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Synthesis of 1-substituted 2-azaspiro[4.5]deca-6,9-diene-8-ones and 2-azaspiro[4.5]deca-1,6,9-triene-8-ones by a three-component condensation of 1,2,3-, 1,2,4- or 1,3,5-trimethoxybenzene with isobutyric aldehyde and nitriles

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ABSTRACT

A three-component condensation of 1,2,3- or 1,2,4-trimethoxybenzene with isobutyric aldehyde and alkyl cyanoacetates in the presence of sulfuric acid resulted in the formation of substituted 2-azaspiro[4.5]deca-6,9-diene-8-ones. The same reaction of aromatic nitriles yielded 2-azaspiro[4.5]deca-1,6,9-triene-8-ones; in the case of 1,2,3-trimethoxybenzene corresponding Ritter amides were also observed. The condensation of 1,3,5-trimethoxybenzene with isobutyric aldehyde and alkyl cyanoacetates provided the compounds of the formal Knöevenagel condensation.

1. Introduction

The 2-azaspiro[4.5]decane skeleton is found in natural products (alkaloids spirostaphylotrichin A[1] and annosqualine[2]); some azaspirocyclic derivatives are immunomodulators[3] or HIV-1 protease inhibitors.[4] Current synthetic methods leading to 2-azaspiro[4.5]decanes and 2-azaspiro[5.5]undecanes include radical cyclizations of chloroacetamides,[5] *N*-allylamides[6] or *para*-methoxybenzylamides,[7] acid-catalyzed cyclizations of aromatic diazoacetamides,[8] intramolecular Heck reaction.[9] Last years some new synthetic approaches to azaspirocyclization were introduced: one-pot Lewis acid or site-isolated base–acid-catalyzed cyclizations,[10] the Pummerer reaction,[11] olefin metathesis,[12] *ipso*-iodocyclization,[13] multicomponent reactions,[14] cyclization of Fe–diene complexes,[15] dearomatization of Ru complexes.[16] Sometimes 2-azaspiro[4.5]decanes appeared as the intermediates in the synthesis of isoquinolines.[17]

2. Results and discussion

Most of the above-mentioned methods are based on the dearomatization of suitable aromatic substrates. Recently we have introduced a new protocol for the construction of 2-azaspiro[4.5]deca-6,9-diene-8-one framework by a three-component [C_2+C_2+CN] domino condensation of anisole with dicarbon synthon (isobutyric aldehyde or isobutylene oxide) and nitriles in the presence of concentrated sulfuric acid.[18] This original one-pot approach resulted in the formation of the substituted 2-azaspiro[4.5]deca-6,9-diene-8-ones in good yields from the simple starting aromatic compounds. 2-Methylanisole[19] or 1-methoxy, and 2-methoxynaphthalenes[20] were also successfully involved in this transformation. In a similar manner 2-azaspiro[5.5]undecanes can be synthesized.[21] It was found that the result of the three-component condensation depended on the character of the aromatic compound: in the case of veratrole or 1,4-dimethoxybenzene the reaction gave rise to substituted 3,4-dihydroisoquinolines.[22] Here we report the extension of this methodology to 1,2,3-, 1,2,4- and 1,3,5-trimethoxybenzene. The aim of present work was to evaluate the influence of the

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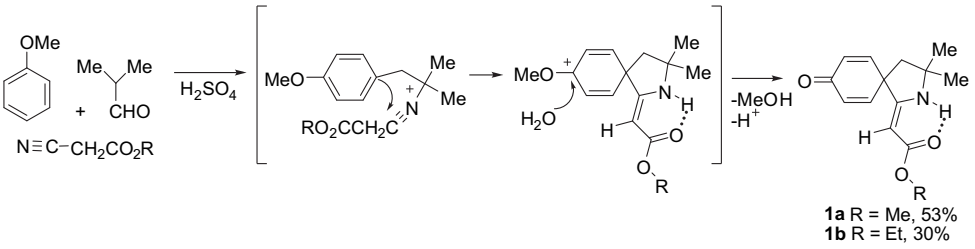
substitution pattern of the aromatic moiety in this three-component condensation. The same reaction of anisole is also discussed. Part of this work has been the subject of a preliminary communication.[23]

We have tested methylcyanoacetate, ethyl cyanoacetate, methylthiocyanate, and aromatic nitriles. In some cases (compounds **13a**–**c**) better results were obtained when we used 2,2-dimethyloxirane (isobutylene oxide) as a dicarbon synthon. 2,2-Dimethyloxirane is known to convert into isobutyric aldehyde (undergo the Meinwald rearrangement) under the reaction conditions.[18a,24,25] The proposed mechanism of the reaction was discussed previously.[18] Anisole, isobutyric aldehyde, and alkyl cyanoacetates afforded 2-azaspiro[4.5]decanes **1a**,**b** (Scheme 1). The structure of compound **1b** was unambiguously confirmed by the single-crystal X-ray diffraction analysis (Fig. 1).

In all these cases nucleophilic attack of water on the transient intermediate **B** is responsible for spirane formation.[26]

Compounds **1a**,**b** and **2a**,**b** exist in an enamine form, which was confirmed by ^{1}H NMR spectrum analysis. Enamines **1a**,**b** and **2a**,**b** showed the singlet of an unsaturated proton =CH δ 4.18–4.23 ppm and broadened singlet at δ 7.91–7.99 ppm (NH). Protons C(9)H, C(10)H of the cyclohexadienone ring resonate at δ 6.03 and 6.45 ppm, respectively (J=9.6 Hz). Compounds **2a**,**b** are formed as a mixture (1:1) of enantiomers relative to the spiro-C(5) atom; as a consequence diastereotopic protons $H_2C(4)$ resonate as two discrete doublets at δ 1,95 and 2.35 ppm (J 14 Hz). The (*Z*)-configuration of compounds **2a**,**b** is due to an intramolecular hydrogen bond (IHB). Indeed, the absorption band of the ester group in the IR spectra of **2a**,**b** is shifted to the low-frequency region (1640–1656 cm^{-1}), which indicates the existence of IHB between the carbonyl and NH group.



Scheme 1.

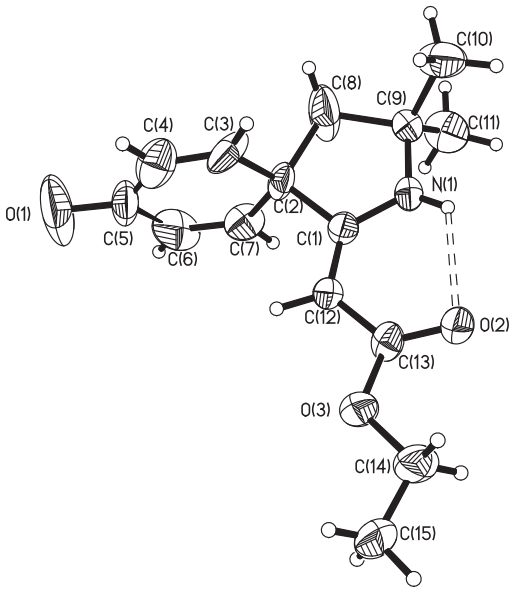
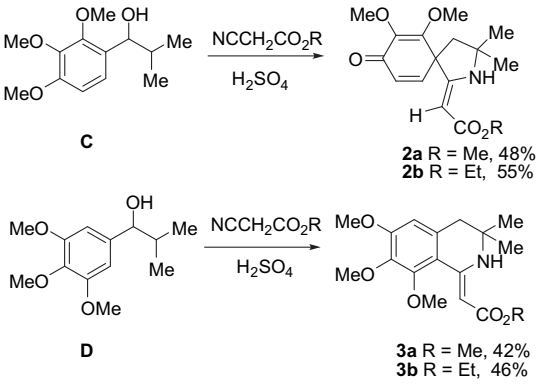


Figure 1. Structure of compound **1b.**

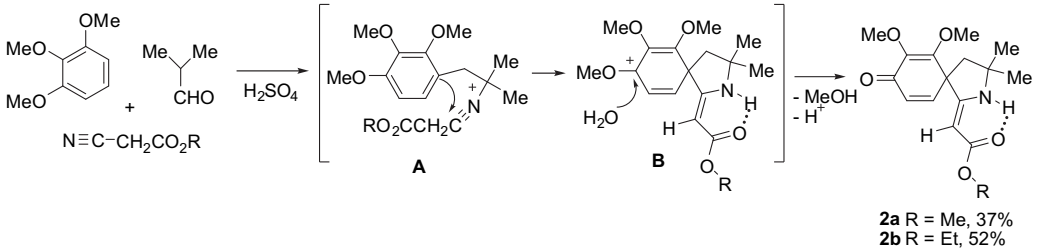
The three-component condensation of 1,2,3-trimethoxybenzene, isobutyric aldehyde, and alkyl cyanoacetates in the presence of concentrated sulfuric acid afforded 2-azaspiro[4.5]deca-6,9-diene-8-ones (**2a**,**b**) (Scheme 2).

The two-component condensation of alkyl cyanoacetates with alcohol **C** afforded spiranes **2a**,**b**, while the same reaction of alcohol **D**[27] gave isoquinolines **3a**,**b** exclusively (Scheme 3).



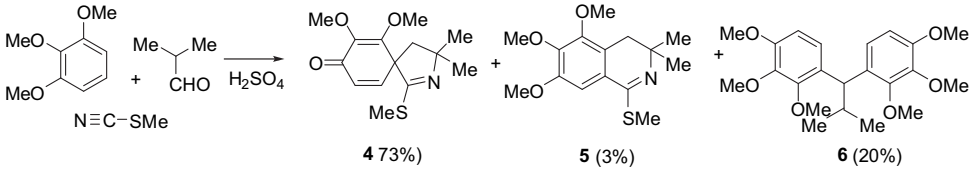
Scheme 3.

Isoquinolines **3a**,**b** were not formed in the three-component condensation (Scheme 2), but **3a**,**b** were the main products of the two-component reaction of alcohol **D** (Scheme 3). After the correlation of these results we reached the conclusion that the protonated isobutyric aldehyde attacks 1,2,3-trimethoxybenzene exclusively at C(4) position of the aromatic ring.



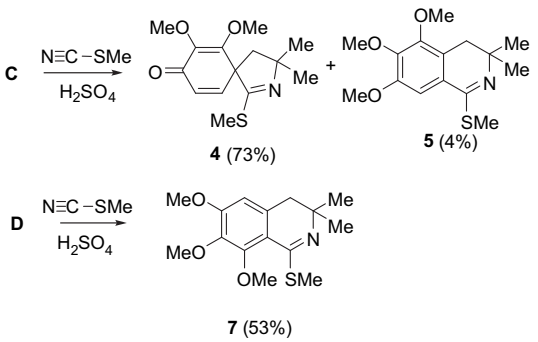
Scheme 2.

Methylthiocyanate reacts in much the same way (Scheme 4), but some quantity of a corresponding isoquinoline **5** was still obtained, along with a condensation product **6**.



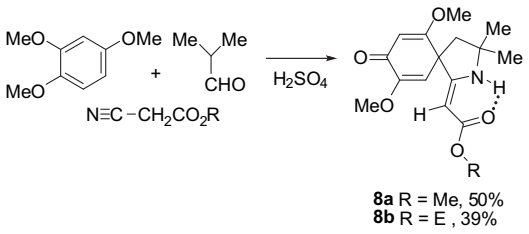
Scheme 4.

In a similar manner, alcohols **C**,**D** react with methylthiocyanate (Scheme 5). Alcohol **C** afforded spirane **5**; isoquinoline **6** was a minor product (4% yield); the mixture was separated by column chromatography. Alcohol **D** gave isoquinoline **7** exclusively, due to the interplay of the two methoxy groups.



Scheme 5.

Next, the reactions of 1,2,4-trimethoxybenzene were studied. Spiranes **8a**,**b** were found to be the single products of the three-component condensation with isobutyric aldehyde and alkyl cyanoacetates (Scheme 6).

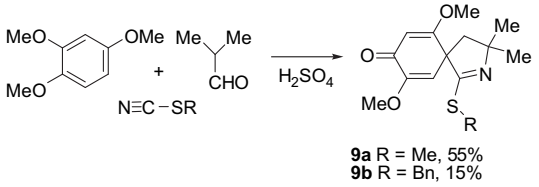


Scheme 6.

As for spiranes **1** and **2**, compounds **8a**,**b** exist in an enamine form (^{1}H NMR spectra showed one singlet of unsaturated proton =CH δ 5.46–5.55 ppm and a broad singlet at δ 8.00–8.27 ppm (NH)). Compounds **8a**,**b** form a mixture (1:1) of enantiomers relative to the spiro-C(5) atom, as it was previously found for spiranes **2a**,**b**, and the diastereotopic protons $H_2C(4)$ gave two discrete doublets at δ 1,95 and 2.35 ppm (J 14 Hz) in the ^{1}H NMR spectra of spiranes **8a**,**b**.

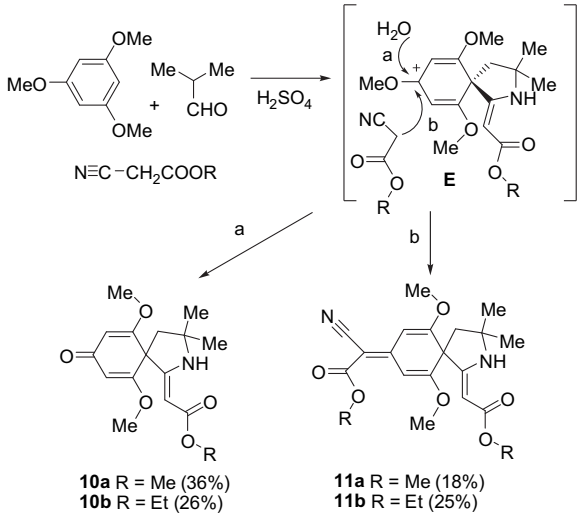
As for enamines **2a**,**b**, the (*Z*)-configuration of compounds **8a**,**b** is due to intramolecular hydrogen bond, so the absorption band of the ester group in the IR spectra of **8a**,**b** is shifted to the low-frequency region (1645–1650 cm^{-1}). The IR spectra of **8a**,**b** also display absorption bands at 3325–3340 (NH), 1630 (C=O) and 1590–1625 (C=C) cm^{-1}.

Unlike for 1,2,3-trimethoxybenzene, a three-component condensation of 1,2,4-trimethoxybenzene with isobutyric aldehyde and methyl (benzyl) thiocyanates afforded unequivocally spiranes **9a**,**b**, formed as a mixture of enantiomers (1:1) at the spiro-C(5) atom (Scheme 7).



Scheme 7.

1,3,5-Trimethoxybenzene was found to react with alkyl cyanoacetates in an unusual way: besides the spiranes **10a**,**b** (yields 26–36%), the products of a four-component condensation **11a**,**b** (18–25%) were isolated, which can be regarded as a result of formal Knöevenagel condensation (Scheme 8). Compounds **11a**,**b** have been characterized by ^{1}H NMR spectra and by single-crystal X-ray crystallography (for **11b**, Fig. 2).



Scheme 8.

It is evident that the initially formed spiro-intermediate **E** is attacked by the alkyl cyanoacetate as a nucleophile (Scheme 8). Such an uncommon behavior can be explained by the two competitive reaction pathways **a** and **b** (Scheme 8) and the high stability (along with relatively strong electrophilicity) of the intermediate **E** (carbocations on the base of 1,3,5-trimethoxybenzene usually can be regarded as the species of high stability[28]). It should be mentioned that in the case of 1,2,3-trimethoxybenzene, the corresponding Knöevenagel products were barely observed. According to our results, 1,2,4-trimethoxybenzene was not inclined to react by route **b**. This fact can be explained by electron-donating properties of the *ortho*-methoxy group; the steric bulk of this substituent must also be taken into account.

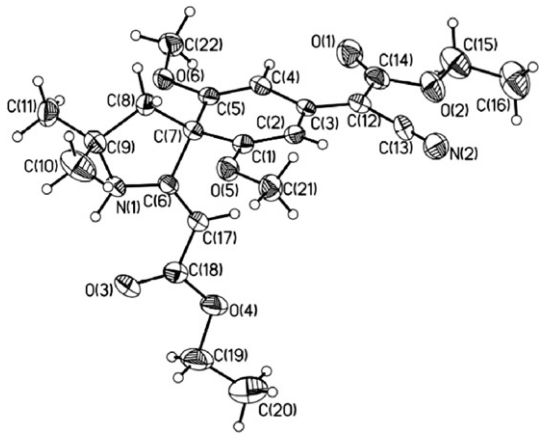
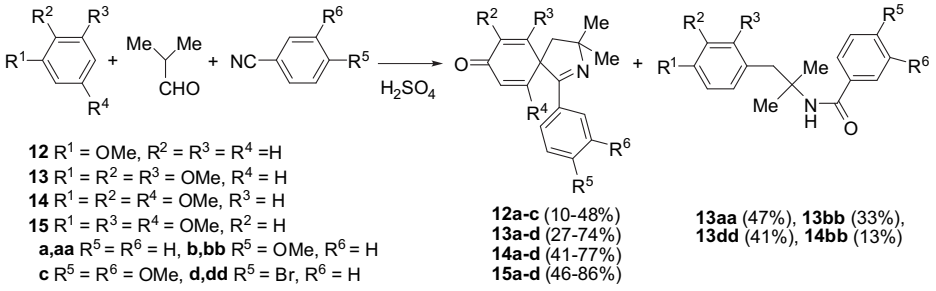


Figure 2. Structure of compound **11b** in thermal ellipsoid of 50% probability.

Finally, we studied the three-component condensation of aromatic nitriles with isobutyric aldehyde and anisole, 1,2,3-trimethoxybenzene, 1,2,4-trimethoxybenzene or 1,3,5-trimethoxybenzene. Spiranes **12**–**15** were obtained as expected (Scheme 9). In the case of 1,2,3- and 1,2,4-trimethoxybenzene, along with spiranes **13a**–**d** and **14a**–**d**, Ritter amides (**13aa**, **13bb**, **13dd**, **14bb**) were isolated as byproducts (yields 9–47%, Scheme 9). Anisole gives a poor yield of spiranes **12a**–**c** (22–48%). The reaction of anisole with isobutyric aldehyde and 4-bromobenzonitrile was sluggish, and we failed to obtain 1-(4-bromophenyl)-3,3-dimethyl-2-azaspiro[4.5]deca-1,6,9-triene-8-one (compound **12d**) by this method.



12 R^1 = OMe, R^2 = R^3 = R^4 =H
13 R^1 = R^2 = R^3 = OMe, R^4 = H
14 R^1 = R^2 = R^4 = OMe, R^3 = H
15 R^1 = R^3 = R^4 = OMe, R^2 = H
a,aa R^5 = R^6 = H, **b,bb** R^5 = OMe, R^6 = H
c R^5 = R^6 = OMe, **d,dd** R^5 = Br, R^6 = H

12a-c (10-48%)
13a-d (27-74%)
14a-d (41-77%)
15a-d (46-86%)

13aa (47%), **13bb** (33%),
13dd (41%), **14bb** (13%)

Scheme 9.

3. Conclusion

In summary, we have described the three-component condensation of 1,2,3-, 1,2,4- and 1,3,5-trimethoxybenzene with isobutyric aldehyde and a variety of nitriles in the presence of concentrated sulfuric acid. This method offers an elegant approach to the 1-substituted 2-azaspiro[4.5]deca-6,9-diene-8-ones and 2-azaspiro[4.5]deca-1,6,9-triene-8-ones. The substitution pattern in arene changes the conversion and the reactivity profile: anisole gives poor yields of spiro-compounds; 1,2,3-trimethoxybenzene is prone to Ritter amides formation, and 1,3,5-trimethoxybenzene provides the compounds of the formal Knöevenagel condensation.

4. Experimental

4.1. General

All the chemicals used were reagent grade as supplied from Alfa Aesar (Lancaster). Analytical thin-layer chromatography was performed using silica gel plates *Sorbfil* in chloroform/acetone mixture (9:1, v/v); compound spots were visualized by UV light (254 nm) and/or by staining with a solution of chloranil in toluene. Flash chromatography was performed on silica gel 60 (220–440 mesh, Alfa Aesar). IR spectra were recorded on Specord M-80 spectrometer in Nujol. ^{1}H and ^{13}C NMR spectra were obtained on a Varian Mercury+300 instrument at 300 and 75 MHz, respectively, in $CDCl_3$ or DMSO-d_6 and were referenced to HMDS (^{1}H NMR δ=0.055 ppm), residual $CHCl_3$ (^{13}C NMR δ=77.0 ppm) or residual DMSO (^{13}C NMR δ=39,6 ppm). Mass-spectra were recorded on GC–MS system Agilent 6890N series with mass-selective detector MSD 5975B (EI, 70 eV). Elemental analyses (C, H, N) were obtained using Leco CHNS 9321P elemental analyzer at the Institute of Technical Chemistry, Perm.

4.2. General procedures for the three-component condensation

Procedure A. A mixture of anisole (1.09 mL, 1.08 g, 10 mmol) or trimethoxybenzene (1.68 g, 10 mmol), isobutyric aldehyde (0.79 g, 1.00 mL, 11 mmol), nitrile (10 mmol), and dichloromethane (3 mL) was added to concentrated H_2SO_4 (6 mL) and stirred for 5 min in a cold water bath followed by 40 min at room temperature. The reaction mixture was poured into a mixture of 100 g crushed ice, 25% NH_4OH (30 mL), concentrated aqueous NH_4Cl (30 mL), and CH_2Cl_2 (50 mL) (pH of water phase ~8). The organic phase was separated, the water phase was extracted with CH_2Cl_2 (20 mL), the combined organic phase was washed with 50 mL of brine, dried over $MgSO_4$, and filtered. The residue after evaporation of organic solvent was crystallized (compounds **1a**, **2a**,**b**, **8a**,**b**, **9a**,**b**, **12a**) or purified by flash chromatography on silica gel (compounds **4**, **5**, **6**, **10a**,**b**, **11a**,**b**, **12b**,**c**, **13a**–**d**, **13aa**, **13bb**, **13dd**, **14a**–**d**, **14bb**).

Procedure B. A mixture of carbinols C or D (2.40 g, 10 mmol) and 10 mmol of nitrile and dichloromethane (3 mL) was added to concentrated H_2SO_4 (6 mL) and stirred for 5 min in a cold water bath followed by 40 min at room temperature. The subsequent workup was performed according to procedure A. The residue after evaporation of organic solvent was crystallized (compounds **2a**,**b**, **3b**, **7**) or purified by flash chromatography on silica gel (compound **3a**, **4**, **5**; eluent hexanes/ethylacetate, 5/1).

Procedure C (for compounds **15a**–**d**). Synthesis was performed according to procedure A; the reaction mixture was poured into cold water, treated by solid $NaHCO_3$ (pH ~7), extracted with CH_2Cl_2 (20 mL), the combined organic phase was washed with 50 mL of brine, dried over $MgSO_4$, and filtered. The residue after evaporation of organic solvent was crystallized.

Products of alkyl cyanoacetate condensation (**1a**, **2a**,**b**, **3a**,**b**, **8a**,**b**, **10a**,**b**, **11a**,**b**) are not stable under conditions of mass-spectrometric experiments; compounds **13**,**14** decompose mainly through loss of aromatic nitriles and the methyl groups.

For compound **1b** see Ref. 18b.

*4.2.1. Methyl [(2Z)-(3,3-dimethyl-8-oxo-2-azaspiro[4,5]deca-6,9-dien-1-ylidene)] acetate (**1a**). Procedure A.* Yield 1.31 g (53%), colorless plates, mp 157–159 °C (from ethanol), R_f 0.60; ν_{max} (Nujol) 3320 (NH), 1630 (C=O), 1575, 1250, 1200, 1140, 1045 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.91 (1H, br s, NH), 6.77 (2H, d, ^3J=10.2 Hz, C(6)H and C(10)H), 6.18 (2H, d, ^3J=10.2 Hz, C(7)H and C(9)H), 4.23 (1H, s, CH=), 3.56 (3H, s, OMe), 2.41 (2H, s, CH_2), 1.41 (6H, s, 2Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.9, 170.8, 161.5, 149.8, 127.9, 77.9, 61.3, 52.9, 50.3, 46.6, 31.1. Anal. Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 68.14; H, 6.81; N, 5.66.

*4.2.2. Methyl-(2Z)-[5-(R,S)-(6,7-dimethoxy-3,3-dimethyl-8-oxo-2-azaspiro[4,5]deca-6,9-dien-1-ylidene)] acetate (**2a**). Procedure A.* Yield 1.14 g (37%), colorless plates, mp 139–140 °C (from ethanol), R_f 0.50; ν_{max} (Nujol) 3320 (NH), 1640 (C=O), 1610, 1585, 1315, 1265, 1215, 1140, 1060, 850, 810 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.94 (1H, br s, NH), 6.46 (1H, d, ^3J=9.6 Hz, C(10)H), 6.03 (1H, d, ^3J=9.6 Hz, C(9)H), 4.18 (1H, s, CH=), 4.01 (3H, s, OMe), 3.69 (3H, s, OMe), 3.56 (3H, s, OMe), 2.35 (1H, d, ^2J=13.8 Hz, C(4)H), 1.95 (1H, d, ^2J=13.8 Hz, C(4)H), 1.38 (3H, s, Me), 1.37 (3H, s, Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.2, 184.1, 170.9, 162.1, 160.7, 145.3, 138.1, 125.6, 75.7, 61.7, 61.2, 60.6, 57.5, 50.1, 45.1, 31.8, 30.3. Anal. Calcd for $C_{16}H_{21}NO_5$: C, 62.53; H, 6.89; N, 4.56. Found: C, 62.59; H, 6.74; N, 4.57. Procedure B afforded 48% yield of **2a** from alcohol **C**.

*4.2.3. Ethyl (2Z)-[5-(R,S)-(6,7-dimethoxy-3,3-dimethyl-8-oxo-2-azaspiro[4,5]deca-6,9-dien-1-ylidene)] acetate (**2b**). Procedure A.* Yield 1.67 g (52%), transparent prisms, mp 140–143 °C (from ethanol), R_f 0.66; ν_{max} (Nujol) 3396 (NH), 1656 (C=O), 1604, 1324, 1260, 1212, 1144, 1056, 856, 840 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.99 (br s, 1H, NH), 6.51 (1H, d, ^3J=9.9 Hz, C(10)H), 6.08 (1H, d, ^3J=9.9 Hz, C(9)H), 4.23 (1H, s, CH=), 4.07 (5H, m, OMe+O$\underline{CH_2}$$CH_3$), 3.74 (3H, s, OMe), 2.40 (1H, d, ^2J=13.5 Hz, C(4)H), 1.99 (1H, d, ^2J=13.5 Hz, C(4)H), 1.43 (3H, s, Me), 1.42 (3H, s, Me), 1.23 (3H, t, J=7.5 Hz, $OCH_2\underline{CH_3}$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 183.6, 169.0, 161.4, 160.9, 146.6, 137.5, 124.8, 74.4, 62.1, 61.1, 60.2, 57.9, 57.4, 44.5, 30.9, 29.8, 14.6. Anal. Calcd for $C_{17}H_{23}NO_5$: C, 63.54; H, 7.21; N, 4.36. Found: C, 63.89; H, 7.01; N, 4.39. Procedure B afforded 55% yield of **2b** from alcohol **C**.

*4.2.4. Methyl (2Z)-(3,3-dimethyl-6,7,8-trimethoxy-1,2,3,4-tetrahydroisoquinoline-1-ylidene) acetate (**3a**). Procedure B.* Yield 1.35 g (42%) from alcohol **D**, colorless prisms, 107–109 °C (hexanes), R_f 0.80; ν_{max} (Nujol) 3267 (NH), 1641 (C=O), 1595 (C=C), 1561 (C=C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.12 (1H, s, NH), 6.38 (1H, s, C(5)H), 5.66 (1H, s, CH=), 3.80 (3H, s, OMe), 3.77 (3H, s, OMe), 3.76 (3H, s, OMe), 3.58 (3H, s, OMe), 2.63 (2H, s, CH_2), 1.16 (6H, s, 2Me); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.2, 154.6, 153.6, 153.2, 141.6, 132.9, 115.3, 107.6, 80.2, 60.9, 60.8, 55.8, 50.0, 48.7, 43.5, 28.2. Anal. Calcd for $C_{17}H_{23}NO_5$: C, 63.54; H, 7.21; N, 4.36. Found: C, 63.64; H, 7.07; N, 4.38.

*4.2.5. Ethyl (2Z)-(3,3-dimethyl-6,7,8-trimethoxy-1,2,3,4-tetrahydroisoquinoline-1-ylidene) acetate (**3b**). Procedure B.* Yield 1.54 g (46%) from alcohol **D**, colorless prisms, mp 174–175 °C (aq MeOH), R_f 0.74; ν_{max} (Nujol) 3260 (NH), 1640 (C=O), 1596, 1332, 1280, 1256, 1232, 1192, 1176, 1156, 1140, 1112, 1032, 896, 868 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 9.13 (1H, s, NH), 6.39 (1H, s, C(5)H), 5.66 (1H, s, CH=), 4.08 (2H, q, ^3J=7.6 Hz, OCH_2), 3.82 (3H, s, OMe), 3.79 (6H, s, 2OMe), 2.65 (2H, s, CH_2), 1.22 (3H, t, ^3J=7.6 Hz, Me), 1.18 (6H, s, 2Me). Anal. Calcd for $C_{18}H_{25}NO_5$: C, 64.46; H, 7.51; N, 4.18. Found: C, 63.79; H, 7.59; N, 4.05.

The reaction of 1,2,3-trimethoxybenzene (1.68 g, 10 mmol), isobutyric aldehyde (0.79 g, 1.00 mL, 11 mmol), and methylthiocyanate (0.73 g, 0.68 mL, 10 mmol) according to procedure A afforded after flash chromatography on silica gel (hexanes/ethylacetate, 5/1) compounds **5** (yield 4%, R_f 0.73), **6** (yield 20%, R_f 0.67), and **4** (yield 73%, R_f 0.57).

*4.2.6. 6,7-Dimethoxy-3,3-dimethyl-1-methylsulfanyl-2-azaspiro[4.5]deca-1,6,9-triene-8-one (**4**).* Colorless prisms, mp 70–71 °C (from hexanes), ν_{max} (Nujol) 1645 (C=O), 1625 (C=C), 1590 (C=N) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 6.65 (1H, d, ^3J=10 Hz, C(10)H), 6.10 (1H, d, ^3J=10 Hz, C(9)H), 4.00 (3H, s, OMe), 3.65 (3H, s, OMe), 2.32 (3H, s, SMe), 2.23 (1H, d, ^2J=14 Hz, C(4)H), 2.08 (1H, d, ^2J=14 Hz, C(4)H), 1.35 (3H, s, Me), 1.32 (3H, s, Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.1, 165.7, 159.6, 144.5, 138.4, 127.0, 74.5, 66.2, 60.9, 60.3, 47.5, 31.2, 30.1, 13.7; m/z (I,%): 208 (100) ($M^+\cdot-CH_3SCN$). Anal. Calcd for $C_{14}H_{19}NO_3S$: C, 59.76; H, 6.81; N, 4.98; S, 11.39. Found: C, 59.85; H, 6.83; N, 4.89; S, 12.46. Procedure B from alcohol **C** gives rise to compounds **4** (yield 73%) and **5** (yield 4%).

*4.2.7. 3,3-Dimethyl-1-methylsulfanyl-5,6,7-trimethoxy-3,4-dihydroisoquinoline (**5**).* Colorless oil, ^1H NMR (300 MHz, $CDCl_3$) δ 7.01 (1H, s, C(8)H), 3.90 (3H, s, OMe), 3.87 (3H, s, OMe), 3.81 (3H, s, OMe), 2.62 (2H, s, CH_2), 2.41 (3H, s, SMe), 1.19 (6H, s, 2Me); m/z 295 (M^+). Anal. Calcd for $C_{15}H_{21}NO_3S$: C, 60.99; H, 7.17; N, 4.72; S, 10.85. Found: C, 60.77; H, 7.32; N, 4.53; S, 11.12.

*4.2.8. 1,1-Bis-(2,3,4-trimethoxyphenyl)-2-methylpropane (**6**).* Colorless oil, ν_{max} (slim film) 2959, 2938, 2872, 2836, 1598, 1493, 1464, 1435 (w), 1413, 1384 (w), 1281, 1256, 1227 (w), 1199, 1170 (w), 1120, 1094, 1040, 1017, 964, 906, 797, 757, 688 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 6.97 (2H, d, ^3J=9 Hz, C(6′)H), 6.59 (2H, d, ^3J=9 Hz, C(5′)H), 4.25 (1H, d, ^3J=10.4 Hz, CH), 3.81 (6H, s, OMe), 3.80 (6H, s, OMe), 3.77 (6H, s, OMe), 2.27 (1H, m, CH), 0.86 (6H, d, ^3J=6.3 Hz, 2Me); m/z 390 (M^+).

*4.2.9. 3,3-Dimethyl-1-methylsulfanyl-6,7,8-trimethoxy-3,4-dihydroisoquinoline (**7**). Procedure B.* Yield 1.56 g (53%) from alcohol **D**, transparent prisms, mp 84–85 °C (hexanes), R_f 0.62; ν_{max} (Nujol) 1584, 1556, 1340, 1316, 1252, 1196, 1132, 1088, 1040 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.40 (1H, s, 5-H), 3.89 (3H, s, OMe), 3.82 (3H, s, OMe), 3.78 (3H, s, OMe), 2.48 (2H, s, CH_2), 2.28 (3H, s, SMe), 1.11 (6H, s, 2Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.8, 151.5, 140.7, 133.3, 115.3, 107.0, 61.2, 60.7, 55.8, 55.0, 40.0, 27.9, 13.3; m/z 295 (M^+). Anal. Calcd for $C_{15}H_{21}NO_3S$: C, 60.99; H, 7.17; N, 4.72; S, 10.85. Found: C, 60.80; H, 7.27; N, 4.72; S, 11.42.

*4.2.10. Methyl (2Z)-[5-(R,S)-(6,9-dimethoxy-3,3-dimethyl-8-oxo-2-azaspiro[4,5]deca-6,9-dien-1-ylidene)]acetate (**8a**). Procedure A.* Yield 1.54 g (50%), colorless prisms, mp 190–192 °C (from ethanol), R_f 0.59; ν_{max} (Nujol) 3340 (NH), 1650 (O–C=O), 1615 (C=C), 1595 (C=C) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 8.00 (1H, br s, NH), 5.63 (1H, s, C(10)H), 5.46 (1H, s, C(7)H), 4.20 (1H, s, CH=), 3.73 (3H, s, OMe), 3.65 (3H, s, OMe), 3.61 (3H, s, OMe), 2.44 (1H, d, C(4)H, ^2J=13.5 Hz), 2.04 (1H, d, C(4)H, ^2J=13.5 Hz), 1.46 (3H, s, Me), 1.44 (3H, s, Me); ^{13}C NMR (75 MHz, DMSO-d_6) δ 180.9, 174.5, 169.6, 163.5, 148.5, 115.6, 102.0, 74.2, 62.0, 56.7, 55.4, 54.9, 49.6, 46.7, 31.2, 29.8. Anal. Calcd for $C_{16}H_{21}NO_5$: C, 62.53; H, 6.89; N, 4.56. Found: C, 62.70; H, 6.69; N, 4.57.

*4.2.11. Ethyl (2Z)-[5-(R,S)-(6,9-dimethoxy-3,3-dimethyl-8-oxo-2-azaspiro[4,5]deca-6,9-dien-1-ylidene)]acetate (**8b**). Procedure A.* Yield 1.25 g (39%), bright yellow plates, mp 179–180 °C (from ethanol), R_f 0.44; ν_{max} (Nujol) 3325 (NH); 1645 (O–C=O); 1630 (C=O); 1640, 1625, 1590 (C=C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.27 (1H, s, NH), 5.56 (1H, s, CH=), 5.55 (1H, s, CH=), 3.88 (2H, q, ^3J=7.2 Hz, OCH_2), 3.82 (1H, s, CH=), 3.67 (3H, s, OMe), 3.50 (3H, s, OMe), 2.24 (1H, d, ^2J=13.8 Hz, C(4)H), 2.02 (1H, d, ^2J=13.8 Hz, C(4)H), 1.38 (3H, s, Me), 1.33 (3H, s, Me), 1.06 (3H, t, ^3J=7.2 Hz, $OCH_2\underline{CH_3}$); ^{13}C NMR (75 MHz, DMSO-d_6) δ 181.5, 175.0, 170.0, 164.1,

149.2, 116.3, 102.6, 75.1, 62.5, 58.4, 57.3, 56.0, 55.6, 47.4, 31.9, 30.5, 15.2; *m/z* 321 (M^+). Anal. Calcd for $C_{17}H_{23}NO_5$: C, 63.54; H, 7.21; N, 4.36. Found: C, 63.28; H, 6.87; N, 4.24.

*4.2.12. 5-(R,S)-6,9-Dimethoxy-3,3-dimethyl-1-methylsulfanyl-2-azaspiro[4.5]deca-1,6,9-triene-8-one (**9a**). Procedure A.* Yield 1.54 g (55%), white solid, mp 190–191 °C (EtOAc/hexanes), R_f 0.43; ν_{max} (Nujol) 1640 (C=O), 1615 (C=C), 1590 (C=N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.66 (1H, s, C(10)H), 5.34 (1H, s, C(7)H), 3.74 (3H, s, OMe), 3.68 (3H, s, OMe), 2.44 (1H, d, ^2J=14.5 Hz, C(4)H), 2.37 (3H, s, SMe), 2.07 (1H, d, ^2J=14.5 Hz, C(4)H), 1.42 (3H, s, Me), 1.41 (3H, s, Me); ^{13}C NMR (75 MHz, DMSO-d_6): δ 180.8, 172.8, 166.3, 149.4, 114.1, 102.8, 74.2, 63.7, 56.7, 55.0, 49.3, 31.4, 30.2, 13.5; *m/z* 281 (M^+). Anal. Calcd for $C_{14}H_{19}NO_3S$: C, 59.76; H, 6.81; N, 4.98; S, 11.39. Found: C, 59.53; H, 6.88; N, 4.94; S, 12.30.

*4.2.13. 5-(R,S)-1-Benzylsulfanyl-6,9-dimethoxy-3,3-dimethyl-2-azaspiro[4.5]deca-1,6,9-triene-8-one (**9b**). Procedure A.* Yield 0.54 g (15%), colorless solid, mp 124–125 °C (EtOAc/hexanes), R_f 0.55; ν_{max} (Nujol) 1645 (C=O), 1625 (C=C), 1590 (C=N) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 7.21 (5H, m, Ph), 5.56 (1H, s, C(10)H), 5.49 (1H, s, C(7)H), 4.16 (1H, d, *J*=13.2 Hz, SCH), 4.05 (1H, d, *J*=13.2 Hz, SCH), 3.59 (3H, s, OMe), 3.47 (3H, s, OMe), 2.28 (1H, d, *J*=13.2 Hz, C(4)H), 2.07 (1H, d, *J*=13.2 Hz, C(4)H), 1.34 (3H, s, Me), 1.29 (3H, s, Me), ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.8, 173.1, 166.0, 150.2, 137.7, 129.0, 128.2, 127.1, 113.2, 103.2, 74.6, 56.2, 55.2, 49.7, 35.6, 31.6, 30.1; Anal. Calcd for $C_{20}H_{23}NO_3S$: C, 67.20; H, 6.49; N, 3.92; S, 8.97. Found: C, 67.14; H, 6.58; N, 3.87; S, 9.18.

The reaction of 1,3,5-trimethoxybenzene (1.68 g, 10 mmol), isobutyric aldehyde (0.79 g, 1.00 mL, 11 mmol), and methylcyanoacetate (0.99 g, 0.88 mL, 10 mmol) according to procedure A afforded after flash chromatography on silica gel (hexanes/ethylacetate, 5/1) compounds **10a** (yield 36%, R_f 0.48) and **11a** (yield 18%, R_f 0.73).

*4.2.14. Methyl (2Z)-(3,3-dimethyl-6,10-dimethoxy-8-oxo-2-azaspiro[4,5]deca-6,9-diene-1-ylidene) acetate (**10a**).* Colorless plates, mp 188–190 °C (from ethanol); ν_{max} (Nujol) 3340 (NH), 1630 (C=O), 1565 (C=C) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.96 (1H, br s, NH), 5.41 (2H, s, C(7)H, C(9)H), 4.12 (1H, s, HC=), 3.65 (6H, s, 2OMe), 3.55 (3H, s, OMe), 2.20 (2H, s, C(4)H_2), 1.38 (6H, s, 2Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.6, 171.5, 171.1, 162.6, 100.3, 73.8, 62.2, 57.9, 56.1, 50.0, 44.8, 30.3; Anal. Calcd for $C_{16}H_{21}NO_5$: C, 62.53; H, 6.89; N, 4.56. Found: C, 62.16; H, 6.95; N, 4.47.

*4.2.15. Methyl {(1Z)-6,10-dimethoxy-3,3-dimethyl-1-(2-methoxy-2-oxoethylidene)-2-azaspiro[4,5]-deca-6,9-diene-8-ilidene}-cyanoacetate (**11a**).* Bright yellow plates, mp 185.5–187 °C (from ethanol), ν_{max} (Nujol) 3320 (NH), 2180 (C≡N), 1690 (O–C=O), 1660 (O–C=O); 1630 (C=C); 1580 (C=C) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 8.36 (1H, s, NH), 7.35 (1H, s, CH=, C(9)H or C(7)H), 5.94 (1H, s, CH=, C(7)H or C(9)H), 3.81 (4H, m, OMe and CH=), 3.78 (3H, s, OMe), 3.74 (3H, s, OMe), 3.45 (3H, s, OMe), 2.17 (2H, s, CH_2), 1.38 (6H, s, 2Me); ^{13}C NMR (75 MHz, DMSO-d_6) δ 170.1, 170.0, 169.5, 164.0, 162.0, 158.3, 117.5, 95.4, 93.7, 89.0, 73.3, 62.7, 58.6, 56.79, 56.75, 51.9, 49.6, 45.5, 30.0; *m/z* 289 (M^+–$NCCH_2CO_2Me$). Anal. Calcd for $C_{20}H_{24}N_2O_6$: C, 61.85; H, 6.23; N, 7.21. Found: C, 61.20; H, 6.10; N, 7.21.

The reaction of 1,3,5-trimethoxybenzene (1.68 g, 10 mmol), isobutyric aldehyde (0.79 g, 1.00 mL, 11 mmol), and ethyl cyanoacetate (1.13 g, 1.06 mL, 10 mmol) according to procedure A afforded after flash chromatography on silica gel (hexanes/ethylacetate, 5/1) compounds **10b** (yield 26%, R_f 0.41) and **11b** (yield 24%, R_f 0.69).

*4.2.16. Ethyl (2Z)-(3,3-dimethyl-6,10-dimethoxy-8-oxo-2-azaspiro[4,5]-deca-6,9-diene-1-ylidene) acetate (**10b**).* Colorless plates, mp 192–195 °C (from ethanol); ν_{max} (Nujol) 3320 (NH), 1640 (C=O), 1610, 1585 (C=C) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.96 (1H, s, NH), 5.41 (2H, s, C(7)H, C(9)H), 4.11 (1H, s, CH=), 4.00 (2H, q, ^2J=7.5 Hz, OCH_2), 3.64 (6H, s, 2OMe), 2.23 (1H, d, ^2J=13.5 Hz, C(4)H), 2.19 (1H, d, ^2J=13.5 Hz, C(4)H), 1.37 (6H, s, 2Me), 1.16 (3H, t, ^3J=7.5 Hz, Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.4, 171.6, 170.9, 162.6, 100.5, 74.6, 62.1, 58.5, 58.2, 56.1, 45.1, 30.4, 14.4. Anal. Calcd for $C_{17}H_{23}NO_5$: C, 63.54; H, 7.21; N, 4.36. Found: C, 63.66; H, 7.53; N, 4.32.

*4.2.17. Ethyl {(1Z)-6,10-dimethoxy-3,3-dimethyl-1-(2-methoxy-2-oxoethylidene)-2-azaspiro[4,5]-deca-6,9-diene-8-ilidene}-cyanoacetate (**11b**).* Bright yellow plates, mp 167–169 °C (from ethanol), ν_{max} (Nujol) 3310 (NH), 2175 (C≡N), 1700 (shoulder, O–C=O), 1670 (O–C=O), 1600 (C=C), 1265, 1170, 1075, 860 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 8.30 (1H, s, NH), 7.33 (1H, s, CH=, C(9)H or C(7)H), 5.95 (1H, s, CH=, C(7)H or C(9)H), 4.21 (2H, q, ^3J=7.8 Hz, OCH_2), 3.93 (2H, q, ^3J=7.8 Hz, OCH_2), 3.82 (3H, s, OMe), 3.79 (4H, m, OMe+CH=), 2.18 (2H, s, CH_2), 1.38 (6H, s, 2Me), 1.27 (3H, t, ^3J=7.8 Hz, Me), 1.12 (3H, t, ^3J=7.8 Hz, Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9, 169.9, 168.9, 163.4, 161.77, 158.0, 117.6, 95.1, 93.4, 88.9, 73.0, 62.7, 60.7, 58.4, 57.8, 56.7, 45.1, 29.8, 14.5, 14.1; *m/z* 416 (M^+). Anal. Calcd for $C_{22}H_{28}N_2O_6$: C, 63.45; H, 6.78; N, 6.73. Found: C, 63.22; H, 6.64; N, 6.75.

*4.2.18. 3,3-Dimethyl-1-phenyl-2-azaspiro[4.5]deca-1,6,9-triene-8-one (**12a**). Procedure A.* The residue after evaporation of organic solvent crystallized on standing. It was filtered and crystallized from hexanes. Yield 0.25 g (10%), colorless needles, mp 132–134 °C, R_f 0.53; ν_{max} (Nujol) 1660 (C=O), 1625 (C=N), 1605 (C=C), 1575 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.64 (2H, m, Ph), 7.40 (1H, m, Ph), 7.32 (2H, m, Ph), 7.15 (2H, d, ^3J=10.2 Hz, C(6)H, C(10)H), 6.28 (2H, d, ^3J=10.2 Hz, C(7)H, C(9)H), 2.23 (2H, s, CH_2), 1.45 (6H, s, 2Me); ^{13}C NMR (75 MHz, DMSO-d_6) δ 183.8, 164.0, 152.0, 133.5, 130.3, 128.0, 127.9, 127.3, 72.4, 60.7, 49.0, 30.2; *m/z* 148 (M^+–PhCN). Anal. Calcd for $C_{17}H_{17}NO$: C, 81.24; H, 6.82; N, 5.57. Found: C, 81.35; H, 6.90; N, 5.42.

*4.2.19. 3,3-Dimethyl-1-(4-methoxyphenyl)-2-azaspiro[4.5]deca-1,6,9-triene-8-one (**12b**). Procedure A.* The residue after evaporation of organic solvent was purified by flash chromatography on silica gel (hexanes/ethylacetate/Et_3N, 80/20/1, R_f 0.58). Yield 22%, colorless powder, mp 142–143 °C (hexanes–CH_2Cl_2); ν_{max} (Nujol) 1670 (C=O), 1630 (C=N), 1600 (C=C), 1260, 1175, 1030, 860 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.59 (2H, d, ^3J=9 Hz, C(2′)H, C(6′)H), 6.95 (2H, d, ^3J=9.6 Hz, C(6)H, C(10)H), 6.72 (2H, d, ^3J=9 Hz, C(3′)H, C(5′)H), 6.33 (2H, d, ^3J=9.6 Hz, C(7)H, C(9)H), 3.73 (3H, s, OMe), 2.17 (2H, s, CH_2), 1.43 (6H, s, 2Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.9, 164.4, 161.5, 152.0, 129.3, 128.3, 126.1, 113.5, 72.3, 61.0, 55.1, 49.9, 30.6; Anal. Calcd for $C_{18}H_{19}NO_2$: C, 76.84; H, 6.81; N, 4.98. Found: C, 76.77; H, 6.62; N, 5.02. If we used 2,2-dimethyloxirane as C_2-synthon, the yield of compound **12b** was 32%.

*4.2.20. 1-(3,4-Dimethoxyphenyl)-3,3-dimethyl-2-azaspiro[4.5]deca-1,6,9-triene-8-one (**12c**). Procedure A.* The residue after evaporation of organic solvent was purified by flash chromatography on silica gel (hexanes/ethylacetate/Et_3N, 80/20/1, R_f 0.53). Yield 48%, colorless plates, mp 190–192 °C (hexanes); ν_{max} (Nujol) 1650 (C=O), 1620, 1600, 1570, 1510 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33 (1H, d, ^4J=2 Hz, C(2′)H), 7.14 (1H, dd, ^3J=9 Hz, ^4J=2 Hz, C(6′)H), 6.97 (2H, d, ^3J=10 Hz, C(6)H, C(10)H), 6.67 (1H, d, ^3J=9 Hz, C(5′)H), 6.34 (2H, d, ^3J=10 Hz, C(7)H, C(9)H), 3.80 (3H, s, OMe), 3.78 (3H, s, OMe), 2.17 (2H, s, CH_2), 1.44 (6H, s, 2Me). Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.40; H, 6.55; N, 4.45.

The reaction of 1,2,3-trimethoxybenzene (1.68 g, 10 mmol), isobutyric aldehyde (0.79 g, 1.00 mL, 11 mmol), and benzonitrile (1.03 g, 1.02 mL, 10 mmol) according to procedure A afforded after

flash chromatography on silica gel (hexanes/ethylacetate, gradient elution from 100/0 to 50/50, v/v) compounds **13aa** (yield 47%, R_f 0.65) and **13a** (yield 27%, R_f 0.56). The same method was used for the synthesis and purification of compounds **13b–d**, **13bb**, **13dd**, **14a–d**, **14bb**.

*4.2.21. 5-(R,S)-6,7-Dimethoxy-3,3-dimethyl-1-phenyl-2-azaspiro[4.5]-deca-1,6,9-triene-8-one (**13a**).* Colorless prisms, mp 100–102 °C (hexanes); ν_{max} (Nujol) 1664 (C=O), 1636 (C=C), 1620 (C=N), 1600, 1576, 1496, 1324, 1280, 1218, 1212, 1204, 1176, 1156, 1136, 1052, 1016, 940, 900, 836 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 7.67 (2H, m, C(2′), C(6′)H), 7.36 (1H, m, C(4′)H), 7.27 (2H, m, C(3′)H, C(5′)H), 6.71 (1H, d, C(10)H, ^3J=10 Hz), 6.26 (1H, d, C(9)H, ^3J=10 Hz), 3.91 (3H, s, OMe), 3.70 (3H, s, OMe), 2.32 (1H, d, ^2J=13.2 Hz, C(4)H), 2.14 (1H, d, ^2J=13.2 Hz, C(4)H), 1.49 (3H, s, Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.2, 164.2, 162.3, 146.2, 138.1, 133.5, 130.5, 128.3, 127.2, 126.9, 72.8, 66.4, 60.9, 60.5, 49.6, 30.8, 30.3; *m/z* 208 ($M^+-C_6H_5CN$). Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.35; H, 6.74; N, 4.60.

*4.2.22. N-[2-Methyl-1-(2,3,4-trimethoxyphenyl)-propan-2-yl]benzamide (**13aa**).* Colorless oil; ν_{max} (Nujol) 3380 (NH), 1664 (C=O), 1604, 1580, 1536, 1496, 1284, 1256, 1232, 1200, 1128, 1092, 1048, 1012 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 7.79 (2H, m, Ph), 7.48 (1H, br s, NH), 7.32–7.42 (3H, m, Ph), 6.85 (1H, d, ^3J=8.7 Hz, C(6′)H), 6.64 (1H, d, ^3J=8.7 Hz, C(5′)H), 3.96 (3H, s, OMe), 3.86 (3H, s, OMe), 3.83 (3H, s, OMe), 2.82 (2H, s, CH_2), 1.52 (6H, s, 2Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 126.6, 152.5, 151.1, 141.9, 135.7, 130.6, 128.0, 126.8, 126.6, 122.7, 107.4, 60.8, 60.6, 55.8, 54.9, 42.5, 25.8; *m/z* 343 (M^+). Anal. Calcd for. $C_{20}H_{25}NO_4\cdot 1/2H_2O$: C, 68.20; H, 7.44; N, 3.97. Found: C, 68.72; H, 7.87; N, 3.96.

*4.2.23. 5-(R,S)-6,7-Dimethoxy-3,3-dimethyl-1-(4-methoxyphenyl)-2-azaspiro[4.5]deca-1,6,9-triene-8-one (**13b**).* Yield 37%, colorless plates, mp 130–131 °C (hexanes–AcOEt), R_f 0.50; ν_{max} (Nujol) 1640 (C=O), 1590, 1500, 1310, 1260, 1205, 1170, 1055 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.58 (2H, dd, ^3J=9.0 Hz, ^4J=1.8 Hz, C(2′,6′)H), 6.71 (2H, dd, ^3J=9.0 Hz, ^4J=1.8 Hz, C(3′,5′)H), 6.65 (1H, d, ^3J=9.6 Hz, C(10)H), 6.20 (1H, d, ^3J=9.6 Hz, C(9)H), 3.87 (3H, s, OMe), 3.72 (3H, s, OMe), 3.66 (3H, s, OMe), 2.34 (1H, d, ^2J=13.8 Hz, C(4)H), 2.06 (1H, d, ^2J=13.8 Hz, C(4)H), 1.41 (3H, s, Me), 1.37 (3H, s, Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.3, 163.6, 162.7, 161.4, 146.6, 138.1, 128.9, 126.2, 113.6, 72.5, 65.3, 61.0, 60.5, 55.2, 49.8, 30.9, 30.4; *m/z* 341 (M^+). Anal. Calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.12; H, 6.89; N, 3.98.

*4.2.24. 4-Methoxy-N-[2-methyl-1-(2,3,4-trimethoxyphenyl)-propan-2-yl]benzamide (**13bb**).* Yield 33%, colorless oil, R_f 0.64; ν_{max} (Nujol) 3350 (NH), 1660 (C=O), 1602, 1496 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.75 (2H, d, ^3J=8.4 Hz, C(2′,6′)H), 6.83–6.88 (3H, m, C(6)H+ C(3′,5′)H), 6.63 (1H, d, ^3J=8.4 Hz, C(5)H), 3.97 (3H, s, OMe), 3.87 (3H, s, OMe), 3.84 (3H, s, OMe), 3.82 (3H, s, OMe), 2.80 (2H, s, C(4)H_2), 1.51 (6H, s, 2Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 161.5, 152.6, 151.2, 142.0, 128.4, 128.1, 126.82, 122.9, 113.2, 107.4, 60.9, 60.7, 55.8, 55.1, 54.8, 42.6; *m/z* 373 (M^+). Anal. Calcd for $C_{21}H_{27}NO_5$: C, 67.54; H, 7.29; N, 3.75. Found: C, 67.45; H, 7.33; N, 3.54.

*4.2.25. 5-R,S-6,7-Dimethoxy-1-(3,4-dimethoxyphenyl)-3,3-dimethyl-2-azaspiro[4.5]deca-1,6,9-triene-8-one (**13c**).* Yield 74%, transparent plates, mp 139–140 °C (hexanes–AcOEt), R_f 0.51; ν_{max} (Nujol) 1652 (C=O), 1592, 1520, 1320, 1276, 1256, 1224, 1176, 1128, 1052, 1024, 836 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33 (1H, d, ^3J=8.4 Hz, C(2′)H), 7.14 (1H, dd, ^3J=8.4 Hz, ^4J=1.2 Hz, C(6′)H), 6.67 (1H, d, ^3J=9.6 Hz, C(10)H), 6.66 (1H, d, ^3J=8.4 Hz, C(5′)H), 6.20 (1H, d, ^3J=9.6 Hz, C(9)H), 3.90 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 3.67 (3H, s, OCH_3), 2.35 (1H, d, J=13.2 Hz, C(4)H), 2.07 (1H, d, J=13.2 Hz, C(4)H), 1.42 (3H, s, CH_3), 1.40 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.2, 162.9, 151.1, 148.7, 146.9, 138.0, 126.6, 126.3, 120.4, 110.3, 110.2, 72.5, 65.3, 61.0, 60.5, 55.8, 55.7, 49.9, 30.9, 30.4; *m/z* 371 (M^+). Anal. Calcd for $C_{21}H_{25}NO_5$: C, 67.91; H, 6.78; N, 3.77. Found: C, 68.20; H, 6.52; N, 3.66.

*4.2.26. 5-(R,S)-1-(4-Bromophenyl)-6,7-dimethoxy-3,3-dimethyl-2-azaspiro[4.5]deca-1,6,9-triene-8-one (**13d**).* Yield 41%, colorless prisms, mp 143–144 °C (hexanes), R_f 0.58; ν_{max} (Nujol) 1653 (C=O), 1639, 1618, 1596 (C=C), 1565, 1324, 1312, 1285, 1217, 1178, 1139, 1069, 1052, 1009, 838 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.55 (2H, d, ^3J=8.4 Hz, C(2′)H, C(6′)H), 7.41 (2H, d, ^3J=8.4 Hz, C(3′)H, C(5′)H), 6.68 (1H, d, ^3J=9.6 Hz, C(10)H), 6.26 (1H, d, ^3J=9.6 Hz, C(9)H), 3.94 (3H, s, OCH_3), 3.71 (3H, s, OCH_3), 2.41 (1H, d, J=13.5 Hz, C(4)H), 2.14 (1H, d, J=13.5 Hz, C(4)H), 1.47 (3H, s, CH_3), 1.45 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 184.0, 163.6, 161.9, 145.8, 138.0, 132.3, 131.5, 128.8, 127.1, 125.1, 72.9, 65.2, 61.0, 60.5, 49.7, 30.7, 30.2; *m/z* 389 (M^+). Anal. Calcd for $C_{19}H_{20}BrNO_3$: C, 58.47; H, 5.17; N, 3.59. Found: C, 58.23; H, 4.86; N, 3.77.

*4.2.27. 4-Bromo-N-[2-methyl-1-(2,3,4-trimethoxyphenyl)-propan-2-yl]benzamide (**13dd**).* Yield 41%, colorless powder, mp 77–78 °C (hexanes), R_f 0.67; ν_{max} (Nujol) 3350 (NH), 1664 (C=O), 1592, 1536 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 (2H, d, J=8.4 Hz, 2′,6′-H), 7.56 (1H, br s, NH), 7.50 (2H, d, J=8.4 Hz, 3′,5′-H), 6.84 (1H, d, J=8.4 Hz, C(6)H), 6.65 (1H, d, J=8.4 Hz, C(5)H), 3.97 (3H, s, OMe), 3.87 (3H, s, OMe), 3.85 (3H, s, OMe), 2.79 (2H, s, CH_2), 1.51 (6H, s, 2Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.6, 152.7, 151.0, 142.0, 134.7, 131.2, 128.4, 126.9, 125.3, 122.7, 107.8, 61.0, 60.7, 55.9, 55.1, 42.9, 25.7; *m/z* 421 (M^+). Anal. Calcd for $C_{20}H_{24}BrNO_4$: C, 56.88; H, 5.73; N, 3.32. Found: C, 57.24; H, 5.61; N, 3.26.

*4.2.28. 5-(R,S)-6,9-Dimethoxy-3,3-dimethyl-1-phenyl-2-azaspiro[4.5]-deca-1,6,9-triene-8-one (**14a**).* Yield 41%, colorless plates, mp 182–183 °C (hexanes/chloroform), R_f 0.42; ν_{max} (Nujol) 1640 (C=O), 1620 (C=C), 1585 (C=N) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 7.59 (2H, d, ^3J=8.4 Hz, Ph) 7.36 (3H, m, Ph), 5.83 (1H, s, C(10)H), 5.72 (1H, s, C(7)H), 3.56 (3H, s, OMe), 3.53 (3H, s, OMe), 2.34 (1H, d, ^2J=13.5 Hz, C(4)H), 2.17 (1H, d, ^2J=13.5 Hz, C(4)H), 1.44 (3H, s, Me), 1.38 (3H, s, Me); ^{13}C NMR (75 MHz, DMSO-d_6) δ 180.6, 175.3, 164.0, 149.2, 133.3, 130.3, 128.3, 127.1, 115.1, 102.3, 72.2, 61.3, 56.7, 55.0, 51.2, 30.7, 30.2; *m/z* 208 ($M^+-C_6H_5CN$). Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.29; H, 6.80; N, 4.50. Found: C, 73.03; H, 6.59; N, 4.48.

*4.2.29. 5-(R,S)-6,9-Dimethoxy-3,3-dimethyl-1-(4-methoxyphenyl)-2-azaspiro[4.5]deca-1,6,9-triene-8-one (**14b**).* Yield 71%, colorless prisms, mp 144–145 °C (hexanes–AcOEt), R_f 0.52; ν_{max} (Nujol) 1653 (C=O), 1618, 1598 (C=C), 1514, 1298, 1259, 1247, 1193, 1170, 1136, 1113, 1046, 1010, 934, 873, 810, 784, 742 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.63 (2H, dd, ^3J=9.0 Hz, ^4J=2.1 Hz, C(2′,6′)H), 6.76 (2H, dd, ^3J=9.0 Hz, ^4J=2.1 Hz, C(3′,5′)H), 5.74 (1H, s, C(10)H), 5.61 (1H, s, C(7)H), 3.78 (3H, s, OMe), 3.66 (3H, s, OMe), 3.65 (3H, s, OMe), 2.44 (1H, d, ^2J=13.5 Hz, C(4)H), 2.15 (1H, d, ^2J=13.5 Hz, C(4)H), 1.47 (6H, s, 2Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.8, 176.1, 164.0, 161.1, 149.3, 128.8, 125.6, 114.8, 113.4, 102.1, 71.9, 62.4, 56.2, 55.0, 54.9, 51.7, 30.9, 30.2; *m/z* 341 (M^+). Anal. Calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.33; H, 6.65; N, 4.20.

*4.2.30. 4-Methoxy-N-[2-methyl-1-(2,4,5-trimethoxyphenyl)-propan-2-yl]benzamide (**14bb**).* Yield 13%, colorless plates, mp 111–112 °C (hexanes), R_f 0.68; ν_{max} (Nujol) 3340 (NH), 1665 (C=O), 1598, 1498 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.63 (2H, dd, ^3J=9.0 Hz, 2′,6′-H), 6.87 (2H, dd, ^3J=9.0 Hz, 3′,5′-H), 6.66 (1H, s, $H_{arom.}$), 6.56 (1H, s, $H_{arom.}$), 3.88 (3H, s, OMe), 3.85 (3H, s, OMe), 3.83 (3H, s, OMe), 3.72 (3H, s, OMe), 2.89 (2H, s, C(4)H_2), 1.51 (6H, s, 2Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.9, 160.2, 129.7, 129.6, 128.7, 121.5, 116.0,

115.8, 113.8, 113.5, 94.7, 70.0, 56.7, 55.3, 55.2, 48.7, 39.9, 30.0, 27.4; *m/z* 373 (M^+). Anal. Calcd for $C_{21}H_{27}NO_5$: C, 67.54; H, 7.29; N, 3.75. Found: C, 67.88; H, 7.15; N, 3.85.

*4.2.31. 5-(R,S)-6,9-Dimethoxy-1-(3,4-dimethoxyphenyl)-3,3-dimethyl-2-azaspiro[4.5]deca-1,6,9-triene-8-one (**14c**).* Yield 77%, transparent prisms, mp 169–171 °C (hexanes–$CHCl_3$), R_f 0.36; ν_{max} (Nujol) 1635 (C=O), 1605 (C=C), 1580 (C=N) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.41 (1H, d, ^4J=1.8 Hz, C(2′)H), 7.13 (1H, dd, ^3J=8.4 Hz, ^4J=1.8 Hz, C(6′)H), 6.68 (1H, d, ^3J=8,4 Hz, C(5′)H), 5.75 (1H, s, C(10)H), 5.63 (1H, s, C(7)H), 3.85 (3H, s, OMe), 3.84 (3H, s, OMe), 3.67 (3H, s, OMe), 3.66 (3H, s, OMe), 2.45 (1H, d, ^2J=13,2 Hz, C(4)H), 2.15 (1H, d, ^2J=13,2 Hz, C(4)H), 1.48 (6H, s, 2Me); ^{13}C NMR (75 MHz, DMSO-d_6) δ 181.8, 176.4, 164.0, 150.9, 149.4, 148.5, 126.0, 120.3, 115.7, 110.3, 110.2, 102.1, 72.1, 62.5, 56.3, 55.8, 55.7, 55.1, 52.0, 31.0, 30.3; *m/z* 371 (M^+). Anal. Calcd for $C_{21}H_{25}NO_5$: C, 67.91; H, 6.78; N, 3.77. Found: C, 67.88; H, 6.55; N, 3.65.

*4.2.32. 5-(R,S)-1-(4-Bromophenyl)-6,9-dimethoxy-3,3-dimethyl-2-azaspiro[4.5]deca-1,6,9-triene-8-one (**14d**).* Yield 50%, colorless plates, mp 186–188 °C (hexanes–CH_2Cl_2), R_f 0.60; ν_{max} (Nujol) 1635 (C=O), 1620 (C=N), 1590 (C=C) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 7.53 (2H, d, ^3J=8.4 Hz, C(2′)H, C(6′)H), 7.38 (2H, d, ^3J=8.4 Hz, C(3′)H, C(5′)H), 5.73 (1H, s, C(6)H), 5.57 (1H, s, C(9)H), 3.65 (6H, s, 2OMe), 2.46 (1H, d, ^2J=13.5 Hz, C(4)H), 2.17 (1H, d, ^2J=13.5 Hz, C(4)H), 1.48 (6H, s, 2Me); ^{13}C NMR (75 MHz, DMSO-d_6) δ 180.5, 174.9, 163.4, 149.4, 132.5, 131.4, 129.1, 124.0, 114.8, 102.1, 72.4, 62.3, 56.7, 55.1, 51.3, 30.7, 30.1; *m/z* 390 (M^+). Anal. Calcd for $C_{19}H_{20}BrNO_3$: C, 58.47; H, 5.17; N, 3.59. Found: C, 58.67; H, 5.00; N, 3.65.

*4.2.33. 6,10-Dimethoxy-3,3-dimethyl-1-phenyl-2-azaspiro[5.4]deca-1,6,9-triene-8-one (**15a**). Procedure C.* Yield 86%, colorless prisms, mp 176–178 °C (hexanes–CH_2Cl_2), R_f 0.47; ν_{max} (Nujol) 1648 (C=O), 1620 (C=N), 1588 (C=C), 1284, 1232, 1212, 1188, 1160, 1064, 1000, 936, 852 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.66 (2H, m, C(2′)H, C(6′)H), 7.33 (1H, m, C(4′)H), 7.26 (2H, m, C(3′)H, C(5′)-H), 5.55 (2H, s, C(7)H, C(9)H), 3.64 (6H, s, 2OMe), 2.29 (2H, s, $C(4)H_2$), 1.47 (6H, s, 2Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.9, 172.6, 133.1, 130.8, 130.2, 128.3, 127.1, 100.4, 73.2, 65.3, 56.2, 50.8, 30.0; *m/z* 311 (M^+). Anal. Calcd for $C_{19}H_{21}NO_3$: C, 73.20; H, 6.80; N, 4.50. Found: C, 73.05; H, 6.56; N, 4.42.

*4.2.34. 6,10-Dimethoxy-3,3-dimethyl-1-(4-methoxyphenyl)-2-azaspiro[5.4]deca-1,6,9-triene-8-one (**15b**). Procedure C.* Yield 77%, colorless plates, mp 169–171 °C (hexanes–EtOAc), R_f 0.43; ν_{max} (Nujol) 1648 (C=O), 1624 (C=N), 1592, 1516 (C=C), 1312, 1292, 1260, 1232, 1208, 1180, 1160, 1068, 1024, 940, 860 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.65 (2H, dd, ^3J=8.7 Hz, 2′,6′-H), 6.77 (2H, dd, ^3J=8.7 Hz, 3′,5′-H), 5.55 (2H, s, C(7)H, C(9)H), 3.78 (3H, s, OMe), 3.64 (6H, s, 2OMe), 2.27 (2H, s, $C(4)H_2$), 1.45 (6H, s, 2Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 188.0, 173.0, 161.6, 161.1, 128.7, 125.7, 113.6, 100.3, 72.9, 65.2, 56.2, 55.1, 50.9, 30.0; *m/z* 341 (M^+). Anal. Calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.27; H, 6.59; N, 4.02.

*4.2.35. 6,10-Dimethoxy-1-(3,4-dimethoxyphenyl)-3,3-dimethyl-2-azaspiro[5.4]deca-1,6,9-triene-8-one (**15c**). Procedure C.* Yield 63%, colorless prisms, mp 155–156 °C (hexanes–CH_2Cl_2), R_f 0.44; ν_{max} (Nujol) 1652 (C=O), 1624 (C=N), 1588, 1524 (C=C), 1340, 1280, 1240, 1212, 1156, 1068, 1028, 848 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.42 (1H, d, ^4J=2.1 Hz, 2′-H), 7.18 (1H, dd, ^3J=8.4 Hz, ^4J=2.1 Hz, 6′-H), 6.69 (1H, d, ^3J=8.4 Hz, 5′-H), 5.56 (2H, s, C(7)H, C(9)H), 3.85 (3H, s, OMe), 3.84 (3H, s, OMe), 3.66 (6H, s, 2OMe), 2.28 (2H, s, $C(4)H_2$), 1.46 (6H, s, 2Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.6, 173.0, 162.5, 133.4, 130.1, 128.3, 127.2, 120.3, 110.8, 100.6, 73.2, 65.6, 56.1, 55.9, 55.8, 51.1, 30.1; *m/z* 371 (M^+). Anal. Calcd for $C_{21}H_{25}NO_5$: C, 67.91; H, 6.78; N, 3.77. Found: C, 67.59; H, 6.61; N, 3.67.

*4.2.36. 1-(4-Bromophenyl)-6,10-dimethoxy-3,3-dimethyl-2-azaspiro[5.4]deca-1,6,9-triene-8-one (**15d**). Procedure C.* Yield 46%, colorless powder, mp 162–163 °C (hexanes–CH_2Cl_2); R_f 0.50; ν_{max} (Nujol) 1590 (C=N), 1620 (C=C), 1635 (C=O) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.55 (2H, d, ^3J=8.4 Hz, C(2′)H, C(6′)H), 7.39 (2H, d, ^3J=8.4 Hz, C(3′)H, C(5′)H), 5.55 (2H, s, C(7)H, C(9)H), 3.65 (6H, s, 2OMe), 2.28 (2H, s, CH_2), 1.45 (6H, s, 2Me); ^{13}C NMR (75 MHz, $CDCl_3$) δ 187.3, 172.2, 161.5, 132.3, 131.5, 128.7, 124.8, 100.7, 73.3, 65.3, 56.1, 51.0, 29.9; *m/z* 390 (M^+). Anal. Calcd for $C_{19}H_{20}BrNO_3$: C, 58.47; H, 5.17; N, 3.59. Found: C, 58.78; H, 4.94; N, 3.75.

4.3. X-ray crystallography

Intensity data for compound **1b** (Fig. 1) were collected on an Enraf-Nonius CAD-4 diffractometer using the ω scan method ($2\theta_{max}$=59.9°). Structure solution and structure refinement were performed by the direct method using *SHELX-97* program package.[29] Nonhydrogen atoms were refined by full-matrix least-squares procedures (with F^2) in an anisotropic approximation (*SHELXL-97*).[30] The position of hydrogen NH atom was found by a difference Fourier synthesis and refined in an isotropic approximation. Co-ordinates and thermal parameters of the hydrogen atoms were fixed (U_H 0.08 Å, C–H 0.96 Å). Molecular packing of the compound **1b** is formed by the intermolecular hydrogen bond (3.107 Å) between NH group of pyrrolidine and C=O group of cyclohexadienone. Intramolecular H–bond NH···O=C(OEt) (2.207 Å) was also found. Crystallographic data for compound **1b** are given in Table 1. The parameters for hydrogen bonds are given in Table 2.

The molecular structure of compound **11b** determined by crystallography is shown in Figure 2. Main sp^3-atom C(7) is tetrahedral with lengths of C–C bonds 1.50–1.55 Å. Cyclohexadienyl and cyanoacetic fragments form general planar system of π-conjugated bonds. Bond lengths and angles of cyclohexadienyl moiety are typical for system of π-conjugated C–C bond.

Molecular packing of the compound **11b** is formed by polymeric chain through hydrogen bond association of CN groups and NH groups of pyrrolidine moiety (Fig. 3). Also NH group forms intramolecular H bond with O(3) of COOEt group to fix cis-conformation

Table 1
Crystal data and structure refinement for compounds **1b** and **11b**

	1b	**11b**
Empirical formula	$C_{15}H_{18}NO_3$	$C_{22}H_{28}N_2O_6$
Formula weight	261.31	416.46
Temperature, K	293	120(2)
Crystal system	Rhombic	Monoclinic
Space group	$P2_12_12_1$	P2(1)/c
a, Å	9.199 (1)	10.0832 (14)
b, Å	9.469 (2)	12.6658 (11)
c, Å	16.801 (3)	17.622 (3)
Volume Å^3	1463.6 (5)	2225.9 (5)
Z	4	4
Density (calculated) g/cm^3	1.186	1.243
Absorption coefficient, mm^{-1}	0.082	0.091
θ Range for data collection	2–29°	2.72–26.37°
Limiting indices	$0\le h\le 12$, $0\le k\le 13$, $0\le l\le 23$	$-12<h<12$, $-15<k<15$, $-22<l<21$
Reflections collected	2405	15,807
Independent reflections	659 (R_{int}=0.069)	4491 (R_{int}=0.0551)
Data/restraints/parameters	659/0/177	4491/0/283
Goodness-of-fit on F^2	0.948	1.006
R_1 [I>2σ(I)]	0.048	0.0513
wR_2 [I>2σ(I)]	0.127	0.1097
R_1 (all data)	0.237	0.1207
wR_2 (all data)	0.204	0.1209
Largest diff. peak and hole, eÅ^{-3}	0.178 and −0.171	0.505 and −0.287

Table 2
Hydrogen bonds with H···A<r(A)+2.000 Å and<DHA> 110 deg for compounds **1b** and **11b**

D–H	d (D–H), Å	d (H···A), Å	<DHA, °	d(D···A), Å	A
			1b		
N1–H1	0.905	2.211	123.03	2.809	O3
N1–H1	0.905	2.399	147.53	3.200	N2 [$-x+1$, $y+1/2$, $-z+3/2$]
			11b		
N1–H1	0.89 (4)	2.22 (4)	123	2.806 (3)	O2
N1–H1	0.89 (4)	2.44 (4)	131	3.108 (3)	O1 [x, $y+1$, z]

of C═C–C═O fragment. The parameters for these hydrogen bonds are given in Table 2. The π-system of substituted vinyl moiety of compound **11b** formed π–π stacking interactions with (*1*−*x*, *2*−*y*, *1*−*z*) symmetry equivalents with 3.383 Å between planes (Fig. 4).

X-ray structure of compound **11b** was determined using the Oxford Diffraction Xcalibur S system (Mo Kα radiation, λ=0.71093

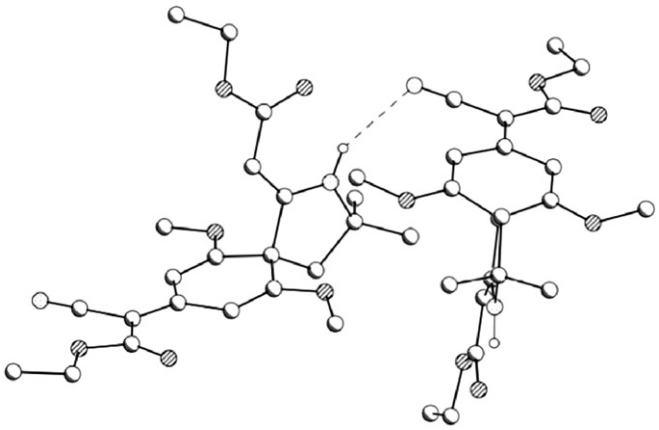


Figure 3. Intermolecular H bonds in molecular packing of compound **11b** (H-atoms, with exception NH groups, are omitted for clarity).

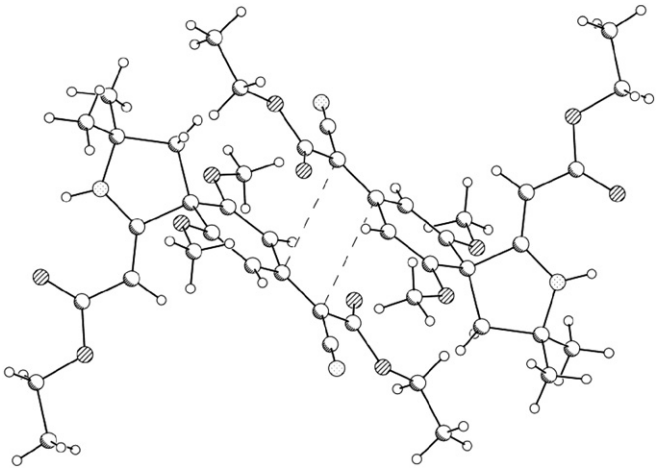


Figure 4. π–π Stacking in molecular packing of compound **11b**.

A, graphite monochromator, $\omega/2\theta$ scan). Structure solution and structure refinement were performed using *SHELX-97* program package. Nonhydrogen atoms were refined by full-matrix least-squares procedures (with F^2) in an anisotropic approximation. The positions of hydrogen atoms were found by a difference Fourier synthesis and refined in an isotropic approximation. Abbreviated crystallographic data for compound **11b** are given in Table 1.

Crystallographic data (excluding structure factors) for structures **1b** and **11b** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. 733250 (**1b**) and 726668 (**11b**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax:+44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

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Supplementary data

Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2009.11.055.

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