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Chemical resolution of inherently racemic dihydropyrimidinones via a site selective functionalization of Biginelli compounds with chiral electrophiles: a case study

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ABSTRACT

Lithiation/substitution of 4-aryl-6-methyl-3,4-dihydropyrimidin-2(1*H*)-one ester derivatives with *n*-BuLi can be directed selectively at N-3 or C-6 positions, depending upon nature and equivalents of the base used and 'hardness or softness' of the metalated site/electrophile used. Biginelli dihydropyrimidinone substrate appended with enantiopure *N*-protected L-phenylalanine amino acid chloride, at N-3 position after resolution and deprotection yielded both enantiomers of 3,4-dihydropyrimidinones.

1. Introduction

The Biginelli reaction, known for over 100 years,[1] is much sought after multicomponent reaction for accessing dihydropyrimidinones (DHPMs). Dihydropyrimidinones are a class of heterocyclic compounds[2] that possess wide ranging biological activities.[3] Many derivatives have been identified as calcium channel modulators **1**,[4] antihypertensive agents **2**–**3**,[5] mitotic kinesin Eg5 inhibitors **4**,[6] and melanin concentrating hormone receptor **5** (MCH1-R) antagonists.[7] The individual enantiomers of inherently racemic DHPMs exhibit different pharmacological profiles. For example, only (*R*)-enantiomer of SQ 32547 **2** and SQ 32926 **3** possesses the desired antihypertensive effect (Fig. 1).[4b,5] In some related DHPM analogs, the individual enantiomers have in fact been demonstrated to have opposing (antagonist vs agonist) pharmacological activity.[4a] For instance the α_{1A}-selective adrenoceptor antagonist L-771,668 **6**, the (*S*)-enantiomer is significantly more active than the (*R*)-enantiomer,[6c] and recent work on the mitotic kinesin Eg5 inhibitor monastrol **4**[6a,b] has shown that the (*S*)-enantiomer is a more potent inhibitor of Eg5 activity.[8] A similar effect was also observed for Bay 41-4109 **7**, a non-nucleosidic inhibitor of hepatitis B virus replication, where the (*S*)-enantiomer was found to be more active than the (*R*)-enantiomer (Fig. 1).[9]

The Biginelli reaction, which involves the three-component cyclocondensation of ureas, β-ketoesters, and aldehydes exclusively furnishes racemic DHPMs. In recent decades, many efforts have focused on developing protocols for the preparation of optically pure Biginelli products. However, only a limited number of synthetic methods provide access to enantiomerically pure DHPMs with high optical purity. Such approaches have thus far relied either on catalytic enantioselective synthetic routes or through chemical or enzymatic resolution methods and have recently been reviewed.[10]

Initial classical approaches in the synthesis of enantiomerically pure DHPM derivatives were based on resolution of the DHPM diastereomers of N-3 menthyl carboxylate[5a] or (*R*)-α-methyl benzyl amine derivatives.[5b] Resolution of diastereomeric salts of DHPM 5-carboxylate with chiral amine[11] however was of limited success. A useful preparative scale resolution of diastereomeric N-3 ribofuranosyl amide derivative of DHPM led to the resolution of racemic monastrol.[12] In a study aimed at enantioselective total synthesis of polycyclic marine alkaloid (−) batzelladine, construction of an enantiomerically enriched DHPM has been achieved through regioselective (N-3) sulfonylation with (1*S*)-(+) camphorsulfonyl chloride.[13] Biocatalytic pathways employing *protease subtilisin* (lipases and esterases were unreactive!), wherein a C-5 methyl ester could be hydrolyzed selectively via hydrolysis of the undesired (*R*)-enantiomer has been reported[14] that allowed the recovery of the desired (*S*)-enantiomer in 80–90% chemical yield and high (98%) enantioselectivity, which was further manipulated

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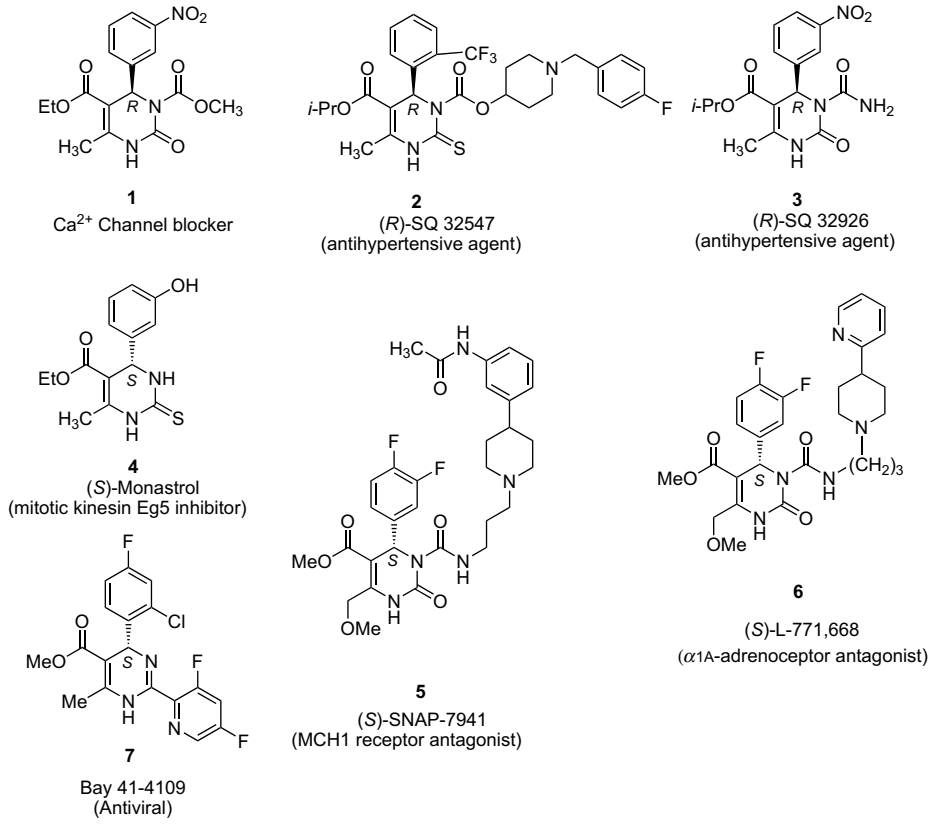


Figure 1. Therapeutically potent enantiomers of DHPMs.

into (*S*)-L-771,668 **6**.[16] Similarly, a lipase-catalyzed kinetic resolution strategy has been reported to yield optically pure DHPMs.[15,16]

Analytical separation of DHPM derivatives has also been achieved by enantioselective HPLC using a variety of different chiral stationary phases (CSPs).[17] The implementation of 'designer-CSPs'[18] paved way for useful and efficient separation of DHPMs.

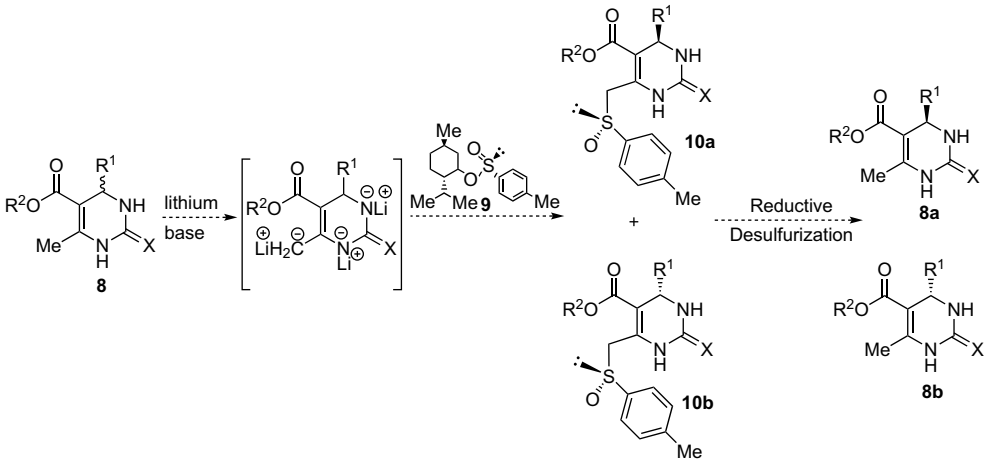
Asymmetric multicomponent reaction using sugar appended reactants has also been shown to induce chirality at C4 of the DHPM ring.[19] A catalytic enantioselective version of the Biginelli reaction has been reported[20] by Juaristi et al. using $CeCl_3$ and $InCl_3$ as Lewis acids in the presence of chiral ligands. Moderate enantioselectivities (up to 40% ee) of DHPMs were obtained by performing the reaction at low temperature under the conditions of kinetic control. The asymmetric Mannich reaction of β-ketoesters to acylimines catalyzed by the *Cinchona* alkaloids as a means of constructing chiral DHPM heterocycles has been reported.[7c,21] Another catalytic approach to highly enantioselective multicomponent Biginelli condensation using a recyclable ytterbium triflate with a chiral hexadentate ligand has been developed (ee up to 99%).[22] Versatile organocatalytic asymmetric reactions using chiral phosphoric acid,[23] 5-(pyrrolidin-2-yl) tetrazole derivatives,[24] and a *trans*-4-hydroxyproline derived secondary amine in combination with achiral Bronsted acid[25] have furnished DHPMs in moderate-to-good yields and very high (up to 98%) enantioselectivity. These methods strongly rely on the accessibility of the chiral reagents and/or catalysts to obtain DHPMs possessing useful levels of enantioselectivity. Thus access to diastereomerically/enantiomerically pure DHPM derivatives utilizing the tools of asymmetric synthesis is of general current interest and a formidable task. Herein we report a chemical resolution method allowing accessibility to both enantiomers of a DHPM derivative by appending chiral auxiliary at N-3 position through highly selective metalation–substitution reaction of a DHPM derivative. However, selective attachment of the chiral auxiliary at C-6 methyl position of DHPM did not effect diastereomeric separation.

2. Results and discussion

We have already demonstrated lithiation of Biginelli compounds resulting in regioselective elaboration of key diversity oriented C-6[26] and N-3[27] and other positions of the DHPM core, depending upon the equivalents of the base used and 'hardness/softness' of the electrophiles implemented. Thus whereas C-6 anion of DHPMs reacted regioselectively with 'soft' electrophiles, N-3 site was substituted with relatively 'hard' counterparts. The lithiation–substitution of Biginelli compounds has also been extended for the synthesis of bicyclic DHPM analogs,[26b] which constitute an important synthetic sequence reminiscent of key structural feature of certain marine alkaloids such as betzelladine A and crambescin A.[28] Utilizing the promising regioselective differentiation of lithiation–substitution of Biginelli DHPMs, toward a variety of electrophiles we appended an appropriate, removable, enantiopure chiral auxiliary at the 'soft' (C-6) and the 'hard' (N-3) sites of DHPMs, leading to the resolution of the diastereomers. The factors affecting stereoselection and our efforts to isolate enantiomerically pure DHPMs have also been described.

2.1. Incorporation of chiral auxiliary at C-6 position

Chiral sulfoxides have been used in numerous enantioselective transformations of synthetic and biological interest.[29] Many reactions can be stereocontrolled using a sulfinyl moiety, which can at a later stage be removed by reductive methods or β-elimination, etc. A barrage of information is available on the synthesis and use of



Scheme 1. Strategy for resolution of racemic DHPMs by trick through C-6 position.

chiral sulfoxides.[29] Also in certain instances the biological properties of some natural products are correlated to the absolute configuration at sulfur atom.[29a] Utilizing our standard conditions[26a] of regioselective alkylation of C-6 position of DHPMs, we envisaged that incorporation of a chiral sulfoxide shall furnish diastereomers such as **10a** and **10b** of **8** (Scheme 1), which subsequent to chromatographic separation and removal of chiral auxiliary shall provide access to enantiomers **8a** and **8b**. The sequence would also offer an opportunity to probe the effect of remote stereocenter created at C6-methyl of DHPM **8** on the resolution of diastereomers.

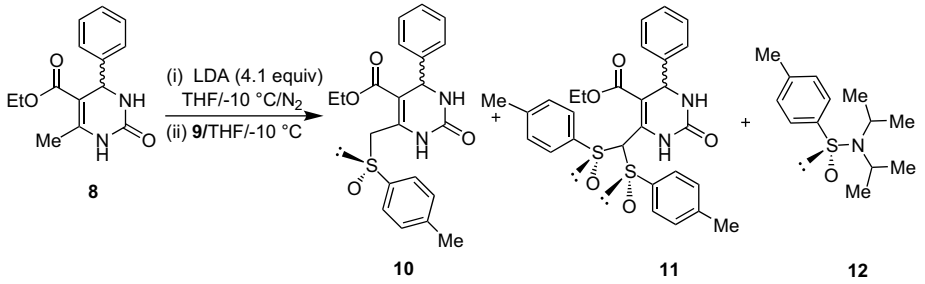
In order to test this hypothesis, DHPM **8** (R^1=Ph, R^2=Et, X=O) was treated with 4.0 equiv of freshly prepared LDA in anhydrous THF at −10 °C, under a blanket of dry nitrogen gas followed by stirring at room temperature for 3 h.[26] The resultant red colored anionic solution was subsequently quenched with 3.0 equiv of optically pure (1*R*,2*S*,5*R*)-(−)-menthyl (*S*)-*p*-toluenesulfinate **9**[30] at −10 °C, which upon stirring for 12 h at room temperature furnished a mixture of three products **10**, **11**, and **12** along with unreacted starting DHPM **8** (Scheme 2). Product **12** was identified as adduct of LDA with **9**, thus depriving the anion of **8** to undergo complete quenching with **9**, leading to incomplete reaction. The formation of **12** (10–12% yield) was further corroborated through an alternate synthesis involving a direct reaction of diisopropylamine with **9** (vide Experimental). In an attempt to improve the reaction and to avoid the formation of **12**, we switched over to the use of *n*-BuLi (3.5 equiv) as the base. In this reaction, metalation of **8** followed by treatment with **9** furnished only **10** and **11**, in 40% and 25% yields, respectively, and the formation of **12** was avoided.

The reaction depicted smooth reactivity of C-6 carbanion with **9** resulting in the formation of diastereomeric mixture of **10** thus creating a chiral center at C-6 position of DHPM. The formation of diastereomers was attested from the appearance of duplicated signals in their ^{1}H and ^{13}C NMR spectra. All attempts to separate the diastereomers using chromatography and/or fractional crystallization failed to yield any significant separation of the diastereomers.

The other product **11** too was a complex mixture of diasteromers as observed from its NMR data. However, one of the diastereomers rapidly crystallized out from hot methanol and corroborated the structure of DHPM **11**, bearing two *p*-tolyl-sulfinyl moieties at C-6 methyl position.[31] The formation of **11** could be envisaged through the second deprotonation of C-6 methylene protons of initially formed **10**, by the unreacted excess base in the reaction, which is invariably required to drive the reaction to completion. The second deprotonation of **10** obviously represents a case of favorable formation of sulfur (sulfoxide) stabilized α-carbanion. In order to gain unequivocal corroboration of its structure, single crystal of **11** was grown from its solution in 1:1 v/v mixture of methanol and dichloromethane. The X-ray crystal structure analysis[32] confirmed the incorporation of two *p*-tolyl-sulfinyl substituents at the C-6 methyl of DHPM **8** (Fig. 2).

Removal of both sulfur stereocenters from **11** with Raney-Ni in methanol furnished DHPM **8** in 75% yield, which did not exhibit any specific optical rotation.

In order to develop an alternative route for exclusive synthesis of **10** and to probe the effect of chiral auxiliary at remote position C-6 on the diastereoselectivity of the process, a three-component Biginelli reaction was performed as depicted in Scheme 3. For this, ethyl (+)-(*R*)-4-(*p*-tolylsulfinyl)-3-oxobutyrate **13** was synthesized by reacting the dianion of ethylacetoacetate with **9**, following a reported protocol.[33] The oxobutyrate **13** was then reacted with benzaldehyde and urea using the standard three-component Biginelli protocol employing dysprosium triflate as Lewis acid catalyst



Scheme 2. Reaction of lithiated DHPM **8** with (1*R*,2*S*,5*R*)-(−)-menthyl (*S*)-*p*-toluenesulfinate **9**.

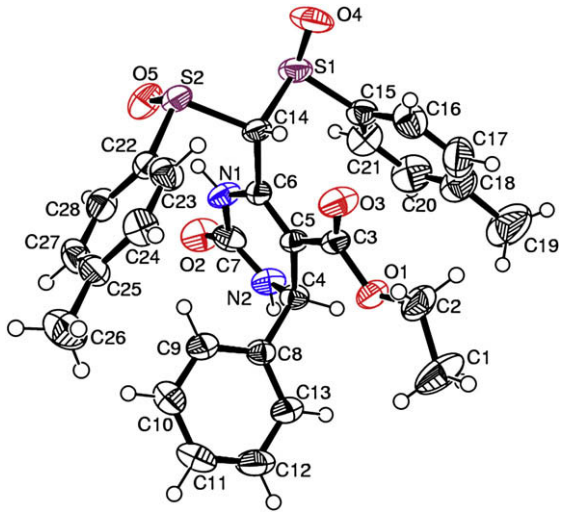
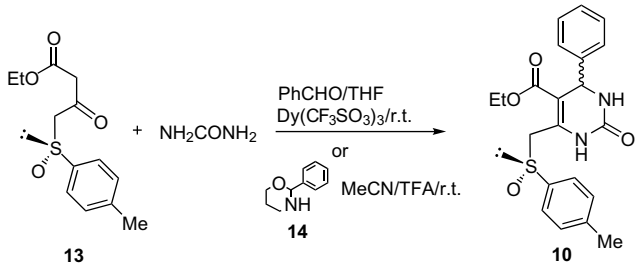


Figure 2. X-ray structure of **11** showing the stereoview of the molecule and the labeling scheme used in the structure analysis.

to obtain **10** in 80% yield. Alternatively, the use of protected benzaldehyde, as 1,3-oxazinane derivative **14** in simple three-component reaction using TFA as acid catalyst also furnished **10** in 75% yield (Scheme 3).[34] Unfortunately, **10** obtained using these routes showed complete lack of stereoselection of the reaction.



Scheme 3. An alternative route for synthesis of DHPM **10**.

Thus appending chiral sulfoxide at C-6 methyl of DHPM **8** did not allow separation of diastereomers **10** and **11**. We reason that the absence of stereoselection in this reaction could be owing to the distance of the chiral auxiliary from the C4 stereocenter[19a] as observed by others during the synthesis of DHPM glycoconjugates employing three-component Biginelli condensations.

2.2. Incorporation of chiral auxiliary at N-3 position

If distance of the chiral auxiliary from the stereogenic C-4 center was any determinant of the stereocontrol of the reaction depicted in Scheme 3, appending a chiral auxiliary at N-3 position might result in separation of diastereomers, which subsequent to the removal of chiral auxiliary may furnish enantiomers of DHPMs. Recently, we have developed a mild and general one-pot protocol for N-3 acylation of Biginelli DHPMs, which tolerates various substituents around the DHPM nucleus.[27] Employing this strategy, when the N-3 anion (generated using 1.1 equiv of *n*-BuLi)[27] of **15** was reacted with the enantiopure **9** (Scheme 4), only starting materials were recovered. We envisaged, choosing a relatively 'hard' and bulky electrophile such as optically pure *N*-protected amino acid chloride **17**, might furnish diastereomeric mixtures of DHPM derivative **18** (Scheme 4).

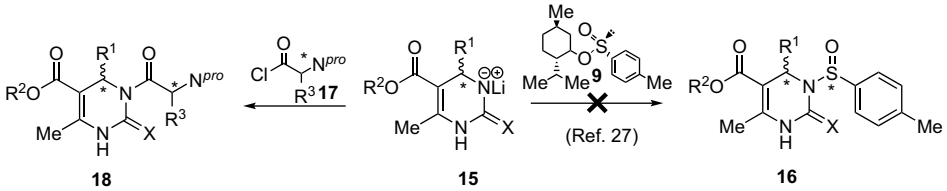
Thus the DHPM derivative **15** bearing the substitution pattern of the potent calcium channel blocker SQ 32926, i.e., a 3-nitrophenyl group at C4 and *i*-propyl ester at C-5 position was metalated [*n*-BuLi (1.1 equiv)/THF/−78 °C] and quenched with 1.5 equiv of *N*-phthaloyl L-phenylalanine acid chloride[35] **17a** (R^3=benzyl) at −78 °C (Scheme 5). The reaction furnished a diastereomeric mixture comprising of **18a** and **18b**, which was resolved on TLC [R_f: 0.4 and 0.25 (ethyl acetate/hexane/50:50)]. Careful chromatographic separation of the mixture resulted in the isolation of the diastereomers **18a** (45%) and **18b** (42%) yield, respectively.

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,[11,17b] through correlation with DHPM derivatives of known configuration.[12,15] However, correlation of specific optical rotation could also be used for predicting the configuration at C-4. Since the chiral auxiliary used in this reaction has (*S*)-configuration at one chiral carbon, the two diastereomers **18a** and **18b** have been assigned, (*R*) and (*S*) configuration, respectively, at C4. Reductive deacylation of the diastereomers **18a** and **18b** could be accomplished using lithium aluminum hydride ($LiAlH_4$) (Scheme 5). Thus treatment of **18a** with $LiAlH_4$ at 0 °C in anhydrous THF under the atmosphere of dry nitrogen gas furnished a single product, 5-isopropoxycarbonyl-6-methyl-4-(3-nitrophenyl)-3,4-dihydropyrimidin-2(1*H*)-one **19a** in 92% yield {$[\alpha]_D^{25}$ +104 (methanol, *c* 0.5)}. In analogy with the sign of optical rotation of the known (*S*)-enantiopure DHPMs,[36] the configuration (*S*) is assigned at C-4 position of DHPM **19a**.

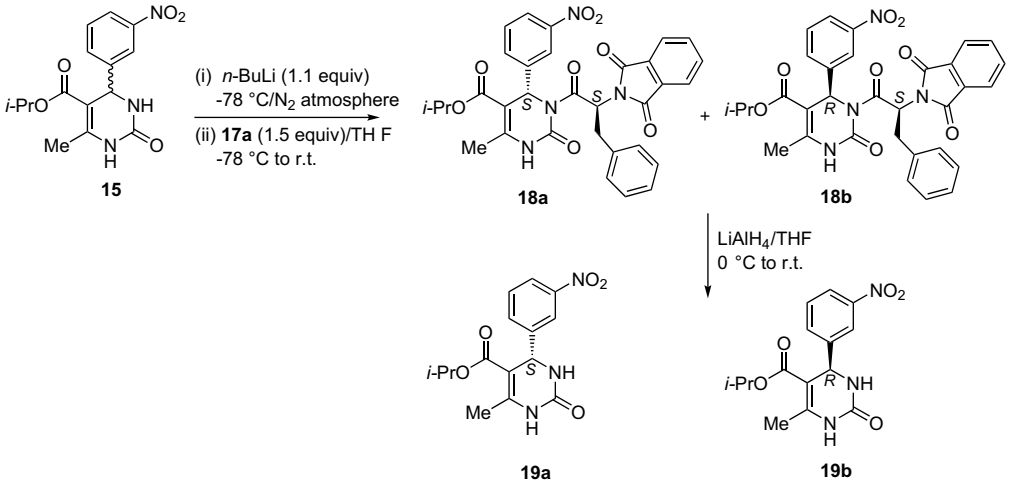
Likewise, reductive deacylation of the diastereomer **18b** with $LiAlH_4$ furnished a single product. The spectral data of this compound was exactly similar to that of **19a** and it was identified as the enantiomer: 5-isopropoxycarbonyl-6-methyl-4-(3-nitrophenyl)-3,4-dihydropyrimidin-2(1*H*)-one **19b** {$[\alpha]_D^{25}$ −103 (methanol, *c* 0.4)}. Comparing the specific optical rotation with a known C-4 (*R*) DHPM,[22] configuration (*R*) is assigned at C-4 position of **19b**.

3. Conclusions

Following the C-6 and N-3 metalation approach, enantiopure chiral auxiliaries could be appended at C-6 and N-3 positions of DHPMs, leading to the formation of diastereomers, which only in the latter case, could be expeditiously resolved, chromatographically to obtain both the enantiomers of medicinally potent DHPM nucleus. The close proximity of the chiral auxiliary appended at N-3 position was found to be effective for separation of diastereomers, in comparison to the distant C-6 position. The applicability of this



Scheme 4. Strategy to append chiral auxiliary at closest proximal N-3 position.



Scheme 5. Regioselective N-3 acylation of DHPM **15** and reductive deacylation. Synthesis of enantiomers **19a** and **19b**.

approach for resolution of diastereomers of a number of DHPM derivatives is currently in progress.

4. Experimental

4.1. General information

Melting points were determined in open capillaries and are uncorrected. $^{1}H/^{13}C$ NMR (300/75 MHz; $CDCl_3$+DMSO-d_6) spectra were recorded using commercial deuterated solvents on multinuclear spectrometer Jeol FT-AL-300 and Bruker AC 200 instrument using tetramethylsilane as internal standard. Data are reported as follows: chemical shifts (multiplicity [singlet (s), doublet (d), double doublet (dd) triplet (t), quartet (q), AB quartet (ABq), broad (br), and multiplet (m)], coupling constant [Hz], integration). The diastereomeric ratios were determined from the comparison of intensity ratio of the key signals in ^{1}H NMR spectrum of the compounds. Mass spectra (MS) were recorded on Bruker Daltonics esquire 3000 spectrometer. Elemental analyses were performed on FLASH EA 1112 (Thermo Electron Corporation) analyzer at Department of Chemistry, Guru Nanak Dev University, Amritsar. Optical rotation was recorded on Atago (AP-100), digital polarimeter at 25 °C.

Thin layer chromatography (TLC) was performed on Merck ($60F_{254}$, 0.2 mm) using an appropriate solvent system. The chromatograms were visualized under UV light. Separation of various products was carried out by column chromatography on silica gel (60–120 mesh). All solvents and electrophiles were dried with appropriate reagents before use. Reactions were run under a blanket of dry nitrogen gas in a sealed (rubber septum, Aldrich) round-bottomed flasks. Organometallic reagents were added using cannula. The low temperature (−10 °C and −78 °C) was attained in Dewar flasks using organic solvent–liquid N_2 slush.

4.2. Typical procedure for C6-substitution of DHPMs with chiral sulfoxide

To a suspension of DHPM **8** (1.3 g, 5 mmol, Scheme 2) in dry THF (50 ml) under a blanket of dry N_2, 2.1 N *n*-BuLi (8.33 ml, 17.5 mmol) was added drop-wise at −10 °C. After the addition, reaction mixture was warmed to room temperature and stirred for additional 3 h until red colored carbanion was generated. To this carbanion, 4.4 g (15 mmol) of (1*R*,2*S*,5*R*)-(−)-menthyl (*S*)-*p*-toluenesulfinate **9**, dissolved in 10 ml dry THF was added drop-wise using cannula at −10 °C. Upon addition of the electrophile, the red color was quenched, indicating the consumption of the carbanion. Reaction was warmed to room temperature and stirring was continued for additional 12 h, to complete the reaction (TLC), after which a saturated aqueous solution of NH_4Cl was introduced to terminate the reaction. The reaction was extracted with ethyl acetate (3×25 ml) treated in sequence with brine and water. The extracts were dried over anhydrous Na_2SO_4 and the mixture concentrated under reduced pressure. The products **10** (0.79 g, 40%), **11** (0.67 g, 25%), and **12** (0.14 g, 12%) were isolated by chromatography using silica gel-G (60–120 mesh) and mixtures of ethyl acetate and hexane as eluent. For preparing samples for micro-analytical analysis, crystallization was done using combinations of dry DCM/methanol and DCM/hexane.

*4.2.1. 5-Ethoxycarbonyl-6-(toluene-4-sulfinylmethyl)-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (1:1 diastereomeric mixture) (**10**)*

Found: C, 63.35; H, 5.48; N, 6.91; S, 8.13. $C_{21}H_{22}N_2O_4S$ requires C, 63.31; H, 5.52; N, 7.03; S, 8.04%; R_f (60% ethyl acetate/hexane) 0.24; mp: 181 °C (acetone). ν_{max} (KBr) 3100, 1730, 1695 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.43 (10H, m, ArH+1H, D_2O exchangeable, N1–H), 5.29 (1H, m, C4–H+1H, D_2O exchangeable, N3–H), 4.52 and 4.36 (2H, ABq, *J* 14.1 and 13.2 Hz, CH_2SO), 4.01 (2H, q, *J* 7.2 Hz, $-OCH_2$), 2.40 and 2.42 (3H, s, CH_3), 1.13 and 1.10 (3H, t, *J* 7.2 Hz, CH_3); δ_C (75 MHz, $CDCl_3$) 14.4, 21.9, 56.0, 60.8, 104.6, 124.7, 124.9, 127.0, 127.1, 128.2, 128.5, 129.0, 129.2, 130.3, 139.7, 141.7, 142.1, 142.3, 143.6, 152.6, 152.9, 165.4; *m*/*z* 398 (M^+).

*4.2.2. 5-Ethoxycarbonyl-6-[bis-(toluene-4-sulfinyl)methyl]-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (**11**)*

Found: C, 62.88; H, 5.01; N, 5.41; S, 12.05. $C_{28}H_{28}N_2O_5S_2$ requires C, 62.68; H, 5.22; N, 5.22; S, 11.94%; R_f (60% ethyl acetate/hexane) 0.6; mp: 183 °C (DCM/methanol). ν_{max} (KBr) 3018, 1703, 1681 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.51 (1H, br, D_2O exchangeable, N1–H), 7.08 (13H, m, ArH), 6.40 (1H, s, CH), 5.03 (1H, br, D_2O exchangeable, N3–H), 4.95 (1H, d, *J* 2.4 Hz, C4–H), 3.60 (2H q, *J* 7.2 Hz, $-OCH_2$), 2.42 (3H, s, CH_3), 2.37 (3H, s, CH_3), 0.90 (3H, t, *J* 7.2 Hz, CH_3); δ_C (75 MHz, $CDCl_3$) 13.6, 21.5, 55.4, 60.3, 82.5, 124.6, 125.3, 126.1, 127.9, 128.5, 129.6, 130.1, 141.9, 143.2, 150.2; *m*/*z* 536 (M^+).

*4.2.3. (+)-(R)-Methyl benezenesulfinic acid diisopropylamide (**12**)*

Found: C, 65.45; H, 8.71; N, 6.01; S, 13.28. $C_{13}H_{21}NOS$ requires C, 65.27; H, 8.78; N, 5.85; S, 13.38%; R_f (60% ethyl acetate/hexane) 0.89; mp: 110 °C (ethyl acetate/hexane). $[\alpha]_D^{25}$ +92 (*c* 0.5, $CHCl_3$).

ν_{max} (KBr) 3200, 1060 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.40 (4H, m, ArH), 3.55 (2H, m, 2×CH), 2.40 (3H, s, CH_3), 1.40 (6H, d, *J* 6.6 Hz, 2×CH_3), 1.11 (6H, d, *J* 6.6 Hz, 2×CH_3); δ_C (75 MHz, $CDCl_3$) 21.1, 23.6, 23.7, 46.3, 126.4, 129.2, 140.2, 141.3; *m*/*z* 239 (M^+).

4.3. Alternative preparation of 12

2.1 N *n*-BuLi (4.7 ml, 10 mmol) was treated with diisopropylamine (1.39 ml, 10 mmol) in 30 ml dry THF at 0 °C and stirred for 30 min to generate LDA. **9** (4.41 g, 15 mmol) dissolved in 10 ml THF was added to the reaction at −20 °C, and contents were warmed to room temperature and stirred for additional 30 min. The reaction was quenched with saturated aqueous solution of NH_4Cl, brine and extracted with ethyl acetate (3×25 ml), followed by evaporation and chromatographic purification furnished **12** (3.2 g, 89%). The characteristic data of **12** is provided in Section 4.2.3.

4.4. Synthesis of 5-ethoxycarbonyl-6-(toluene-4-sulfinylmethyl)-4-phenyl-3,4-dihydropyrimidin-2(1*H*)-one (1:1 diastereomeric mixture) 10

4.4.1. Method A

A mixture of ethyl(+)-(*R*)-4-(*p*-tolylsulfinyl)-3-oxobutyrate **13** (0.268 g, 1 mmol), benzaldehyde (0.106 g, 1 mmol), and catalytic amount of $Dy(CF_3SO_3)_3$ (0.005 g) was stirred in 30 ml THF at room temperature for 2 h, followed by addition of urea (0.09 g, 1.5 mmol) and stirring was continued for 10 h at room temperature. The solvent was evaporated and crude reaction was chromatographed to obtain **10** (0.32 g, 80%).

4.4.2. Method B

A mixture of ethyl(+)-(*R*)-4-(*p*-tolylsulfinyl)-3-oxobutyrate **13** (0.268 g, 1 mmol), 1,3-oxazinane **14**[34] (0.163 g, 1 mmol), urea (0.09 g, 1.5 mmol), and catalytic amount of TFA (0.5 ml) was stirred in acetonitrile 50 ml at 35 °C for 12 h. The reaction contents were washed with aqueous $NaHCO_3$ solution and organic phase was extracted with ethyl acetate (3×25 ml) and washed with water (1×25 ml). The organic extracts were dried with sodium sulfate and solvent was evaporated to yield crude product, which upon chromatographic purification furnished **10** (0.29 g, 75%). The characteristic data of **10** is provided in Section 4.2.1.

4.5. Reductive desulfurization

To a solution of compound **11** (1.6 g, 3 mmol) in methanol (50 ml) was added excess of Raney-Ni (5 g) at room temperature. The reaction was shifted to 60 °C and stirred for 1 h under nitrogen atmosphere. After completion (TLC) reaction was filtered through a bed of Celite and the solvent was removed under reduced pressure. The crude product was purified by column chromatography to furnish **8** (0.59 g, 75%) as white crystalline solid.

*4.5.1. 5-Ethoxycarbonyl-6-methyl-4-phenyl-3,4-dihydropyrimidin-2(1H)-one (**8**)*

Found: C, 64.64; H, 6.25; N, 10.92. $C_{14}H_{16}N_2O_3$ requires C, 64.61; H, 6.15; N, 10.76%; R_f (50% ethyl acetate/hexane) 0.6; mp: 210 °C (methanol). ν_{max} (KBr) 3300, 1730, 1700 cm^{-1}; δ_H (300 MHz, $CDCl_3$+DMSO-d_6) 8.44 (1H, br, D_2O exchangeable, N1–H), 7.29 (5H, m, ArH), 6.41 (1H, br, D_2O exchangeable, N3–H), 5.34 (1H, d, *J* 3.0 Hz, C4–H), 4.04 (2H, q, *J* 7.1 Hz, –OCH_2), 2.33 (3H, s, C6–CH_3), 1.15 (3H, t, *J* 7.1 Hz, CH_3); δ_C (75 MHz, $CDCl_3$+DMSO-d_6) 13.8, 18.1, 55.0, 59.4, 100.3, 126.3, 127.2, 128.1, 144.0, 146.9, 152.6, 165.5; *m*/*z* 260 (M^+).

4.6. Typical procedure for N3-substitution of DHPMs with enantiopure amino acid chloride

To a suspension of DHPM **15** (1.6 g, 5 mmol, Scheme 5) in 50 ml dry THF under a blanket of dry N_2, 2.1 N *n*-BuLi (2.62 ml, 5.5 mmol) was added drop-wise at −78 °C whereupon pale yellow anion was formed. After the addition, reaction mixture was stirred at −78 °C for 30 min and treated at −78 °C with enantiopure amino acid chloride **17a**[35] (2.34 g, 7.5 mmol), dissolved in 10 ml dry THF. The reaction was warmed slowly to room temperature till it was completed (TLC). A cold saturated aqueous solution of NH_4Cl (30 ml) was introduced. 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 **18a** (1.34 g, 45%) and **18b** (1.19 g, 40%) were isolated by column chromatography using silica gel-G (60–120 mesh) and mixtures of ethyl acetate/hexane as eluent.

*4.6.1. (2S,4S)-5-Isopropoxycarbonyl-6-methyl-3-[2-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-3-phenylpropionyl]-4-(3-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one (**18a**)*

Found: C, 64.35; H, 4.71; N, 9.69. $C_{32}H_{28}N_4O_8$ requires C, 64.42; H, 4.69; N, 9.39%; R_f (50% ethyl acetate/hexane) 0.4; mp: 119 °C (DCM/hexane). $[\alpha]_D^{25}$ +186 (*c* 0.5, $CHCl_3$). ν_{max} (KBr) 3300, 2920, 1770, 1720, 1640, 1535, 1380 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.70 (1H, br, D_2O exchangeable, N1–H), 7.67 (13H, m, ArH), 6.55 (1H, dd, *J* 11.4 Hz, *J* 4.2 Hz, CH), 6.47 (1H, s, C4–H), 5.05 (1H, m, CH), 3.85 (1H, dd, *J* 13.5 Hz, *J* 12.0 Hz, CH), 3.38 (1H, dd, *J* 13.5 Hz, *J* 3.9 Hz, CH), 2.48 (3H, s, C6–Me), 1.17 (3H, d, *J* 6.0 Hz, CH_3), 1.33 (3H, d, *J* 6.0 Hz, CH_3); δ_C (75 MHz, $CDCl_3$) 18.0, 21.7, 21.9, 34.0, 55.6, 57.2, 68.8, 105.3, 122.4, 123.2, 123.3, 128.5, 128.6, 129.6, 131.5, 133.2, 134.0, 136.3, 141.8, 150.9, 163.6, 168.0, 170.7, 179.3; *m*/*z* 596 (M^+).

*4.6.2. (2S,4R)-5-Isopropoxycarbonyl-6-methyl-3-[2-(1,3-dioxo-1,3-dihydroisoindol-2-yl)-3-phenylpropionyl]-4-(3-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one (**18b**)*

Found: C, 64.30; H, 4.52; N, 9.24. $C_{32}H_{28}N_4O_8$ requires C, 64.42; H, 4.69; N, 9.39%; R_f (50% ethyl acetate/hexane) 0.25; mp: 98 °C (DCM/hexane). $[\alpha]_D^{25}$ −276 (*c* 0.5, $CHCl_3$). ν_{max} (KBr) 3300, 2928, 1765, 1720, 1640, 1535, 1390 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 7.67 (13H, m, ArH), 7.43 (1H, br, D_2O exchangeable, NH), 6.56 (1H, s, C4–H), 6.06 (1H, m, CH), 5.04 (1H, m, CH), 3.57 (2H, m, CH_2), 2.30 (3H, s, C6–CH_3), 1.30 (3H, d, *J* 6.0 Hz, CH_3), 1.15 (3H, d, *J* 6.0 Hz, CH_3); δ_C (75 MHz, $CDCl_3$) 17.7, 21.7, 21.9, 34.1, 54.9, 57.0, 68.6, 104.9, 122.0, 123.2, 123.4, 126.8, 128.3, 129.0, 129.7, 131.3, 133.2, 134.2, 136.5, 142.0, 145.3, 148.3, 150.6, 163.7, 167.5, 171.5; *m*/*z* 596 (M^+).

4.7. Reductive deacylation

To a solution of DHPM **18a** (0.5 g, 0.83 mmol) in dry THF (50 ml), $LiAlH_4$ (0.76 g, 20 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. Column chromatographic separation of the residue using silica gel-G (60–120 mesh) and mixtures of ethyl acetate/hexane as eluent furnished enantiomer **19a** (0.24 g, 92%). Following the similar procedure, reductive deacylation of **18b** (0.5 g, 0.83 mmol) furnished **19b** (0.237 g, 90%).

*4.7.1. (4S)-5-Isopropoxycarbonyl-6-methyl-4-(3-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one (**19a**)*

Found: C, 56.30; H, 5.52; N, 13.23. $C_{15}H_{17}N_3O_5$ requires C, 56.42; H, 5.32; N, 13.16%; R_f (65% ethyl acetate/hexane) 0.5; mp: 187 °C

(methanol). $[\alpha]_D^{25}$ +104 (*c* 0.5, methanol). ν_{max} (KBr) 3250, 3100, 2950, 1690, 1630, 1535, 1350 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.10 (1H, br, D_2O exchangeable, N1–H), 7.84 (4H, m, ArH), 6.10 (1H, br, D_2O exchangeable, N3–H), 5.51 (1H, s, C4–H), 4.96 (1H, m, CH), 2.37 (3H, s, C6–CH_3), 1.23 (3H, d, *J* 6.3 Hz, CH_3), 1.06 (3H, d, *J* 6.3 Hz, CH_3); δ_C (75 MHz, $CDCl_3$) 18.7, 21.6, 21.9, 23.9, 55.1, 67.8, 100.7, 121.8, 122.9, 129.8, 132.7, 145.8, 147.0, 148.2, 153.1, 182.6; *m*/*z* 319 (M^+).

*4.7.2. (4R)-5-Isopropoxycarbonyl-6-methyl-4-(3-nitrophenyl)-3,4-dihydropyrimidin-2(1H)-one (**19b**)*

Found: C, 56.32; H, 5.47; N, 13.31. $C_{15}H_{17}N_3O_5$ requires C, 56.42; H, 5.32; N, 13.16%; R_f (65% ethyl acetate/hexane) 0.5; mp: 187 °C (methanol). $[\alpha]_D^{25}$ −103 (*c* 0.4, methanol). ν_{max} (KBr) 3245, 3100, 2950, 1690, 1630, 1530, 1350 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 8.08 (1H, br, D_2O exchangeable, N1–H), 7.84 (4H, m, ArH), 6.10 (1H, br, D_2O exchangeable, N3–H), 5.51 (1H, d, *J* 2.7 Hz, C4–H), 4.96 (1H, m, CH), 2.37 (3H, s, C6–CH_3), 1.23 (3H, d, *J* 6.3 Hz, CH_3), 1.06 (3H, d, *J* 6.3 Hz, CH_3); δ_C (75 MHz, $CDCl_3$) 18.7, 21.6, 22.0, 23.9, 55.1, 67.9, 100.7, 121.8, 122.9, 129.8, 132.7, 145.8, 147.0, 148.2, 153.1, 182.6; *m*/*z* 319 (M^+).

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31. When ^1H NMR spectrum was recorded in the presence of a chiral shift reagent europium tris[3-heptafluoropropylhydroxymethylene)-(+)camphorate] ($Eu(hfc)_3$), a distinct separation of the ester signal upon increasing the equivalent of ($Eu(hfc)_3$) indicated the presence of the diastereomeric mixture.
32. Crystallographic data for **11** have been deposited with the Cambridge Crystallographic Data Centre (CCDC). The coordinates can be obtained on request from the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK. The CCDC number is 269204.
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