* $\Delta\delta$ (*R-S*) value, though, additional investigations are necessary to examine the consistency of the trend. Studies are ongoing to elucidate the structural properties underlying the spectroscopic differences described here and to examine other trends in the spectral and chromatographic properties of the diastereomeric conjugates of **1**.
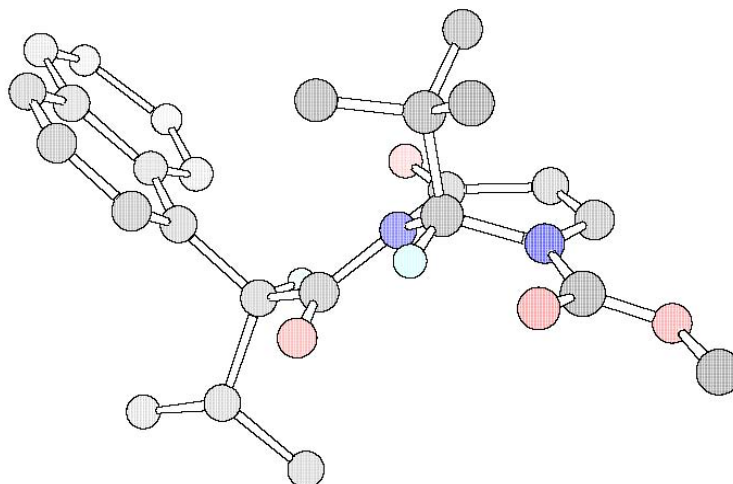
Figure 2. View of **9B** displayed on CHEM 3D® using coordinates from X-ray crystallography. Most hydrogen atoms are removed for clarity.

Experimental Section

General Procedures. Proton (^{1}H NMR) and carbon-13 (^{13}C NMR) magnetic resonance spectra were recorded at 300 MHz and 75 MHz respectively in acetone-d_6 or CDCl$_3$ at 25 °C. Chemical shift values are reported in ppm with TMS as an internal reference. *J* values are given in Hz. COSY spectroscopy was used to identify overlapping proton signals where appropriate. Optical rotation was recorded on a JASCO DIP-1000 digital polarimeter. Kieselgel 60F$_{254}$ silica gel TLC plates were used for monitoring reaction progress. Flash chromatography was performed using silica gel (Aldrich, 200–300 mesh) with ethyl acetate-hexanes gradients. Reactions were routinely effected under a dry nitrogen atmosphere with magnetic stirring.

Materials. Tetrahydrofuran (THF) was distilled from sodium metal with benzophenone, and dichloromethane (DCM) from CaH immediately prior to use. Sodium hexamethyldisilazide (NaHMDS) and lithium hexamethyldisilazide (LiHMDS) were purchased from Aldrich Chemical Company and titrated prior to use with diphenylacetic acid. (±)-2-Phenylpropionic acid, (*R*)-2-phenylpropionic acid, (±)-2-phenylbutanoic acid, (*R*)-2-phenylpropionic acid, (±)-2-(4-nitrophenyl)propionic acid, (±)-(*O*)-methylmandelic acid, (*R*)-(*O*)-methylmandelic acid, (±)-2-methylbutanoyl chloride, (*R*)-2-methylbutanoyl chloride, and (*S*)-2-[2-(6-methoxynapthyl)]-propionic acid were purchased from the Sigma-Aldrich Chemical Company.

(*S*)-2-*tert*-Butyl-1-carbomethoxy-2,3-dihydro-4(1*H*)-pyrimidinone (1). The title compound was prepared following the method of Konopelski[15] in yields ranging from 30% to 55% from asparagine. ^{1}H NMR and ^{13}C NMR data were identical to the published data.

General method for the preparation of chiral 2-aryl carboxylic acids via ester enolate alkylation. The appropriate arylacetic acid was dissolved in methanol (5 mL per mmol acid),

catalytic sulfuric acid was added, and the reaction was stirred and heated at 60 °C. Upon complete esterification as determined by TLC, the reaction was concentrated to 1/5 volume, diluted with ethyl acetate, and washed with a saturated sodium bicarbonate solution then brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting methyl ester was dissolved in THF and added dropwise to a cooled (-46 °C) solution of LiHMDS (1.0 equiv., 1.0 M in THF) and HMPA (1.0 equiv.) diluted to 0.02 M in THF. The cooled reaction was stirred for an additional 1 h. An appropriate alkyl iodide (2 equiv.) was added and the reaction was stirred for 1 h at -46 °C then allowed to gradually warm to room temperature with stirring until judged complete by TLC. The reaction was quenched with saturated ammonium chloride, diluted with ethyl acetate, and washed sequentially with saturated ammonium chloride then brine. Evaporation of solvent under reduced pressure left behind mixtures of alkylated and non-alkylated esters. Reaction mixtures with poor conversion to the desired alkylated ester were separated by flash chromatography (5-10% ethyl acetate in hexanes) prior to hydrolysis as described below. Reaction mixtures with complete or nearly complete alkylation were hydrolyzed (10 equiv. NaOH, 1:1 $THF-H_2O$, reflux) and extractively isolated. Crystallizations were attempted from the slow evaporation of ethyl acetate where applicable.

(±)-2-(1-Naphthyl)propionic acid. Following the general method above from 1-naphthylacetic acid and methyl iodide, without purification as the methyl ester, 65% yield after crystallization, as colorless crystals. ^{1}H NMR (CDCl$_3$) δ 1.66 (d, J = 7.2, 3H), 4.53 (q, J = 7.2, 1H), 7.41–8.10 (m, 7H) in agreement with the literature values.[20]

(±)-2-(1-Pyrenyl)propionic acid. Following the general method above from 1-pyrenylacetic acid and methyl iodide, with flash column purification (5–10% ethyl acetate in hexanes) as the methyl ester, 35% yield after hydrolysis, as a tan solid that darkened upon exposure to light. ^{1}H NMR (CDCl$_3$, methyl ester) δ 1.76 (d, J = 6.9, 3H), 3.65 (s, 3H), 4.80 (q, J = 7.2, 1H), 7.96–8.12 (m, 9H); ^{13}C NMR (acetone-d_6, methyl ester) δ 19.4, 42.2, 52.4, 123.8, 125.9, 125.9, 126.1, 126.3, 126.4, 127.2, 127.2, 128.3, 128.5, 128.5, 128.9, 131.5, 131.9, 132.5, 136.5, 175.8.

(±)-3-Methyl-2-phenylbutanoic acid. Following the general method above from phenylacetic acid and 2-iodopropane, after flash column purification of the methyl ester (5% ethyl acetate in hexanes), 50% yield as a colorless oil resisting crystallization. ^{1}H NMR (CDCl$_3$, methyl ester) δ0.71 (d, J = 6.6, 3H), 1.04 (d, J = 6.6, 3H), 2.34 (m, 1H), 3.15 (d, J = 10.5, 1H), 3.62 (s, 3H), 7.32 (m, 5H) in agreement with the literature values.[21]

(R)-3-Methyl-2-phenylbutanoic acid. Following the protocol of Newman[22] a solution of (±)-3-methyl-2-phenylbutanoic acid (1.25 g, 7.0 mmol), (R)-(+)-α-methylbenzylamine (850 mg, 7.0 mmol), and 63% aqueous ethanol (3.8 mL) was warmed and allowed to cool slowly. The salts that separated were removed and recrystallized two additional times from 63% aqueous ethanol. The purified diastereomer salts were added to a cooled (0 °C) 10% sulfuric acid solution and extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated to an oil that upon standing solidified to give

274 mg of a mixture predicted to be enriched with (*R*)-3-methyl-2-phenylbutanoic acid; $[\alpha]_{D25°}$(CHCl$_3$, *c* 4.46) = -46.2 (lit.[22] -62.4).

(±)-3-Methyl-2-(1-naphthyl)butanoic acid. Following the general method above from 1-naphthylacetic acid and 2-iodopropane, after flash column purification of the methyl ester with 5% ethyl acetate in hexanes, 73% yield as a colorless oil that resisted crystallization; ^{1}H NMR (CDCl$_3$, methyl ester) δ 0.73 (d, *J* = 6.9, 3H), 1.20 (d, *J* = 6.3, 3H), 2.60 (m, 1H), 3.63 (s, 3H), 4.15 (d, *J* = 10.2, 1H), 7.46–8.26 (m, 7H).

(*R*)-3-Methyl-2-(1-naphthyl)butanoic acid. Following the protocol of Picollo[19] a solution of (±)-3-methyl-2-(1-naphthyl)butanoic acid (1.18 g, 5.17 mmol), (*R*)-(+)-α-methylbenzylamine (626 mg, 5.17 mmol) and 50% aqueous ethanol (13 mL) was warmed and allowed to cool slowly. The separated salts were removed and recrystallized two additional times from 50% aqueous ethanol. The purified diastereomer salts were added to a cooled (0 °C) 10% sulfuric acid solution and extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over MgSO$_4$, filtered, and concentrated to an oil that upon standing solidified to give 330 mg of a mixture predicted to be enriched with (*R*)-3-methyl-2-naphthylbutanoic acid; ^{1}H NMR (CDCl$_3$, acid) δ 0.69 (d, *J* = 6.9, 3H), 1.18 (d, *J* = 6.6, 3H), 2.56 (m, 1H), 4.08 (d, *J* = 10.5, 1H), 7.42– 8.15 (m, 7H); $[\alpha]_D^{25°}$ (PhH, *c* 2.363) = -178.3 (lit.[19] -212.44).

(±)-2-(4-Isobutylphenyl)propionic acid. Two 200 mg over-the-counter Ibuprofen tablets were pulverized in a mortar and pestle and dissolved in 200 mL 1 N aqueous NaOH. The aqueous layer was washed 3 times with ethyl acetate then acidified to pH<2 with sulfuric acid and extracted three times with ethyl acetate. The organic layers were combined, dried over MgSO$_4$, filtered, and concentrated to an oil that solidified upon standing to give 420 mg of a white solid. ^{1}H NMR (CDCl$_3$, acid) δ 0.89 (d, *J* = 6.6, 6H), 1.49 (d, *J* = 7.2, 3H), 1.84 (m, 1H), 2.44 (d, *J* = 7.2, 2H), 3.70 (q, *J* = 6.9, 1H), 7.22 (d, *J* = 7.8, 2H), 7.10 (d, *J* = 8.1, 2H) in agreement with the literature values.[23]

(±)-2,3-Dimethylbutanoic acid. 3-methylbutanoic acid (550 mg, 3.87 mmol) and DMF (305 mg, 3.87 mmol) were dissolved in DCM (7.7 ml) and cooled to 0 °C. Oxalyl chloride (982 mg, 7.74 mmol) was added and the solution was stirred at room temperature for 1 h. The reaction was concentrated to 1/4 volume, filtered rapidly to remove precipitated solids, and the filtrate stored under N$_2$ for use in the proceeding step. In a separate reaction vessel, 2-oxazolidinone (337 mg, 3.87 mmol) was dissolved in THF (7.7 mL) and cooled to -46 °C. NaHMDS (4.64 mL, 4.64 mmol, 1 M in THF) was added to the cooled reaction which was allowed to warm to room temperature for 10 min while stirring then cooled back to -46 °C. The acid chloride made previously was diluted to 0.5 mL with THF and added to the cooled oxazolidinone anion via cannula. The reaction was stirred 30 min at -46 °C then allowed to stir a further 1 h at 0 °C. The reaction was quenched with saturated sodium bicarbonate, diluted with ethyl acetate and washed with brine. The organic layer was dried over MgSO$_4$, filtered, and concentrated to an oil. Flash chromatography using 20% ethyl acetate in hexanes hexanes provided 670 mg 3-(3-methylbutanoic)-2-oxazolidinone (82%) as a white solid; ^{1}H NMR (CDCl$_3$) δ 0.97 (d, *J* = 6.6, 6H), 2.17 (m, 1H), 2.80 (d, *J* = 6.9, 2H), 4.01 (t, *J* = 8.1, 2H), 4.39 (t,

J = 8.1, 2H); ^{13}C NMR (CDCl$_3$) δ 22.4, 24.9, 42.5, 43.5, 61.9, 153.5, 172.8. The acylated oxazolidinone (660 mg, 3.12 mmol) was dissolved in THF (15 mL) and cooled to -46 °C. NaHMDS (3.27 mL, 3.27 mmol, 1.0 M in THF) was added to the cooled solution that was stirred at this temperature for 1 h. Methyl iodide (885 mg, 6.24 mmol) was added and the reaction was stirred 1 h at -46 °C then allowed to gradually warm to room temperature and stirred an additional 1 h. The reaction was quenched with saturated ammonium chloride and extracted twice with ethyl acetate. The combined organic layers were washed with brine, dried over MgSO$_4$, filtered, and concentrated to an oily residue which was purified with flash chromatography (15–20% ethyl acetate in hexanes) to give 667 mg 3-(2,3-dimethylbutyryl)-2-oxazolidinone (95%); ^{1}H NMR (CDCl$_3$) δ 0.90 (d, J = 6.6, 3H), 0.94 (d, J = 6.6, 3H), 1.98 (m, 1H), 3.61 (m, 1H), 4.02 (dt, J = 8.1, 2.4, 2H), 4.39 (t, J = 8.1, 2H) ^{13}C NMR 22.9, 25.4, 42.9, 43.9, 62.3, 153.9, 173.2. The acylated oxazolidinone (600 mg, 2.66 mmol) was dissolved in 12 mL 1:1 THF-H$_2$O and treated with 2.7 mL of 10 N aqueous NaOH and stirred at 110 °C for 3 h after which the reaction was cooled, diluted to 100 mL with 1N NaOH, and washed two times with ethyl acetate. The aqueous layer was acidified to pH<2 with sulfuric acid and extracted three times with ethyl acetate. The combined organic layers were washed with brine, dried over MgSO$_4$, filtered, and concentrated give 261 mg (63 %) of the title compound as an oil that solidified upon standing; ^{1}H NMR (CDCl$_3$) δ 0.93 (d, J = 6.3, 6H), 1.12 (d, J = 6.6, 3H), 1.88 (m, 1H), 3.44 (m, 1H); ^{13}C NMR (CDCl$_3$) δ 13.3, 19.0, 20.6, 30.7, 46.0, 183.2.

(±)-2-Cyclohexylpropionic acid. Following the procedure for the synthesis of (±)-2,3-dimethylbutanoic acid, the achiral intermediate 3-(cyclohexylaceto)-2-oxazolidone was obtained in 82% yield; ^{1}H NMR (CDCl$_3$) δ 0.95–1.80 (m, 11H), 2.81 (d, J = 6.4, 2H), 4.02 (t, J = 8.0, 2H), 4.41 (t, J = 8.0, 2H). Methylation as above provided 3-(2-cyclohexylpropionyl)-2-oxazolidinone (95%); ^{1}H NMR (CDCl$_3$) δ 0.80–1.80 (m, 11H), 1.11 (d, J = 6.8, 3H), 3.67 (m, 1H), 4.02 (m, 2H), 4.40 (t, J = 7.8, 2H). Finally, the free acid was obtained after hydrolysis and work-up as above in 63% yield; ^{1}H NMR (CDCl$_3$) δ 0.90–1.80 (m, 11H), 1.13 (d, J = 6.9, 3H), 2.28 (m, 1H).

General method for the preparation of carboxylic acid chlorides

The appropriate carboxylic acid (1.0 equiv.) was treated with KOH (1.0 equiv., 2 N in water) and heated at 60 °C with stirring for 30 min. Water was removed by sequential azeotropic concentrations with methanol and toluene under reduced pressure and heat followed by storage under high vacuum for 12 hours. The dried carboxylic acid salt was suspended in toluene (to 0.4 M), a catalytic amount of pyridine was added and the reaction was cooled to 0 °C. Oxalyl chloride (2 equiv.) was added dropwise to the cooled solution that was then allowed to warm to room temperature and stirred for 2 h. The reaction was concentrated under reduced pressure to 1/5 the original volume, filtered, and further concentrated to a slightly viscous liquid with some solids. The crude acid chloride was dissolved in dry THF to an approximately 2 M concentration and used in this form for further reactions.

General methods for the formation of diastereomeric derivatives of 1

Method A*:* NaHMDS (1.1 equiv., 1.0 M in THF) was added to a cooled (-78° C) solution of **1** (1.0 equiv., 0.2 M in THF). The solution was stirred 1 h at -78° C after which the appropriate acid chloride (1.2 equiv., 2 M in THF) was added. The reaction was allowed to gradually warm to room temperature and monitored by TLC until completion (1–2 h) after which the reaction was quenched with saturated ammonium chloride and extracted with ethyl acetate. The organic layer was washed sequentially with saturated sodium bicarbonate and brine, dried over MgSO$_4$, filtered, and concentrated to an oil. Purification by flash chromatography using 5–20% ethyl acetate in hexanes provided yields between 82–95%.

Method B: Dicyclohexylcarbodiimide (DCC, 1.2 equiv., 2 M in DCM) was added to a cooled solution (0° C) of **1** (1.0 equiv.), 4-(*N,N'*-dimethylamino)pyridine (DMAP, 0.1 equiv.) and the appropriate carboxylic acid (1.1 equiv.) in DCM (to 0.2 M in **1**). The reaction was allowed to gradually warm to room temperature and stirred for 12 h. The resultant mixture was filtered to remove the urea by-product and concentrated to an oily solid. Purification by flash chromatography (10–30% ethyl acetate in hexanes) provided isolated yields between 45–85%.

Method C*:* The appropriate prochiral carboxylic acid or acid chloride was coupled to **1** following either method A or method B to generate acylated-**1**. NaHMDS (1.1 equiv., 1.0 M in THF) was added to a cooled solution (-78° C) of the acylated-**1** (0.2 M in THF) and stirred for 30 min. The appropriate alkyl iodide (2 equiv.) was added and the reaction was brought to room temperature with stirring until completion (30 min–1 h). After work-up (as in method A), the diastereomeric products were isolated by flash chromatography (10–30% ethyl acetate in hexanes) with the 2'*R* diastereomer in excesses ranging from 10:1 to 3:1 over the 2'*S* diastereomer as determined by ^{1}H NMR.

(2*R*)-2-*tert*-Butyl-1-carbomethoxy-3-[(*R*)-2-phenylpropionyl]-2,3-dihydro-4(1*H*)-pyrimidinone (1A). Following Method A; ^{1}H NMR (acetone-d_6) δ 0.95 (s, 9H), 1.45 (d, *J* = 7.2, 3H), 3.83 (s, 3H), 5.00 (q, *J* = 6.9, 1H), 5.12 (d, *J* = 8.0, 1H), 6.71 (d, *J* = 1.6, 1H), 7.12–7.26 (aromatic, 5H), 7.58 (dd, *J* = 7.6, 1.2, 1H); ^{13}C NMR (acetone-d_6) δ 20.5, 27.3, 40.4, 45.9, 54.8, 70.7, 104.9, 127.6, 128.6, 129.1, 140.5, 141.9, 153.1, 164.7, 176.0.

(2*R*)-2-*tert*-Butyl-1-carbomethoxy-3-[(*S*)-2-phenylpropionyl]-2,3-dihydro-4(1*H*)-pyrimidinone (1B). Following Method A; ^{1}H NMR (acetone-d_6) δ 0.79 (s, 9H), 1.38 (d, *J* = 6.8, 3H), 3.88 (s, 3H), 4.81 (q, *J* = 6.9, 1H), 5.33 (d, *J* = 7.6, 1H), 6.93 (d, *J* = 1.2, 1H), 7.19–7.46 (aromatic, 5H), 7.76 (dd, *J* = 8.0, 1.2, 1H); ^{13}C NMR (acetone-d_6) δ 21.2, 27.2, 41.3, 46.4, 54.8, 69.6, 105.3, 127.5, 129.1, 129.2, 140.6, 142.8, 153.3, 164.1, 175.5.

(2*R*)-2-*tert*-Butyl-1-carbomethoxy-3-[(*R*)-2-phenylbutyryl]-2,3-dihydro-4(1*H*)-pyrimidinone (4A). Following Method A; ^{1}H NMR δ (acetone-d_6)) 0.88 (t, *J* = 7.2, 3H), 0.96 (s, 9H), 1.72 (m, *J* = 5.6, 1H), 2.16 (m, *J* = 5.6, 1H), 3.80 (s, 3H), 4.86 (t, *J* = 7.2, 1H), 5.15 (d, *J* = 7.6, 1H), 6.74 (d, *J* = 1.2, 1H), 7.13–7.35 (aromatic, 5H), 7.58 (dd, *J* = 7.8, 1.0, 1H); ^{13}C NMR (acetone-d_6) δ 12.8, 27.3, 28.4, 40.8, 53.1, 54.8, 70.5, 104.9, 127.7, 129.2, 129.6, 140.1, 140.5, 153.2, 164.7, 175.3.

(2R)-2-*tert*-Butyl-1-carbomethoxy-3-[(S)-2-phenylbutyryl]-2,3-dihydro-4(1H)-pyrimidinone (4B). Following Method A; ^{1}H NMR δ (acetone-d_6) 0.75 (t, J = 7.2, 3H), 0.79 (s, 9H), 1.76 (m, J = 5.7, 1H), 2.03 (m, J = 5.6, 1H), 3.88 (s, 3H), 4.58 (t, J = 7.4, 1H), 5.35 (d, J = 8.0, 1H), 6.92 (d, J = 1.2, 1H), 7.19–7.48 (aromatic, 5H), 7.78 (dd, J = 7.8, 1.4, 1H); ^{13}C NMR (acetone-d_6) δ 12.7, 27.2, 29.5, 41.3, 53.8, 54.8, 69.6, 105.3, 127.4, 128.0, 128.8, 140.6, 141.3, 154.6, 164.2, 175.2.

(2R)-2-*tert*-Butyl-1-carbomethoxy-3-[(R)-3-methyl-2-phenylbutyryl]-2,3-dihydro-4(1H)-pyrimidinone (5A). Following Method A; ^{1}H NMR δ (acetone-d_6) 0.65 (d, J = 6.8, 1H), 0.96 (s, 9H), 1.09 (d, J = 6.4, 1H), 2.46 (m, J = 6.6, 1H), 3.78 (s, 3H), 4.74 (d, J = 10.0, 1H), 5.19 (d, J = 8.0, 1H), 6.72 (d, J = 1.2, 1H), 7.14–7.33 (aromatic, 5H), 7.57 (dd, J = 7.6, 1.2, 1H); ^{13}C NMR (acetone-d_6) δ 20.7, 22.3, 27.4, 32.7, 40.8, 54.8, 58.5, 70.3, 104.8, 127.9, 129.1, 129.5, 139.4, 140.6, 153.0, 164.9, 175.1.

(2R)-2-*tert*-Butyl-1-carbomethoxy-3-[(S)-3-methyl-2-phenylbutyryl]-2,3-dihydro-4(1H)-pyrimidinone (5B). Following Method A; ^{1}H NMR δ (acetone-d_6) 0.63 (d, J = 6.8, 1H), 0.77 (s, 9H), 0.88 (d, J = 6.4, 1H), 2.41 (m, J = 6.6, 1H), 3.88 (s, 3H), 4.32 (d, J = 10.8, 1H), 5.38 (d, J = 8.0, 1H), 6.90 (d, J = 1.2, 1H), 7.17–7.52 (aromatic, 5H), 7.81 (dd, J = 7.8, 1.4, 1H); ^{13}C NMR (acetone-d_6) δ 20.7, 21.8, 27.2, 34.1, 41.2, 54.9, 59.7, 69.8, 105.3, 127.6, 128.7, 130.1, 139.7, 140.8, 153.2, 164.5, 175.5.

(2R)-2-*tert*-Butyl-1-carbomethoxy-3-[(R)-2-methoxy-2-phenylacetyl]-2,3-dihydro-4(1H)-pyrimidinone (6A). Following Method A; ^{1}H NMR δ (acetone-d_6) 0.97 (s, 9H), 3.38 (s, 3H), 3.81 (s, 3H), 5.17 (d, J = 7.8, 1H), 6.04 (s, 1H), 6.71 (d, J = 1.2, 1H), 7.25–7.35 (aromatic, 5H), 7.62 (dd, J = 7.8, 1.2, 1H); ^{13}C NMR (acetone-d_6) δ 27.3, 40.9, 54.9, 57.7, 70.8, 83.7, 104.7, 128.7, 129.2, 129.4, 137.7, 141.1, 153.3, 164.7, 172.9.

(2R)-2-*tert*-Butyl-1-carbomethoxy-3-[(S)-2-methoxy-2-phenylacetyl]-2,3-dihydro-4(1H)-pyrimidinone (6B). Following Method A; ^{1}H NMR δ (acetone-d_6 0.77 (s, 9H), 3.22 (s, 3H), 3.88 (s, 3H), 5.38 (d, J = 7.8, 1H), 5.78 (s, 1H), 6.86 (d, J = 1.5, 1H), 7.28–7.59 (aromatic, 5H), 7.81 (dd, J = 7.8, 1.5, 1H); ^{13}C NMR (acetone-d_6) δ 27.1, 41.3, 54.9, 57.5, 70.0, 83.8, 105.0, 128.9, 129.0, 129.8, 138.2, 141.3, 153.5, 164.1, 172.5.

(2R)-2-*tert*-Butyl-1-carbomethoxy-3-[(R)-2-(1-naphthyl)propionyl]-2,3-dihydro-4(1H)-pyrimidinone (7A). Following Method A; ^{1}H NMR δ (acetone-d_6)) 0.97 (s, 9H), 1.58 (d, J = 7.2, 3H), 3.84 (s, 3H), 4.91 (d, J = 7.6, 1H), 5.70 (q, J = 6.9, 1H), 6.76 (d, J = 1.2, 1H), 7.52 (COSY, 1H), 7.16–8.02 (aromatic, 5H); ^{13}C NMR (acetone-d_6) δ 19.5, 27.3, 40.9, 43.0, 54.8, 71.1, 104.7, 123.9, 124.9, 126.0, 126.4, 126.9, 128.2, 129.5, 132.3, 134.9, 138.8, 140.5, 153.1, 164.6, 176.7.

(2R)-2-*tert*-Butyl-1-carbomethoxy-3-[(S)-2-(1-naphthyl)propionyl]-2,3-dihydro-4(1H)-pyrimidinone (7B). Following Method A; ^{1}H NMR δ (acetone-d_6 0.90 (s, 9H), 1.48 (d, J = 7.2, 3H), 3.89 (s, 3H), 5.32 (d, J = 7.6, 1H), 5.62 (q, J = 6.8, 1H), 6.96 (d, J = 1.2, 1H), 7.80 (COSY, 1H), 7.43–8.24 (aromatic, 5H); ^{13}C NMR (acetone-d_6) δ 19.8, 27.5, 41.2, 42.5, 54.8, 69.9, 105.2, 124.4, 124.7, 126.0, 126.3, 126.7, 127.9, 129.5, 132.3, 135.1, 139.3, 140.8, 153.3, 164.4, 175.5.

(2R)-2-*tert*-Butyl-1-carbomethoxy-3-[(R)-2-(1-pyrenyl)propionyl]-2,3-dihydro-4(1H)-pyrimidinone (8A). Following Method A; ^{1}H NMR δ (acetone-d_6) 0.97 (s, 9H), 1.69 (d, J = 6.8,

3H), 3.82 (s, 3H), 4.71 (d, J = 7.6, 1H), 5.99 (q, J = 7.1, 1H), 6.81 (d, J = 1.2, 1H), 7.35 (d, J = 7.2, 1H), 8.04–8.31 (aromatic, 5H); ^{13}C NMR (acetone-d_6) δ 20.2, 27.3, 40.9, 43.6, 54.9, 71.4, 104.7, 123.9, 125.6, 125.8, 125.9, 126.0, 126.0, 126.3, 127.2, 128.2, 128.4, 128.7, 129.5, 131.3, 131.9, 132.4, 136.8, 140.7, 153.4, 164.8, 177.3.

(2R)-2-*tert*-Butyl-1-carbomethoxy-3-[(S)-2-(1-pyrenyl)propionyl]-2,3-dihydro-4(1H)-pyrimidinone (8B). Following Method A; ^{1}H NMR δ (acetone-d_6) 0.88 (s, 9H), 1.62 (d, J = 6.9, 3H), 3.90 (s, 3H), 5.32 (d, J = 7.8, 1H), 5.92 (q, J = 7.0, 1H), 7.03 (d, J = 1.2, 1H), 7.80 (d, J = 8.0, 1H), 8.04-8.54 (aromatic, 5H); ^{13}C NMR (acetone-d_6) δ 20.8, 27.4, 41.3, 43.2, 54.9, 70.0, 105.4, 124.8, 125.3, 125.8, 125.8, 125.9, 126.1, 126.1, 127.1, 128.0, 128.3, 128.5, 129.5, 131.2, 132.0, 132.5, 137.6, 141.0, 153.6, 164.6, 176.0.

(2R)-2-*tert*-Butyl-1-carbomethoxy-3-[(R)-3-methyl-2-(1-naphthyl)butyryl]-2,3-dihydro-4(1H)-pyrimidinone (9A). Following Method A; ^{1}H NMR δ (acetone-$d_6$0.63 (d, J = 6.8, 1H), 0.97 (s, 9H), 1.23 (d, J = 6.4, 1H), 2.60 (m, J = 6.6, 1H), 3.72 (s, 3H), 4.98 (d, J = 8.0, 1H), 5.62 (d, J = 10.0, 1H), 6.67 (s, 1H), 7.40 (COSY, 1H), 7.39–8.14 (aromatic, 5H); ^{13}C NMR (CDCl$_3$) δ 20.3, 22.0, 26.9, 33.5, 40.0, 52.9, 54.2, 70.2, 104.2, 123.0, 124.6, 125.3, 125.5, 126.2, 127.5, 128.8, 131.3, 133.9, 137.6, 139.2, 152.2, 164.7, 175.7.

(2R)-2-*tert*-Butyl-1-carbomethoxy-3-[(S)-3-methyl-2-(1-naphthyl)butyryl]-2,3-dihydro-4(1H)-pyrimidinone (9B). Following Method A; ^{1}H NMR δ (acetone-d_6) 0.62 (d, J = 6.8, 1H), 0.76 (s, 9H), 1.01 (d, J = 6.4, 1H), 2.50 (m, J = 6.6, 1H), 3.90 (s, 3H), 5.38 (d, J = 8.0, 1H), 5.43 (d, J = 10.0, 1H), 7.00 (d, J = 1.2, 1H), 7.82 (COSY, 1H), 7.45–8.51 (aromatic, 5H); ^{13}C NMR (CDCl$_3$) δ 20.3, 21.6, 26.7, 35.1, 40.5, 54.0, 54.3, 69.1, 105.1, 123.4, 123.7, 125.2, 125.5, 126.1, 127.4, 128.9, 131.2, 134.1, 137.8, 139.2, 152.6, 163.8, 175.1.

(2R)-2-*tert*-Butyl-1-carbomethoxy-3-[(R)-2-(4-*iso*-butylphenyl)propionyl]-2,3-dihydro-4(1H)-pyrimidinone (10A). Following Method A; ^{1}H NMR δ (acetone-d_6) 0.85 (d, J = 6.6, 3H), 0.94 (s, 9H), 1.43 (d, J = 7.2, 3H), 1.88 (m, J = 6.6, 1H), 2.41 (d, J = 7.5, 2H), 3.82 (s, 3H), 4.95 (q, J = 7.0, 1H), 5.11 (d, J = 7.8, 1H), 6.67 (d, J = 1.2, 1H), 7.13 (d, J = 8.1, 2H), 7.25 (d, J = 7.8, 2H), 7.39–7.27 (aromatic, 5H), 7.55 (dd, J = 7.8, 1.2, 1H); ^{13}C NMR (acetone-d_6) δ 20.3, 22.7, 22.8, 27.3, 31.1, 40.9, 45.6, 45.7, 54.8, 71.0, 105.1, 128.6, 130.0, 139.5, 140.6, 141.1, 153.4, 165.1, 176.7.

(2R)-2-*tert*-Butyl-1-carbomethoxy-3-[(S)-2-(4-*iso*-butylphenyl)propionyl]-2,3-dihydro-4(1H)-pyrimidinone (10B). Following Method A; ^{1}H NMR δ (acetone-d_6) 0.78 (s, 9H), 0.87 (d, J = 6.6, 3H), 0.88 (d, J = 6.6, 3H), 1.38 (d, J = 6.9, 3H), 1.90 (m, J = 6.8, 1H), 2.45 (d, J = 7.2, 2H), 3.88 (s, 3H), 4.84 (q, J = 6.9, 1H), 5.33 (d, J = 7.8, 1H), 6.93 (d, J = 1.2, 1H), 7.11 (d, J = 8.4, 2H), 7.37 (d, J = 8.1, 2H), 7.09–7.39 (aromatic, 5H), 7.76 (dd, J = 7.8, 1.5, 1H); ^{13}C NMR (acetone-d_6) δ 20.9, 22.7, 22.8, 27.2, 31.1, 41.3, 45.7, 45.9, 54.8, 69.6, 105.6, 129.1, 129.8, 140.1, 140.7, 140.8, 153.6, 164.4, 176.1.

(2R)-2-*tert*-Butyl-1-carbomethoxy-3-[(R)-2-(2-(6-methoxynaphthyl))propionyl]-2,3-dihydro-4(1H)-pyrimidinone (11A). Following Method B; ^{1}H NMR δ (acetone-d_6) 0.94 (s, 9H), 1.52 (d, J = 7.2, 3H), 3.82 (s, 3H), 3.90 (s, 3H), 5.06 (q, J = 6.9, 1H), 5.14 (d, J = 8.0, 1H), 7.46 (dd, J = 8.4, 2.0, 1H), 7.09–7.84 (aromatic, 5H); ^{13}C NMR (acetone-d_6) δ 20.9, 26.1, 39.8, 45.4, 54.8,

55.7, 68.4, 105.4, 119.7, 126.6, 127.1, 127.2, 127.8, 129.6, 129.8, 131.0, 134.4, 139.0, 140.6, 158.0, 164.2, 176.0.

(2*R*)-2-*tert*-Butyl-1-carbomethoxy-3-[(*S*)-2-(6-methoxy-2-naphthyl)propionyl]-2,3-dihydro-4(1*H*)-pyrimidinone (11B). Following Method A; ^{1}H NMR δ (acetone-d_6) 0.78 (s, 9H), 1.46 (d, *J* = 6.8, 3H), 3.88 (s, 3H), 3.90 (s, 3H), 4.95 (q, *J* = 6.9, 1H), 5.34 (d, *J* = 8.0, 1H), 6.96 (s, 1H) , 7.56 (dd, *J* = 8.6, 1.8, 1H), 7.11–7.83 (aromatic, 5H); ^{13}C NMR (acetone-d_6) δ 21.1, 27.2, 41.3, 46.3, 54.8, 55.7, 69.6, 106.4, 119.4, 126.6, 127.3, 127.4, 128.0, 130.0, 131.9, 134.5, 137.8, 138.6, 140.6, 158.4, 164.1, 175.6.

(2*R*)-2-*tert*-Butyl-1-carbomethoxy-3-[(*R*)-2-methylbutyryl]-2,3-dihydro-4(1*H*)-pyrimidinone (12A). Following Method A; ^{1}H NMR δ (acetone-d_6) 0.77 (t, *J* = 7.3, 3H), 0.93 (s, 9H), 1.20 (d, *J* = 6.6, 3H), 1.36 (m, *J* = 7.3, 1H), 1.64 (m, *J* = 7.4, 1H), 3.36 (m, *J* = 7.2, 1H), 3.87 (s, 3H), 5.35 (d, *J* = 7.8, 1H), 6.84 (d, *J* = 1.5, 1H), 7.78 (dd, *J* = 7.8, 1.5, 1H); ^{13}C NMR (acetone-d_6) δ 12.4, 18.8, 27.5, 28.1, 41.3, 42.7, 55.1, 70.1, 105.7, 141.1, 153.8, 165.1, 178.7.

(2*R*)-2-*tert*-Butyl-1-carbomethoxy-3-[(*S*)-2-methylbutyryl]-2,3-dihydro-4(1*H*)-pyrimidinone (12B). Following Method A; ^{1}H NMR δ (acetone-d_6) 0.95 (t, *J* = 7.3, 3H), 0.93 (s, 9H), 1.01 (d, *J* = 6.6, 3H), 1.41 (m, *J* = 7.3, 1H), 1.89 (m, *J* = 6.8, 1H), 3.43 (m, *J* = 7.0, 1H), 3.87 (s, 3H), 5.33 (d, *J* = 7.8, 1H), 6.88 (d, *J* = 1.2, 1H), 7.77 (dd, *J* = 7.8, 1.5, 1H); ^{13}C NMR (acetone-d_6) δ 12.3, 17.1, 27.5, 28.6, 41.3, 42.1, 55.1, 69.9, 105.7, 141.0, 153.8, 165.0, 178.4.

(2*R*)-2-*tert*-Butyl-1-carbomethoxy-3-[(*R*)-2,3-dimethylbutyryl]-2,3-dihydro-4(1*H*)-pyrimidinone (13A). Following Method B from **1** and (±)-2,3-dimethylbutanoic acid for larger amounts, and Method C for assignment of stereochemistry; ^{1}H NMR (acetone-d_6) δ 0.77 (d, *J* = 6.6, 3H), 0.84 (d, *J* = 6.9, 3H), 0.94 (s, 9H), 1.16 (d, *J* = 6.9, 3H), 1.84 (m, *J* = 7.0, 1H), 3.25 (m, *J* = 7.1, 1H), 3.87 (s, 3H), 5.36 (d, *J* = 7.8, 1H), 6.79 (d, *J* = 0.9, 1H), 7.80 (dd, *J* = 7.8, 1.2, 1H); ^{13}C NMR (acetone-d_6) δ 15.7, 19.4, 21.6, 27.3, 32.3, 41.1, 47.0, 54.9, 70.1, 105.4, 141.0, 153.5, 165.2, 178.5.

(2*R*)-2-*tert*-Butyl-1-carbomethoxy-3-[(*S*)-2,3-dimethylbutyryl]-2,3-dihydro-4(1*H*)-pyrimidinone (13B). Following Method B from **1** and (±)-2,3-dimethylbutanoic acid for larger amounts, and Method C for assignment of stereochemistry; ^{1}H NMR δ (acetone-d_6) 0.87 (d, *J* = 6.9, 3H), 0.95 (d, *J* = 6.9, 3H), 0.94 (s, 9H), 1.00 (d, *J* = 6.6, 3H), 2.18 (m, *J* = 6.5, 1H), 3.39 (m, *J* = 5.2, 1H), 3.86 (s, 3H), 5.33 (d, *J* = 8.1, 1H), 6.90 (s, 1H), 7.76 (dd, *J* = 8.0, 1.0, 1H); ^{13}C NMR (acetone-d_6) δ 13.1, 17.9, 21.8, 27.3, 31.3, 41.0, 45.9, 54.9, 69.5, 110.6, 140.8, 153.5, 164.9, 177.7.

(2*R*)-2-*tert*-Butyl-1-carbomethoxy-3-[(*R*)-2-cyclohexylpropionyl]-2,3-dihydro-4(1*H*)-pyrimidinone (14A). Following Method B from **1** and (±)-2,3-dimethylbutanoic acid for larger amounts, and Method C for assignment of stereochemistry; ^{1}H NMR δ (acetone-d_6) 0.80 - 1.85 (cyclohexyl, 11H), 0.94 (s, 9H), 1.15 (d, *J* = 6.4, 3H), 3.28 (q, *J* = 5.1, 1H), 3.87 (s, 3H), 5.36 (d, *J* = 8.0, 1H), 6.78 (d, *J* = 1.2, 1H), 7.80 (dd, *J* = 7.6, 1.2, 1H); ^{13}C NMR (acetone-d_6) δ 15.7, 27.0, 27.1, 27.2, 27.2, 30.3, 32.2, 40.9, 42.0, 45.9, 54.8, 69.9, 105.3, 140.7, 153.1, 164.9, 178.1.

(2*S*)-2-*tert*-Butyl-1-carbomethoxy-3-[(*R*)-2-cyclohexylpropionyl]-2,3-dihydro-4(1*H*)-pyrimidinone (14B). Following Method B from **1** and (±)-2,3-dimethylbutanoic acid for larger

amounts, and Method C for assignment of stereochemistry; ^{1}H NMR δ (acetone-d_6) 0.92 - 1.85 (cyclohexyl, 11H), 0.94 (s, 9H), 0.96 (d, J = 7.2, 3H), 3.41 (q, J = 4.1, 1H), 3.86 (s, 3H), 5.33 (d, J = 7.6, 1H), 6.89 (d, J = 1.2, 1H), 7.76 (dd, J = 7.8, 1.4, 1H); ^{13}C NMR (acetone-d_6) δ 13.9, 27.3, 27.3, 27.3, 27.5, 28.9, 32.5, 40.8, 41.5, 45.2, 54.7, 69.4, 105.4, 140.4, 153.1, 164.5, 177.2.

Acknowledgements

References and Notes

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17. Procedure: DCC (0.1 equiv) was added in one portion to a cooled solution (0° C) of **1** (1 equiv), carboxylic acid (1.1 equiv) and DMAP (1.2 equiv) in CH_2Cl_2. The reaction was

allowed to gradually warm to room temperature and stirred for 12 h. The resultant mixture was filtered to remove the urea by-product and concentrated to an oily solid. Purification by flash chromatography provided isolated yields between 64-85%. All compounds were analyzed by ^{1}H- and ^{13}C-NMR.

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