

Design and Synthesis of a Conformationally Rigid Mimic of the Dihydropyrimidine Calcium Channel Modulator SQ 32,926[‡]

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Abstract: A conformationally rigid polyheterocycle (**3**) which mimics the putative receptor-bound conformation of dihydropyridine-type calcium channel modulators is prepared in a seven-step reaction sequence based on a Biginelli-type cyclocondensation reaction.

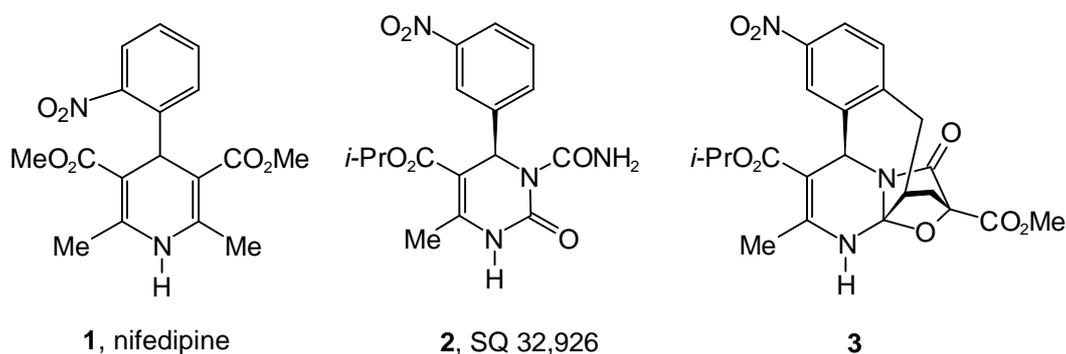
Keywords: Dihydropyrimidines, Biginelli reaction, isomünchnones, 1,3-dipolar cycloaddition reactions, AM1 calculations, conformation.

Introduction

4-Aryl-1,4-dihydropyridines (DHPs, e.g. nifedipine, **1**) are the most studied class of organic calcium channel modulators and, since their introduction into clinical medicine in 1975, have become almost indispensable for the treatment of cardiovascular diseases such as hypertension, cardiac arrhythmias, or angina [1]. More than 25 years after the introduction of nifedipine (**1**), many DHP analogs have now

been synthesized and numerous second-generation commercial products have appeared on the market [2].

In recent years interest has also focused on aza-analogs such as dihydropyrimidines of type 2 (DHPMs) which show a very similar pharmacological profile to classical dihydropyridine calcium channel modulators [3-9]. Over the past few years several lead-compounds were developed (*i.e.* SQ 32,926) [6-8] that are superior in potency and duration of antihypertensive activity to classical DHP drugs, and compare favorably with second-generation analogs such as amlodipine and nicardipine [6,7]. These inherently asymmetric DHPM derivatives are not only very potent calcium channel modulators, but also have been studied extensively to expand the existing structure-activity relationships and to get further insight into molecular interactions at the receptor level [3-9].



DHP calcium channel antagonists (*e.g.* 1, nifedipine) are flexible molecules, in which the C4-aryl moiety and the C3/C5 ester substituents can rotate, and the conformation of the 1,4-dihydropyridine ring can change [10]. Despite many studies on the structure-activity relationships for DHPs and DHPMs with respect to calcium channel antagonist-agonist modulation, there still remains debate on the exact stereochemical/conformational requirements for activity [9-12]. It was recently proposed that calcium channel modulation (antagonist *vs.* agonist activity) is dependent on the absolute configuration at C4, whereby the orientation of the 4-aryl group (*R*- versus *S*-enantiomer) acts as a "molecular switch" between antagonist and agonist activity [9]. In the receptor-bound conformation the substituted aryl ring should be positioned axially, perpendicular to, and bisecting the boat-like dihydropyridine ring, with the 4-aryl substituent (X) preferring the synperiplanar (*sp*) orientation relative to C4-H (Figure 1) [9].

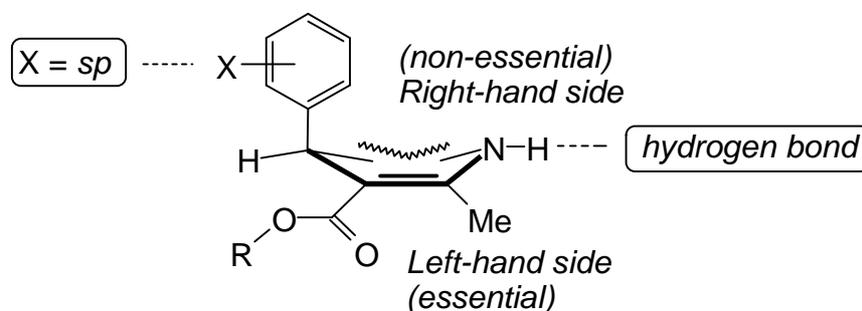


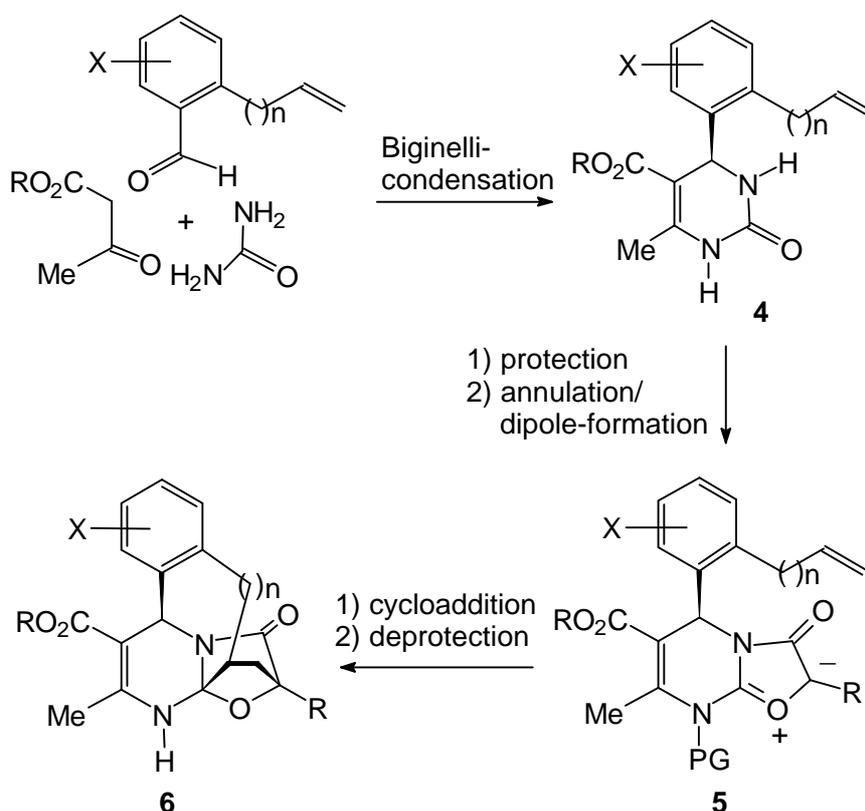
Figure 1. Proposed receptor-bound conformation of DHP/DHPM calcium channel modulators.

A *cis*-carbonyl ester orientation (with respect the C5=C6 bond) was also found mandatory for calcium channel modulatory activity, whereas the right-hand side of the dihydropyridine ring was proposed non-essential [9], providing a rationale for the similar pharmacological profile observed for DHPs and DHPMs.

In the present article we detail the synthesis of the polycyclic DHPM derivative **3** that represents a conformationally rigid analog of SQ 32,926 [6], "frozen" in the putative bioactive conformation shown in Figure 1. All structural changes on **2** are made on the non-essential right hand side of the molecule, thereby not interfering with the receptor-sensitive groups on the left-hand side.

Results and Discussion

The synthetic strategy towards the polycyclic DHPM derivative **3** is based on an intramolecular 1,3-dipolar cycloaddition reaction of an *o*-alkenylaryl-tethered dihydropyrimidine-fused isomünchnone dipole ("cyclization-cycloaddition cascade", see Scheme 1 [13]).

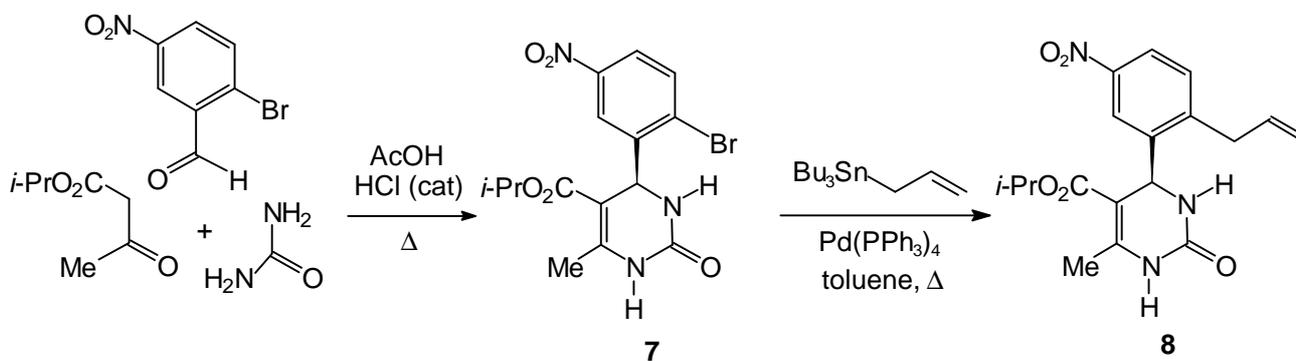


Scheme 1.

In recent publications we have described model studies dealing with bimolecular and intramolecular dipolar cycloaddition reactions of a variety of dihydropyrimidine-fused mesomeric betaines, including 1,3-thiazolium-4-olates, 1,3-oxazolium-4-olates, and cross-conjugated heteroaromatic 1,3-thiazinium

betaines [14]. These studies have led to the synthesis of biologically inactive polyheterocycles of type **6** where the crucial *N1* position of the pyrimidine nucleus (*cf.* Figure 1) is blocked by a methyl group [14]. More recently we have devised a modified protection group strategy in order to access derivatives where this position is unblocked [15]. These targets, however, still lacked the all important electron-withdrawing substituent on the aromatic ring (**6**, X = H) and therefore proved inactive.

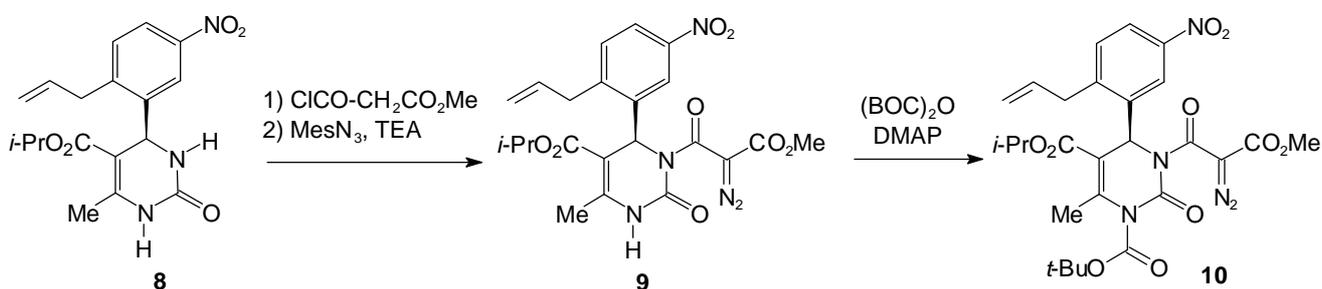
In order to prepare a conformationally rigid mimic of the orally active antihypertensive agent and calcium channel modulator SQ 32,926 (**2**) [6], a nitro group had to be introduced into the *meta*-position of the aromatic ring. We initially considered to use the corresponding 5-nitro-2-alkenylbenzaldehydes as suitable building blocks in a classical Biginelli-type cyclocondensation reaction (Scheme 1, \rightarrow **4**, X = NO₂) [16]. Apparently, such aldehydes are too unstable and have never been reported in the literature, and all our attempts to synthesize *e.g.* 5-nitro-2-vinyl-benzaldehyde failed. We have therefore chosen to introduce the *ortho*-alkenyl tether required for the intramolecular 1,3-dipolar cycloaddition at a later stage in the synthesis. The corresponding *ortho*-bromo substituted analog **7** was readily prepared by Biginelli condensation of 2-bromo-5-nitrobenzaldehyde with isopropyl acetoacetate and urea. Although a number of improved protocols for carrying out the one-pot Biginelli reaction have recently been reported [17], the method described by Folkers et al. in 1932 using acetic acid as solvent [18] proved to be superior to all other procedures, producing DHPM **7** in 66% yield. 2-Bromo-5-nitrobenzaldehyde was readily available by nitration of commercially 2-bromo-benzaldehyde with fuming HNO₃/H₂SO₄ [19]. In the next step the allyl tether was introduced on the DHPM scaffold via Stille reaction [20], using allyltributylstannane as reagent. The palladium-catalyzed cross coupling process was best performed in refluxing toluene using tetrakis(triphenylphosphine)palladium, as catalyst. Despite considerable variations in experimental conditions [20], the maximum yield of DHPM **8** obtained was 47%.



Scheme 2.

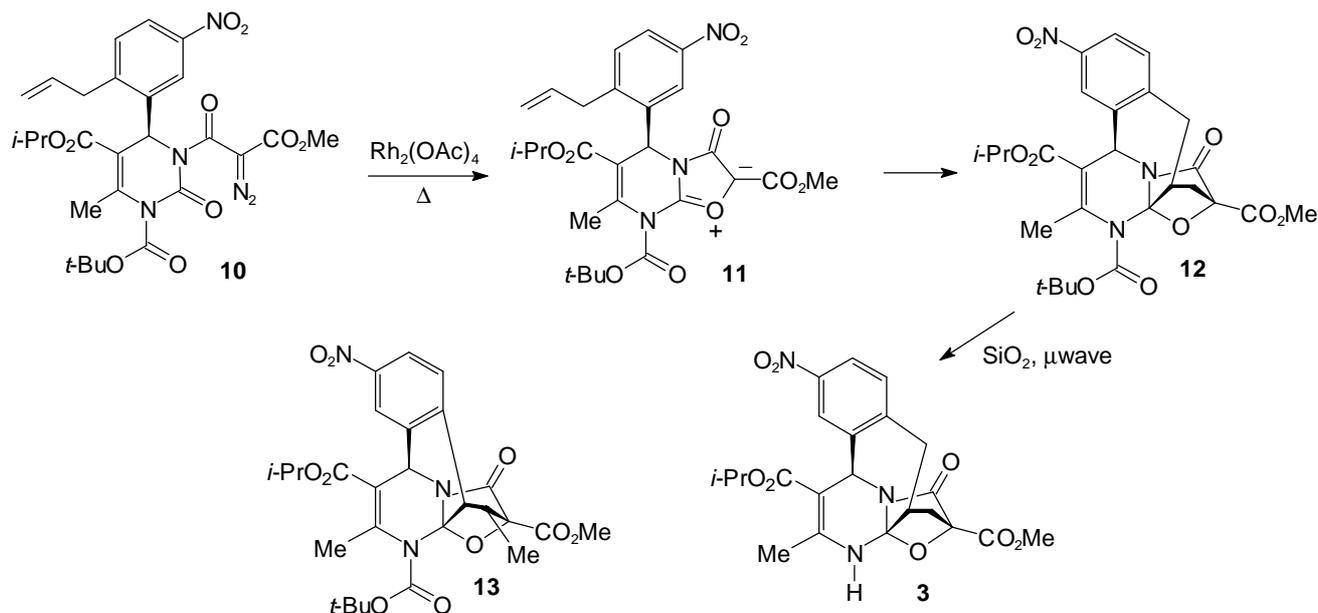
In order to set up the cyclization-cycloaddition cascade for the construction of polycycle **3** the urea moiety was functionalized at *N3* by regioselective malonylacylation [21] with commercially available methyl malonyl chloride. Even when a large excess of acylating reagent was used, the *N3*-acylated product was obtained in a regioselective manner, without any *N1*- or bis-acylation products being formed. In a subsequent step the diazo functionality was introduced by standard diazo transfer with

mesyl azide [22]. As we have previously noted, the protection of the *N1* nitrogen at this stage of the synthesis is crucial for the success of the cyclization-cycloaddition cascade [15]. In the absence of a protective group the isomünchone intermediate (*i.e.*, **5**, PG = H, Scheme 1) will undergo a rapid, thermally allowed 1,5-sigmatropic hydrogen shift to form an isomeric oxazole, which cannot participate in the anticipated cycloaddition sequence **5** → **6** [14]. In contrast to the CBZ-based (benzyloxycarbonyl) protection method that we have devised in our model studies [15], we have now employed the *N*-BOC-functionality (*tert*-butyloxycarbonyl) as protective group. The corresponding *N1*-BOC protected DHPM **10** was synthesized in standard fashion by treatment of DHPM **9** with (BOC)₂O/DMAP [23]. The advantage of this protection method is that the BOC group can easily be removed in the final product (see below) under conditions that do not require palladium-catalyzed hydrogenolysis, which here may not be compatible with the presence of a nitro group on the aromatic ring.



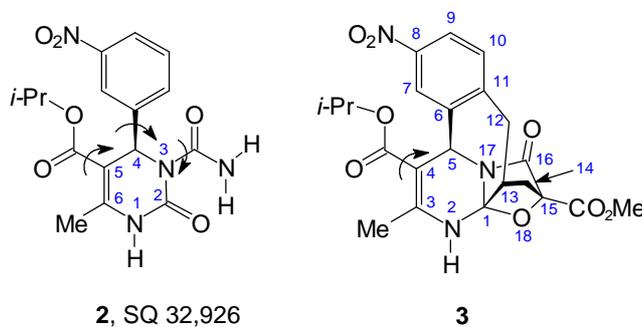
Scheme 3.

The final steps in the synthesis, the cyclization-cycloaddition cascade, is shown in Scheme 4. Decomposition of the BOC-protected diazo imide precursor **10** with a catalytic amount of rhodium acetate in refluxing benzene furnished directly the protected pentacyclic DHPM analog **12** in 55% yield, without isolation of the initially generated transient isomünchone dipole **11**. Note that in the absence of suitable dipolarophiles (*i.e.* an internal π -bond) such cyclic carbonyl ylide dipoles **11** can be isolated, and, in fact, are quite stable crystalline compounds [24]. In contrast to the cycloaddition reactions carried out on the earlier model systems [14,15], here an isomeric pentacycle **13** was additionally isolated in 38% yield. The formation of **13** can be rationalized in terms of a double bond isomerization in the allyl-tethered side chain, probably catalyzed by the transition metal (Rh^{2+}) present in the reaction medium. Regardless of the choice of catalyst (rhodium acetate or rhodium perfluorobutyrate) and reaction conditions (*e.g.* inverse addition) the ratio of these cycloaddition products remained unchanged. The structures of both cycloadducts were confirmed by comparison of their ¹H and ¹³C NMR spectra with spectroscopic data obtained for close analogs for which X-ray structure determinations had been carried out [14]. For pentacycle **13**, the position of the newly formed methyl group at C13 *anti* to the bridged aryl substituent follows from the observed small coupling constant for the two vicinal hydrogen atoms at C12 and C13 ($J = 2.9$ Hz, torsion angle ca. 115°). Finally, gentle removal of the BOC group in **12** was carried out by microwave-promoted deprotection following a recently reported protocol [25] to furnish the target compound **3** in 90% yield.



Scheme 4.

Molecular models based on semiempirical calculations of pentacycle **3** demonstrate that the geometry of this conformationally rigid DHPM derivative is very similar to the receptor-bound conformation proposed in Figure 1 for DHP/DHPM calcium channel modulators (see Figure 3). The aryl group is "tied" into the axial position and is (nearly) perpendicular to and bisecting the boatlike dihydropyrimidine ring. The nitro substituent on the aromatic ring is forced into the synperiplanar (*sp*) orientation relative to the C4-H atom. At the same time, the amide functionality on the right-hand side in SQ 32,926 here is fixed into the *trans* position. Only the isopropyl ester moiety on the left-hand side retains its conformational freedom (see Figure 2). According to semiempirical AM1 calculations, the *cis* carbonyl ester orientation in **3** is favoured over the corresponding *trans* orientation by 1.68 kcal/mol. In DHPMs these energy differences are generally small, and the rotational barriers have also been calculated to be relatively minor (2-4 kcal/mol) [26-28]. In a biological environment, both calculated minimum energy ester conformers therefore seem accessible.

Figure 2. Conformationally flexible bonds and functional groups in SQ 32,926 and DHPM **3**.

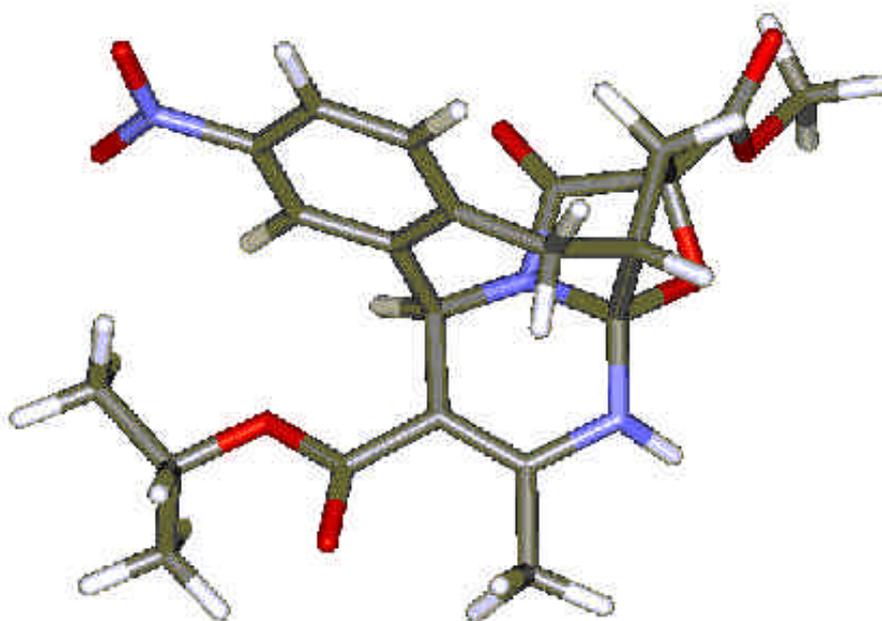


Figure 3. AM1 optimized geometry of the conformationally rigid pentacycle **3**.

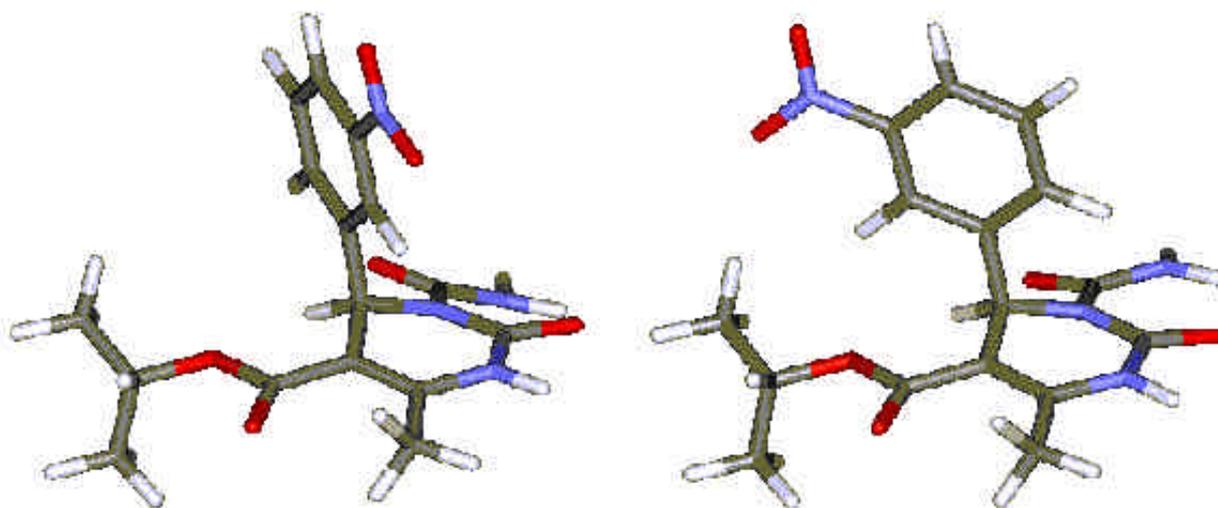


Figure 4. AM1 optimized geometries for the two lowest energy conformers of SQ 32,926 (*cis/ap*, left, $\Delta H_f = -109.55$ kcal/mol; *cis/sp*, right, $\Delta H_f = -109.11$ kcal/mol).

For comparison purposes, we have calculated the minimum energy geometries for the conformationally non-restricted SQ 32,926. Based on the presence of three conformationally flexible bonds (Figure 2) eight minimum conformers were located [26-28]. Since the intramolecular H-bond between the *N3*-carbamoyl NH and the C2 carbonyl oxygen stabilized the *trans* carbonyl arrangement shown in Figure 3 by at least 6 kcal/mol (AM1), the relatively high energy conformers with an *N3 cis* carbonyl oriented carbamoyl functionality (strong dipole-dipole repulsion) were discounted. Of the remaining

four conformers, the lowest energy conformer was the one having a C5 *cis* carbonyl oriented ester group with the nitro group on the C4-aryl ring oriented in antiperiplanar (*ap*) orientation with respect to C4-H (Figure 4). Note that this conformation does not correspond to the proposed bioactive *cis/sp* arrangement shown in Figure 1. However, the putative bioactive *cis/sp* conformer (Figure 4) is only 0.44 kcal/mol higher in energy than the lowest energy *cis/ap* conformer. The respective *trans* C5 ester carbonyl rotamers (not shown) were ca. 1.5-2.0 kcal/mol higher in energy than the corresponding *cis* isomers.

In conclusion, we have reported the synthesis and structural characterization of a conformationally rigid analog of the calcium channel modulator SQ 32,926. All modifications on the SQ 32,926 scaffold were performed on the putative [9] nonessential right-hand side of the molecule, thereby not interfering with the receptor sensitive groups on the left hand side. The current model compound mimics the proposed bioactive conformation of SQ 32,926 and therefore provides a tool to test the validity of the currently accepted binding site model for DHP/DHPM calcium channel modulators [9]. Preliminary electrophysiological measurements have confirmed that **3** has calcium channel antagonistic activity in the micromolar range. Further structural modifications on these dihydropyrimidine analogs are currently being considered in our laboratory in order to increase their activity (modification of the right-hand side). In addition, in order to test the binding site model depicted in Figure 1 it will be necessary to access enantiomerically pure **3** with known absolute configuration. Work along these lines is currently in progress in our laboratories [29].

Experimental

General Procedures and Materials

Melting points were determined on a Gallenkamp melting point apparatus, Mod. MFB-595, and are uncorrected. IR spectra were recorded on a Perkin-Elmer 298 spectrophotometer as KBr pellets. ¹H and ¹³C NMR spectra were obtained on a Varian XL-200 Gemini instrument at 200 MHz and 50 MHz, respectively (*J* values are given in Hz). Microanalyses were obtained on a Fisons Mod. EA 1108 elemental analyzer. Reactions were monitored by thin layer chromatography (TLC) on 0.2mm silica gel F-252 (Merck) plates. Flash chromatography was performed with silica gel 60 (40-63 μm, Aldrich) using mixtures of hexane and ethyl acetate as eluent. Methylene chloride, benzene, and THF were distilled and dried over 4 Å molecular sieves. Triethylamine was distilled from KOH before use. All moisture-sensitive reactions were carried out under dry argon atmosphere employing flame-dried glassware.

Computational Methods

Semiempirical AM1 calculations were carried out using the PC Spartan Pro package (Version 1.0.1) on a Pentium PC. Starting geometries were obtained using Spartans interactive building mode, and

preoptimized using the SYBYL force field. For pentacycle **3** the starting geometries were obtained from X-ray structure coordinates of close analogs [14]. Geometries were completely optimized without molecular mechanics corrections for amide bonds. Convergence was achieved in all optimizations.

2-Bromo-5-nitrobenzaldehyde

This material was prepared following a literature procedure [19]. 2-Bromobenzaldehyde (8.94 g, 48 mmol) was added dropwise under stirring at 5–10°C to a mixture of fuming HNO₃ (4 mL) and concentrated H₂SO₄ (30 mL). The resulting yellow solution was allowed to warm to rt and subsequently was poured onto ice-water, mp 98°C (cyclohexane); ¹H NMR (CDCl₃): δ 7.89 (d, *J* = 8.5 Hz, 1H, C3-H), 8.30 (dd, *J* = 3.0 and 8.5 Hz, 1H, C4-H), 8.73 (d, *J* = 3.0 Hz, 1H, C6-H), 10.40 (s, 1H, CHO).

Isopropyl 4-(2-Bromo-5-nitrophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (7)

A mixture of isopropyl acetoacetate (2.30 g, 16 mmol), 2-bromo-5-nitrobenzaldehyde (2.43 g, 11 mmol), urea (0.95 g, 11 mmol), and acetic acid (20 mL) containing conc. HCl (100 µL, ca. 4 drops) was heated under reflux for 24 h (after the first 6 h an additional quantity of conc HCl (100 µL) was added). After the mixture was allowed to stand at rt overnight, the precipitate was filtered and recrystallized from acetic acid to give 2.89 g (66%) of DHPM **7** as a colorless solid, mp 241°C; IR (KBr) 3380, 3080, 2950, 1710, 1650, 1520, 1450 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 0.79 and 1.12 (2 d, *J* = 6.4 Hz each, 6H, CH(CH₃)₂), 2.36 (s, 3H, C6-CH₃), 4.75 (m, *J* = 6.4 Hz, 1H, CH(CH₃)₂), 5.70 (s, 1H, C4-H), 7.80–8.10 (m, 4H, 3 ArH and N3-H), 9.45 (brs, 1H, N1-H) ppm. Anal. Calcd for C₁₅H₁₆BrN₃O₅: C, 45.20; H, 4.00; N, 10.60. Found: C, 45.58; H, 4.00; N, 10.24.

Isopropyl 4-(2-Allyl-5-nitrophenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (8)

To a suspension of DHPM **7** (1.15 g, 2.9 mmol) in dry toluene (20 mL) was added allyltributylstannane (0.95 g, 2.9 mmol), and Pd(PPh₃)₄ (67 mg, 2 mol%). The resulting mixture was heated at reflux for 48 h under an argon atmosphere. After all starting material had been consumed (¹H NMR analysis, if necessary additional catalyst was added) the dark solution was filtered and washed successively with 3% HCl (2 x 10mL), H₂O (2 x 10mL), and saturated NaHCO₃ (2 x 10mL). The organic layer was dried (Na₂SO₄) and toluene removed under reduced pressure. The crude material crystallized upon titration with hexane. Purification by silica gel flash chromatography (CHCl₃/acetone 7:3) furnished 0.49 g (47%) of DHPM **8** as a colorless solid, mp 175°C; IR (KBr) 3250, 3100, 2950, 1705, 1640, 1520, 1450 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 0.79 and 1.12 (2 d, *J* = 6.4 Hz each, 6H, CH(CH₃)₂), 2.34 (s, 3H, C6-CH₃), 3.73 (m, 2H, CH₂CH=CH₂) 4.77 (m, *J* = 6.4 Hz, 1H, CH(CH₃)₂), 5.19 (m, 2H, CH₂CH=CH₂), 5.59 (s, 1H, C4-H), 5.95–6.18 (m, 1H, CH₂CH=CH₂), 7.41–8.17 (m, 4H, 3 ArH and N3-H), 9.38 (brs, 1H, N1-H) ppm. Anal. Calcd for C₁₈H₂₁N₃O₅: C, 60.16; H, 5.88; N, 11.69. Found: C, 59.84; H, 5.91; N, 11.65.

Isopropyl 4-(2-Allyl-5-nitrophenyl)-3-[2-diazo-2-[(methoxy)carbonyl]acetyl]-6-methyl-2-oxo-1,2,3,4-tetrahydro-5-pyrimidinecarboxylate (9)

A mixture of DHPM **8** (1.08 g, 3.00 mmol), distilled methyl malonyl chloride (0.68 g, 5.00 mmol), and benzene (30 mL) was heated at reflux for 2 h. After all starting material had been consumed (TLC), the solution was cooled to ambient temperature. The solvent was evaporated under reduced pressure and the crude product purified by silica gel flash chromatography (hexane/EtOAc 2:1) to yield 980 mg (71%) of isopropyl 4-(2-allyl-2-nitrophenyl)-6-methyl-3-(2-methoxyacetyl)-2-oxo-1,2,3,4-tetrahydro-5-pyrimidine-carboxylate as colorless solid, mp 130°C; IR (KBr) 3260, 3150, 2960, 1760, 1740, 1705, 1640, 1520 cm⁻¹; ¹H NMR (DMSO-*d*₆) δ 1.08 and 1.20 (2 d, *J* = 6.4 Hz each, 6H, CH(CH₃)₂), 2.36 (s, 3H, C6-CH₃), 3.54 (s, 2H, COCH₂CO), 3.86 (s, 3H, OCH₃), 3.73-4.00 (m, 2H, CH₂CH=CH₂), 4.91 (m, *J* = 6.4 Hz, 1H, CH(CH₃)₂), 5.16-5.31 (m, 2H, CH₂CH=CH₂), 5.90-6.15 (m, 1H, CH₂CH=CH₂), 6.63 (s, 1H, C4-H), 7.45 (m, 1H, ArH), 8.12 (m, 2H, ArH), 10.56 (brs, 1H, N1-H) ppm. Anal. Calcd for C₂₂H₂₅N₃O₈: C, 57.51; H, 5.48; N, 9.14. Found: C, 57.18; H, 5.54; N, 8.85.

A mixture of the above 1,3-dicarbonyl compound (460 mg, 1.00 mmol), mesyl azide (145 mg, 1.20 mmol), triethylamine (250 mg, 2.50 mmol), and methylene chloride (5 mL) was stirred in the dark at rt for 24-48 h. After all starting material had been consumed (¹H NMR), an additional amount of solvent was added and the diazo-transfer reaction mixture was washed rapidly with ice-cold 5% aq. KOH (3 x 5 mL) and brine (3 x 10 mL). The organic layer was dried (Na₂SO₄) and the solvent evaporated under reduced pressure. The crude product was purified by flash chromatography (hexane/EtOAc, 1:1) to yield the diazo imide **9** (460 mg, 95%) as a yellow oil that slowly crystallizes, mp 121-122°C; IR (KBr) 3210, 3140, 2980, 2140, 1715, 1670, 1640, 1520 cm⁻¹; ¹H NMR (CDCl₃) δ 1.02 and 1.12 (2 d, *J* = 6.4 Hz each, 6H, CH(CH₃)₂), 2.42 (s, 3H, C6-CH₃), 3.82 (s, 3H, OCH₃), 3.73-4.21 (m, 2H, CH₂CH=CH₂), 5.00 (m, *J* = 6.4 Hz, 1H, CH(CH₃)₂), 5.22-5.36 (m, 2H, CH₂CH=CH₂), 5.93-6.15 (m, 1H, CH₂CH=CH₂), 6.31 (brs, 1H, C4-H), 7.35-8.28 (m, 4H, 3 ArH and N1-H) ppm, and minor rotamers.

1-tert.-Butyl 5-Isopropyl 4-(2-Allyl-5-nitrophenyl)-6-methyl-3-[2-diazo-2-[(methoxy)carbonyl]acetyl]-2-oxo-1,2,3,4-tetrahydro-1,5-pyrimidinedicarboxylate (10)

A solution of diazo imide **9** (340 mg, 0.70 mmol), 2.0 equiv. of (BOC)₂O (320 mg, 1.40 mmol), DMAP (90 mg, 0.70 mmol), and triethylamine (70 mg, 0.70 mmol) in dry CH₂Cl₂ (10 mL) was allowed to stir at rt for 2 h. It was then washed with cold 1M HCl, brine, dried (Na₂SO₄), evaporated to dryness and purified by silica gel flash chromatography (hexane/EtOAc 2:1) to yield 370 mg (90%) of the protected DHPM **10** as a yellow oil, IR (film) 2980, 2140, 1770, 1720, 1700, 1670, 1640, 1520 cm⁻¹; ¹H NMR (CDCl₃) δ 1.18 and 1.28 (2 d, *J* = 6.4 Hz each, 6H, CH(CH₃)₂), 1.67 (s, 9H, *t*-BuO), 2.54 (s, 3H, C6-CH₃), 3.82 (s, 3H, OCH₃), 3.73-4.20 (m, 2H, CH₂CH=CH₂), 5.05 (m, *J* = 6.4 Hz, 1H, CH(CH₃)₂), 5.22-5.37 (m, 2H, CH₂CH=CH₂), 5.92-6.17 (m, 1H, CH₂CH=CH₂), 6.28 (brs, 1H, C4-H),

7.35-8.28 (m, 3H, ArH) ppm, and minor rotamers.

4-Isopropyl 15-Methyl 2-tert.-Butyl 3-Methyl-8-nitro-16-oxo-18-oxa-2,17-diazapentacyclo[13.2.1.0^{1,13}.0^{5,17}.0^{6,11}]octadeca-3,6,8,10-tetraene-2,4,15-tricarboxylate (12)

A solution of diazo compound **10** (175 mg, 0.3 mmol) in dry benzene (10 mL) containing a catalytic amount of rhodium acetate (< 5 mg) was heated at reflux under argon for 4 h. After all starting material was consumed (TLC), the solvent was evaporated under reduced pressure and the crude product purified by flash chromatography (hexane/EtOAc, 1:1) to give pentacycle **12** ($R_f = 0.47$, 92 mg, 55%) as a colorless solid, mp 170-172°C, and the isomeric pentacycle **13** ($R_f = 0.55$, 63 mg, 38%) as a colorless solid, mp. 104-106°C; Data for **12**: IR (KBr) 2980, 1770, 1750, 1590, 1520 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.18 and 1.28 (2 d, $J = 6.4$ Hz each, 6H, $\text{CH}(\text{CH}_3)_2$), 1.43 (dd, $J = 5.5$ and 13.0 Hz, 1H, C14- H_a), 1.67 (s, 9H, *t*-BuO), 2.43 (dd, $J = 10.0$ and 13.0 Hz, 1H, C14- H_b), 2.64 (3 H, s, C3-Me), 2.98 (dd, $J = 5.5$ and 16.0 Hz, 1H, C12- H_a), 3.20 (m, 1H, C13-H), 3.37 (dd, $J = 2.0$ and 16.0 Hz, 1H, C12- H_b), 3.74 (3 H, s, OCH_3), 4.98 (m, $J = 6.4$ Hz, 1H, $\text{CH}(\text{CH}_3)_2$), 5.79 (s, 1H, C5-H), 7.22 (d, $J = 8.5$ Hz, 1H, C10-H), 8.04 (dd, $J = 3.0$ and 8.5 Hz, 1H, C9-H), 8.38 (d, $J = 3.0$ Hz, 1H, C7-H) ppm; ^{13}C NMR (CDCl_3) δ 18.6, 21.6, 22.0, 27.8, 31.5, 32.7, 41.9, 53.1, 54.2, 68.7, 85.0, 85.2, 97.9, 103.5, 122.9, 127.0, 133.6, 139.1, 141.6, 146.4, 147.2, 149.2, 164.2, 164.6, 166.5 ppm. Anal. Calcd. for $\text{C}_{27}\text{H}_{31}\text{N}_3\text{O}_{10}$: C, 58.16; H, 5.60; N, 7.53. Found: C, 58.29; H, 5.70; N, 7.53. Data for **13**: (KBr) 2980, 1770, 1750, 1590, 1520 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.44 (d, $J = 7.0$ Hz, 3H, C13-Me), 1.41 and 1.46 (2 d, $J = 6.4$ Hz each, 6H, $\text{CH}(\text{CH}_3)_2$), 1.55 (s, 9H, *t*-BuO), 2.30 (dd, $J = 2.9$ and 7.0 Hz, 1H, C13-H), 2.46 (3 H, s, C3-Me), 3.74 (d, $J = 2.9$ Hz, 1H, C12-H), 3.91 (3 H, s, OCH_3), 5.22 (m, $J = 6.4$ Hz, 1H, $\text{CH}(\text{CH}_3)_2$), 6.04 (s, 1H, C5-H), 7.31 (d, $J = 8.5$ Hz, 1H, C10-H), 8.09 (dd, $J = 3.0$ and 8.5 Hz, 1H, C9-H), 8.41 (d, $J = 3.0$ Hz, 1H, C7-H) ppm; ^{13}C NMR (CDCl_3) δ 16.7, 21.8, 22.1, 22.2, 28.1, 47.2, 48.9, 53.1, 53.5, 69.3, 85.3, 89.3, 97.2, 114.2, 122.6, 123.1, 130.4, 134.5, 139.9, 147.6, 150.0, 150.1, 163.2, 163.8, 166.6 ppm. Anal. Calcd. for $\text{C}_{27}\text{H}_{31}\text{N}_3\text{O}_{10}$: C, 58.16; H, 5.60; N, 7.53. Found: C, 58.40; H, 5.90; N, 7.23.

4-Isopropyl 15-Methyl 3-Methyl-8-nitro-16-oxo-18-oxa-2,17-diazapentacyclo[13.2.1.0^{1,13}.0^{5,17}.0^{6,11}]octadeca-3,6,8,10-tetraene-4,15-dicarboxylate (3)

To a solution of pentacycle **12** (56 mg, 0.1 mmol) in CH_2Cl_2 (10 mL) was added 1.50 g of silica gel 60. After evaporation of the solvent the dry powder was irradiated in a domestic microwave oven at 800 W for 3-5 min (TLC monitoring). Purification by silica gel flash chromatography provided 41 mg (90%) of the target compound **3** as a colorless solid, mp 155-157°C; IR (KBr) 3550-3200, 2980, 1750, 1720, 1695, 1600, 1520 cm^{-1} ; ^1H NMR (CDCl_3) δ 1.06 and 1.34 (2 d, $J = 6.4$ Hz each, 6H, $\text{CH}(\text{CH}_3)_2$), 1.47 (dd, $J = 5.5$ and 13.0 Hz, 1H, C14- H_a), 2.45 (dd, $J = 10.0$ and 13.0 Hz, 1H, C14- H_b), 2.46 (3 H, s, C3-Me), 2.68 (m, 1H, C13-H), 2.99 (dd, $J = 5.5$ and 16.0 Hz, 1H, C12- H_a), 3.38 (dd, $J = 2.0$ and 16.0 Hz, 1H, C12- H_b), 3.86 (3 H, s, OCH_3), 4.97 (m, $J = 6.4$ Hz, 1H, $\text{CH}(\text{CH}_3)_2$), 5.51 (s, 1H, N2-H), 5.79

(s, 1H, C5-H), 7.23 (d, $J = 8.5$ Hz, 1H, C10-H), 8.01 (dd, $J = 3.0$ and 8.5 Hz, 1H, C9-H), 8.41 (d, $J = 3.0$ Hz, 1H, C7-H) ppm; ^{13}C NMR (CDCl_3) δ 20.8, 21.8, 22.2, 31.4, 32.5, 43.8, 53.2, 53.9, 67.7, 86.1, 94.7, 96.2, 122.6, 126.9, 133.5, 140.7, 141.4, 146.4, 150.9, 164.7, 165.1, 166.0 ppm. Anal. Calcd. for $\text{C}_{22}\text{H}_{23}\text{N}_3\text{O}_8$: C, 57.77; H, 5.07; N, 9.19. Found: C, 57.70; H, 5.00; N, 9.03.

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