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Design and synthesis of alkyl 7,7-dihalo-3-methyl-5-(nitrophenyl)-2-azabicyclo[4.1.0]hept-3-ene-4-carboxylates with calcium channel antagonist activity

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Abstract—A group of alkyl 7,7-dihalo-3-methyl-5-(2- or 3-nitrophenyl)-2-azabicyclo[4.1.0]hept-3-ene-4-carboxylates were prepared by reaction of dihalocarbenes (:CX_2, X = Br, Cl) with alkyl 2-methyl-4-(2- or 3-nitrophenyl)-1,4-dihydropyridine-3-carboxylates. In vitro calcium channel antagonist activities were determined using a guinea pig ileum longitudinal smooth muscle assay. The title compounds exhibited weaker CC antagonist activity (10^{-5} to 10^{-7} M range) than the reference drug nifedipine (1.4×10^{-8} M). Structure–activity relationships showed that the position (*ortho* or *meta*) of the nitro-substituent on the C-5 phenyl ring, the size (van der Waal's radius for Br and Cl are 1.95 and 1.80 Å, respectively) and/or electronegativity (Cl > Br) of the C-7 geminal halogen atoms do not appear to have a significant effect on CC antagonist activity. In contrast, the effect of the alkyl ester substituent was more pronounced where compounds having a Me or Et alkyl ester group showed superior potency (IC_{50} in the 10^{-7} M range) relative to the reference drug nifedipine ($IC_{50} = 1.40 \times 10^{-8}$ M). Replacement of a 2-methyl-3-methoxycarbonylvinyl moiety present in nifedipine by a bioisosteric geminal-dihalocyclopropyl moiety provided a novel class of calcium channel antagonists that do not exhibit any inotropic effect on guinea pig atria.

1. Introduction

The geometrical requirements of the 1,4-dihydropyridine (1,4-DHP) calcium channel binding site[1–4] have been investigated extensively following discovery of the first-generation calcium channel antagonist nifedipine (**1**) (Fig. 1) that is used to treat hypertension.[5] Structure–activity correlations acquired in these studies indicated that the collective combination of the 1,4-DHP C-3, C-4, and C-5 substituents modulated activity,[1] tissue selectivity,[6–12] and the conformation[13–15] of the 1, 4-DHP ring system. The isomeric potency order, with respect to the nature and position of C-4 aryl ring substituents that are determinants of calcium channel antagonist activity, was generally *ortho* ⩾ *meta* ≫ *para*.[2] In the solid state, Hantzsch 1,4-DHPs have a boat conformation where the C-4 substituted-phenyl ring is perpendicular (pseudoaxial) to the 1,4-DHP ring. Strain between the C-3, C-4, and C-5 1,4-DHP substituents, arising from non-bonded interactions, is relieved primarily by puckering of the 1,4-DHP ring and distortion of the bond angles about C-4 with the most potent compounds showing the smallest degree of ring distortion from planarity.[2,13] Synperiplanar (*sp*) carbonyl groups are a common characteristic of DHP calcium channel antagonists, whereas an antiperiplanar (*ap*) carbonyl group such as the lactone moiety in the rigid CGP 28 392 (**2**) may be a requirement for calcium channel agonist activity.[14] Molecular orbital (MOPAC) conformational calculations suggested that the nitro group of the calcium channel agonist Bay K 8644 (**3**) is orientated in the plane of the DHP ring. On the other hand, both carbonyl groups in calcium channel antagonists are preferentially orientated in a plane that intersects the DHP ring with an angle between 30° and 60°.[16] It has been suggested that differences in molecular electrostatic potentials between calcium channel antagonist and agonist agents, with respect to binding at the C-3 and C-5 regions, may constitute a mechanism by which the receptor distinguishes between agonist and antagonist ligands. In this regard, antagonists show a positive

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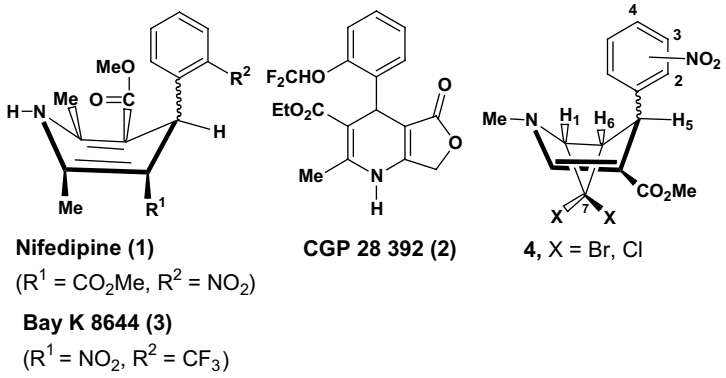


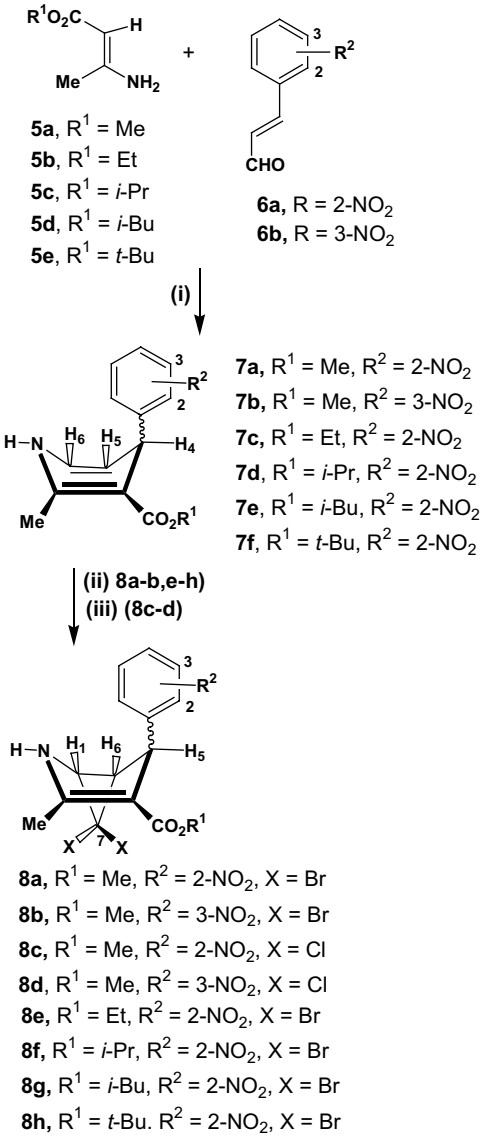
Figure 1. Structures of Nifedipine (**1**), CGP 28 392 (**2**), Bay K 8644 (**3**), and Methyl 7,7-dihalo-2-methyl-5-(nitrophenyl)-2-azabicyclo[4.1.0]hept-3-ene-4-carboxylates (**4**).

potential in this region when a C-3 ester group is present, but calcium channel activators show a strong negative potential in the region adjacent to the C-3 nitro substituent.[17] In an earlier study, we showed that replacement of the 1-amino-2-methyl-3-methoxycarbonyl-2,3-vinyl moiety present in nifedipine (**1**) by a bioisosteric 1-methylamino-2,3-dihalocyclopropyl moiety provided a group of methyl 2-methyl-7,7-dihalo-5-(nitrophenyl)-2-azabicyclo[4.1.0]hept-3-ene-4-carboxylates (**4**) that exhibited weaker calcium channel antagonist activity ($IC_{50} = 10^{-5}$ to 10^{-6} M range) than the reference drug nifedipine ($IC_{50} = 1.40 \times 10^{-8}$ M).[18] This study has now been extended where the 1-amino-2-methyl-3-methoxycarbonyl-2,3-vinyl moiety present in nifedipine (**1**) has been replaced by a more structurally comparable 1-amino-2-methyl-2,3-dihalocyclopropyl bioisosteric moiety. In this regard, we now report the synthesis and calcium channel antagonist activities for a group of rigid bicyclic alkyl 7,7-dihalo-3-methyl-5-(nitrophenyl)-2-azabicyclo[4.1.0]hept-3-ene-4-carboxyla- tes (**8a**–**h**) that are closer structural mimics of nifedipine.

2. Chemistry

The piperidine catalyzed condensation[19] of an alkyl 3-aminocrotonate (**5**, R^1 = Me, Et, *i*-Pr, *i*-Bu, *t*-Bu) with either 2-nitrocinnamaldehyde (**6a**), or 3-nitrocinnamaldehyde (**6b**),[20] afforded the respective alkyl 2-methyl-4-(2-, or 3-nitrophenyl)-1,4-dihydropyridine-3-carboxylate (**7a**, 29%; **7b**, 34%; **7c**, 19%; **7d**, 13%; **7e**, 14%; **7f**, 21%) as illustrated in Scheme 1.

Carbenes often undergo undesirable insertion reactions, due to their extreme reactivity, that decrease the yield of the olefin addition product.[21] In contrast, dihalocarbenes ($:CX_2$) are much less reactive species that do not produce insertion products.[22–24] The reaction of olefins with singlet state carbenes yield stereospecific *syn* addition products[25,26] that likely proceed via a concerted mechanism.[27] Accordingly, the thermal in situ generation of dihalocarbenes ($:CX_2$, X = Br, Cl)[28,29] from the Seyferth reagents[30] $PhHgCBr_3$, or $PhHgCBrCl_2$, in the presence of an alkyl 2-methyl-4-(2- or 3-nitrophenyl)-1,4-dihydropyridine-3-carboxylate (**7a**–**f**) afforded the



Scheme 1. Reagents and conditions: (i) piperidine, MeOH, reflux, 3 h (**7a**) and piperidine, EtOH, reflux, 6 h (**7b**–**f**); (ii) $PhHgCBr_3$, dry benzene, reflux, 8 h; (iii) $PhHgCBrCl_2$, dry benzene, reflux, 8 h.

respective alkyl 7,7-dihalo-3-methyl-5-(2- or 3-nitrophenyl)-2-azabicyclo[4.1.0]hept-3-ene-4-carboxylate (**8a**–**b**,

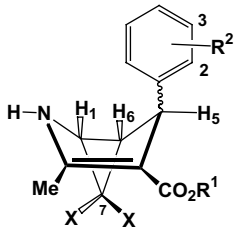
e–**h**, X = Br; **8c**–**d**, X = Cl) in 8–12% chemical yield (see Scheme 1). Electronegative halogen substituents decrease the rate of reaction of carbenes, which are electrophilic species.[31,32] Therefore, it is expected that dihalocyclopropanation (:CX_2) should occur exclusively at the C5–C6 olefinic bond of **7a**–**f**, rather than the deactivated C2–C3 olefinic bond to which the 3-alkoxycarbonyl substituent is attached. Regiospecific dihalocyclopropanation of the C5–C6 olefinic bond, rather than the C=O bond of the 3-methoxycarbonyl substituent, is also consistent with the observation that dihalocarbenes rarely add to the C=O bond of aldehydes or lactones.[33] 1,4-Dihydropyridines such as **7a**–**f** exist in a boat conformation where the C-4 aryl ring is pseudoaxial to the 1,4-DHP ring.[2,13,33,34] The concerted addition of :CX_2 should therefore occur from the sterically least hindered lower face of the boat-shaped 1,4-DHP ring such that the orientation of the C-4 aryl ring remains unchanged. A ^{1}H NMR difference nuclear Overhauser enhancement (NOE) experiment was performed for **8a** where irradiation of the phenyl H-6 proton at δ 7.33 resulted in a 3.6% NOE for the 2-azabicyclo-[4.1.0]hept-3-ene H-6 proton at δ 2.39. This NOE result clearly shows that a significant rotamer fraction is present in which the phenyl H-6 of **8a** is oriented above the 2-azabicyclo[4.1.0]hept-3-ene ring near its H-6 proton. Accordingly, the dibromocylcopropyl ring must be located on the opposite lower face of the 2-azabicyclo[4.1.0]hept-3-ene ring. These stereochemical and regiochemical assignments are consistent with the X-ray structure of 2-benzoyl-5-benzyl-7,7-dibromo-4-ethoxycarbonyl-2-azabicyclo[4.1.0]hept-3-ene that was prepared by reaction of 1-benzoyl-4-benzyl-3-ethoxycarbonyl-1,4-dihydropyridine with :CBr_2, in which the C=O moiety of the C-4 CO_2Et substituent is antiperiplanar (*ap*) to the C3–C4 olefinic bond.[35]

3. Results and discussion

In a program to design novel calcium channel modulators, it was anticipated that replacement of the C5–C6 olefinic bond of 2-methyl-3-alkoxycarbonyl-4-(2- or 3-nitrophenyl)-1,4-dihydropyridines (**7a**–**f**) by a potentially bioisosteric dihalocyclopropyl moiety would provide a novel class of alkyl 7,7-dihalo-3-methyl-5-(2- or 3-nitrophenyl)-2-azabicyclo[4.1.0]hept-3-ene-4-carboxylates (**8**) that mimic the essential structural features present in the calcium channel antagonist nifedipine (**1**). This drug design concept is based on the premise that cyclopropyl C–C bonds share some similarities with olefinic bonds that include: (i) the hybridization of cyclopropyl C–C bonds is intermediate in character between a sigma (σ) and a pi (π) bond,[33] (ii) a cyclopropyl C–C bond, like a C=C bond, is able to conjugate with an olefinic bond to which it is attached,[33] but unlike a C=C it does not transmit electronic effects,[36] and (iii) a cyclopropyl ring interacts with adjacent π-electron systems and p-electron centers much like a vinyl group.[37,38] For these reasons, a cyclopropane group has been investigated as an alkene bioisostere.[39–41] Rigid tetracyclic compounds derived from structural analogs of the calcium channel antagonist nifedipine having a fused cyclopropane ring have been synthesized but no pharmacological properties were reported.[42] It was therefore anticipated, that the fused dihalocyclopropyl ring in the bicyclic compounds (**8**), which is orientated below the plane of the boat-shaped tetrahydropyridine ring, may serve as a bioisostere of the 2-methyl-3-methoxycarbonyl-2,3-olefinic moiety present in nifedipine (**1**). In compounds **8**, one C-7 halo substituent on the fused planar cyclopropyl ring system is *syn* to the H-1 and H-6 hydrogen atoms, while the other C-7 halogen substituent is *syn* to the C3–C4 vinyl bond.

The in vitro calcium channel antagonist activities exhibited by compounds **8a**–**h** were determined using a guinea pig ileum longitudinal smooth muscle (GPILSM) assay,[6] and the results are summarized in Table 1. Compounds **8a**–**h** exhibited weaker calcium channel antagonist activity (10^{-5} to 10^{-7} M range) relative to the reference drug nifedipine ($IC_{50} = 1.40 \times 10^{-8}$ M). Structure–activity relationships showed that the position of a nitro-substituent on the C-5 phenyl ring was variable since the 2-nitrophenyl and 3-nitrophenyl regioisomers in the 7,7-dibromocyclopropyl compounds **8a** and **8b** were equipotent, but the 3-nitrophenyl compound (**8d**) was more potent than the 2-nitrophenyl regioisomer (**8c**) for the 7,7-dihalocyclopropyl compounds. The size (van der Waal's radius for Br and Cl are 1.95 and 1.80 Å, respectively) and/or electronegativity (Cl > Br) of the C-7 halogen atoms do not appear to have a significant effect on the CC antagonist activity of compounds **8a**–**d**. It is well documented that strain arising from non-bonded interactions between the C-3, C-4, and C-5 substituents in monocyclic 1,4-DHP CC antagonists is relieved primarily by puckering of the 1,4-DHP ring and distortion of the bond angles about C-4 with the most potent compounds showing the smallest degree of ring distortion from 1,4-DHP ring planarity.[2,13] It is plausible that the rigid bicyclic 2-azabicyclo[4.1.0] hept-3-ene ring present in compounds **8** is not able to adopt a more planar shape to relieve non-bonded steric interactions between the C-5 nitrophenyl and C-7 diahalo substituents. This possibility may explain the observations noted above that the steric and/or electronic properties of the geminal C-7 halogen atoms (Br, Cl), and the position of the nitro substituents on the C-5 phenyl ring, did not appreciably alter CC antagonist activity. The dibromocyclopropyl compound **8a** having a methyl ester substituent (R^1 = Me) was elabo- rated to determine whether the alkyl ester substituent (R^1) was a determinant of CC antagonist activity. These structure–activity studies showed that compounds having a R^1 = Et or *i*-Pr ester moiety provided optimal activity (IC_{50} in the 10^{-7} M range), relative to compounds having R^1 = Me, *i*-Bu or *t*-Bu ester substituents (IC_{50} in the 10^{-6} M range). The most active CC antagonist ethyl 7,7-dibromo-3-methyl-5-(2-nitrophenyl)-2-azabicyclo[4.1.0]hept-3-ene-4-carboxylate (**8e**, $IC_{50} = 6.25 \times 10^{-7}$ M) was approximately 45-fold less active than the reference drug nifedipine ($IC_{50} = 1.40 \times 10^{-8}$ M). This class of compounds **8a**–**h** did not exhibit a cardiac inotropic effect (antagonist or agonist) on guinea pig left atria.

Table 1. In vitro calcium channel antagonist activities for alkyl 7,7-dihalo-3-methyl-5-(nitrophenyl)-2-azabicyclo[4.1.0]hept-3-ene-4-carboxylates (**8a–h**)



Compd.	R^1	R^2	X	Calcium channel antagonist activity GPILSM: IC_{50} (M)[a]
8a	Me	2-NO_2	Br	$3.61 \pm 0.23 \times 10^{-6}$
8b	Me	3-NO_2	Br	$3.47 \pm 0.09 \times 10^{-6}$
8c	Me	2-NO_2	Cl	$1.16 \pm 0.18 \times 10^{-5}$
8d	Me	3-NO_2	Cl	$3.95 \pm 0.93 \times 10^{-6}$
8e	Et	2-NO_2	Br	$6.25 \pm 0.17 \times 10^{-7}$
8f	*i*-Pr	2-NO_2	Br	$8.32 \pm 0.21 \times 10^{-7}$
8g	*i*-Bu	2-NO_2	Br	$4.30 \pm 0.50 \times 10^{-6}$
8h	*t*-Bu	2-NO_2	Br	$8.18 \pm 0.36 \times 10^{-6}$
Nifedipine				$1.40 \pm 0.19 \times 10^{-8}$

[a] The molar concentration of the test compound causing a 50% decrease in the slow component or tonic contractile response ($IC_{50} \pm$ SEM, $n = 3$) in guinea pig ileum longitudinal smooth muscle (GPILSM) induced by the muscarinic agonist carbachol (1.6×10^{-7} M) was determined graphically from the dose–response curve.

4. Conclusions

A geminal-dihalocyclopropyl moiety (i) is a bioisostere for a 2-methyl-3-methoxycarbonylvinyl moiety of nifedipine (**1**), and (ii) the dihalocyclopropyl compounds **8** provides further structure–activity data that may be of value to probe the structure–function relationship of calcium channel modulation. The group of alkyl 7,7-dibromo-3-methyl-5-(2-nitrophenyl)-2-azabicyclo[4.1.0]hept-3-ene-4-carboxylates (**8**) described in this study possess the two structural requirements deemed to be essential for CC antagonist activity in 1,4-DHPs that include an up-oriented pseudoaxial aryl group (normal DHP boat) in conjunction with an essential 2-methyl-3-alkoxycarbonyl-2,3-vinyl moiety in which the orientation of the C=O moiety is synperiplanar with respect to the 2,3-olefinic bond to which it is attached.[43]

5. Experimental

Melting points were determined using a Thomas–Hoover capillary apparatus and are uncorrected. Infrared (IR) spectra were recorded using a Nicolet 550 Series II Magna FT-IR spectrometer. ^{1}H NMR nuclear magnetic resonance spectra were recorded on a Bruker AM-300 spectrophotometer. The assignment of exchangeable protons (N*H*) was confirmed by the addition of D_2O. The NOE experiment was performed under steady-state conditions using the Bruker NOE DIFF. AU software program (signal:noise ratio of 136 for a single pulse). The NMR solvent $CDCl_3$ was degassed by passage of dry argon gas at 22 °C just prior to use. Molecular tumbling time was not altered. Silica gel column chromatography was performed using Silicycle® silica gel (70–230 mesh). Elemental analyses were determined for C, H, and N (microanalytical service laboratory, Department of Chemistry, University of Alberta). 3-Nitrocinnamaldehyde (**6b**),[20] phenyl(tribromomethyl)-mercury ($PhHgCBr_3$),[30] phenyl(bromodichloromethyl) mercury ($PhHgCBrCl_2$),[30] and the alkyl 3-aminocrotonates (**5c–e**)[44] were prepared according to literature procedures. All other reagents, including methyl 3-aminocrotonate (**5a**), ethyl 3-aminocrotonate (**5b**) and 2-nitrocinnamaldehyde (**6a**), were purchased from Aldrich Chemical (Milwaukee, WI) and used without further purification. In vitro calcium channel antagonist activities were determined using protocols approved by the Health Sciences Animal Welfare Committee at the University of Alberta.

5.1. General method for the synthesis of alkyl 2-methyl-4-(2- or 3-nitrophenyl)-1,4-dihydropyridine-3-carboxylates (7a–f)

A mixture of the alkyl 3-aminocrotonate (**5a–e**, 25 mmol), a nitrocinnamaldehyde (**6a** or **6b**; 4.43 g, 25 mmol) and piperidine (120 μL, 1.0 mmol) in methanol (12 mL) was refluxed for 3 h (**7a–b**), or in ethanol (15 mL) was refluxed for 6 h (**7c–f**). The solvent was removed in vacuo, and the respective product (**7a–f**) was purified by elution from a silica gel column using ethyl acetate/hexanes (35:65, v/v) as an eluent for compounds **7a–b**, or ethyl acetate/hexanes (3:7, v/v) for the compounds **7c–f**. Products **7a–b** were recrystallized from MeOH, and products **7c**, **e–f** were recrystallized from dichloromethane/hexanes. Some physical and spectroscopic data for **7a–f** are listed below.

5.1.1. Methyl 2-methyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3-carboxylate (7a). Yellow crystals (MeOH); mp 148–150 °C; yield 29%; IR (NaCl) ν 3339 (NH), 1672 (C=O), 1597 (C=C aromatic), 1523, 1358 (NO_2) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.68 (d, $J_{3,4} = 8.1$ Hz, 1H, phenyl

H-3), 7.61 (dd, $J_{5,6}$ = 8.1, $J_{4,6}$ = 1.5 Hz, 1H, phenyl H-6), 7.54 (dd, $J_{4,5}$ = 7.2, $J_{5,6}$ = 8.1 Hz, 1H, phenyl H-5), 7.27 (ddd, $J_{3,4}$ = 8.1, $J_{4,5}$ = 7.2, $J_{4,6}$ = 1.5 Hz, 1H, phenyl H-4), 6.08 (dd, $J_{5,6}$ = 7.2, $J_{6,NH}$ = 1.5 Hz, 1H, DHP H-6), 5.41 (br s, 1H, N*H*), 5.06–5.13 (m, 2H, DHP H-4, H-5), 3.43 (s, 3H, OCH_3), 2.36 (s, 3H, CH_3). Anal. Calcd for $C_{14}H_{14}N_2O_4$: C, 61.31; H, 5.15; N, 10.21. Found: C, 61.16; H, 5.02; N, 10.04. This compound is sensitive to light and should be placed in a dark container and stored in a cool place prior to use.

5.1.2. Methyl 2-methyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylate (7b). Yellow crystals (MeOH); mp 162–164 °C; yield 34%; IR (NaCl) *v* 3339 (NH), 1672 (C=O), 1597 (C=C aromatic), 1523, 1341 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.13 (dd, $J_{2,4}$ = 2.1, $J_{2,6}$ = 2.1 Hz, 1H, phenyl H-2), 8.03 (ddd, $J_{2,4}$ = 2.1, $J_{4,5}$ = 8.1, $J_{4,6}$ = 1.2 Hz, 1H, phenyl H-4), 7.62 (dd, $J_{5,6}$ = 8.1, $J_{4,6}$ = 1.2 Hz, 1H, phenyl H-6), 7.43 (dd, $J_{4,5}$ = 8.1, $J_{5,6}$ = 8.1 Hz, 1H, phenyl H-5), 6.12 (dd, $J_{5,6}$ = 7.2, $J_{6,NH}$ = 4.8 Hz, 1H, DHP H-6), 5.49 (br s, 1H, N*H*), 4.89–4.94 (m, 1H, DHP H-5), 4.69 (d, $J_{4,5}$ = 5.4 Hz, 1H, DHP H-4), 3.58 (s, 3H, OCH_3), 2.35 (s, 3H, C-2 CH_3). Anal. Calcd for $C_{14}H_{14}N_2O_4$: C, 61.31; H, 5.15; N, 10.21. Found: C, 61.45; H, 5.29; N, 10.07. This compound is sensitive to light and should be placed in a dark container and stored in a cool place prior to use.

5.1.3. Ethyl 2-methyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3-carboxylate (7c). Yellow crystals (CH_2Cl_2/hexanes); mp 154–155 °C; yield 29%; IR ($CHCl_3$) *v* 3354 (NH), 3069 (aromatic CH), 1669 (C=O), 1604 (C=C aromatic), 1525, 1361, 744 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.71 (d, $J_{3,4}$ = 7.9 Hz, 1H, phenyl H-3), 7.60 (ddd, $J_{5,6}$ = 7.9, $J_{4,5}$ = 7.3, $J_{3,5}$ = 1.5 Hz, 1H, phenyl H-5), 7.53 (dd, $J_{5,6}$ = 7.9 Hz, 1H, phenyl H-6), 7.27 (ddd, $J_{3,4}$ = 7.9, $J_{4,5}$ = 7.3, $J_{4,6}$ = 1.5 Hz, 1H, phenyl H-4), 6.04 (dd, $J_{5,6}$ = 7.6, $J_{6,NH}$ = 2.7 Hz, 1H, DHP H-6), 5.43 (br s, 1H, N*H*), 5.12 (d, $J_{4,5}$ = 4.9, $J_{5,6}$ = 7.6, $J_{5,NH}$ = 0.8 Hz, 1H, DHP H-5), 5.06 (d, $J_{4,5}$ = 4.9 Hz, 1H, DHP H-4), 3.87 (q, J = 7.3 Hz, 2H, OCH_2), 2.37 (s, 3H, C-2 CH_3), 0.93 (t, J = 7.3 Hz, 3H, CH_2CH_3). This compound is sensitive to light and it should be used as soon as possible after purification. When **7c** is stored, it should be placed in a dark container in a cool place prior to use.

5.1.4. Isopropyl 2-methyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3-carboxylate (7d). Yellow foam; yield 13%; IR ($CHCl_3$) *v* 3344 (NH), 3069 (aromatic CH), 1673 (C=O), 1604 (C=C aromatic), 1521, 1353, 743 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.73 (d, $J_{3,4}$ = 7.9 Hz, 1H, phenyl H-3), 7.59 (ddd, $J_{5,6}$ = 7.9, $J_{4,5}$ = 7.4, $J_{3,5}$ = 1.2 Hz, 1H, phenyl H-5), 7.53 (d, $J_{5,6}$ = 7.9 Hz, 1H, phenyl H-6), 7.27 (dd, $J_{3,4}$ = 7.9, $J_{4,5}$ = 7.4 Hz, 1H, phenyl H-4), 6.01 (dd, $J_{5,6}$ = 7.8, $J_{6,NH}$ = 2.7 Hz, 1H, DHP H-6), 5.37 (br s, 1H, N*H*), 5.13 (dd, $J_{4,5}$ = 4.9, $J_{5,6}$ = 7.8 Hz, 1H, DHP H-5), 5.02 (d, $J_{4,5}$ = 4.9 Hz, 1H, DHP H-4), 4.77 (heptet, J = 6.4 Hz, 1H, OC*H*), 2.38 (s, 3H, C-2 CH_3), 1.06 [d, J = 6.4 Hz, 3H, $CH(CH_3)_2$], 0.67 [d, J = 6.4 Hz, 3H, $CH(CH_3)_2$]. This compound is sensitive to light and it should be used as soon as possible after purification. When **7d** is stored, it should be placed in a dark container in a cool place prior to use.

5.1.5. Isobutyl 2-methyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3-carboxylate (7e). Yellow crystals, mp 114–115 °C; yield 14%; IR ($CHCl_3$) *v* 3346 (NH), 3069 (aromatic CH), 1678 (C=O), 1607 (C=C aromatic), 1521, 1358, 747 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.46 (d, $J_{3,4}$ = 7.9 Hz, 1H, phenyl H-3), 7.57 (dd, $J_{5,6}$ = 7.3, $J_{4,5}$ = 7.3 Hz, 1H, phenyl H-5), 7.54 (d, $J_{5,6}$ = 7.3 Hz, 1H, phenyl H-6), 7.27 (dd, $J_{3,4}$ = 7.9, $J_{4,5}$ = 7.3 Hz, 1H, phenyl H-4), 6.20 (dd, $J_{5,6}$ = 7.6, $J_{6,NH}$ = 4.6 Hz, 1H, DHP H-6), 5.42 (br s, 1H, N*H*), 5.17 (dd, $J_{4,5}$ = 4.9, $J_{5,6}$ = 7.6 Hz, 1H, DHP H-5), 5.12 (d, $J_{4,5}$ = 4.9 Hz, 1H, DHP H-4), 3.64 (m, 2H, OCH_2), 2.40 (s, 3H, C-2 CH_3), 1.65 [m, 1H, CH(CH_3)$_2$], 0.66 [d, J = 6.7 Hz, 3H, CH(CH_3)$_2$], 0.61 [d, J = 6.7 Hz, 3H, CH(CH_3)$_2$]. Anal. Calcd for $C_{17}H_{20}N_2O_4$: C, 64.54; H, 6.37; N, 8.86. Found: C, 64.53; H, 6.43; N, 8.72.

5.1.6. *tert*-Butyl 2-methyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3-carboxylate (7f). Yellow crystals, mp 149–150 °C; yield 21%; IR ($CHCl_3$) *v* 3357 (NH), 3072 (aromatic CH), 1684 (C=O), 1605 (C=C aromatic), 1526, 1351, 756 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.79 (d, $J_{3,4}$ = 8.2 Hz, 1H, phenyl H-3), 7.54–7.78 (m, 2H, phenyl H-5, H-6), 7.28 (dd, $J_{3,4}$ = 8.2, $J_{4,5}$ = 6.7 Hz, 1H, phenyl H-4), 5.98 (dd, $J_{5,6}$ = 7.3, $J_{6,NH}$ = 4.9 Hz, 1H, DHP H-6), 5.29 (br s, 1H, N*H*), 5.17 (dd, $J_{4,5}$ = 4.9, $J_{5,6}$ = 7.3 Hz, 1H, DHP H-5), 5.01 (d, $J_{4,5}$ = 4.9 Hz, 1H, DHP H-4), 2.36 (s, 3H, C-2 CH_3), 1.12 (s, 9H, *t*-C_4H_9). Anal. Calcd for $C_{17}H_{20}N_2O_4$: C, 64.54; H, 6.37; N, 8.86. Found: C, 64.23; H, 6.56; N, 8.79.

5.2. General method for the preparation of alkyl 7,7-dihalo-3-methyl-5-(2- or 3-nitrophenyl)-2-azabicyclo-[4.1.0]hept-3-ene-4-carboxylates (8a–h)

Phenyl(tribromomethyl)mercury (1.38 g, 2.6 mmol), or phenyl(bromodichloromethyl)mercury (1.15 g, 2.6 mmol), was added to a stirred solution of an alkyl 2-methyl-4-(2- or 3-nitrophenyl)-1,4-dihydropyridine-3-carboxylate (**7a**–**f**, 2.6 mmol) in dry benzene (30 mL) under an atmosphere of nitrogen gas, the reaction flask was sealed with a rubber septum, and the mixture was refluxed for 8 h. Additional aliquots (1.3 mmol) of either $PhHgCBr_3$, or $PhHgCBrCl_2$, in dry benzene (10 mL) were added using a syringe to the reaction mixture at 2 and 4 h, respectively. The reaction mixture was cooled to 25 °C, and the PhHgBr which precipitated during the reaction was removed by filtration. Removal of the solvent in vacuo gave a brownish oil, which was purified by silica gel column chromatography using ethyl acetate/hexanes (35:65, v/v) as eluent for products **8a**–**d**, or ethyl acetate/hexanes (3:7, v/v) as eluent for products **8e**–**h**. Each product (**8a**–**h**) was recrystallized from the solvent(s) specified along with the physical and spectral data that are listed below.

5.2.1. Methyl 7,7-dibromo-3-methyl-5-(2-nitrophenyl)-2-azabicyclo[4.1.0]hept-3-ene-4-carboxylate (8a). Yellow crystals (Et_2O); mp 163–165 °C (dec); yield 10%; IR (NaCl) *v* 3318 (NH), 1683 (C=O), 1600 (C=C

aromatic), 1525, 1353 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.78 (d, $J_{3,4} = 8.1$ Hz, 1H, phenyl H-3), 7.47 (dd, $J_{4,5} = 8.1$, $J_{5,6} = 7.2$ Hz, 1H, phenyl H-5), 7.29–7.36 (m, 2H, phenyl H-4, H-6), 4.89 (br s, 1H, N*H*), 4.49 (s, 1H, H-5), 3.37 (s, 3H, OCH_3), 3.33 (dd, $J_{1,6} = 10.2$, $J_{1,NH} = 2.4$ Hz, 1H, H-1), 2.39 (d, $J_{1,6} = 10.2$ Hz, 1H, H-6), 2.33 (s, 3H, C-3 CH_3). Anal. Calcd for $C_{15}H_{14}Br_2N_2O_4$: C, 40.39; H, 3.16; N, 6.28. Found: C, 40.66; H, 3.01; N, 6.13.

5.2.2. Methyl 7,7-dibromo-3-methyl-5-(3-nitrophenyl)-2-azabicyclo[4.1.0]hept-3-ene-4-carboxylate (8b). Yellow crystals (Et_2O); mp 155–157 °C (dec); yield 8%; IR (NaCl) ν 3302 (NH), 1677 (C=O), 1676 (C=C aromatic), 1530, 1346 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.11 (d, $J_{2,4} = 2.1$, 1H, phenyl H-2), 8.07 (dd, $J_{2,4} = 2.1$, $J_{4,5} = 7.8$ Hz, 1H, phenyl H-4), 7.64 (d, $J_{5,6} = 7.8$ Hz, 1H, phenyl H-6), 7.46 (dd, $J_{4,5} = 7.8$, $J_{5,6} = 7.8$ Hz, 1H, phenyl H-5), 4.87 (br s, 1H, N*H*), 4.20 (s, 1H, H-5), 3.49 (s, 3H, OCH_3), 3.35 (dd, $J_{1,6} = 10.5$, $J_{1,NH} = 2.1$ Hz, 1H, H-1), 2.33 (s, 3H, CH_3), 2.19 (d, $J_{1,6} = 10.5$ Hz, 1H, H-6). Anal. Calcd for $C_{15}H_{14}Br_2N_2O_4$: C, 40.39; H, 3.16; N, 6.28. Found: C, 40.36; H, 2.98; N, 6.06.

5.2.3. Methyl 7,7-dichloro-3-methyl-5-(2-nitrophenyl)-2-azabicyclo[4.1.0]hept-3-ene-4-carboxylate (8c). Yellow crystals (Et_2O/hexanes); mp 166–168 °C (dec); yield 10%; IR (NaCl) ν 3318 (NH), 1683 (C=O), 1608 (C=C aromatic), 1518, 1345 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.77 (d, $J_{3,4} = 8.1$ Hz, 1H, phenyl H-3), 7.47 (dd, $J_{4,5} = 7.5$, $J_{5,6} = 7.5$ Hz, 1H, phenyl H-5), 7.29–7.36 (m, 2H, phenyl H-4, H-6), 4.81 (br s, 1H, N*H*), 4.57 (s, 1H, H-5). 3.37 (s, 3H, OCH_3), 3.28 (dd, $J_{1,6} = 10.2$, $J_{1,NH} = 2.4$ Hz, 1H, H-1), 2.34 (s, 3H, C-3 CH_3), 2.30 (d, $J_{1,6} = 10.2$ Hz, 1H, H-6). Anal. Calcd for $C_{15}H_{14}Cl_2N_2O_4$: C, 50.44; H, 3.95; N, 7.84. Found: C, 50.59; H, 4.22; N, 7.54.

5.2.4. Methyl 7,7-dichloro-3-methyl-5-(3-nitrophenyl)-2-azabicyclo[4.1.0]hept-3-ene-4-carboxylate (8d). Yellow crystals (Et_2O/hexanes); mp 162–164 °C (dec); yield 12%; IR (NaCl) ν 3326 (NH), 1678 (C=O), 1602 (C=C aromatic), 1527, 1348 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.11 (dd, $J_{2,4} = 2.1$, $J_{2,6} = 2.1$ Hz, 1H, phenyl H-2), 8.06 (dd, $J_{2,4} = 2.1$, $J_{4,5} = 7.8$ Hz, 1H, phenyl H-4), 7.64 (d, $J_{5,6} = 7.8$ Hz, 1H, phenyl H-6), 7.46 (dd, $J_{4,5} = 7.8$, $J_{5,6} = 7.8$ Hz, 1H, phenyl H-5), 4.80 (br s, 1H, N*H*), 4.28 (s, 1H, H-5), 3.50 (s, 3H, OCH_3), 3.30 (dd, $J_{1,6} = 10.5$, $J_{1,NH} = 2.4$ Hz, 1H, H-1), 2.34 (s, 3H, C-3 CH_3), 2.10 (d, $J_{1,6} = 10.5$ Hz, 1H, H-6). Anal. Calcd for $C_{15}H_{14}Cl_2N_2O_4$: C, 50.44; H, 3.95; N, 7.84. Found: C, 50.61; H, 3.79; N, 7.65.

5.2.5. Ethyl 7,7-dibromo-3-methyl-5-(2-nitrophenyl)-2-azabicyclo[4.1.0]hept-3-ene-4-carboxylate (8e). Yellow crystals (CH_2Cl_2/hexanes); mp 148–149 °C (dec); yield 10%; IR ($CHCl_3$) ν 3331 (NH), 3012 (aromatic CH), 1690 (C=O), 1605 (C=C aromatic), 1527, 1348, 757 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 8.55 (d, $J_{3,4} = 8.5$ Hz, 1H, phenyl H-3), 7.47 (dd, $J_{4,5} = 7.0$, $J_{5,6} = 7.0$ Hz, 1H, phenyl H-5), 7.29–7.39 (m, 2H, phenyl H-4, H-6), 4.87 (br s, 1H, N*H*), 4.49 (s, 1H, H-5). 3.71–3.91 (m, 2H, OCH_2), 3.30 (dd, $J_{1,6} = 10.4$, $J_{1,NH} = 2.4$ Hz, 1H, H-1), 2.39 (d, $J_{1,6} = 10.4$ Hz, 1H, H-6), 2.34 (s, 3H, C-3 CH_3), 0.85 (t, $J = 7.3$ Hz, 3H, CH_2CH_3). Anal. Calcd for $C_{16}H_{16}Br_2N_2O_4 \cdot 3/4H_2O$: C, 40.57; H, 3.72; N, 5.93. Found: C, 40.40; H, 3.37; N, 5.53.

5.2.6. Isopropyl 7,7-dibromo-3-methyl-5-(2-nitrophenyl)-2-azabicyclo[4.1.0]hept-3-ene-4-carboxylate (8f). Yellow crystals (CH_2Cl_2/hexanes); mp 73–74 °C (dec); yield 9%; IR ($CHCl_3$) ν 3118 (NH), 3027 (aromatic CH), 1672 (C=O), 1605 (C=C aromatic), 1530, 1356, 757 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.63 (d, $J_{3,4} = 7.6$ Hz, 1H, phenyl H-3), 7.47 (dd, $J_{4,5} = 7.3$, $J_{5,6} = 7.6$ Hz, 1H, phenyl H-5), 7.29–7.39 (m, 2H, phenyl H-4, H-6), 4.84 (br s, 1H, N*H*), 4.71 (heptet, $J = 6.4$ Hz, 1H, OC*H*Me$_2$), 4.40 (s, 1H, H-5). 3.28 (dd, $J_{1,6} = 10.4$, $J_{1,NH} = 2.4$ Hz, 1H, H-1), 2.38 (d, $J_{1,6} = 10.4$ Hz, 1H, H-6), 2.35 (s, 3H, C-3 CH_3), 1.43 [d, $J = 6.4$ Hz, 3H, CH(*Me*)$_2$], 0.58 [d, $J = 6.4$ Hz, 3H, CH(*Me*)$_2$]. Anal. Calcd for $C_{17}H_{18}Br_2N_2O_4$: C, 43.06; H, 3.83; N, 5.51. Found: C, 43.10; H, 3.51; N, 5.71.

5.2.7. Isobutyl 7,7-dibromo-3-methyl-5-(2-nitrophenyl)-2-azabicyclo[4.1.0]hept-3-ene-4-carboxylate (8g). Yellow crystals (CH_2Cl_2/hexanes); mp 158–159 °C (dec); yield 11%; IR ($CHCl_3$) ν 3316 (NH), 3010 (aromatic CH), 1673 (C=O), 1597 (C=C aromatic), 1524, 1351, 751 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.84 (d, $J_{3,4} = 7.9$ Hz, 1H, phenyl H-3), 7.48 (dd, $J_{4,5} = 7.4$, $J_{5,6} = 7.9$ Hz, 1H, phenyl H-5), 7.38 (d, $J_{5,6} = 7.9$ Hz, 1H, phenyl H-6), 7.32 (ddd, $J_{3,4} = 7.9$, $J_{4,5} = 7.4$, $J_{4,6} = 1.5$ Hz, 1H, phenyl H-4), 4.84 (br s, 1H, N*H*), 4.51 (s, 1H, H-5), 3.58 (d, $J = 6.7$ Hz, 2H, OCH_2), 3.29 (dd, $J_{1,6} = 10.4$, $J_{1,NH} = 2.4$ Hz, 1H, H-1), 2.39 (d, $J_{1,6} = 10.4$ Hz, 1H, H-6), 2.36 (s, 3H, C-3 CH_3), 1.60 [m, 1H, C*H*(Me)$_2$], 0.65 [d, $J = 6.7$ Hz, 3H, CH(*Me*)$_2$], 0.57 [d, $J = 6.7$ Hz, 3H, CH(*Me*)$_2$]. Anal. Calcd for $C_{18}H_{20}Br_2N_2O_4$: C, 44.29; H, 4.13; N, 5.74. Found: C, 44.58; H, 4.14; N, 5.67.

5.2.8. *tert*-Butyl 7,7-dibromo-3-methyl-5-(2-nitrophenyl)-2-azabicyclo[4.1.0]hept-3-ene-4-carboxylate (8h). Yellow crystals (MeOH/H_2O); mp 78–79 °C (dec); yield 11%; IR ($CHCl_3$) ν 3328 (NH), 3056 (aromatic CH), 1684 (C=O), 1616 (C=C aromatic), 1528, 1352, 762 (NO_2) cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.90 (d, $J_{3,4} = 7.9$ Hz, 1H, phenyl H-3), 7.49 (dd, $J_{4,5} = 7.3$, $J_{5,6} = 7.6$ Hz, 1H, phenyl H-5), 7.38 (d, $J_{5,6} = 7.6$ Hz, 1H, phenyl H-6), 7.35 (ddd, $J_{3,4} = 7.8$, $J_{4,5} = 7.3$, $J_{4,6} = 1.5$ Hz, 1H, phenyl H-4), 4.72 (br s, 1H, N*H*), 4.34 (s, 1H, H-5), 3.23 (dd, $J_{1,6} = 10.4$, $J_{1,NH} = 2.4$ Hz, 1H, H-1), 2.36 (d, $J_{1,6} = 10.4$ Hz, 1H, H-6), 2.32 (s, 3H, C-3 CH_3), 1.06 (s, 9H, *t-Bu*). Anal. Calcd for $C_{18}H_{20}Br_2N_2O_4$: C, 44.29; H, 4.13; N, 5.74. Found: C, 44.70; H, 4.12; N, 5.56.

5.3. In vitro calcium channel antagonist assay

Smooth muscle calcium channel antagonist activity was determined as the molar (M) concentration of the test compound required to produce 50% inhibition of the muscarinic receptor-mediated (carbachol,

1.6×10^{-7} M) Ca^{+2}-dependent contraction (tonic response) of guinea pig ileum longitudinal smooth muscle (GPILSM) using the procedure previously reported.[6] The IC_{50} (±SEM, $n = 3$) was determined graphically from the dose–response curve.

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References and notes

1. Ferry, D. R.; Glossmann, H. *Naunyn.-Schmiedeberg's Arch. Pharmacol.* **1982**, *321*, 80.
2. Janis, R. A.; Triggle, D. J. *J. Med. Chem.* **1983**, *26*, 775.
3. Murphy, K. M. M.; Gould, R. J.; Largent, B. L.; Snyder, S. H. *Proc. Natl. Acad. Sci. U.S.A.* **1983**, *80*, 860.
4. Venter, J. C.; Fraser, C. M.; Schaber, J. S.; Jung, C. Y.; Bolger, G.; Triggle, D. J. *J. Biol. Chem.* **1983**, *258*, 9344.
5. Van Houtte, P. M.; Cohen, R. A. *Am. J. Cardio.* **1983**, *52*, 99A.
6. Vo, D.; Matowe, W. C.; Ramesh, M.; Iqbal, N.; Wolowyk, M. W.; Howlett, S. E.; Knaus, E. E. *J. Med. Chem.* **1995**, *38*, 2851.
7. Shan, R.; Howlett, S. E.; Knaus, E. E. *J. Med. Chem.* **2002**, *45*, 955.
8. Shan, R.; Velazquez, C.; Knaus, E. E. *J. Med. Chem.* **2004**, *47*, 254.
9. Itil, T.; Michael, S.; Hoffmeister, F.; Kunitz, A.; Erlap, E. *Curr. Ther. Res.* **1984**, *35*, 405.
10. Heusch, G.; Deussen, A. *J. Cardiovasc. Pharmacol.* **1984**, *6*, 378.
11. Schramm, M.; Thomas, G.; Towart, R.; Franckowiak, G. *Nature* **1983**, *303*, 535.
12. Bolger, G. T.; Weissman, B. A.; Skolnick, P. *Naunyn.-Schmiedeberg's Arch. Pharmacol.* **1985**, *328*, 373.
13. Fossheim, R.; Svarteng, K.; Mostad, A.; Romming, C.; Shefter, E.; Triggle, D. J. *J. Med. Chem.* **1982**, *25*, 126.
14. Fossheim, R. *J. Med. Chem.* **1986**, *29*, 305.
15. Iqbal, N.; Akula, M. R.; Vo, D.; Matowe, W. C.; McEwen, C.-A.; Wolowyk, M. W.; Knaus, E. E. *J. Med. Chem.* **1998**, *41*, 1827.
16. Mahmoudian, M.; Richards, W. G. *J. Chem. Soc., Chem. Commun.* **1986**, 739.
17. Holtje, H.-D.; Marrer, S. A. *J. Comput.-Aided Mol. Des.* **1987**, *1*, 23.
18. Mojarrad, J. S.; Miri, R.; Knaus, E. E. *Bioorg. Med. Chem.* **2004**, *12*, 3215.
19. Weller, D. D.; Rapoport, H. *J. Am. Chem. Soc.* **1976**, *98*, 6650.
20. Kinkelin, F. *Berichte* **1885**, *18*, 483.
21. Bell, J. A. *Prog. Phys. Org. Chem.* **1964**, *2*, 1.
22. Moss, R. A. *Acc. Chem. Res.* **1980**, *2*, 58.
23. Moss, R. A.; Perez, L. A.; Turro, N. J.; Gould, I. R.; Hacker, N. P. *Tetrahedron Lett.* **1983**, *24*, 685.
24. Schoeller, W. W.; Aktekin, N.; Friege, H. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 932.
25. Woodworth, R. C.; Skell, P. S. *J. Am. Chem. Soc.* **1959**, *81*, 3383.
26. Jones, M.; Ando, W.; Hendrick, M. E.; Kulczyki, A.; Howley, P. M.; Hummenl, K. F.; Malamert, D. S. *J. Am. Chem. Soc.* **1972**, *94*, 7469.
27. Giese, B.; Lee, W. B.; Neuman, C. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 310.
28. Lambert, J. B.; Larson, E. G.; Bosch, R. J.; Tevrucht, M. L. E. *J. Am. Chem. Soc.* **1985**, *107*, 5443.
29. Agudoawu, S.; Li, H.; Habeeb, A. G.; Rao, P. N. P.; Suresh, M. R.; Knaus, E. E. *Drug Dev. Res.* **2000**, *49*, 75.
30. Seyferth, D.; Lambert, R. L., Jr. *J. Organomet. Chem.* **1969**, *16*, 21.
31. Skell, P. S.; Garner, A. Y. *J. Am. Chem. Soc.* **1956**, *78*, 5430.
32. Doering, W. E.; Henderson, W. A. *J. Am. Chem. Soc.* **1958**, *80*, 5274.
33. March, J. *Advanced Organic Chemistry. Reaction Mechanisms and Structure*, 3rd ed.; John Wiley & Sons: New York, 1985, pp 131, 975.
34. Agudoawu, S. A.; Knaus, E. E. *Pharm. Sci.* **1995**, *1*, 277.
35. McCullough, K. J.; MacTavish, J.; Proctor, G. R.; Redpath, J. *J. Chem. Soc., Perkin Trans. 1* **1986**, 2553.
36. Noller, C. R. *Chemistry of Organic Compounds*, 3rd ed.; W. B. Saunders: Philadelphia, 1966.
37. DeMeijerre, A. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 909.
38. Gassman, P. G. *Chem. Commun.* **1967**, 793.
39. Beres, J. A.; Daggett, J. U.; Dax, S. L.; Mueller, J.; Dombroski, B. A.; Graboski, G. G.; Schram, T. J.; Diehl, B. H.; True, W. R. *J. Pa. Acad. Sci.* **1992**, *66*, 21.
40. Perly, B.; Smith, I. C. P.; Jarrell, H. C. *Biochemistry* **1985**, *24*, 1055.
41. Wipf, P.; Reeves, J. T.; Balachandran, B.; Day, B. W. *J. Med. Chem.* **2002**, *45*, 1901.
42. Remy, D. C.; King, S. W.; Cochran, D. *J. Org. Chem.* **1985**, *50*, 4120.
43. Rovnyak, G. C.; Kimball, S. D.; Beyer, B.; Cucinotta, G.; DiMarco, J. D.; Gougoutas, J.; Hedberg, A.; Malley, M.; McCarthy, J. P.; Zhang, R.; Moreland, S. *J. Med. Chem.* **1995**, *38*, 119.
44. Koo, J. *J. Am. Chem. Soc.* **1953**, *75*, 2000.