DOI: 10.1002/ejoc.200900208

An Efficacious Protocol for 4-Substituted 3,4-Dihydropyrimidinones: Synthesis and Calcium Channel Binding Studies

Kamaljit Singh,*[a] Divya Arora,[a] Danielle Falkowski,[b] Qingxin Liu,[b] and Robert S. Moreland[b]

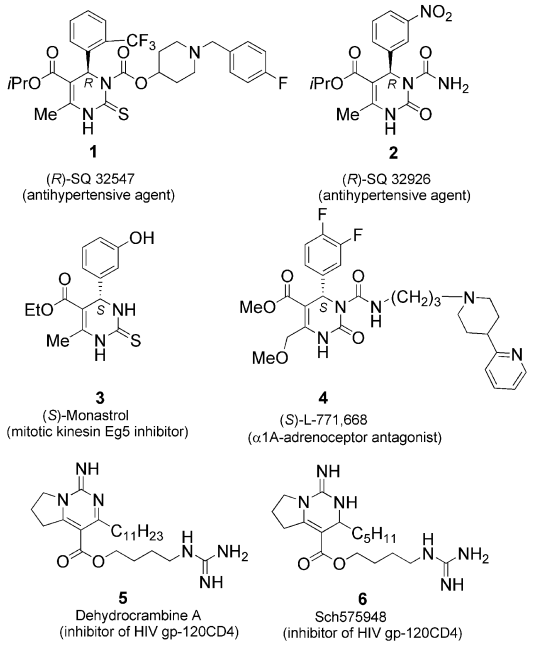
Keywords: Multicomponent reactions / Lithiation / Regioselectivity / Chiral auxiliaries / Medicinal chemistry / Vascular smooth muscles

Ethyl 1,2-dihydro-1,6-dimethyl/6-methyl-2-oxopyrimidine-5-carboxylates react with C-nucleophiles as well as the anion of the enantiopure chiral auxiliary (1*R*,2*S*,5*R*)-(–)-methyl (*S*)-*p*-toluenesulfinate to afford 4-substituted and enantiopure congeners of medicinally potent Biginelli dihydropyrimidinones. The calcium channel blocking activity of some of the compounds was evaluated and compared with nifedipine for their ability to relax a membrane depolarization-induced contraction.

Introduction

The scaffold decoration of bioactive molecules represents one of the most vibrant research areas in organic chemistry and has a rich history within the realm of fragment-based drug design. The Biginelli 3,4-dihydropyrimidin-2(1*H*)-ones (DHPMs) have been known for more than a century.[1] These compounds and their appropriately functionalized derivatives have interesting pharmacological profiles such as antihypertensive agent **1** and **2**,[2] mitotic kinesin inhibitors **3**,[3] α_{1a}-adrenergic receptor antagonists **4**[4] and hepatitis B virus replication inhibitors.[5]

The synthesis and scaffold decoration of the DHPM core has played an important role in the total synthesis of polycyclic guanidine-containing marine alkaloids such as batzelladine A.[6] These are also common moieties in some of the most bioactive natural products including dehydrocrambine A (**5**) and Sch575948 (**6**),[7] which are inhibitors of HIV gp-120-CD4 interaction. As a result of their diverse pharmacological profile, synthetic investigations on DHPMs have received extensive attention by both synthetic organic chemists and medicinal chemists. Synthetic approaches to DHPMs can be divided into two major strategies.



Whereas multicomponent reactions (multi = three; see Figure 1) for the construction of Biginelli libraries through solution- and solid-phase strategies are amenable to a high throughput or combinatorial format, the post-Biginelli condensation scaffold decoration tools are prized for appending tailor-made fragments at all possible (N-1, C-2, N-3, C-4, C-5 and C-6) diversity-oriented centres[8] from simple starting materials. By using the latter tools, we previously described both racemic and diastereoselective methods for DHPM synthesis.[9]

[a] Organic Synthesis Laboratory, Department of Applied Chemical Sciences & Technology, Guru Nanak Dev University, Amritsar 143005, India
Fax: +91-183-2258853
E-mail: kamaljit19in@yahoo.co.in
[b] Department of Pharmacology and Physiology, Drexel University College of Medicine, Philadelphia, PA 19102, USA

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.200900208.

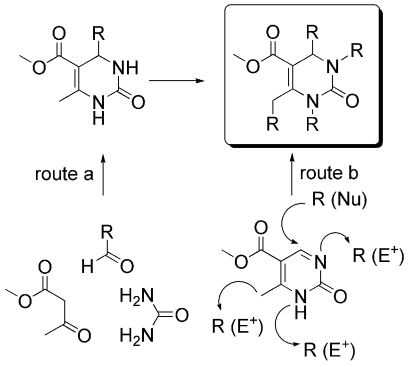


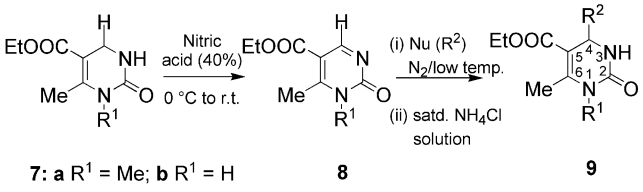
Figure 1. Multistep (route a) construction of functionalized 3,4-dihydropyrimidin-2(1*H*)-one derivatives and post-Biginelli condensation scaffold decoration pathway (route b).

In a preliminary communication,[10] we recently reported a nucleophilic addition sequence for the regioselective incorporation of substituents at the C-4 position of DHPMs, and herein we provide a full account of our development of this process and its further extension to asymmetric synthesis. In addition, we describe highly regioselective addition reactions of a number of Grignard reagents to synthesize DHPM derivatives, which in fact, are formed with greater efficiency. Finally, we report on calcium channel blocking studies of selected compounds to further extend the existing understanding on structure–activity relationships.

Results and Discussion

The current understanding of calcium channel modulation (antagonist vs. agonist activity) of DHPM derivatives, like 1,4-dihydropyridine drugs such as nifedipine, points to the nature (size, polarity, etc.) of the substituent at C-4 as well as the absolute configuration of ring position 4.[11] Different enantiomers of some DHPMs are found to possess opposing biological effects.[11] Whereas the approach to C-4-elaborated DHPMs by using the three-component Biginelli condensation and its variants has thus far been mainly through the use of aldehydes,[12] the C-4 addition method proved to be a highly useful and dependable method with the added advantage that it proceeds with remarkably high regio- as well as chemoselectivity and does not require any chemical activation.

The synthetic route of the current approach starts with the synthesis of 4-unsubstituted ethyl 1,2,3,4-tetrahydro-1,6-dimethyl-2-oxopyrimidine-5-carboxylate (**7a**) and ethyl 1,2,3,4-tetrahydro-6-methyl-2-oxopyrimidine-5-carboxylate (**7b**), for which we have relied on a formyl equivalent, a 1,3-oxazinane derivative,[13] rather than direct use of formaldehyde. Compounds **7a**,**b**, upon further oxidation with nitric acid[14] were readily transformed into ethyl 1,2-dihydro-1,6-dimethyl-2-oxopyrimidine-5-carboxylate (**8a**) and ethyl 1,2-dihydro-6-methyl-2-oxopyrimidine-5-carboxylate (**8b**), respectively (Scheme 1). Oxidation of **7** to **8** was also successfully achieved by us recently by using pyridinium chlorochromate (PCC).[15] The addition of stabilized carbanions, aryllithium reagents and heterocyclic anions to **8a**,**b** furnished exclusively C-4-elaborated DHPM derivatives and made available those DHPMs that are otherwise not accessible through traditional methods employing aldehydes as a result of their unavailability and operational difficulties with aliphatic counterparts. Therefore, the reactions in the present case represent addition of only carbon nucleophiles. Further, whereas the addition reactions of pyridines with aryllithium[16] reagents require activation of the pyridine moiety as a 1-alkoxycarbonyl derivative, the regioselectivity of the reactions of 1-acylpyridinium salts with Grignard reagents[17] was additionally influenced by the structures of the Grignard reagent and the 1-acyl group. However, the addition reactions of pyrimidin-2(1*H*)-ones **7** with carbon nucleophiles proceeded regioselectively without activation of the pyrimidinone substrates.

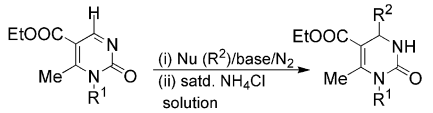


Scheme 1. Synthetic strategy for C-4-elaborated DHPMs **9**.

Addition of Carbon Nucleophiles to Pyrimidine-2(1*H*)-ones 8: Formation of C-4-Elaborated DHPM Derivatives

Treatment of the appropriate DHPM derivative **8a** or **8b** with the intensely yellow dianions of ethyl/methyl acetoacetate,[18] generated by using NaH and *n*BuLi (2.5 equiv. each) in sequence in anhydrous THF at low temperature (Table 1) under a blanket of nitrogen gas, furnished after extractive workup 4-substituted **9** and **10**, depicting a clean addition of the carbanion to ring position 4. No other product arising from addition at the C-5 ester or any other position was detected, pointing to the observed high regio- and chemoselectivity of the transformation. Likewise, reactions of the anions of acetone,[19] acetonitrile,[19] acetophenone,[19] methyl phenyl sulfone,[20] thiophene[21] and furan,[22] generated by using standard methods, furnished the corresponding C-4-elaborated DHPM derivatives in a synthetically useful manner. Only in the reactions of thiophene and furan were products of ester displacement detected (^{1}H NMR spectroscopy) and only in trace amounts. Similarly, the reaction of phenyllithium[23] proceeded with complete regioselectivity to furnish 4-substituted DHPM derivative **9g**. All the products were characterized by IR, ^{1}H NMR and ^{13}C NMR spectroscopy, MS and elemental analysis.

Table 1. Addition of carbon nucleophiles to pyrimidine-2(1*H*)-ones **8**. Formation of 4-substituted DHPM derivatives **9**.



Entry	Nu substrate	Reaction conditions[a]	Product **9/10**, R^2	Yield [%][b]
1	$MeCOCH_2COOEt$	–78 °C/NaH/*n*BuLi/THF	**9a**,[c] CH_2COCH_2COOEt	73
2	$MeCOCH_2COOEt$	–78 °C/NaH/*n*BuLi/THF	**10a**, CH_2COCH_2COOEt	57
3	$MeCOCH_2COOMe$	–78 °C/NaH/*n*BuLi/THF	**10b**, CH_2COCH_2COOMe	35
4	MeCOMe	–78 °C/LDA/THF	**9b**, CH_2COMe	75
5	MeCN	–78 °C/LDA/THF	**10c**, CH_2CN	50
6	PhCOMe	–78 °C/LDA/THF	**9c**, CH_2COPh	96
7	$PhSO_2Me$	–78 °C/*n*BuLi/THF	**9d**, CH_2SO_2Ph	77
8	$PhSO_2Me$	–78 °C/*n*BuLi/THF	**10d**, CH_2SO_2Ph	52
9	thiophene	–40 °C/*n*BuLi/THF	**9e**, (C_4H_3S-2yl)	80
10	thiophene[d]	–40 °C/*n*BuLi/THF	**10e**, (C_4H_3S-2yl)	40
11	furan	–40 °C/*n*BuLi/THF	**9f**, (C_4H_3O-2yl)	81
12	furan[d]	–40 °C/*n*BuLi/THF	**10f**, (C_4H_3O-2yl)	35
13	PhLi[e]	–78 °C/THF	**9g**, Ph	78

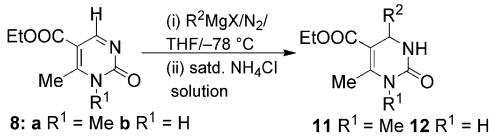
[a] Equivalents of base used are mentioned in the experimental section. [b] Isolated yields. [c] Mixture of keto–enol tautomers (^{1}H NMR spectroscopy). [d] Trace amounts of products of ester displacement[9a] were detected (see the Supporting Information). [e] Freshly prepared from bromobenzene and lithium.

Addition of Grignard Reagents to Pyrimidine-2(1*H*)-ones 8: Formation of DHPM Derivatives Bearing Aliphatic Chains at C-4

Whereas the DHPM derivatives listed in Table 1, particularly Entries 6–13, were designed to evaluate calcium channel blocking properties, the derivatives outlined in Entries 1–5 were designed as probes to determine the effect of aliphatic-functionalized chains at C-4 on the calcium channel blocking activity. The importance of appending alkyl chains at the C-4 position can also be gauged from the fact that naturally occurring marine alkaloids such as **5** and **6** have long aliphatic chains (C_5 and C_{11}, respectively) appended at C-4. The reactions to append such chains through the use of aliphatic aldehydes, under acid-catalyzed conditions of the traditional Biginelli condensation reaction, are prone to side reactions owing to the vulnerability of the aldehydes.[8b] Herein we describe a useful protocol for appending long aliphatic chains with the use of the above methodology by using Grignard reagents[24] as nucleophiles, and the examples mentioned in Table 2 (Entries 7 and 9) demonstrate a useful protocol for appending long chains at C-4, a synthetic sequence that is of considerable importance in connection with the total synthesis of **5/6** and their analogues.

Treatment of **8a**,**b** with freshly prepared Grignard reagents[24] of aliphatic groups with carbon chain lengths of $C_{1–5}$, C_{10} and C_{11} at –78 °C under an atmosphere of nitrogen furnished the corresponding DHPMs (Table 2, Entries 1–9) in good yields. Similar reaction with allylmagnesium bromide furnished C-4 addition product **12i** in 65% yield after column chromatography. The reaction of phenylmagnesium bromide with **8b** leading to the exclusive formation of **12j** was very facile, as no side product was detected.

Table 2. Addition of Grignard reagents to pyrimidine-2(1*H*)-ones **8**. Formation of 4-substituted DHPM derivatives **11** and **12**.



Entry	R^2MgX (equiv.)[a]	Product **11/12**, R^2	Yield [%][b]
1	MeMgI (2.5)	**11a**, Me	92
2	MeMgI (1.0)	**12a**, Me	51
3	EtMgBr (1.0)	**12b**, Et	88
4	*n*PrMgBr (1.0)	**12c**, *n*Pr	85
5	*n*BuMgBr (1.0)	**12d**, *n*Bu	79
6	*s*BuMgBr (1.0)	**12e**, *s*Bu	77
7	*n*-$C_5H_{11}MgBr$ (1.0)	**12f**, *n*-C_5H_{11}	90
8	*n*-$C_{10}H_{21}MgBr$ (1.0)	**12g**, *n*-$C_{10}H_{21}$	85
9	*n*-$C_{11}H_{23}MgBr$ (1.0)	**12h**, *n*-$C_{11}H_{23}$	80
10	AllMgBr (1.0)	**12i**, allyl	65
11	PhMgBr (2.5)	**12j**, Ph	45

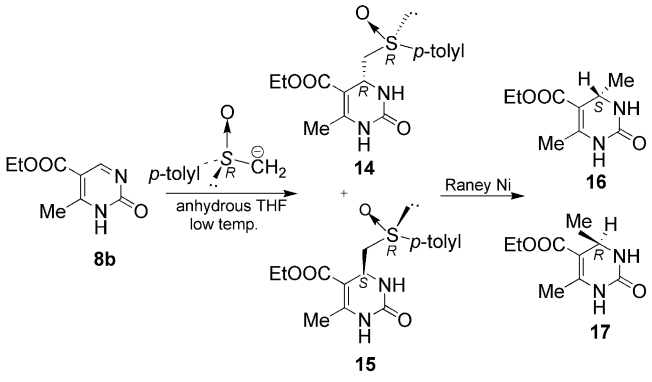
[a] Freshly prepared reagent was used. [b] Isolated yields.

Addition of the Monoanion of (*R*)-(+)-Methyl *p*-Tolyl Sulfoxide to 8b: Synthesis of (*R*)- and (*S*)-Enantiomers

Access to diastereomerically/enantiomerically pure DHPM derivatives by utilizing the tools of asymmetric synthesis is of general current interest and has been a formidable task. The literature reports on the use of resolution methods employing fractional crystallization of the diastereomeric salts[25] and the use of chiral aldehydes.[26] Chiral auxiliaries at the N-3 position can be used to resolve diastereomers to obtain ultimately enantiomerically enriched DHPM derivatives.[27] Analytical separation through the use of designer chiral stationary phases in chiral HPLC

has allowed useful and efficient separation of enantiomers.[28] Biocatalytic and chemical catalytic methods employing proteases,[29] Lewis acids in the presence of chiral ligands,[30] enantioselective organocatalytic Biginelli reactions[31a,31b,31c,31d] or cinchona alkaloid-catalyzed Mannich reactions[31e,31f,31g] have also been advantageously employed.

Chiral sulfoxides have been used in numerous enantioselective transformations of synthetic and biological interest.[32] To further expand the scope of the C-4 elaboration methodology, we sought to employ chiral sulfoxides for the enantioselective synthesis of DHPMs.[33] Lithiation of enantiomerically pure (*R*)-(+)-methyl *p*-tolyl sulfoxide (**13**) was achieved with LDA by using a standard method. Addition of this anion to **8b** resulted in the smooth formation of a diastereomeric mixture comprising **14** {$[a]_D^{25}$ = +10 (methanol, *c* = 0.2)} and **15** {$[a]_D^{25}$ = +185 (methanol, *c* = 0.2)} in a 80:20 ratio determined from the ^{1}H NMR spectrum of the crude reaction mixture (Scheme 2). Major diastereomer **14** separated out from a hot methanol solution, and it was recrystallized to obtain an analytically pure sample. The remaining mixture was resolved by column chromatography to obtain an additional amount of **14** and minor diastereomer **15**.



Scheme 2. Addition of the monoanion of (*R*)-(+)-methyl *p*-tolyl sulfoxide to **8b**.

The assignment of the absolute configuration at the C-4 position of a series of DHPM derivatives was performed on the basis of the combination of enantioselective HPLC and circular dichroism (CD) spectroscopy,[28b] through correlation with DHPM derivatives of known configuration. A correlation of specific optical rotation was also used for predicting the configuration at C-4 bearing aryl substituents at C-4.[30a] Because the chiral auxiliary used in this reaction has (*R*)-configuration at the sulfur atom, diastereomers **14** and **15** were assigned the (*R*) and (*S*) configurations, respectively, at C-4. The assignment of absolute configuration of major diastereomer **14** was unambiguously assigned from the single-crystal X-ray structure determination (Figure 2).

Desulfurization of major diastereomer **14** with Raney Ni in methanol led to the corresponding optically active (*S*)-enantiomer **16** {$[a]_D^{25}$ = –205.00 (methanol, *c* = 0.2)}. The purity of **16** was also confirmed by ^{1}H NMR spectroscopy with the addition of the chiral shift reagent europium tris(3-

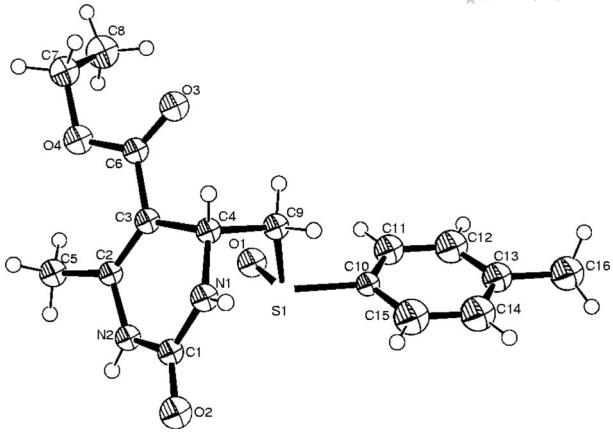


Figure 2. X-ray crystal structure of **14**.

heptafluoropropylhydroxymethylene)-(+)camphorate [Eu(hfc)$_3$]. Similarly, desulfurization of minor diastereomer **15** with Raney Ni furnished (*R*)-enantiomer **17** {$[a]_D^{25}$ = +160 (methanol, *c* = 0.2)}. (There is considerable variability in the magnitude of the specific rotation of the minor enantiomer, which can presumably be attributed to purity.) The (4*S*) configuration of the major enantiomer was also corroborated by CD spectroscopic analysis (Figure 3) of **16** with that of a 4-methyl DHPM of known absolute configuration.[34]

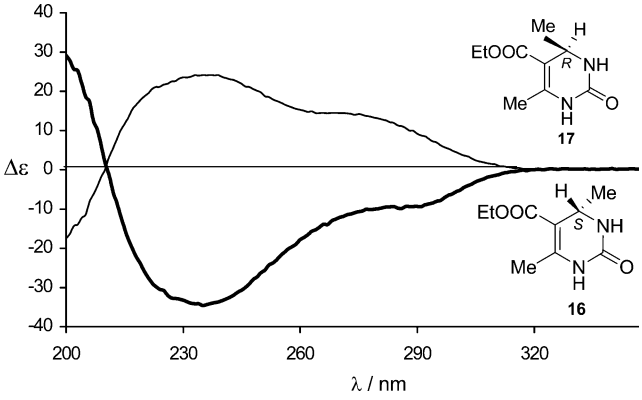


Figure 3. Experimental CD spectra of **16** and **17**.

Further, in view of the exceptional stabilization influence of the sulfoxide sulfur to the *α*-carbanions, synthesis of a number of derivatives of **14** could be envisaged.

Biological Results and Discussion

Some of the newly synthesized compounds were screened for their calcium channel blocking activity on the basis of their ability to relax a membrane-depolarization-induced contraction of vascular smooth muscle. Swine carotid arteries were obtained from a local slaughterhouse and transported to the laboratory in an ice-cold physiological salt solution (PSS) buffered (pH 7.4) with 3-[*N*-morpholino]-propane sulfonic acid (MOPS). The PSS contained NaCl (140 mM), KCl (4.7 mM), $MgSO_4$ (1.2 mM), $CaCl_2$ (1.6 mM), Na_2HPO_4 (1.2 mM), MOPS, D-glucose (5 mM) and diso-

dium ethylenediaminetetraacetate (EDTA; 0.02 mM). Arteries were cleaned of connective tissue, and then dissected free of both intima and adventitia leaving a thin medial layer for experimentation. Intact medial strips of swine carotid artery (7 × 0.7 mm) were suspended between a Grass FT.03 force transducer and a stationary clip in water jacketed organ baths. The strips were equilibrated in PSS at 37 °C, pH 7.4 and bubbled with 100% O_2 for 90–120 min. A passive force of ca. 2 g was applied to all tissues. This passive force sets the muscle at a length that approximates L_o, the length at which maximal active force is generated. During the equilibration period, tissues were maximally contracted with 110 mM KCl (equimolar substitution for NaCl) several times until similar levels of force were attained.

The equilibrated vascular strips were contracted with 110 mM KCl containing PSS, allowed to achieve a stable level of force and then subjected to the cumulative addition of calcium channel blocker (1 μM–30 mM) or DMSO as a vehicle control. Data are presented (Figure 4) as a percent of the initial maximal response to 110 mM KCl at each dose of compound.

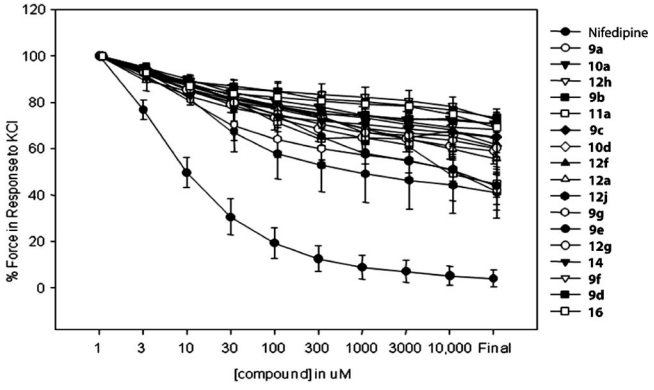


Figure 4. Medial strips from the swine carotid artery were contracted with 110 mM KCl-PSS and then subjected to the cumulative addition of calcium channel blocker to determine their potential for relaxation. Nifedipine and **17** novel calcium channel blockers were tested.

The calcium channel blockers were compared against nifedipine for their ability to relax a membrane-depolarization-induced contraction, which is almost exclusively dependent on the influx of extracellular calcium.[35] The novel compounds and nifedipine were tested across a concentration range of 1 μM to 30 mM. Nifedipine completely relaxed the KCl-induced contraction with an IC_{50} value in the 10 μM range. In contrast, these compounds maximally relaxed the KCl-induced contractions by only 40% with IC_{50} values ranging from 100–300 μM (Figure 4).

Conclusions

In summary, inspired by the biological potential of a number of dihydropyrimidinone-based natural products, we developed a method for the highly regio- and chemoselective synthesis of C-4-elaborated DHPMs. This approach allows incorporation of aliphatic, aromatic and heterocyclic substituents with the possibility of further synthetic transformations on the C-4 substituents. Also, this approach was extended to synthesize both enantiomers of DHPM through the use of optically pure sulfoxide carbanions. Finally, DHPMs with variation in the substituents at C-4 were tested for their ability to relax a membrane-depolarization-induced contraction, which is almost exclusively dependent on the influx of extracellular calcium. Long aliphatic chains appended at C-4 do not seem to be particularly useful for calcium channel blocking activity in so far as their comparison with 4-aryl derivatives of DHPMs is concerned.

Experimental Section

General: Freshly prepared *n*-butyllithium (2.0 N in hexanes), phenyllithium, LDA and Grignard reagents were employed. Tetrahydrofuran and diethyl ether were dried (sodium benzophenone ketyl) under an atmosphere of nitrogen and transferred with hypodermic glass syringes. All liquid reagents were dried/purified following recommended drying agents and/or distilled from 4 Å molecular sieves. Reactions were run under an atmosphere of dry nitrogen in a single-necked round-bottomed flask, sealed with a rubber septum (Aldrich). The reagents were introduced through hypodermic syringes and/or cannula. The low temperature was achieved by using a slush of liquid nitrogen with the appropriate solvent or alternatively by using dry ice. Precoated aluminum TLC plates (60 F_{254}, 0.2 mm) were used for TLC monitoring of the reactions. The compounds were purified by flash chromatography with the use of silica gel (60–120 mesh) and mixtures of ethyl acetate/hexane as eluent. Melting points were determined in open capillaries and are uncorrected. ^1H and ^{13}C NMR spectra were recorded with a JEOL FTNMR AL-300 MHz spectrometer by using TMS as an internal standard. The mass spectra were recorded with an Esquire 3000–00037 mass spectrometer. Elemental analysis was performed with a Thermo Flash EA 112. Analyses indicated by the symbols of the elements were within ±0.4% of the theoretical values. Optical rotations were recorded with an Atago (AP-100) digital polarimeter at 25 °C. The CD spectra were recorded with an Applied Photophysics Chirascan circular dichroism spectrometer with stop flow.

Typical Procedure for the Synthesis of 8a,b

Method A: To a stirred aqueous solution of nitric acid (40% v/v, 6.5 mL) maintained at 0 °C was added powdered DHPM **7a** or **7b** (4.0 mmol) portionwise over 5–10 min. The reaction was stirred for an additional 5 min at the same temperature, after which the mixture was warmed to room temperature over 30 min. The mixture was poured onto crushed ice (10 g) and neutralized to pH 7.0 by using solid potassium carbonate. The resulting aqueous solution was subsequently extracted with dichloromethane (3 × 30 mL), the organic layer was dried with anhydrous sodium sulfate, and the solvents were evaporated under reduced pressure. The residual product was purified by recrystallization from ethanol to obtain **8**.

Method B: A solution of DHPM **7** (1.97 mmol) in dichloromethane was stirred with PCC (5.90 mmol) (Aldrich) until the reaction was complete (16–25 h, TLC). The reaction mixture was filtered through Celite to remove any suspension, and the residue obtained after removal of the solvent was purified by flash chromatography to obtain corresponding pyrimidinone **8**.

Ethyl 1,2-Dihydro-1,6-dimethyl-2-oxopyrimidine-5-carboxylate (8a): Cream-coloured solid. R_f = 0.5 (70% ethyl acetate/hexane). Yield: 80%. M.p. 212 °C (dichloromethane). IR (KBr): $\tilde{\nu}$ = 1680,

1690 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.37 (t, J = 7.2 Hz, 3 H), 2.71 (s, 3 H), 3.61 (s, 3 H), 4.33 (q, J = 7.2 Hz, 2 H), 8.39 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 14.2, 26.1, 39.1, 61.2, 108.1, 152.6, 155.0, 163.1, 176.6 ppm. MS: m/z = 219 [M + 23]. $C_9H_{12}N_2O_3$ (196.21): calcd. C 55.10, H 6.12, N 14.28; found C 54.75, H 6.01, N 14.14.

Ethyl 1,2-Dihydro-6-methyl-2-oxopyrimidine-5-carboxylate (8b): Cream-coloured solid. R_f = 0.5 (80% ethyl acetate/hexane). Yield: 75%. M.p. 210 °C (methanol). IR (KBr): $\tilde{\nu}$ = 1675, 1680 cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO, 25 °C): δ = 1.23 (t, J = 7.2 Hz, 3 H), 2.49 (s, 3 H), 4.18 (q, J = 7.2 Hz, 2 H), 8.69 (s, 1 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$/[D_6]DMSO, 25 °C): δ = 14.0, 20.8, 60.4, 106.2, 152.6, 155.5, 163.5, 165.0 ppm. MS: m/z = 205 [M + 23]. $C_8H_{10}N_2O_3$ (182.18): calcd. C 52.74, H 5.53, N 15.38; found C 52.45, H 5.42, N 15.14.

Synthesis of 9a: A solution of ethyl acetoacetate (6.37 mmol) in anhydrous THF (10 mL) under an atmosphere of dry nitrogen was cooled to 0 °C and treated with NaH (6.37 mmol). After the cessation of hydrogen gas, freshly prepared *n*BuLi (2.0 N in hexanes, 6.37 mmol) was introduced through a hypodermic syringe at the same temperature, and the reaction was then stirred at ambient temperature for 30 min, whereupon an intense yellow-coloured anion formed. The dianion suspension was cooled to –78 °C and quenched by the addition of **8a** (2.5 mmol) dissolved in THF (20 mL). The progress of the reaction was monitored by TLC. After completion of the reaction, it was quenched with cold saturated aqueous solution of NH_4Cl at low temperature. The organic phase was washed with brine and extracted with ethyl acetate. The extract was dried with anhydrous sodium sulfate, and the mixture was concentrated under reduced pressure. Corresponding product **9a** was isolated in 73% yield after column chromatography (silica gel; ethyl acetate/hexane).

Formation of DHPM Derivatives 9 and 10: For the synthesis of **9** and **10** (Table 1), appropriate **8a** and **8b** (Table 1) was similarly treated with anions of various carbon acids [read: carbon acid (equivalents of base used) product]: ethyl acetoacetate (2.0), **10a**; methyl acetoacetate (2.0), **10b**; acetone (2.5), **9b**; acetonitrile (1.5), **10c**; acetophenone (2.5), **9c**; methyl phenyl sulfone (2.5), **9d**; methyl phenyl sulfone (2.0), **10d**; thiophene (2.5), **9e**; thiophene (2.5), **10e**; furan (2.5), **9f**; furan (2.5), **10f**; PhLi (2.5 mmol), **9g**.

Formation of DHPM Derivatives 11 and 12 – Typical Procedure for the Synthesis of 11a: Grignard reagent[24] (6.37 mmol) prepared by using activated magnesium metal (6.37 mmol) and iodomethane (6.37 mmol) in anhydrous ether was transferred to a solution of **8a** (2.55 mmol) in anhydrous THF maintained at –78 °C under a nitrogen atmosphere. Extractive workup from ethyl acetate and column chromatography furnished product **11a** in 92% yield. Similar reaction of **8** with other Grignard reagents (Table 2) furnished corresponding products **12a**–**j**.

Synthesis of DHPM Diastereomers 14 and 15: (*R*)-(+)-Methyl *p*-tolyl sulfoxide was prepared from (1*R*,2*S*,5*R*)-(–)-menthyl (*S*)-*p*-toluenesulfinate following the procedure of Solladie.[33] To a solution of diisopropylamine (8.35 mmol) in THF (2 mL) was added *n*BuLi (8.25 mmol) dropwise at –78 °C under a nitrogen atmosphere. The solution was warmed to 0 °C and stirred for an additional 10 min. The solution was cooled to –78 °C and precooled THF (25 mL at –78 °C) was added with stirring. (*R*)-(+)-Methyl *p*-tolyl sulfoxide (5.50 mmol) dissolved in THF (10 mL) was then introduced by hypodermic syringe, and the solution was stirred for an additional 10 min to ensure complete deprotonation to the monoanion. A solution of **8b** (2.75 mmol) dissolved in THF (20 mL) was introduced with the help of cannula. The reaction was warmed to room temperature and stirring was continued to complete the reaction (TLC), after which a saturated aqueous solution of NH_4Cl was introduced. The reaction was extracted with ethyl acetate (3 × 25 mL) and treated in sequence with brine. The extracts were dried with anhydrous Na_2SO_4, and the mixture was concentrated under reduced pressure. Diastereomers **14** and **15** were resolved by crystallization (methanol) of the column chromatographed mixture.

(4*R*,S*R*)-Ethyl 1,2,3,4-Tetrahydro-6-methyl-2-oxo-4-(*p*-tolylsulfinylmethyl)pyrimidine-5-carboxylate (14): Major diastereomer, white solid. R_f = 0.5 (45% ethyl acetate/hexane). Yield: 70%. M.p. 216–219 °C (methanol). $[\alpha]_D^{25}$ = +10 (methanol, c = 0.2). IR (KBr): $\tilde{\nu}$ = 1676, 1706 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.29 (t, J = 7.2 Hz, 3 H), 2.25 (s, 3 H), 2.41 (s, 3 H), 2.87–3.18 (AB part of ABX, J_{AX} = 13.2 Hz, J_{BX} = 3.6 Hz, 2 H), 4.14–4.24 (m, 2 H), 5.03 (dd, J_{AX+BX} = 9.0 Hz, 1 H), 6.18 (s, NH, exchanged with D_2O), 7.29–7.54 (m, 4 H), 7.67 (br., 1 H, NH, exchanged with D_2O) ppm. ^{13}C NMR (75 MHz, $CDCl_3$/[D_6]DMSO, 25 °C): δ = 14.1, 18.5, 21.2, 49.2, 59.9, 62.7, 97.8, 123.7, 129.9, 140.6, 141.6, 149.1, 152.7, 165.1 ppm. MS: m/z = 359 [M + 23]. $C_{16}H_{20}N_2O_4S$ (336.41): calcd. C 57.14, H 5.95, N 8.33, S 9.52; found C 57.15, H 6.00, N 8.50, S 9.38.

(4*S*,S*R*)-Ethyl 1,2,3,4-Tetrahydro-6-methyl-2-oxo-4-(*p*-tolylsulfinylmethyl)pyrimidine-5-carboxylate (15): Minor diastereomer, white solid. R_f = 0.5 (45% ethyl acetate/hexane). Yield: 20%. M.p. 180–181 °C (methanol). $[\alpha]_D^{25}$ = +185 (methanol, c = 0.2). ^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.07 (t, J = 7.2 Hz, 3 H), 2.27 (s, 3 H), 2.43 (s, 3 H), 2.71–3.34 (AB part of ABX, J_{AX} = 13.2 Hz, J_{BX} = 3.6 Hz, 2 H), 3.88–4.03 (m, 2 H), 4.84 (dd, J_{AX+BX} = 9.6 Hz, 1 H), 6.27 (s, NH, exchanged with D_2O), 7.35–7.53 (m, 4 H), 7.67 (br., 1 H, NH, exchanged with D_2O) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C): δ = 14.2, 18.6, 21.3, 47.5, 59.8, 97.9, 124.1, 130.0, 139.2, 141.5, 149.5, 153.4, 164.7 ppm. MS: m/z = 359 [M + 23]. $C_{16}H_{20}N_2O_4S$ (336.41): calcd. C 57.14, H 5.95, N 8.33, S 9.52; found C 57.20, H 6.92, N 8.28, S 9.56.

Synthesis of Enantiomeric DHPMs 16 and 17 by the Reductive Desulfurization of 14 and 15: A solution of compound **14** or **15** (0.14 mmol) in dry methanol (50 mL) was treated with an excess amount of Raney Ni (2 g) at 0 °C. Whereas complete desulfurization of **14** required stirring at room temperature followed by overnight reflux, the desulfurization of **15** was complete at 0 °C. After completion (TLC), reaction mixtures were filtered through Celite, and the solvent was removed under reduced pressure. The crude product was purified by crystallization in methanol.

(4*S*)-Ethyl 1,2,3,4-Tetrahydro-4,6-dimethyl-2-oxopyrimidine-5-carboxylate (16): White solid. R_f = 0.5 (60% ethyl acetate/hexane). Yield: 51%. M.p. 206–210 °C (methanol). $[\alpha]_D^{25}$ = –205.00 (methanol, c = 0.2).^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.25–1.31 (m, 6 H), 2.28 (s, 3 H), 4.15–4.23 (m, 2 H), 4.41–4.44 (m, 1 H), 5.25 (br., 1 H, NH, exchanged with D_2O), 7.14 (br., 1 H, NH, exchanged with D_2O) ppm. ^{13}C NMR (75 MHz, $CDCl_3$/[D_6]-DMSO, 25 °C): δ = 13.7, 17.6, 22.9, 46.4, 59.0, 101.2, 146.5, 153.7, 165.4 ppm. MS: m/z = 221 [M + 23]. $C_9H_{14}N_2O_3$ (198.22): calcd. C 54.53, H 7.12, N 14.13; found C 54.65, H 7.14, N 14.20.

(4*R*)-Ethyl 1,2,3,4-Tetrahydro-4,6-dimethyl-2-oxopyrimidine-5-carboxylate (17): White solid. R_f = 0.5 (60% ethyl acetate/hexane). Yield: 45%. M.p. 195–198 °C (methanol). $[\alpha]_D^{25}$ = +160 (methanol, c = 0.2).^1H NMR (300 MHz, $CDCl_3$, 25 °C): δ = 1.25–1.31 (m, 6 H), 2.28 (s, 3 H), 4.15–4.23 (m, 2 H), 4.40–4.44 (m, 1 H), 5.08 (br., 1 H, NH, exchanged with D_2O), 6.57 (br., 1 H, NH, exchanged with D_2O) ppm. ^{13}C NMR (75 MHz, $CDCl_3$ 25 °C): δ = 14.3, 18.5, 23.6, 47.5, 59.8, 102.6, 146.1, 154.2, 165.7 ppm. MS: m/z = 221 [M

+ 23]. $C_9H_{14}N_2O_3$ (198.22): calcd. C 54.53, H 7.12, N 14.13; found C 54.41, H 7.06, N 14.05.

CCDC-628121 (for **14**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see also the footnote on the first page of this article): All ^1H and ^{13}C NMR spectroscopic data for the products listed in Tables 1 and 2.

Acknowledgments

The authors thank Dr. K. A. Suri, Deputy Director, Institute of Integrated Medicine, Jammu, for his help in acquiring the mass spectrometric data, the National Single-Crystal X-ray diffraction Facility, IIT, Bombay, for X-ray analysis and AIF-USIC, Jawaharlal Nehru University, New Delhi, for recording the CD spectra. Financial support of the University Grants Committee (UGC), New Delhi (31-53/2005/SR) and the National Institutes of Health (NIH) (HL 37956) is gratefully acknowledged. D.A. thanks the Council of Scientific and Industrial Research (CSIR), New Delhi, for a senior research fellowship.

[1] P. Biginelli, *Gazz. Chim. Ital.* **1893**, *23*, 360–416.
[2] K. S. Atwal, B. N. Swanson, S. E. Unger, D. M. Floyd, S. Moreland, A. Hedberg, B. C. O'Reilly, *J. Med. Chem.* **1991**, *34*, 806–811.
[3] a) T. U. Mayer, T. M. Kapoor, S. J. Haggarty, R. W. King, S. L. Schreiber, T. J. Mitchison, *Science* **1999**, *286*, 971–974; b) S. J. Haggarty, T. U. Mayer, D. T. Miyamoto, R. Fathi, R. W. King, T. J. Mitchison, S. L. Schreiber, *Chem. Biol.* **2000**, *7*, 275–286.
[4] J. C. Barrow, P. G. Nantermet, H. G. Selnick, K. L. Glass, K. E. Rittle, K. F. Gilbert, T. G. Steele, C. F. Homnick, R. M. Freidinger, R. W. Ransom, P. Kling, D. Reiss, T. P. Broten, T. W. Schorn, R. S. L. Chang, S. S. O'Malley, T. V. Olah, J. D. Ellis, A. Barrish, K. Kassahun, P. Leppert, D. Nagarathnam, C. Forray, *J. Med. Chem.* **2000**, *43*, 2703–2718.
[5] K. Deres, C. H. Schroeder, A. Paessens, S. Goldmann, H. J. Hacker, O. Weber, T. Kramer, U. Niewoehner, U. Pleiss, J. Stoltefuss, E. Graef, D. Koletzki, R. N. A. Masantschek, A. Reimann, R. Jaeger, R. Grob, B. Beckermann, K.-H. Schlemmer, D. Haebich, H. Ruebsamen-Waigmann, *Science* **2003**, *299*, 893–896.
[6] A. D. Patil, N. V. Kumar, W. C. Kokke, M. F. Bean, A. J. Freyer, C. DeBrosse, S. Mai, A. Truneh, D. J. Faulkner, *J. Org. Chem.* **1995**, *60*, 1182–1188.
[7] S.-W. Yang, T.-M. Chan, S. A. Pomponi, G. Chen, A. E. Wright, M. Patel, V. Gullo, B. Pramanik, M. Chu, *J. Antibiot.* **2003**, *56*, 970–972.
[8] a) D. Dallinger, C. O. Kappe, *Pure Appl. Chem.* **2005**, *77*, 155–161; b) C. O. Kappe, *QSAR Comb. Sci.* **2003**, *22*, 630–645.
[9] a) K. Singh, S. Singh, A. Mahajan, *J. Org. Chem.* **2005**, *70*, 6114–6117; b) K. Singh, D. Arora, S. Singh, *Tetrahedron Lett.* **2006**, *47*, 4205–4207; c) K. Singh, S. Singh, *Tetrahedron Lett.* **2006**, *47*, 8143–8146; d) K. Singh, S. Singh, *Tetrahedron* **2008**, *64*, 1171–1173; e) K. Singh, D. Arora, E. Poremsky, J. Lowery, R. S. Moreland, *Eur. J. Med. Chem.* **2009**, *44*, 1997–2001; f) K. Singh, D. Arora, K. Singh, S. Singh, *Mini-Rev. Med. Chem.* **2009**, *9*, 95–106.
[10] K. Singh, D. Arora, S. Singh, *Tetrahedron Lett.* **2007**, *48*, 1349–1352 (preliminary communication).
[11] G. C. Rovnyak, S. D. Kimball, B. Beyer, G. Cucinotta, J. D. DiMarco, J. Gougoutas, A. Hedberg, M. Malley, J. P. McCarthy, R. Zhang, S. Moreland, *J. Med. Chem.* **1995**, *38*, 119–129.
[12] C. O. Kappe, A. Stadler, *Org. React.* **2004**, *63*, 1–116.
[13] K. Singh, H. Singh, *Adv. Heterocycl. Chem.* **2006**, *91*, 159–188.
[14] A. Puchala, F. Belaj, J. Bergman, C. O. Kappe, *J. Heterocycl. Chem.* **2001**, *38*, 1345–1352.
[15] K. Singh, K. Singh, *Aust. J. Chem.* **2008**, *61*, 910–913.
[16] A. I. Meyers, T. Oppenlaender, *J. Chem. Soc., Chem. Commun.* **1986**, 920–921.
[17] D. L. Comins, A. H. Abdullah, *J. Org. Chem.* **1982**, *47*, 4315–4319.
[18] S. N. Huckin, L. Weiler, *J. Am. Chem. Soc.* **1974**, *96*, 1082–1087.
[19] K. Singh, J. Singh, H. Singh, *Tetrahedron* **1998**, *54*, 3567–3574.
[20] I. W. J. Still (Ed.), *The Chemistry of Sulphones and Sulphoxides* (Eds.: S. Patai, Z. Rappoport, C. Stirling), John Wiley & Sons, Chichester, **1988**.
[21] E. Jones, I. M. Moodie, *Org. Synth.* **1988**, *6*, 979–980.
[22] S. T. Perri, P. Rice, H. W. Moore, *Org. Synth.* **1993**, *8*, 179–181.
[23] B. J. Wakefield, *Organolithium Methods*, Academic Press, London, **1990**, ch. 3, p. 24.
[24] G. S. Hiers, *Org. Synth.* **1941**, *1*, 550–552.
[25] C. O. Kappe, G. Uray, P. Roschger, W. Lindner, C. Kratky, W. Keller, *Tetrahedron* **1992**, *48*, 5473–5480.
[26] a) A. Dondoni, A. Massi, A. Sabbatini, V. Bertolasi, *J. Org. Chem.* **2002**, *67*, 6979–6994; b) A. Dondoni, A. Massi, *Acc. Chem. Res.* **2006**, *39*, 451–463.
[27] P. A. Evans, J. Qin, J. E. Robinson, B. Bazin, *Angew. Chem. Int. Ed.* **2007**, *46*, 7417–7419.
[28] a) O. P. Kleidernigg, C. O. Kappe, *Tetrahedron: Asymmetry* **1997**, *8*, 2057–2067; b) W. Krenn, P. Verdino, G. Uray, K. Faber, C. O. Kappe, *Chirality* **1999**, *11*, 659–662; c) D. Kontrec, V. Vinkovic, V. Sunjic, B. Schuiki, W. M. F. Fabian, C. O. Kappe, *Chirality* **2003**, *15*, 550–557; d) F. Wang, T. O'Brian, T. Dowling, G. Bicker, J. Wyvratt, *J. Chromatogr. A* **2002**, *958*, 69–77; e) F. Wang, R. M. Wenslow, T. M. Dowling, K. T. Mueller, I. Santos, J. Wyvratt, *Anal. Chem.* **2003**, *75*, 5877–5885; f) M. Yarim, S. Sarac, *Chromatographia* **2002**, *56*, 307–312; g) D. M. Forjan, I. Gazic, V. Vinkovic, *Chirality* **2007**, *19*, 446–452.
[29] D. R. Sidler, N. Barta, W. Li, E. Hu, L. Matty, N. Ikemoto, J. S. Campbell, M. Chartrain, K. Gbewonyo, R. Boyd, E. G. Corley, R. G. Ball, R. D. Larsen, P. J. Reider, *Can. J. Chem.* **2002**, *80*, 646–652.
[30] a) Y. Huang, F. Yang, C. Zhu, *J. Am. Chem. Soc.* **2005**, *127*, 16386–16387; b) O. M. Muniz, E. Juaristi, *Arkivoc* **2003**, *11*, 16–26.
[31] a) X.-H. Chen, X.-Y. Xu, H. Liu, L.-F. Cun, L.-Z. Gong, *J. Am. Chem. Soc.* **2006**, *128*, 14802–14803; b) L.-Z. Gong, X.-H. Chen, X.-Y. Xu, *Chem. Eur. J.* **2007**, *13*, 8920–8926; c) J. Xin, L. Chang, Z. Hou, D. Shang, X. Liu, X. Feng, *Chem. Eur. J.* **2008**, *14*, 3177–3181; d) Y.-Y. Wu, Z. Chai, X.-Y. Liu, G. Zhao, S.-W. Wang, *Eur. J. Org. Chem.* **2009**, 904–911; e) S. Lou, P. Dai, S. E. Schaus, *J. Org. Chem.* **2007**, *72*, 9998–10008; f) S. Lou, B. M. Taoka, A. Ting, S. E. Schaus, *J. Am. Chem. Soc.* **2005**, *127*, 11256–11257; g) J. M. Goss, S. E. Schaus, *J. Org. Chem.* **2008**, *73*, 7651–7656.
[32] a) M. C. Carreno, *Chem. Rev.* **1995**, *95*, 1717–1760; b) H. Pellissier, *Tetrahedron* **2006**, *62*, 5559–5601.
[33] G. Solladie, J. Hatt, A. Girardin, *Synthesis* **1987**, 173.
[34] G. Uray, P. Verdino, F. Belaj, C. O. Kappe, W. M. F. Fabian, *J. Org. Chem.* **2001**, *66*, 6685–6694.
[35] S. Moreland, R. S. Moreland, *Am. J. Physiol.* **1987**, *252*, H1049–H1058.

Received: March 1, 2009
Published Online: May 15, 2009

