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Chemical resolution of enantiomers of 3,4-dihydropyrimidin-2(1*H*)-ones using chiral auxiliary approach

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ABSTRACT

Inherently racemic DHPMs have been resolved using chemical resolution methodology by appending enantiopure chiral auxiliary at N-1 or N-3 position of the DHPMs, leading to the formation of both diastereomers, which were separated chromatographically to obtain both enantiomers (*ee* upto 99.9%) of DHPMs, after removal of the auxiliary. Absolute configuration of the enantiomers has been assigned.

1. Introduction

3,4-Dihydropyrimidin-2(1*H*)-ones (DHPMs) are a class of heterocyclic compounds,[1] which possess diverse range of biological properties.[2] DHPMs show very similar pharmacological profile to classical 1,4-dihydropyridine (DHPs) based calcium channel modulators.[3] In general, DHPMs and their derivatives have been found to possess equivalent or even superior calcium channel binding properties than the traditional DHP based drugs. This has fueled considerable interest in creating diversity in these molecules to search for better calcium channel modulators. In addition, these molecules also act as mitotic kinesin inhibitors,[4] α_{1a}-adrenergic receptor antagonists,[5] hepatitis B virus replication inhibitors,[6] and depict a variety of other biological effects.[1] The DHPM core also constitutes a key component of polycyclic guanidine containing marine alkaloids, such as batzelladine A[7] and very active natural products, such as dehydrocrambine A and Sch 575948,[8] which are potent inhibitors of HIV glycoprotein gp120-CD4 receptor interaction. In contrast to DHPs, DHPMs are inherently racemic molecules[3a–c] and the influence of the absolute configuration at the stereogenic center C-4 on biological activity is well documented.[9]

The DHPM enantiomers exhibit different or even opposite pharmacological profiles. For example, only (*R*)-enantiomers of SQ 32926 **1** and SQ 32547 **2** depict antihypertensive effect.[3a–c] The (*S*)-enantiomer of α_{1a}-selective adrenoceptor antagonist L-771, 688 **3**, is significantly more active than the (*R*)-enantiomer,[5] and the (*S*)-enantiomer of the mitotic kinesin Eg5 inhibitor monastrol **4** is a more potent inhibitor of Eg5 activity.[4] Similar effects were also observed for Bay 41-4109 **5**, a non-nucleosidic inhibitor of hepatitis B virus replication, where the (*S*)-enantiomer was found to be more active than the (*R*)-enantiomer[6] (Fig. 1).

Whereas a number of methods have been reported for the synthesis of racemic DHPMs,[10] approaches to the enantiopure DHPMs are relatively scanty and have relied either on catalytic enantioselective synthetic routes or through chemical or enzymatic resolution methods and have been reviewed recently.[11] In fact, access to diastereomerically/enantiomerically pure DHPM derivatives utilizing the tools of asymmetric synthesis has been a formidable task and is still being pursued with vigor. Incorporation of chiral auxiliary, such as menthyl carboxylate,[3b] (*R*)-α-methyl benzyl amine derivatives,[3a] chiral amine,[12] ribofuranosyl amide[13] or sulfonylation with (1*S*)-(+) camphorsulfonyl chloride,[14] at N-3 position were of limited success. Alternatively employing protease subtilisin (lipases and esterases were unreactive), selective hydrolysis of C-5 methyl ester of only (*R*)-enantiomer[15] led to the recovery of the desired (*S*)-enantiomer in 80–90% chemical yield and high (98%) enantioselectivity, which was further manipulated into (*S*)-L-771,668 **3**. Similarly, a lipase-catalyzed kinetic resolution strategy has been reported to yield optically pure DHPMs.[16]

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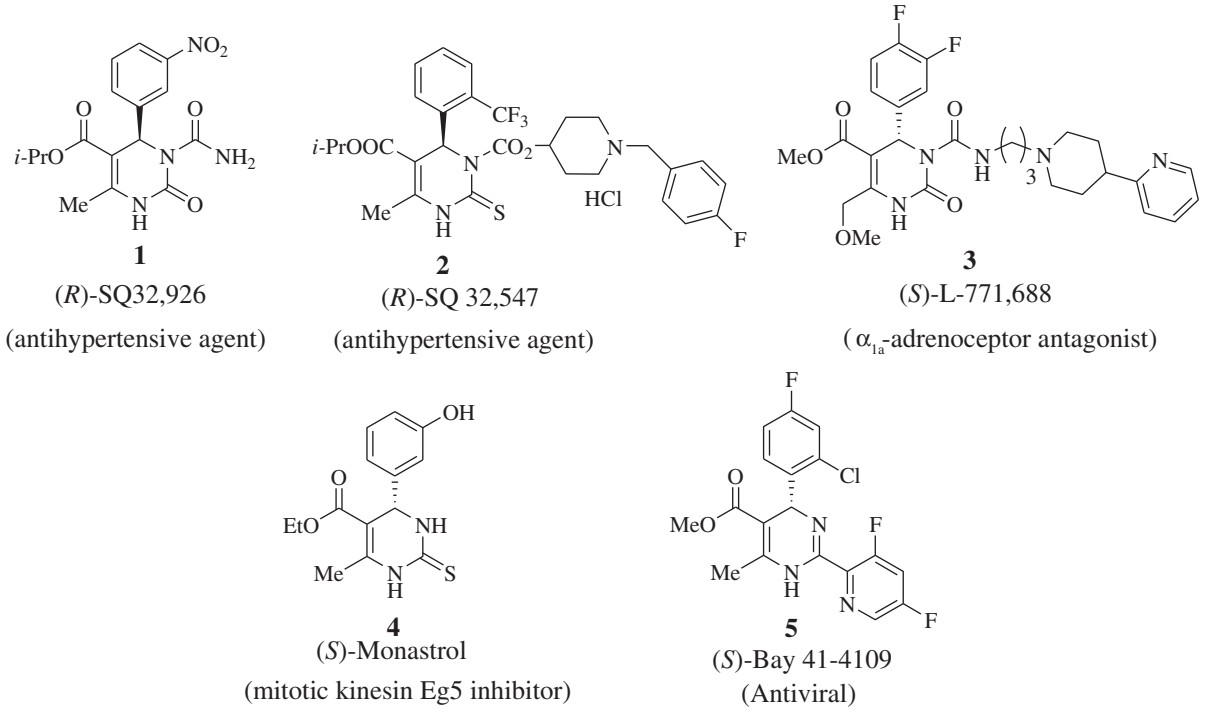


Fig. 1. Therapeutically potent enantiomers of DHPMs.

Direct asymmetric induction using chiral aldehydes[17,18] or enantioselective HPLC separation using chiral stationary phases (CSPs)[19,20] furnished a useful but expensive separation of DHPM enantiomers.

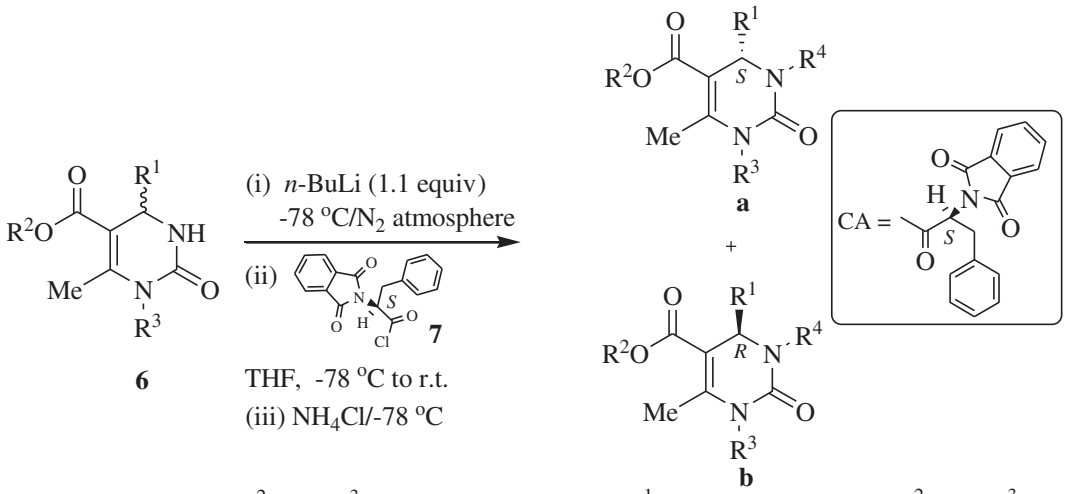
Catalytic enantioselective synthesis of Biginelli DHPMs has relied on the use of acids[21–24] in the presence of different chiral ligands. Moderate to excellent enantioselectivities (upto 99%) have been reported for a wide range of aldehydes and/or β-keto esters. Biginelli reaction has also been catalyzed by a simple chiral secondary amine and achiral bronsted acid by dual activation route,[25] leading to products upto 98% *ee*. Recently, enantioselective (*ee* up to 99%) multicomponent Biginelli reactions catalyzed by chiral catalysts in combination with a Bronsted acid[26] or organocatalyst[27] have been reported. However, in many instances, the reactions lack practicability owing to high cost of catalysts and/or tedious preparative routes. Further, availability of characteristic data of both the enantiomers, which is often required for comparison purposes has been lacking as the reactions are enantioselective. In continuation of our interest toward the structural diversification of DHPMs,[28] herein we have developed a reaction to append a readily available amino acid based chiral auxiliary (CA) at N-1 and N-3 of DHPMs.

2. Result and discussion

We employed *N*-acylation reaction[29] with an optically pure amino acid chloride **7** as electrophile to obtain diastereomeric DHPMs, which subsequent to the removal of the chiral auxiliary furnished both enantiomers of DHPMs. The chiral amino acid chloride **7** could be easily prepared in optically pure form using a reported protocol.[30] In order to position the chiral auxiliary at the two different nitrogen centers of DHPM **6**, we chose both, N-1 unsubstituted and N-1 methyl substituted DHPM. Substitution variation at C-4 position of DHPM by way of choosing bulkier as well as simple alkyl substituents, has also been undertaken to see the effect on resolution outcome (Scheme 1).

Thus, appropriate DHPMs **6a**–**c** (R^3=H), unsubstituted at N-1 position, were treated with *n*-BuLi (1.1 equiv) in anhydrous THF at low temperature (−78 °C) under an atmosphere of dry nitrogen and reaction mixture was stirred for 0.5 h. The pale yellow colored anion was than quenched with the drop wise addition of the acid chloride **7** (1.5 equiv) in anhydrous THF at −78 °C. The reaction was allowed to warm to room temperature and stirred until completion of the reaction (TLC) and then treated with a saturated aqueous solution of ammonium chloride at −78 °C (Scheme 1) and the diastereomeric mixture comprising of **8**–**10a** and **8**–**10b**, which resolved on TLC, was carefully chromatographed leading to the isolation of the diastereomers **8**–**10a** and **8**–**10b** in moderate to good yields (Table 1). The characteristic feature of the ^{1}H NMR spectra of **8**–**10a/b** included the appearance of doublet in case of **8** and **9** and multiplet in case of **10**, which corresponds to C4-H. The appearance of signal corresponding to N3-H and absence of resonance corresponding to N1-H are the other features of the spectrum.

Likewise, when metalated DHPMs, substituted at N-1 position **6d**–**e** (R^3=Me) were similarly reacted with chiral auxiliary **7** using similar set of reaction conditions [*n*-BuLi (1.1 equiv)/−78 °C, **7** (1.5 equiv)/−78 °C], corresponding diastereomers **11**–**12a/b** were isolated through column chromatography (Table 1). The characteristic features of the ^{1}H NMR spectrum of diastereomers **11**–**12a/b** included the presence of singlet signals corresponding to C4-H accompanied by the absence of N3-H resonance. Thus, it has been observed that in the reaction of N-1 unsubstituted DHPM **6a**–**c** (R^3=H), with chiral auxiliary **7**, substitution proceeded at N-1 position while the N-1 substituted DHPM **6d**–**e** (R^3=Me) furnished, N-3 substituted diastereomers upon reaction with **7**. In addition to the specific NMR characteristics of N-1 (**8**–**10**) and N-3 (**11**–**12**) another characteristic feature was the presence of an ABX splitting pattern of CH_2 and CH of the chiral auxiliary. Further, it was also observed that in case of N-1 substituted DHPMs **6d**–**e**, reaction proceeded smoothly, without formation of any byproducts, but in case of N-1 unsubstituted DHPMs **6a**–**c**, corresponding N1,N3-disubstituted DHPM were formed, which led to lowering of



a. R^1 = 3,4,5-$(OMe)_3C_6H_2$, R^2 = Et, R^3 = H
b. R^1 = C_6H_5, R^2 = Et, R^3 = H
c. R^1 = CH_3, R^2 = Et, R^3 = H
d. R^1 = C_6H_5, R^2 = Et, R^3 = Me
e. R^1 = C_6H_5, R^2 = *i*-Pr, R^3 = Me

8 a/b. R^1 = 3,4,5-$(OMe)_3C_6H_2$, R^2 = Et, R^3 = CA, R^4 = H
9 a/b. R^1 = C_6H_5, R^2 = Et, R^3 =CA, R^4 = H
10 a/b. R^1 = CH_3, R^2 = Et, R^3 = CA, R^4 = H
11 a/b. R^1 = C_6H_5, R^2 = Et, R^3 = Me, R^4 = CA
12 a/b. R^1 = C_6H_5, R^2 = *i*-Pr, R^3 = Me, R^4 = CA

Scheme 1. Synthesis of diastereomers of 3,4-dihydropyrimidin-2(1*H*)-ones.

Table 1
Synthesis of diastereomers **8**–**12** from racemic DHPMs

Entry	R^1	R^2	R^3	R^4	Product[a]	Yield (%)	$[\alpha]_D^{20}$ (CH_2Cl_2)
1.	3,4,5-$(OMe)_3C_6H_2$	C_2H_5	CA	H	**8a**	40	+180° (*c*=0.1)
2.	3,4,5-$(OMe)_3C_6H_2$	C_2H_5	CA	H	**8b**	42	+60° (*c*=0.1)
3.	C_6H_5	C_2H_5	CA	H	**9a**	40	+175° (*c*=0.2)
4.	C_6H_5	C_2H_5	CA	H	**9b**	38	−185° (*c*=0.2)
5.	CH_3	C_2H_5	CA	H	**10a**	30	+15° (*c*=0.2)
6.	CH_3	C_2H_5	CA	H	**10b**	28	+5° (*c*=0.2)
7.	C_6H_5	C_2H_5	CH_3	CA	**11a**	52	+205° (*c*=0.2)
8.	C_6H_5	C_2H_5	CH_3	CA	**11b**	48	−245° (*c*=0.2)
9.	C_6H_5	$CH(CH_3)_2$	CH_3	CA	**12a**	45	+160° (*c*=0.2)
10.	C_6H_5	$CH(CH_3)_2$	CH_3	CA	**12b**	44	−250° (*c*=0.2)

[a] (i) *n*-BuLi/THF/−78 °C; (ii) **7**/−78 °C to r.t.; (iii) NH_4Cl/−78 °C.

the isolated yield of **8**–**10** (Table 1). The specific optical rotation of all the diastereomers were recorded using dichloromethane as solvent and are mentioned in Table 1.

The assignment of the absolute configuration at C-4 position of a series of DHPM derivatives, has been based on the combination of enantioselective HPLC and circular dichroism (CD) spectroscopy,[19e,f] through correlation with DHPM derivatives of known configuration.[19b,c] The correlation of specific optical rotation has also been used for predicting the configuration at C-4. Since the chiral auxiliary used in this reaction has (*S*)-configuration at the chiral carbon, the diastereomers **8**–**12a** and **8**–**12b** have been assigned, (*S*)- and (*R*)- configuration, respectively, at C-4.

Reductive deacylation of the diastereomers **8**–**12** was accomplished using lithium aluminum hydride ($LiAlH_4$) (Scheme 2). Thus, treatment of **8**–**12a**/**b** with $LiAlH_4$ at 0 °C in anhydrous THF under the atmosphere of dry nitrogen gas furnished corresponding **13**–**17a**/**b** in good yield. The superimposable spectral data of compounds having equal and opposite specific optical rotations (Table 2) confirmed the formation of enantiomers of **13**–**17**. The plausible mechanism of reduction deacylation is outlined in Scheme 3. The initially formed **18** might get further reduced to *N*-phthalimido protected amino alcohol **19** by action of the excess $LiAlH_4$ used in the reaction.

The absolute configuration (*S*)- and (*R*)- at the C-4 of enantiomers **13**–**17a** and **13**–**17b**, respectively, was assigned in analogy with the sign of optical rotation of the known (*S*)- and (*R*)- enantiopure DHPMs.[22,26] The absolute configuration at C-4 of **13**, **14**, **15**, **16**, **17a**–**b** were also confirmed by recording CD spectra of the enantiomers and comparing them with enantiomers of known absolute configuration. Fig. 2 shows the CD spectra of both enantiomers of DHPM **13**, **14**, **15**, **16** and **17**. Based on comparison with reference CD spectra of DHPMs with known absolute configuration,[19d] enantiomers showing a positive cotton effect around 288 and 300 nm were assigned the (*S*)-configuration and those with mirror image CD spectrum, were assigned the (*R*)-configuration at the C-4. This data corroborated well with the optical rotation data (Table 2).

The enantiomeric purity of enantiomers **13**–**17a** and **13**–**17b** was determined by chiral HPLC using chiracel ODH column and is reported in the Supplementary data. The aryl substituted compounds depicted *ee* upto 99.9% (entry 7, Table 2), however, in case of C-4 alkyl substituted derivative (entries 5 and 6, Table 2), it was miserably low.

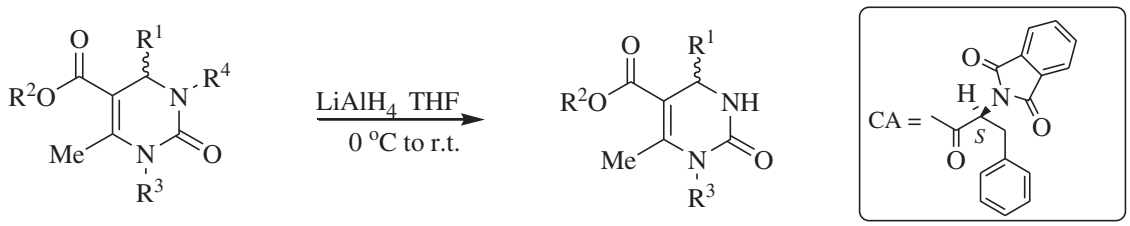
3. Conclusion

Thus, diastereomers of inherently racemic DHPMs were resolved using chiral auxiliary, which after chromatographic separation and removal of chiral auxiliary furnished both enantiomers of DHPMs. DHPMs bearing both aryl and alkyl groups at C-4 position could be resolved using this methodology. Absolute configuration of the enantiomers has also been assigned.

4. Experimental

4.1. General information

All liquid reagents were dried/purified following recommended drying agents and/or distilled over 4 Å molecular sieves. ^1H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were recorded in



Configuration at C-4
8-12a: (*S*)-
8-12b: (*R*)-

Configuration at C-4
13-17a: (*S*)-
13-17b: (*R*)-

8a/b. R^1 = 3,4,5-$(OMe)_3C_6H_2$, R^2 = Et, R^3 = CA, R^4 = H
9a/b. R^1 = Ph, R^2 = Et, R^3 =CA, R^4 = H
10a/b. R^1 = Me, R^2 = Et, R^3 = CA, R^4 = H
11a/b. R^1 = Ph, R^2 = Et, R^3 = Me, R^4 = CA
12a/b. R^1 = Ph, R^2 = *i*-Pr, R^3 = Me, R^4 = CA

13a/b. R^1 = 3,4,5-$(OMe)_3C_6H_2$, R^2 = Et, R^3 = H
14a/b. R^1 = Ph, R^2 = Et, R^3 = H
15a/b. R^1 = Me, R^2 = Et, R^3 = H
16a/b. R^1 = Ph, R^2 = Et, R^3 = Me
17a/b. R^1 = Ph, R^2 = *i*-Pr, R^3 = Me

Scheme 2. Synthesis of enantiomers of 3,4-dihydropyrimidin-2(1*H*)-ones.

Table 2
Specific optical rotation and enantiomeric excess of enantiomer **13**–**17**

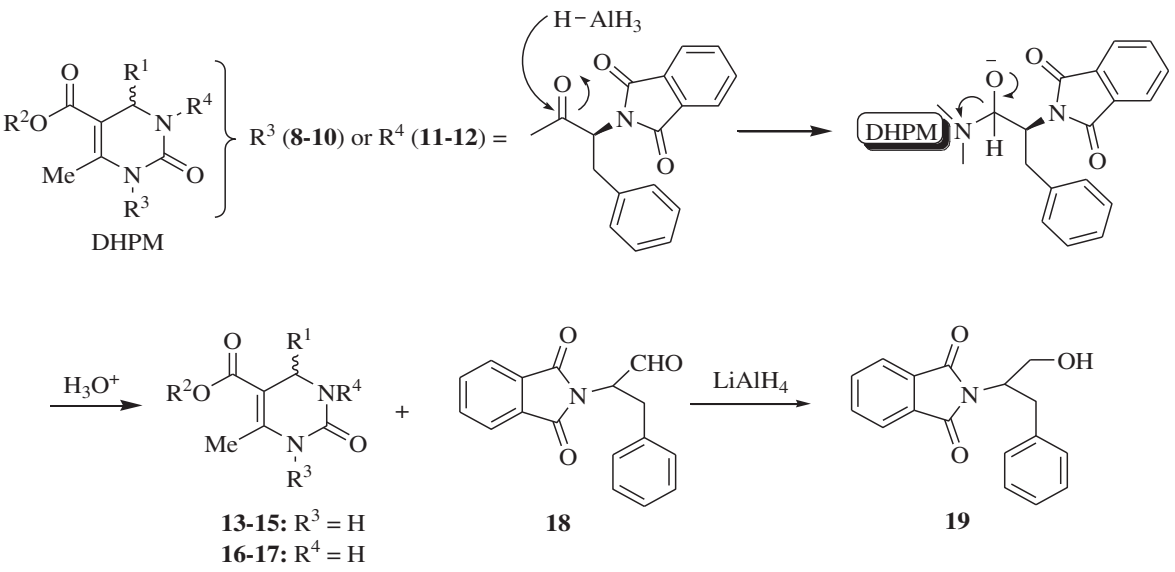
Entry	R^1	R^2	R^3	Product[a]	Yield (%)	$[\alpha]_D^{20}$ (MeOH)	*ee* (%)[b]
1.	3,4,5-$(OMe)_3C_6H_2$	C_2H_5	H	**13a**	90	+30° (*c*=0.2)	96.2
2.	3,4,5-$(OMe)_3C_6H_2$	C_2H_5	H	**13b**	90	−30° (*c*=0.1)	97.4
3.	C_6H_5	C_2H_5	H	**14a**	70	+50° (*c*=0.1)	86.8
4.	C_6H_5	C_2H_5	H	**14b**	70	−50° (*c*=0.1)	83.5
5.	CH_3	C_2H_5	H	**15a**	70	−15° (*c*=0.1)	45.7
6.	CH_3	C_2H_5	H	**15b**	65	+14° (*c*=0.1)	41.7
7.	C_6H_5	C_2H_5	CH_3	**16a**	80	−40° (*c*=0.2)	99.9
8.	C_6H_5	C_2H_5	CH_3	**16b**	75	+40° (*c*=0.2)	89.7
9.	C_6H_5	$CH(CH_3)_2$	CH_3	**17a**	70	−24° (*c*=0.2)	97.0
10.	C_6H_5	$CH(CH_3)_2$	CH_3	**17b**	65	+25° (*c*=0.2)	96.0

[a] $LiAlH_4$/THF/0 °C to r.t.
[b] Enantiomeric excess determined from HPLC using chiracel ODH column (4.6 mm×250 mm, particle size 5 μM).

DMSO-d_6 and $CDCl_3$ on a multinuclear Bruker–Jeol FT-AL-300 instruments with chemical shifts being reported in parts per million (δ) relative to internal tetramethylsilane (TMS, δ 0.0, ^{1}H NMR) or ($CDCl_3$, δ 77.0, ^{13}C NMR). Mass spectra were recorded from Indian Institute of Integrative Medicine (CSIR), Jammu, under electron impact at 70 eV on a Bruker Daltonics Esquire 3000 spectrometer. Elemental analysis was performed on FLASH EA 112 (Thermoelectron Corporation) analyzer at the Department of Chemistry, Guru Nanak Dev University, Amritsar and the results are quoted in %. IR recorded on FTIR Shimadzu 8400 Fourier-transform spectrophotometer in the range 400–4000 cm^{-1} using KBr. The optical rotation was recorded on Atago (AP-100) digital polarimeter at 25 °C. The CD spectra were recorded on Applied Photophysics Chirascan Circular Dichrosim Spectrometer. Enantiomeric excess was determined from chiral HPLC using chiracel ODH column (4.6 mm×250 mm, particle size 5 μM). Melting points were determined in open capillaries and are uncorrected. Pre-coated aluminum sheets Merck ($60F_{254}$, 0.2 mm) and silica gel (60–120 mesh) were employed for TLC and column chromatography, respectively.

4.2. Synthesis of diastereomers of DHPMs 6a–e

To a suspension of DHPM **6** (5.0 mmol) in 50 ml dry THF under a blanket of dry N_2, 2.1 N *n*-BuLi (5.5 mmol) was added drop wise



Scheme 3. Plausible mechanism of deacylation of **8**–**12**.

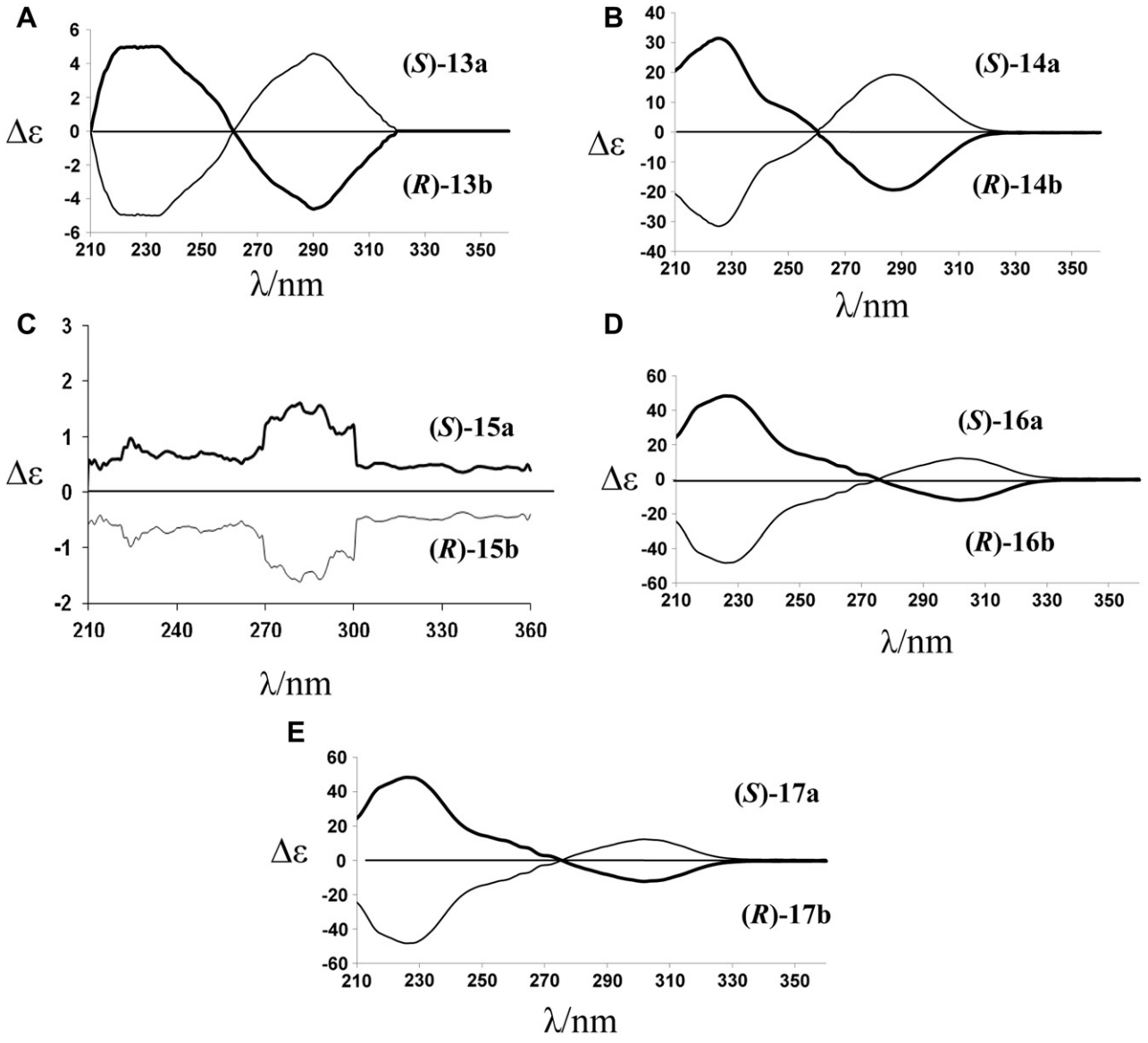


Fig. 2. CD spectra of **13**–**17**.

at −78 °C, whereupon pale yellow anion was formed. After the addition, reaction mixture was stirred at −78 °C for 30 min and quenched at −78 °C with enantiopure amino acid chloride **7** (7.5 mmol), dissolved in 10 ml dry THF. The reaction was stirred at same low temperature till it was completed (TLC). A cold saturated aqueous solution of NH_4Cl (30 ml) was introduced at the same low temperature. The reaction contents were extracted with ethyl acetate (3×25 ml), treated with brine, washed with water (2×25 ml), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The diastereomers were separated by column chromatography using silica gel-G (230–400 mesh) and mixtures of ethyl acetate/hexane as eluent.

*4.2.1. 5-Ethoxycarbonyl-6-methyl-4(S)-(3,4,5-trimethoxyphenyl)-1-[2(S)-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-3-phenylpropionyl]-3,4-dihydropyrimidin-2(1H)-one (**8a**).* White solid; [Found: C, 64.99; H, 5.35; N, 6.35. $C_{34}H_{33}N_3O_9$ requires C, 65.07; H, 5.26; N, 6.70%]; R_f: (60% EtOAc/Hexane) 0.7; mp 183 °C (methanol); $[\alpha]_D^{20}$+180° (*c* 0.1, CH_2Cl_2); ν_{max} (KBr) 3294, 2938, 1720, 1648, 1464, 1228 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.74 (2H, m, ArH), 7.67 (2H, m, ArH), 7.19 (5H, m, ArH), 6.44 (2H, s, ArH), 6.29 (1H, dd, *J* 4.5 Hz, *J* 4.5 Hz, CH), 6.20 (1H, d, *J* 3.9 Hz, exchanged with D_2O, N3-H), 5.35 (1H, d, *J* 3.9 Hz, C4-H), 4.21 (2H, q, *J* 7.2 Hz, ester−CH_2), 3.80 (1H, dd, *J* 6.0 Hz, *J* 13.8 Hz, CH), 3.79 (3H, s, OCH_3), 3.73 (1H, dd, *J* 2.4 Hz, *J* 17.4 Hz, CH), 3.69 (6H, s, 2×OCH_3), 2.51 (3H, s, C6-CH_3), 1.27 (3H, t, *J* 7.2 Hz, ester−CH_3); δ_C (75 MHz, $CDCl_3$) 172.1, 167.8, 164.6, 153.5, 151.3, 147.0, 137.5, 136.8, 135.3, 134.0, 131.4, 128.7, 128.5, 126.8, 123.3, 115.4, 103.0, 61.2, 60.7, 59.1, 55.9, 54.8, 34.1, 19.6, 14.1; *m*/*z* 650 (M^++23).

*4.2.2. 5-Ethoxycarbonyl-6-methyl-4(R)-(3,4,5-trimethoxyphenyl)-1-[2(S)-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-3-phenylpropionyl]-3,4-dihydropyrimidin-2(1H)-one (**8b**).* White solid; [Found: C, 64.78; H, 5.58; N, 6.40. $C_{34}H_{33}N_3O_9$ requires C, 65.07; H, 5.26; N, 6.70%]; R_f: (60% EtOAc/Hexane) 0.6; mp 150 °C (methanol); $[\alpha]_D^{20}$+60° (*c* 0.1, CH_2Cl_2); ν_{max} (KBr) 3264, 2937, 1728, 1642, 1462, 1236 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.77 (2H, m, ArH), 7.67 (2H, m, ArH), 7.14 (5H, m, ArH), 6.45 (2H, s, ArH), 6.07 (1H, d, *J* 3.6 Hz, exchanged with D_2O, N3-H), 5.90 (1H, dd, *J* 6.0 Hz, *J* 5.7 Hz, CH), 5.25 (1H, d, *J* 3.9 Hz, C4-H), 4.18 (2H, q, *J* 7.2 Hz, ester−CH_2), 3.80 (3H, s, OCH_3), 3.73 (6H, s, 2×OCH_3), 3.41 (1H, dd, *J* 6.0 Hz, *J* 5.7 Hz, CH), 3.30 (1H, dd, *J* 9.6 Hz, *J* 9.6 Hz, CH), 2.54 (3H, s, C6-CH_3), 1.23 (3H, t, *J* 7.2 Hz, ester−CH_3); δ_C (75 MHz, $CDCl_3$) 171.1, 167.2, 164.8, 153.6, 151.3, 137.5, 136.4, 135.0,

134.0, 131.6, 129.1, 128.3, 126.8, 123.4, 103.4, 61.1, 60.7, 57.4, 56.0, 54.7, 35.2, 19.0, 14.1; *m*/*z* 650 (M^++23).

*4.2.3. 5-Ethoxycarbonyl-6-methyl-4(S)-phenyl-1-[2(S)-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-3-phenylpropionyl]-3,4-dihydropyrimidin-2(1H)-one (**9a**).* White solid; [Found: C, 69.10; H, 4.82; N, 7.62. $C_{31}H_{27}N_3O_6$ requires C, 69.27; H, 5.03; N, 7.82%]; R_f: (40% EtOAc/Hexane) 0.5; mp 105 °C (methanol); $[\alpha]_D^{20}$+175° (*c* 0.2, CH_2Cl_2); ν_{max} (KBr) 3280, 2960, 1711, 1648, 1375, 1220 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.75 (2H, m, ArH), 7.67 (2H, m, ArH), 7.20 (10H, m, ArH), 6.28 (1H, dd, *J* 5.4 Hz, *J* 5.4 Hz, CH), 5.96 (1H, d, *J* 3.6 Hz, exchanged with D_2O, N3-H), 5.42 (1H, d, *J* 3.3 Hz, C4-H), 4.17 (2H, m, ester−CH_2), 3.75 (2H, dd, *J* 2.1 Hz, *J* 7.5 Hz, CH_2), 2.50 (3H, s, C6-CH_3), 1.22 (3H, t, *J* 7.2 Hz, ester−CH_3); δ_C (75 MHz, $CDCl_3$) 171.2, 167.6, 153.6, 150.7, 136.9, 134.0, 131.5, 129.1, 128.6, 128.3, 126.8, 126.4, 123.3, 105.7, 60.6, 57.3, 54.8, 34.0, 17.8, 14.1; *m*/*z* 560 (M^++23).

*4.2.4. 5-Ethoxycarbonyl-6-methyl-4(R)-phenyl-1-[2(S)-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-3-phenylpropionyl]-3,4-dihydropyrimidin-2(1H)-one (**9b**).* White solid; [Found: C, 68.92; H, 4.70; N, 7.52. $C_{31}H_{27}N_3O_6$ requires C, 69.27; H, 5.03; N, 7.82%]; R_f: (40% EtOAc/Hexane) 0.3; mp 115 °C (methanol); $[\alpha]_D^{20}$−185° (*c* 0.2, CH_2Cl_2); ν_{max} (KBr) 3293, 2981, 1719, 1650, 1382, 1229 cm^{-1} δ_H (300 MHz, $CDCl_3$) 7.76 (2H, m, ArH), 7.66 (2H, m, ArH), 7.27 (10H, m, ArH), 6.07 (1H, dd, *J* 4.5 Hz, *J* 4.5 Hz, CH), 5.92 (1H, d, *J* 3.4 Hz, exchanged with D_2O, N3-H), 5.40 (1H, d, *J* 3.2 Hz, C4-H), 4.15 (2H, q, *J* 7.2 Hz, ester−CH_2), 3.57 (2H, m, CH_2), 2.55 (3H, s, C6-CH_3), 1.22 (3H, t, *J* 7.2 Hz, ester−CH_3); δ_C (75 MHz, $CDCl_3$) 172.3, 166.9, 152.9, 150.4, 135.9, 133.5, 131.9, 129.6, 128.8, 128.2, 127.0, 126.5, 122.9, 105.5, 60.4, 57.3, 54.6, 34.1, 17.7, 14.1; *m*/*z* 560 (M^++23).

*4.2.5. 5-Ethoxycarbonyl-4(S),6-dimethyl-1-[2(S)-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-3-phenylpropionyl]-3,4-dihydropyrimidin-2(1H)-one (**10a**).* White solid; [Found: C, 65.50; H, 5.10; N, 8.54. $C_{26}H_{25}N_3O_6$ requires C, 65.68; H, 5.26; N, 8.84%]; R_f: (40% EtOAc/Hexane) 0.4; mp 180 °C (methanol); $[\alpha]_D^{20}$+15° (*c* 0.2, CH_2Cl_2); ν_{max} (KBr) 3373, 1703, 1442, 1385, 1240 cm^{-1} δ_H (300 MHz, $CDCl_3$) 7.76 (2H, m, ArH), 7.66 (2H, m, ArH), 7.16 (5H, m, ArH), 6.22 (1H, dd, *J* 4.2 Hz, *J* 4.5 Hz, CH), 5.72 (1H, d, *J* 4.2 Hz, exchanged with D_2O, N3-H), 4.35 (1H, m, C4-H), 4.26 (2H, m, ester−CH_2), 3.76 (2H, m, CH_2), 2.43 (3H, s, C6-CH_3), 1.31 (3H, t, *J* 7.2 Hz, ester−CH_3), 1.24 (3H, d, *J* 6.6 Hz, C4-CH_3); δ_C (75 MHz, $CDCl_3$) 171.4, 167.9, 164.7, 152.3, 146.8, 137.0, 133.9, 131.6, 128.8, 128.4, 126.7, 123.3, 117.6, 60.9, 58.7, 47.0, 34.0, 22.4, 19.3, 14.1; *m*/*z* 498 (M^++23).

*4.2.6. 5-Ethoxycarbonyl-4(R),6-dimethyl-1-[2(S)-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-3-phenylpropionyl]-3,4-dihydropyrimidin-2(1H)-one (**10b**).* White solid; [Found: C, 65.40; H, 5.12; N, 8.60. $C_{26}H_{25}N_3O_6$ requires C, 65.68; H, 5.26; N, 8.84%]; R_f: (40% EtOAc/Hexane) 0.3; mp 173 °C (methanol); $[\alpha]_D^{20}$+5° (*c* 0.2, CH_2Cl_2); ν_{max} (KBr) 3216, 1723, 1647, 1495, 1341, 1241 cm^{-1} δ_H (300 MHz, $CDCl_3$) 7.76 (2H, m, ArH), 7.67 (2H, m, ArH), 7.19 (5H, m, ArH), 5.97 (1H, t, *J* 7.8 Hz, CH), 5.91 (1H, d, *J* 4.8 Hz, exchanged with D_2O, N3-H), 4.31 (1H, m, C4-H), 4.24 (2H, m, ester−CH_2), 3.49 (2H, d, *J* 7.8 Hz, CH_2), 2.46 (3H, s, C6-CH_3), 1.31 (3H, t, *J* 7.2 Hz, ester−CH_3), 1.25 (3H, d, *J* 6.3 Hz, C4-CH_3); δ_C (75 MHz, $CDCl_3$) 170.1, 167.4, 164.8, 152.6, 147.4, 145.9, 136.5, 133.9, 131.6, 129.1, 128.4, 126.8, 123.3, 118.6, 60.9, 57.2, 46.9, 35.0, 22.2, 19.2, 14.2; *m*/*z* 498 (M^++23).

*4.2.7. 5-Ethoxycarbonyl-1,6-dimethyl-3-[2(S)-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-3-phenylpropionyl]-4(S)-phenyl-3,4-dihydropyrimidin-2(1H)-one (**11a**).* White solid; [Found: C, 69.57; H, 4.90; N, 7.47. $C_{32}H_{29}N_3O_6$ requires C, 69.69; H, 5.26; N, 7.62%]; R_f: (40% EtOAc/Hexane) 0.5; mp 98 °C (methanol/petroleum ether); $[\alpha]_D^{20}$+205° (*c* 0.2, CH_2Cl_2); ν_{max} (KBr) 3220, 2982, 1625, 1469, 1289 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.76 2H, (m, ArH), 7.64 (2H, m, ArH), 7.21 (10H, m, ArH), 6.63 (1H, dd, *J* 4.5 Hz, *J* 4.5 Hz, CH), 6.54 (1H, s, C4-H), 4.22 (2H, m, ester−CH_2), 3.82 (1H, dd, *J* 11.4 Hz, *J* 11.4 Hz, CH), 3.31 (1H, d, *J* 4.2 Hz, CH), 3.27 (3H, s, N1-CH_3), 2.56 (3H, s, C6-CH_3), 1.27 (3H, t, *J* 7.2 Hz, ester−CH_3); δ_C (75 MHz, $CDCl_3$) 170.7, 168.2, 165.0, 151.9, 148.2, 138.5, 136.7, 133.8, 131.7, 128.8, 128.6, 128.4, 128.0, 126.8, 126.4, 123.3, 109.4, 60.8, 57.0, 53.2, 34.1, 31.4, 16.2, 14.1; *m*/*z* 552 (M^++1).

*4.2.8. 5-Ethoxycarbonyl-1,6-dimethyl-3-[2(S)-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-3-phenylpropionyl]-4(R)-phenyl-3,4-dihydropyrimidin-2(1H)-one (**11b**).* White solid; [Found: C, 69.76; H, 5.34; N, 7.30. $C_{32}H_{29}N_3O_6$ requires C, 69.69; H, 5.26; N, 7.62%]; R_f: (40% EtOAc/Hexane) 0.3; mp 158 °C (methanol); $[\alpha]_D^{20}$−245° (*c* 0.2, CH_2Cl_2); ν_{max} (KBr) 3023, 1719, 1647, 1494, 1290 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.76 (2H, m, ArH), 7.67 (2H, m, ArH), 7.23 (10H, m, ArH), 6.67 (1H, s, C4-H), 5.98 (1H, dd, *J* 6.3 Hz, *J* 6.6 Hz, CH), 4.19 (2H, m, ester−CH_2), 3.70 (2H, m, CH_2), 3.03 (3H, s, N1-CH_3), 2.36 (3H, s, C6-CH_3), 1.24 (3H, t, *J* 7.2 Hz, ester−CH_3); δ_C (75 MHz, $CDCl_3$) 171.3, 167.4, 164.9, 151.5, 148.3, 138.6, 137.0, 133.9, 131.4, 129.2, 128.6, 128.3, 128.0, 126.6, 126.3, 123.3, 109.3, 60.7, 56.8, 52.3, 34.3, 31.1, 15.8, 14.1; *m*/*z* 574 (M^++23).

*4.2.9. 5-Isopropoxycarbonyl-1,6-dimethyl-3-[2(S)-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-3-phenylpropionyl]-4(S)-phenyl-3,4-dihydropyrimidin-2(1H)-one (**12a**).* White solid; [Found: C, 69.95; H, 5.59; N, 7.11$C_{33}H_{31}N_3O_6$ requires C, 70.08; H, 5.48; N, 7.43%]; R_f: (40% EtOAc/Hexane) 0.5; mp 100 °C (methanol/petroleum ether); $[\alpha]_D^{20}$+160° (*c* 0.2, CH_2Cl_2); ν_{max} (KBr) 3473, 2979, 1720, 1639, 1382, 1239 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.76 (2H, m, ArH), 7.64 (2H, m, ArH), 7.18 (10H, m, ArH), 6.64 (1H, dd, *J* 4.2 Hz, *J* 4.2 Hz, CH), 6.49 (1H, s, C4-H), 5.07 (1H, m, CH), 3.83 (1H, t, *J* 13.2 Hz, CH), 3.32 (1H, d, *J* 4.2 Hz, CH), 3.27 (3H, s, N1-CH_3), 2.55 (3H, s, C6-CH_3), 1.32 (3H, d, *J* 6.3 Hz, CH_3), 1.16 (3H, d, *J* 6.3 Hz, CH_3); δ_C (75 MHz, $CDCl_3$) 170.7, 168.2, 164.5, 151.9, 147.8, 138.7, 136.7, 133.8, 131.7, 128.8, 128.5, 128.4, 127.9, 126.7, 126.5, 123.3, 109.9, 68.5, 57.1, 53.4, 34.0, 31.4, 21.9, 21.7, 16.2; *m*/*z* 588 (M^++23).

*4.2.10. 5-Isopropoxycarbonyl-1,6-dimethyl-3-[2(S)-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-3-phenylpropionyl]-4(R)-phenyl-3,4-dihydropyrimidin-2(1H)-one (**12b**).* White solid; [Found: C, 69.88; H, 5.31; N, 7.30. $C_{33}H_{31}N_3O_6$ requires C, 70.08; H, 5.48; N, 7.43%]; R_f: (40% EtOAc/Hexane) 0.3; mp 125 °C (methanol/petroleum ether); $[\alpha]_D^{20}$−250° (*c* 0.2, CH_2Cl_2); ν_{max} (KBr) 3474, 3025, 1719, 1642, 1384, 1288 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.76 (2H, m, ArH), 7.67 (2H, m, ArH), 7.22 (10H, m, ArH), 6.64 (1H, s, C4-H), 6.00 (1H, dd, *J* 5.4 Hz, *J* 5.7 Hz, CH), 5.05 (1H, m, CH), 3.70 (2H, dd, *J* 6.0 Hz, *J* 9.3 Hz, CH_2), 3.05 (s, 3H, N1-CH_3), 2.36 (3H, s, C6-CH_3), 1.28 (3H, d, *J* 6.3 Hz, CH_3), 1.15 (3H, d, *J* 6.3 Hz, CH_3); δ_C (75 MHz, $CDCl_3$) 171.4, 167.4, 164.5, 151.6, 147.9, 138.8, 137.1, 133.9, 131.4, 129.1, 128.6, 128.3, 127.9, 126.6, 126.3, 123.3, 109.7, 68.3, 56.9, 52.4, 34.2, 31.1, 21.9, 21.6, 15.8; *m*/*z* 588 (M^++23).

4.3. Reductive N1/N3-deacylation. Formation of enantiomers

To a solution of DHPM **8**–**12** (0.83 mmol) in dry THF (50 ml), $LiAlH_4$ (9.15 mmol) was added slowly at 0 °C. The reaction contents were warmed to room temperature and stirred till completion (TLC). The cold saturated aqueous solution of sodium potassium tartrate was introduced to terminate the reaction followed by treatment with brine. The extraction was done with ethyl acetate (3×25 ml), organic extracts were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The enantiomers were separated by column chromatography using silica gel-G (60–120 mesh) and mixtures of ethyl acetate/hexane as eluent.

*4.3.1. 5-Ethoxycarbonyl-6-methyl-4(S)-(3,4,5-trimethoxyphenyl)-3,4-dihydropyrimidin-2(1H)-one (**13a**).* Colorless solid; [Found: C, 58.10; H, 5.92; N, 7.74. $C_{17}H_{22}N_2O_6$ requires C, 58.28; H, 6.28; N, 8.00%]; R_f: (80% EtOAc/Hexane) 0.2; mp 185–186 °C (dichloromethane/hexane); $[\alpha]_D^{20}$+30° (*c* 0.2, MeOH); ν_{max} (KBr) 3232, 3100, 2934, 1708, 1664, 1589, 1463, 1285 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.33 (1H, br, exchanged with D_2O, N1-H), 6.53 (2H, s, ArH), 5.48 (1H, br, exchanged with D_2O, N3-H), 5.37 (1H, d, *J* 2.7 Hz, C4-H), 4.10 (2H, m, ester–CH_2), 3.82 (9H, s, 3×OCH_3), 2.36 (3H, s, C6-CH_3), 1.20 (3H, t, *J* 7.2 Hz, ester–CH_3); δ_C (75 MHz, $CDCl_3$) 165.6, 153.5, 153.3, 146.2, 139.3, 137.7, 103.6, 101.1, 60.7, 60.0, 56.0, 55.7, 18.3, 14.1; *m/z* 373 (M^++23); enantiomeric excess: 96.2% determined by HPLC (Chiracel OD-H column, hexane/2-propanol 90:10), λ=254 nm, flow rate 1.0 mL min^{-1}, t_R (major)=29.3 min, t_R (minor)=36.2 min.

*4.3.2. 5-Ethoxycarbonyl-6-methyl-4(R)-(3,4,5-trimethoxyphenyl)-3,4-dihydropyrimidin-2(1H)-one (**13b**).* Colorless solid; [Found: C, 57.92; H, 5.99; N, 7.74. $C_{17}H_{22}N_2O_6$ requires C, 58.28; H, 6.28; N, 8.00%]; R_f: (80% EtOAc/Hexane) 0.2; mp 183–184 °C (dichloromethane/hexane); $[\alpha]_D^{20}$−30° (*c* 0.2, MeOH); ν_{max} (KBr) 3262, 3110, 2954, 1719, 1668, 1579, 1468, 1282 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.64 (1H, br, exchanged with D_2O, N1-H), 6.53 (2H, s, ArH), 5.58 (1H, br, exchanged with D_2O, N3-H), 5.36 (1H, d, *J* 2.4 Hz, C4-H), 4.11 (2H, q, *J* 7.2 Hz, ester–CH_2), 3.82 (9H, s, 3×OCH_3), 2.35 (3H, s, C6-CH_3), 1.20 (3H, t, *J* 7.2 Hz, ester–CH_3); δ_C (75 MHz, $CDCl_3$) 165.6, 153.4, 153.3, 146.1, 139.3, 137.7, 103.6, 101.2, 60.7, 60.0, 56.1, 55.7, 18.5, 14.2; *m/z* 373 (M^++23); enantiomeric excess: 97.4% determined by HPLC (Chiracel OD-H column, hexane/2-propanol 90:10), λ=254 nm, flow rate 1.0 mL min^{-1}, t_R (minor)=30.0 min, t_R (major)=33.1 min.

*4.3.3. 5-Ethoxycarbonyl-6-methyl-4(S)-phenyl-3,4-dihydropyrimidin-2(1H)-one (**14a**).* Colorless solid; [Found: C, 64.40; H, 6.05; N, 10.35. $C_{14}H_{16}N_2O_3$ requires C, 64.61; H, 6.15; N, 10.77%]; R_f: (60% EtOAc/Hexane) 0.4; mp 205–207 °C (methanol); $[\alpha]_D^{20}$+50° (*c* 0.1, MeOH); ν_{max} (KBr) 3243, 3115, 1724, 1701, 1647, 1221, 1091 cm^{-1}; δ_H (300 MHz, $CDCl_3$ and DMSO-d_6) 8.65 (1H, br, exchanged with D_2O, N1-H), 7.27 (5H, m, ArH), 6.47 (1H, br, exchanged with D_2O, N3-H), 5.36 (1H, d, *J* 2.7 Hz, C4-H), 4.05 (2H, q, *J* 7.2 Hz, ester–CH_2), 2.33 (3H, s, C6-CH_3), 1.15 (3H, t, *J* 7.2 Hz, ester–CH_3); δ_C (75 MHz, $CDCl_3$ and DMSO-d_6) 164.4, 151.7, 146.6, 143.6, 127.0, 126.0, 125.3, 98.7, 58.1, 53.4, 16.8, 12.8; *m/z* 261 (M^++1); enantiomeric excess: 86.8% determined by HPLC (Chiracel OD-H column, hexane/2-propanol 90:10), λ=207 nm, flow rate 1.0 mL min^{-1}, t_R (minor)=10.3 min, t_R (major)=11.9 min.

*4.3.4. 5-Ethoxycarbonyl-6-methyl-4(R)-phenyl-3,4-dihydropyrimidin-2(1H)-one (**14b**).* Colorless solid; [Found: C, 64.44; H, 6.09; N, 10.44. $C_{14}H_{16}N_2O_3$ requires C, 64.61; H, 6.15; N, 10.77%]; R_f: (60% EtOAc/Hexane) 0.4; mp 212–214 °C (methanol); $[\alpha]_D^{20}$−50° (*c* 0.1, MeOH); ν_{max} (KBr) 3245, 3125, 1734, 1711, 1642, 1211 cm^{-1}; δ_H (300 MHz, $CDCl_3$ and DMSO-d_6) 8.82 (1H, br, exchanged with D_2O, N1-H), 7.26 (5H, m, ArH), 7.02 (1H, br, exchanged with D_2O, N3-H), 5.31 (1H, d, *J* 2.7 Hz, C4-H), 4.04 (2H, q, *J* 7.2 Hz, ester–CH_2), 2.32 (3H, s, C6-CH_3), 1.16 (3H, t, *J* 7.2 Hz, ester–CH_3); δ_C (75 MHz, $CDCl_3$ and DMSO-d_6) 164.6, 151.9, 146.7, 143.6, 127.1, 126.1, 125.4, 98.9, 58.3, 53.6, 17.0, 13.0; *m/z* 261 (M^++1); enantiomeric excess: 83.5% determined by HPLC (Chiracel OD-H column, hexane/2-propanol 90:10), λ=207 nm, flow rate 1.0 mL min^{-1}, t_R (major)=10.5 min, t_R (minor)=12.3 min.

*4.3.5. 5-Ethoxycarbonyl-4(S),6-dimethyl-3,4-dihydropyrimidin-2(1H)-one (**15a**).* Colorless solid; [Found: C, 54.29; H, 6.83; N, 13.80. $C_9H_{14}N_2O_3$ requires C, 54.54; H, 7.07; N, 14.14%]; R_f: (60% EtOAc/Hexane) 0.3; mp 176–178 °C (methanol); $[\alpha]_D^{20}$−15° (*c* 0.1, MeOH); ν_{max} (KBr) 3332, 2971, 1713, 1626, 1474, 1380, 1237 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.98 (1H, br, exchanged with D_2O, N1-H), 5.65 (1H, br, exchanged with D_2O, N3-H), 4.41 (1H, m, C4-H), 4.18 (2H, m, ester–CH_2), 2.28 (3H, s, C6-CH_3), 1.28 (3H, t, *J* 7.2 Hz, ester–CH_3), 1.26 (3H, d, *J* 5.1 Hz, C4-CH_3); δ_C (75 MHz, $CDCl_3$ and DMSO-d_6) 165.3, 153.5, 146.5, 101.1, 58.8, 46.4, 22.8, 17.5, 13.6; *m/z* 221 (M^++23); enantiomeric excess: 45.7% determined by HPLC (Chiracel OD-H column, hexane/2-propanol 90:10), λ=254 nm, flow rate 1.0 mL min^{-1}, t_R (major)=9.7 min, t_R (minor)=10.9 min.

*4.3.6. 5-Ethoxycarbonyl-4(R),6-dimethyl-3,4-dihydropyrimidin-2(1H)-one (**15b**).* Colorless solid; [Found: C, 54.25; H, 6.87; N, 13.85. $C_9H_{14}N_2O_3$ requires C, 54.54; H, 7.07; N, 14.14%]; R_f: (60% EtOAc/Hexane) 0.3; mp 180–182 °C (methanol); $[\alpha]_D^{20}$+14° (*c* 0.1, MeOH); ν_{max} (KBr) 3339, 2975, 1723, 1628, 1484, 1385, 1235 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.09 (1H, br, exchanged with D_2O, N1-H), 5.70 (1H, br, exchanged with D_2O, N3-H), 4.43 (1H, m, C4-H), 4.18 (2H, m, ester–CH_2), 2.28 (3H, s, C6-CH_3), 1.30 (6H, m, ester–CH_3 and C4-CH_3); δ_C (75 MHz, $CDCl_3$ and DMSO-d_6) 165.1, 153.5, 146.4, 100.9, 58.7, 13.5, 46.2, 22.7, 17.3; *m/z* 221 (M^++23); enantiomeric excess: 41.7% determined by HPLC (Chiracel OD-H column, hexane/2-propanol 90:10), λ=254 nm, flow rate 1.0 mL min^{-1}, t_R (minor)=10.1 min, t_R (major)=11.2 min.

*4.3.7. 5-Ethoxycarbonyl-1,6-dimethyl-4(S)-phenyl-3,4-dihydropyrimidin-2(1H)-one (**16a**).* Colorless solid; [Found: C, 65.39; H, 6.20; N, 9.98. $C_{15}H_{18}N_2O_3$ requires C, 65.69; H, 6.57; N, 10.22%]; R_f: (60% EtOAc/Hexane) 0.5; mp 140–142 °C (dichloromethane/hexane); $[\alpha]_D^{20}$−40° (*c* 0.2, MeOH); ν_{max} (KBr) 3230, 1685, 1624, 1439, 1346, 1299 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.28 (5H, m, ArH), 5.58 (1H, br, exchanged with D_2O, N3-H), 5.38 (1H, d, *J* 3.3 Hz, C4-H), 4.10 (2H, q, *J* 7.2 Hz, ester–CH_2), 3.23 (3H, s, N1-CH_3), 2.51 (3H, s, C6-CH_3), 1.18 (3H, t, *J* 7.2 Hz, ester–CH_3); δ_C (75 MHz, $CDCl_3$) 166.0, 154.0, 149.2, 143.3, 128.5, 127.5, 126.1, 104.1, 60.0, 53.6, 30.1, 16.4, 14.0; *m/z* 297 (M^++23); enantiomeric excess: 99.9% determined by HPLC (Chiracel OD-H column, hexane/2-propanol 90:10), λ=209 nm, flow rate 1.0 mL min^{-1}, t_R (minor)=14.5 min, t_R (major)=16.7 min.

*4.3.8. 5-Ethoxycarbonyl-1,6-dimethyl-4(R)-phenyl-3,4-dihydropyrimidin-2(1H)-one (**16b**).* Colorless solid; [Found: C, 65.35; H, 6.35; N, 9.95. $C_{15}H_{18}N_2O_3$ requires C, 65.69; H, 6.57; N, 10.22%]; R_f: (60% EtOAc/Hexane) 0.5; mp 133–135 °C (dichloromethane/hexane); $[\alpha]_D^{20}$+40° (*c* 0.2, MeOH); ν_{max} (KBr) 3220, 1683, 1621, 1435, 1341, 1298 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.28 (5H, m, ArH), 5.57 (1H, br, exchanged with D_2O, N3-H), 5.38 (1H, d, *J* 3.3 Hz, C4-H), 4.10 (2H, q, *J* 7.2 Hz, ester–CH_2), 3.23 (3H, s, N1-CH_3), 2.51 (3H, s, C6-CH_3), 1.18 (3H, t, *J* 7.2 Hz, ester–CH_3); δ_C (75 MHz, $CDCl_3$) 166.0, 154.0, 149.2, 143.3, 128.5, 127.6, 126.1, 104.1, 60.0, 53.6, 30.1, 16.4, 14.0; *m/z* 297 (M^++23); enantiomeric excess: 89.8% determined by HPLC (Chiracel OD-H column, hexane/2-propanol 90:10), λ=208 nm, flow rate 1.0 mL min^{-1}, t_R (major)=14.1 min, t_R (minor)=17.4 min.

*4.3.9. 5-Isopropoxycarbonyl-1,6-dimethyl-4(S)-phenyl-3,4-dihydropyrimidin-2(1H)-one (**17a**).* Colorless solid; [Found: C, 66.35; H, 6.75; N, 9.45. $C_{16}H_{20}N_2O_3$ requires C, 66.67; H, 6.94; N, 9.72%]; R_f: (80% EtOAc/Hexane) 0.7; mp 120 °C (dichloromethane/hexane); $[\alpha]_D^{20}$−24° (*c* 0.2, MeOH); ν_{max} (KBr) 3220, 3090, 2982, 1686, 1625, 1469, 1347, 1289 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.27 (5H, m, ArH), 5.76 (1H, br, exchanged with D_2O, N3-H), 5.37 (1H, d, *J* 3.0 Hz, C4-H), 4.97 (1H, m, ester–CH), 3.22 (3H, s, N1-CH_3), 2.50 (3H, s, C6-CH_3), 1.22 (3H, d, *J* 6.0 Hz, ester–CH_3), 1.04 (3H, d, *J* 6.3 Hz, ester–CH_3); δ_C (75 MHz, $CDCl_3$) 165.5, 154.0, 148.9, 143.4, 128.4, 127.5, 126.2, 104.4, 67.4, 53.7, 30.1, 21.9, 21.5, 16.3; *m/z* 311 (M^++23); enantiomeric excess: 97.0% determined by HPLC (Chiracel OD-H column, hexane/2-propanol 90:10), λ=254 nm, flow rate 1.0 mL min^{-1}, t_R (minor)=11.0 min, t_R (major)=13.8 min.

*4.3.10. 5-Isopropoxycarbonyl-1,6-dimethyl-4(R)-phenyl-3,4-dihydropyrimidin-2(1H)-one (**17b**).* Colorless solid; [Found: C,

66.45; H, 6.57; N, 9.53. $C_{16}H_{20}N_2O_3$ requires C, 66.67; H, 6.94; N, 9.72%]; R_f: (80% EtOAc/Hexane) 0.7; mp 123–125 °C (dichloromethane/hexane); $[\alpha]_D^{20}$ +25° (*c* 0.2, MeOH); ν_{max} (KBr) 3210, 3099, 2972, 1676, 1620, 1455, 1337, 1279 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.25 (5H, m, ArH), 5.54 (1H, br, exchanged with D_2O, N3-H), 5.37 (1H, d, *J* 3.0 Hz, C4-H), 4.97 (1H, m, ester–CH), 3.23 (3H, s, N1-CH_3), 2.51 (3H, s, C6-CH_3), 1.22 (3H, d, *J* 6.3 Hz, ester–CH_3), 1.04 (3H, d, *J* 6.0 Hz, ester–CH_3); δ_C (75 MHz, $CDCl_3$) 165.5, 153.9, 148.9, 143.4, 128.5, 127.6, 126.2, 104.5, 67.5, 53.9, 30.1, 21.9, 21.5, 16.4; *m*/*z* 311 (M^++23); enantiomeric excess: 96.0% determined by HPLC (Chiracel OD-H column, hexane/2-propanol 90:10), λ=254 nm, flow rate 1.0 mL min^{-1}, t_R (major)=10.7 min, t_R (minor)=14.0 min.

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Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.tet.2012.05.073.

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