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Regioselective synthesis of spiro-cyclopropanated 1-aminopyrrol-2-ones by $Bi(OTf)_3$-catalyzed one-pot 'Mukaiyama–Michael addition/cyclization/ring-contraction' reactions of 1,2-bis(trimethylsilyloxy)cyclobutene with 1,2-diaza-1,3-butadienes

Orazio A. Attanasi [a,*], Gianfranco Favi [a], Gianluca Giorgi [b], Fabio Mantellini [a], Vahuni Karapetyan [c], Peter Langer [c,d,*]

[a] Istituto di Chimica Organica, Università degli Studi di Urbino 'Carlo Bo', Via I Maggetti 24, 61029 Urbino, Italy
[b] Centro Interdipartimentale di Analisi e Determinazioni Strutturali, Università degli Studi di Siena, Via Aldo Moro 53100, Italy
[c] Institut für Chemie, Universität Rostock, Albert-Einstein-Str. 3a, 18059 Rostock, Germany
[d] Leibniz-Institut für Katalyse e. V. an der Universität Rostock, Albert-Einstein-Str. 29a, 18059 Rostock, Germany

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ABSTRACT

Unknown spiro-cyclopropanated 1-aminopyrrol-2-ones are regioselectively prepared in high yields by $Bi(OTf)_3$-catalyzed one-pot 'Mukaiyama–Michael addition/cyclization/ring-contraction' reactions of 1,2-bis(trimethylsilyloxy)cyclobutene with 1,2-diaza-1,3-butadienes at room temperature.

1. Introduction

Spirocyclic compounds occur in diverse natural products and in many drugs.[1] Among them, the spiro-cyclopropyl moiety is present in the skeleton of many biologically significant molecules such as highly cytotoxic sesquiterpene illudins M and S (Chart 1), semisynthetic derivative antitumor agent (−)-irofulven (HMAF), and the taxane-AB fragment.[2] Recently, one of us reported the synthesis of 1-hydroxyspiro[2.5]cyclooct-4-en-3-ones, which show a considerable antiproliferative activity against human HL 60 cells (leukemia) (Chart 1).[3] A strong cancerostatic activity was also reported for the CC-1065 or duocarmycin SA (Chart 2).[4] In a recent paper, de Meijere and co-workers reported the preparation of spiro-cyclopropanated analogues of bioactive demethoxyfumitremorgine C and tadalafil using methyl 2-chloro-2-cyclopropylideneacetate as a building block.[5] Also, a synthesis of spiroannelated analogues of fungicide Iprodione is reported.[6] In addition, spiro[cyclopropan-1,3′-oxindoles] are used as starting materials for alkaloid synthesis of oxindoles[7] as exemplified recently in the first elegant total synthesis of strychnofoline by Carreira and Lerchner.[8]

Therefore, interest in developing new strategies that can give rise to spiro-cyclopropane derivatives[2–11] has risen considerably due to the inherent rigidity displayed together by the spiro and cyclopropane[12] functionality.

On the other hand, pyrroles and their derivatives are important classes of heterocycles broadly used in material science and can be found in many natural and medicinally active compounds.[13] Recently, 1-aminopyrroles have been used as building blocks during the synthesis of analgesic[14] and NMDA receptor antagonists.[15]

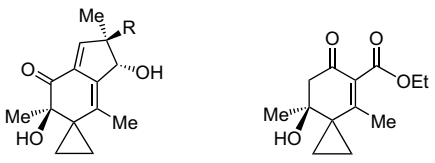

Chart 1.

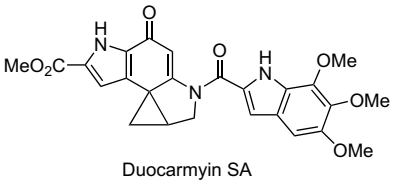

Chart 2.

* Corresponding authors.
E-mail address: orazio.attanasi@uniurb.it (O.A. Attanasi).

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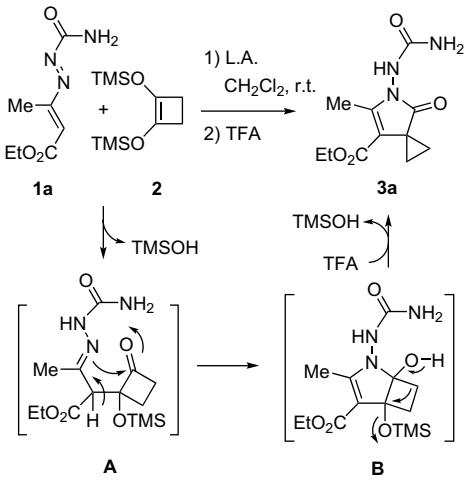


Scheme 1. Possible mechanism for the formation of **3a–n**.

Although numerous methods have been developed for the synthesis of pyrroles, direct syntheses of 1-aminopyrroles are much more rare. In contrast to this literature scenario, no structures of spiro-cyclopropanated pyrrol-2-ones have been found.

The chemistry of 1,2-diaza-1,3-butadienes[16] has been extensively studied by some of us. Recently, we have reported the synthesis of 1-aminopyrrol-2-ones, 1-aminopyrroles and pyrazoles by 'Mukaiyama–Michael addition/cyclization' reactions of 1,2-diaza-1,3-butadienes with silyl enol ethers,[17] Danishefsky's dienes,[18] and 1,3-bis(silyloxy)-1,3-butadienes.[19]

In connection with our ongoing interest in developing new synthetic strategies for the construction of heterocycle rings, herein, we report what are, to the best of our knowledge, the first one-pot 'Mukaiyama–Michael addition/cyclization/ring-contraction' reactions of 1,2-diaza-1,3-butadienes with 1,2-bis(trimethylsilyloxy)-cyclobutene. These reactions provide a convenient approach to functionalized spiro-cyclopropanated 1-aminopyrrol-2-ones, which are not readily available by other methods.

The chemistry of 1,3-bis(silyloxy)-1,3-butadienes has been reviewed.[20,21] Reactions of 1,2-bis(trimethylsilyloxy)cyclobutene, available by the method reported by Rühlmann,[22] are more rare. For example, the geminal acylation of ketones and ketals has been studied in details. These transformations proceed by Lewis acid-mediated reaction of 1,2-bis(trimethylsilyloxy)cyclobutene onto the ketone and subsequent acid-mediated rearrangement with ring-enlargement.[23] Burnell and Gao reported the synthesis of cyclopentane-1,3-diones.[24]

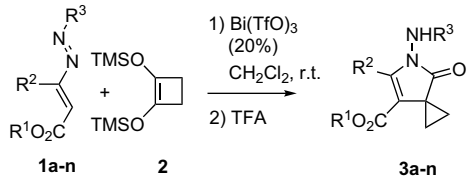
2. Results and discussion

Exploratory reaction between 1,2-bis(trimethylsilyloxy)-cyclobutene **2** and 1,2-diaza-1,3-butadiene **1a** catalyzed by $ZnCl_2$

Table 1
Screening activity of various Lewis acids (L.A.)

Entry	Catalyst	Reaction time	Yield[a] (%)
1	$ZnCl_2$	10 h	50
2	$InCl_3$	—	—
3	$InBr_3$	>48 h	30
4	$LiClO_4$	>48 h	34
5	$Sc(TfO)_3$	0.5 h	84
6	$Y(TfO)_3$	12 h	67
7	$In(TfO)_3$	2 h	49
8	**$Bi(TfO)_3$**	**0.01 h**	**85**
9	$Sm(TfO)_3$	6 h	74
10	$Yb(TfO)_3$	0.5 h	80

[a] Isolated yields.



Scheme 2. Synthesis of **3a–n**.

afforded, after addition of trifluoroacetic acid (TFA), removal of the solvent, and chromatographic purification, new and unexpected spiro-cyclopropanated pyrrol-2-one **3a** in 50% yield (Scheme 1, Table 1, entry 1).

To identify suitable conditions for the process, the series of Lewis acids depicted in Table 1 was screened. Various Lewis acids such as $ZnCl_2$, $InBr_3$, $LiClO_4$, $Sc(TfO)_3$, $Y(TfO)_3$, $In(TfO)_3$, $Bi(TfO)_3$, $Sm(TfO)_3$, or $Yb(TfO)_3$ were found active. Among them, the relatively common and inexpensive $Bi(TfO)_3$[25] gave the best result at room temperature (Table 1, entry 8). The $InCl_3$ catalyst was ineffective for the reaction providing only chloro-hydrazonic adduct (Table 1, entry 2).

The formation of **3a** can be rationalized as shown in Scheme 1. The Lewis acid catalyzed Mukaiyama–Michael addition of **2** at the terminal carbon of the azo–ene system of **1a** gave hydrazonic intermediate **A**. Subsequently, five-membered ring closure affords hydroxy-1-aminopyrroline **B** by internal nucleophilic attack of the nitrogen atom at the carbonyl group. In turn, the addition of TFA results in the cleavage of the silyl groups, and cyclobutane ring contraction with concomitant loss of a water molecule (pinacol-like rearrangement) provided the final spiro-cyclopropanated pyrrol-2-one (Scheme 1).

The conjugate addition of nucleophiles to α,β-unsaturated carbonyl compounds represents one of the most powerful methods for the formation of carbon–carbon bonds.[26] The use of silyl enol ethers in Lewis acid catalyzed conjugate additions, introduced by Mukaiyama and co-workers, offers a mild alternative to base-mediated variants.[27,28]

It is worthy of note that in this case the reaction proceed with cyclobutane ring contraction in concert with cyclization and no cyclobutane ring expansion products were isolated.[23,24] The only example of formation of spiro-cyclopropane derivatives that proceed with an analogous pinacol-like rearrangement has been previously reported by Hanna and Ricard.[29]

Under the optimized conditions, the cyclization of 1,2-diaza-1,3-butadienes **1a–n** with **2** afforded the spiro-cyclopropanated pyrrol-2-ones **3a–n** in 32–98% yield (Scheme 2, Table 2).

Table 2
Synthesis of **3a–n**

3	R^1	R^2	R^3	Yield[a] (%)
a	Et	Me	$CONH_2$	85
b	Me	Me	$CONH_2$	79
c	*i*-Pr	Me	$CONH_2$	98
d	Bn	Me	$CONH_2$	81
e	Me	Et	$CONH_2$	87
f	Et	Me	CONHPh	64
g	Et	Me	Ph	86
h	Et	Me	Ts	32[b]
i	Et	Pr	$CONH_2$	82
j	allyl	Me	$CONH_2$	94
k	Me	CH_2CO_2Me	$CONH_2$	75
l	Et	CH_2CO_2Et	$CONH_2$	54
m	$(CH_2)_2OCH_3$	Me	CONHPh	56
n	*i*-Pr	Me	CONHPh	60

[a] Isolated yields.
[b] Compound **3h** was obtained without quenching with TFA.

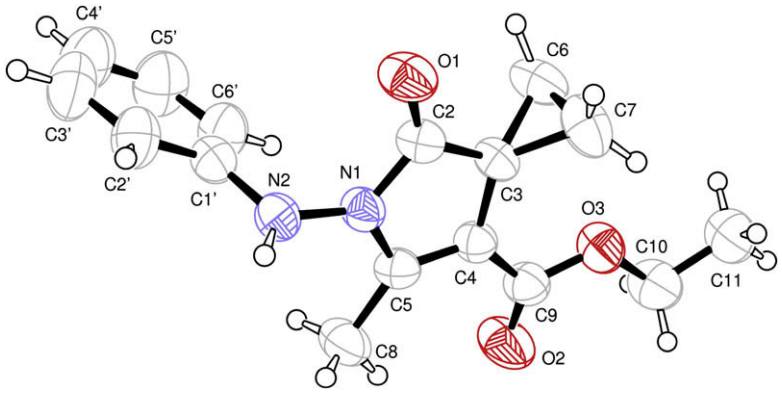
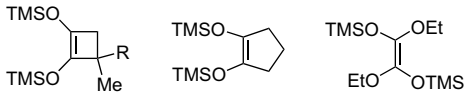


Figure 1. Ortep plot of **3g** (50% probability level).



4a (R = H)
4b (R = Me)

5

6

Chart 3.

A structural requirement for the success of the cyclization is the presence of an ester group bonded to the carbon C-4 and of a methyl, ethyl, propyl or CH_2COOR group linked to the carbon C-3 of the 1,2-diaza-1,3-butadiene. An amido, phenyl or tosyl group must be located at the nitrogen atom N1 (substituent R^3).

The structure of all products (**3a–n**) was assigned on the basis of the spectroscopic data. In particular ^{13}C NMR spectra of **3a** exhibit some peculiarities: (i) the absence of CO signals of ketones; (ii) the presence of four C-sp^2 signals (175.9, 162.6, 157.2, and 103.6 ppm); (iii) the presence of only one C-sp^3 resonance at highfield (26.8 ppm); (iv) the coupling constant value for the CH_2 carbons that resonates at 16.8 and 17.0 ppm is J_{CH}=165 Hz, typical for a CH_2 in a cyclopropane ring.[30]

However, the structure of **3g** was unambiguously confirmed by X-ray crystal structure analysis[31] (Fig. 1).

All attempts to vary the silyl enol ether failed. The employment of substituted 1,2-bis(silyloxy)cyclobutenes **4a**,**b**, 1,2-bis(silyloxy)-cyclopentene **5**, and 1,2-bis(ethoxy)-1,2-bis(silyloxy)ethene **6** resulted in the formation of complex mixtures (Chart 3).

Among spirocyclic compounds,[1] the spiro-cyclopropane-annelated heterocycles' framework[5–9,11] is an important motif in biologically relevant compounds as natural products and pharmaceuticals. Despite of their potential importance, spiro-cyclopropanated 1-aminopyrrol-2-ones are unknown products. Moreover, the presence of the spiro-cyclopropane ring in α position to the carbonyl group in the final azaheterocycles might open new pathways for further and useful synthetic elaborations of the pyrrolone skeleton.

3. Conclusion

In conclusion, we have reported a convenient regioselective synthesis of functionalized spiro-cyclopropanated 1-aminopyrrol-2-ones. The products are formed by a novel $Bi(OTf)_3$-catalyzed one-pot 'Mukaiyama–Michael addition/cyclization/ring-contraction' reaction from 1,2-bis(trimethylsilyloxy)cyclobutene and 1,2-diaza-1,3-butadienes. These reactions are easy, occur under mild conditions, and with excellent yields.

4. Experimental section

4.1. General

All reactions requiring anhydrous conditions were carried out using oven-dried glassware. All the commercially available reagents and solvents were used without further purification. 1,2-Diaza-1,3-butadienes **1a–n** were synthesized as a mixture of *E/Z* isomers as previously reported.[32,33] Chromatographic purification of compounds was carried out on silica gel (60–200 μm). TLC analysis was performed on pre-loaded (0.25 mm) glass supported silica gel plates (Kieselgel 60); compounds were visualized by exposure to UV light and by dipping the plates in 1% $Ce(SO_4)\cdot 4H_2O$, 2.5% $(NH_4)_6Mo_7O_{24}\cdot 4H_2O$ in 10% sulfuric acid followed by heating on a hot plate. All ^1H NMR and ^{13}C NMR spectra were recorded at 400 and 100.56 MHz, respectively. Proton and carbon spectra were referenced internally to solvent signals, using values of δ=2.49 ppm for proton (middle peak) and δ=39.50 ppm for carbon (middle peak) in DMSO-d_6 and δ=7.26 ppm for proton and δ=77.00 ppm for carbon (middle peak) in $CDCl_3$. The following abbreviations are used to describe peak patterns where appropriate: s=singlet, d=doublet, t=triplet q=quartet, sept=septet, m=multiplet and br=broad signal. All coupling constants (*J*) are given in hertz. FTIR spectra were obtained as Nujol mulls. Low- and high-resolution mass spectrometric data were obtained by electron ionization (EI, 70 eV). Melting points were determined in open capillary tubes and are uncorrected.

4.2. General procedure for the 'Mukaiyama–Michael type addition/cyclization/ring-contraction' reaction of 1,2-diaza-1,3-butadienes 1a–n with 1,2-bis[(trimethylsilyl)-oxy]cyclobutene 2

Under a nitrogen atmosphere, to a solution of 1,2-diaza-1,3-butadienes **1a–n** (1.0 mmol) in CH_2Cl_2 (5 mL) 1,2-bis-(trimethylsilyloxy)cyclobutene **2** (1.1 mmol) and $Bi(TfO)_3$ (0.2 mmol) were added. The mixture was stirred at room temperature until complete disappearance of 1,2-diaza-1,3-butadienes **1a–n** (TLC check) and then the reaction was quenched with TFA to obtain **3a–n**. Products **3a–n** were purified by chromatography on silica gel column.

*4.2.1. Ethyl 5-[(aminocarbonyl)amino]-6-methyl-4-oxo-5-azaspiro[2,4]hept-6-ene-7-carboxylate (**3a**)*

Spirocompound **3a** was isolated by column chromatography (ethyl acetate) in 85% yield as a white solid; mp 216–218 °C; IR (Nujol) ν_{max} 3440, 3338, 3287, 3211, 1744, 1683, 1270, 1235, 1133, 1082 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.16–1.26 (m, 5H), 1.70–1.85 (m, 2H), 2.27 (s, 3H), 4.08 (q, *J*=7.0 Hz, 2H), 6.32 (br, 2H), 8.62 (br, 1H);

^{13}C NMR (DMSO-d_6) δ 11.7, 14.0, 16.8, 17.0, 26.8, 59.1, 103.6, 153.8, 157.2, 162.6, 175.9; EIMS *m*/*z* (%) 253 (M^+, 45), 210 (51), 194 (100), 181 (67), 166 (56), 148 (20), 136 (35), 121 (29), 109 (39); Anal. Calcd for $C_{11}H_{15}N_3O_4$: C, 52.17; H, 5.97; N, 16.59. Found: C, 52.02; H, 6.09; N, 16.44.

4.2.2. Methyl 5-[(aminocarbonyl)amino]-6-methyl-4-oxo-5-azaspiro[2,4]hept-6-ene-7-carboxylate (**3b**)

Spirocompound **3b** was isolated by column chromatography (ethyl acetate) in 79% yield as a white solid; mp 213–215 °C; IR (Nujol) ν_{max} 3444, 3337, 3211, 1734, 1685, 1447, 1384 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.18–1.28 (m, 2H), 1.70–1.83 (m, 2H), 2.26 (s, 3H), 3.62 (s, 3H), 6.32 (br, 2H), 8.62 (br, 1H); ^{13}C NMR (DMSO-d_6) δ 11.8, 16.8, 17.0, 26.8, 50.6, 103.5, 153.9, 157.2, 163.1, 175.9; EIMS *m*/*z* (%) 239 (M^+, 32), 222 (3), 208 (12), 196 (42), 180 (100), 164 (30), 148 (30), 135 (29), 120 (26), 109 (30). Anal. Calcd for $C_{10}H_{13}N_3O_4$: C, 50.21; H, 5.48; N, 17.56. Found: C, 50.34; H, 5.37; N, 17.51.

4.2.3. Isopropyl 5-[(aminocarbonyl)amino]-6-methyl-4-oxo-5-azaspiro[2.4]hept-6-ene-7-carboxylate (**3c**)

Spirocompound **3c** was isolated by column chromatography (ethyl acetate) in 98% yield as a white solid; mp 190–192 °C; IR (Nujol) ν_{max} 3428, 3335, 3269, 3196, 1740, 1692, 1622, 1537, 1261, 1231 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.19 (d, *J*=6.0 Hz, 6H), 1.19–1.28 (m, 2H), 1.70–1.85 (m, 2H), 2.26 (s, 3H), 4.92 (sept, *J*=6.0 Hz, 1H), 6.31 (br, 2H), 8.61 (br, 1H); ^{13}C NMR (DMSO-d_6) δ 11.7, 16.9, 17.1, 21.6, 26.8, 66.5, 103.8, 153.8, 157.3, 162.2, 175.9; EIMS *m*/*z* (%) 267 (M^+, 10), 225 (17), 208 (11), 182 (49), 166 (100), 149 (80), 136 (12), 109 (19). Anal. Calcd for $C_{12}H_{17}N_3O_4$: C, 53.92; H, 6.41; N, 15.72. Found: C, 53.79; H, 6.25; N, 15.51.

4.2.4. Benzyl 5-[(aminocarbonyl)amino]-6-methyl-4-oxo-5-azaspiro[2.4]hept-6-ene-7-carboxylate (**3d**)

Spirocompound **3d** was isolated by column chromatography (ethyl acetate) in 81% yield as a white solid; mp 187–189 °C; IR (Nujol) ν_{max} 3338, 3238, 3043, 1739, 1705, 1688, 1363, 1267, 1236 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.18–1.29 (m, 2H), 1.70–1.82 (m, 2H), 2.27 (s, 3H), 5.12 (s, 2H), 6.33 (br, 2H), 7.30–7.40 (m, 5H, Ar), 8.62 (br, 1H); ^{13}C NMR (DMSO-d_6) δ 11.8, 16.9, 17.1, 26.9, 64.9, 103.3, 127.9, 128.0, 128.5, 136.3, 154.6, 157.2, 162.4, 175.9; EIMS *m*/*z* (%) 315 (M^+, 3), 272 (4), 257 (5), 185 (392), 181 (100), 166 (35), 149 (18), 139 (23), 125 (26), 111 (50). Anal. Calcd for $C_{16}H_{17}N_3O_4$: C, 60.94; H, 5.43; N, 13.33. Found: C, 60.71; H, 5.32; N, 13.48.

4.2.5. Methyl 5-[(aminocarbonyl)amino]-6-ethyl-4-oxo-5-azaspiro[2.4]hept-6-ene-7-carboxylate (**3e**)

Spirocompound **3e** was isolated by column chromatography (ethyl acetate) in 87% yield as a white solid; mp 195–197 °C; IR (Nujol) ν_{max} 3345, 3202, 3040, 1738, 1701, 1694, 1617, 1545, 1295, 1240, 1054 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.07 (d, *J*=7.6 Hz, 3H), 1.18–1.25 (m, 2H), 1.70–1.85 (m, 2H), 2.45–2.58 (m, 1H), 2.78–2.90 (m, 1H), 3.62 (s, 3H), 6.31 (br, 2H), 8.66 (br, 1H); ^{13}C NMR (DMSO-d_6) δ 12.2, 17.1, 17.3, 18.8, 26.8, 50.7, 102.8, 157.2, 159.0, 162.9, 176.1; EIMS *m*/*z* (%) 253 (M^+, 30), 210 (45), 194 (100), 178 (17), 162 (33), 149 (17), 134 (25), 123 (15), 106 (18). Anal. Calcd for $C_{11}H_{15}N_3O_4$: C, 52.17; H, 5.97; N, 16.59. Found: C, 52.02; H, 6.05; N, 16.37.

4.2.6. Ethyl 5-[(anilinocarbonyl)amino]-6-methyl-4-oxo-5-azaspiro[2.4]hept-6-ene-7-carboxylate (**3f**)

Spirocompound **3f** was isolated by column chromatography (cyclohexane/ethyl acetate 50:50) in 64% yield as a white solid; mp 179–180 °C; IR (Nujol) ν_{max} 3321, 1711, 1698, 1563, 1411, 1256, 1131, 1073 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.20 (t, *J*=7.2 Hz, 3H), 1.22–1.32 (m, 2H), 1.77–1.88 (m, 2H), 2.32 (s, 3H), 4.11 (q, *J*=7.2 Hz, 2H), 6.97 (t, *J*=7.6 Hz, 1H), 7.25 (t, *J*=7.6 Hz, 2H), 7.42 (d, *J*=7.6 Hz, 2H), 8.84 (s, 1H), 9.31 (br, 1H); ^{13}C NMR (DMSO-d_6) δ 11.8, 14.1, 16.9, 17.2, 26.9, 59.3, 103.8, 118.6, 122.4, 128.7, 139.1, 153.7, 154.0, 162.6, 176.0; EIMS *m*/*z* (%) 329 (M^+, 16), 284 (3), 210 (100), 194 (51), 181 (38), 166 (32), 149 (10), 137 (15), 119 (35), 109 (15). Anal. Calcd for $C_{17}H_{19}N_3O_4$: C, 62.00; H, 5.81; N, 12.76. Found: C, 61.84; H, 5.98; N, 12.54.

4.2.7. Ethyl 5-anilino-6-methyl-4-oxo-5-azaspiro[2.4]hept-6-ene-7-carboxylate (**3g**)

Spirocompound **3g** was isolated by column chromatography (cyclohexane/ethyl acetate 80:20) in 86% yield as a white solid; mp 116–118 °C; IR (Nujol) ν_{max} 3291, 1721, 1701, 1623, 1450, 1386, 1233, 1128, 1067 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.31 (t, *J*=7.2 Hz, 3H), 1.47–1.53 (m, 2H), 1.95–2.05 (m, 2H), 2.47 (s, 3H), 4.20 (q, *J*=7.2 Hz, 2H), 6.47 (s, 1H), 6.67 (d, *J*=7.6 Hz, 2H), 6.93 (t, *J*=7.6 Hz, 1H), 7.23 (t, *J*=7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 12.0, 14.2, 18.3, 27.8, 59.7, 105.3, 112.8, 121.5, 129.3, 146.4, 153.6, 163.3, 177.3; EIMS *m*/*z* (%) 286 (M^+, 100), 271 (3), 257 (5), 241 (9), 211 (9), 194 (38), 166 (32), 148 (15), 138 (14), 122 (13). Anal. Calcd for $C_{16}H_{18}N_2O_3$: C, 67.12; H, 6.34; N, 9.78. Found: C, 67.33; H, 6.17; N, 9.97.

4.2.8. Ethyl 6-methyl-5-{[(4-methylphenyl)sulfonyl]amino}-4-oxo-5-azaspiro[2.4]hept-6-ene-7-carboxylate (**3h**)

Spirocompound **3h** was isolated by column chromatography (cyclohexane/ethyl acetate 80:20) in 32% yield as a white solid; mp 150–154 °C; IR (Nujol) ν_{max} 3231, 1740, 1696, 1343, 1167, 1102 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.09–1.39 (m, 2H), 1.31 (t, *J*=7.2 Hz, 3H), 1.81–1.95 (m, 2H), 2.41 (s, 3H), 2.57 (s, 3H), 4.18 (q, *J*=7.2 Hz, 2H), 7.24 (d, *J*=8.4 Hz, 2H), 7.64 (d, *J*=8.4 Hz, 2H), 7.71 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 12.6, 14.2, 18.0, 19.1, 21.7, 26.8, 59.9, 106.3, 128.4, 129.6, 134.2, 145.2, 151.7, 163.0, 175.7; EIMS *m*/*z* (%) 364 (M^+, 11), 319 (4), 209 (39), 181 (100), 163 (8), 135 (10). Anal. Calcd for $C_{17}H_{20}N_2O_5S$: C, 56.03; H, 5.53; N, 7.69; S, 8.80. Found: C, 56.16; H, 5.37; N, 7.51; S, 8.99.

4.2.9. Ethyl 5-[(aminocarbonyl)amino]-4-oxo-6-propyl-5-azaspiro[2.4]hept-6-ene-7-carboxylate (**3i**)

Spirocompound **3i** was isolated by column chromatography (ethyl acetate) in 82% yield as a white solid; mp 201–203 °C; IR (Nujol) ν_{max} 3432, 3337, 3238, 1736, 1700, 1689, 1619, 1546, 1269, 1239 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 0.90 (t, *J*=7.2 Hz, 3H), 1.19 (t, *J*=7.2 Hz, 3H), 1.19–1.28 (m, 2H), 1.45–1.55 (m, 2H), 1.72–1.90 (m, 2H), 2.45–2.55 (m, 1H), 2.78–2.90 (m, 1H), 4.07 (q, *J*=7.2 Hz, 2H), 6.29 (br, 2H), 8.66 (br, 1H); ^{13}C NMR (DMSO-d_6) δ 13.9, 14.0, 17.1, 17.3, 20.9, 26.9, 27.1, 59.2, 103.6, 157.2, 157.3, 162.4, 176.2; EIMS *m*/*z* (%) 281 (M^+, 46), 252 (9), 238 (68), 222 (100), 209 (59), 193 (46), 176 (30), 165 (25), 148 (35), 136 (35), 120 (27). Anal. Calcd for $C_{13}H_{19}N_3O_4$: C, 55.50; H, 6.81; N, 14.94. Found: C, 55.72; H, 6.63; N, 15.02.

4.2.10. Allyl 5-[(aminocarbonyl)amino]-6-methyl-4-oxo-5-azaspiro[2.4]hept-6-ene-7-carboxylate (**3j**)

Spirocompound **3j** was isolated by column chromatography (ethyl acetate) in 94% yield as a white solid; mp 195–197 °C; IR (Nujol) ν_{max} 3448, 3339, 3252, 1740, 1686, 1544, 1261, 1123 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 1.19–1.29 (m, 2H), 1.72–1.85 (m, 2H), 2.28 (s, 3H), 4.56–4.61 (m, 2H), 5.19–5.23 (m, 1H), 5.25–5.31 (m, 1H), 5.89–6.01 (m, 1H), 6.34 (br, 2H), 8.63 (br, 1H); ^{13}C NMR (DMSO-d_6) δ 11.9, 16.9, 17.2, 26.9, 63.8, 103.3, 117.7, 132.9, 154.4, 157.3, 162.3, 175.9; EIMS *m*/*z* (%) 265 (M^+, 8), 236 (3), 222 (7), 208 (6), 181 (100), 166 (10), 151 (5), 137 (8), 123 (5), 109 (14). Anal. Calcd for $C_{12}H_{15}N_3O_4$: C, 54.33; H, 5.70; N, 15.84. Found: C, 54.16; H, 5.89; N, 16.04.

4.2.11. Methyl 5-[(aminocarbonyl)amino]-6-(2-methoxy-2-oxoethyl)-4-oxo-5-azaspiro[2.4]hept-6-ene-7-carboxylate (**3k**)

Spirocompound **3k** was isolated by column chromatography (ethyl acetate) in 75% yield as a white solid; mp 172–174 °C; IR (Nujol) ν_{max} 3317, 3280, 3194, 1749, 1732, 1693, 1688, 1356, 1253,

1123 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.29–1.35 (m, 2H), 1.78–1.88 (m, 2H), 3.50 (d, J=16.4 Hz, 1H), 3.61 (s, 3H), 3.62 (s, 3H), 4.21 (d, J=16.4 Hz, 1H), 6.29 (br, 2H), 8.74 (br, 1H); ^{13}C NMR (DMSO-d_6) δ 17.6, 17.8, 27.3, 31.1, 51.0, 52.2, 106.2, 149.5, 157.2, 162.6, 168.2, 175.5; EIMS m/z (%) 297 (M^+, 15), 280 (2), 254 (69), 238 (39), 222 (51), 206 (100), 194 (41), 179 (21), 163 (25), 135 (28). Anal. Calcd for $C_{12}H_{15}N_3O_6$: C, 48.48; H, 5.09; N, 14.14. Found: C, 48.67; H, 5.34; N, 14.03.

4.2.12. Ethyl 5-[(aminocarbonyl)amino]-6-(2-ethoxy-2-oxoethyl)-4-oxo-5-azaspiro[2.4]hept-6-ene-7-carboxylate (**3l**)

Spirocompound **3l** was isolated by column chromatography (ethyl acetate) in 54% yield as a white solid; mp 182–184 °C; IR (Nujol) ν_{max} 3423, 3320, 3277, 3191, 1747, 1735, 1692, 1416, 1353, 1255, 1196, 1125 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.18 (t, J=7.2 Hz, 6H), 1.29–1.35 (m, 2H), 1.80–1.90 (m, 2H), 3.47 (d, J=16.4 Hz, 1H), 4.00–4.12 (m, 4H), 4.18 (d, J=16.4 Hz, 1H), 6.28 (br, 2H), 8.73 (br, 1H); ^{13}C NMR (DMSO-d_6) δ 13.9, 14.0, 17.6, 17.8, 27.3, 31.2, 59.6, 60.9, 106.3, 149.4, 157.2, 162.1, 167.8, 175.6; EIMS m/z (%) 325 (M^+, 18), 308 (3), 282 (100), 266 (22), 236 (78), 220 (44), 208 (65), 192 (50), 179 (39), 166 (32), 151 (22), 136 (33). Anal. Calcd for $C_{14}H_{19}N_3O_6$: C, 51.69; H, 5.89; N, 12.92. Found: C, 51.86; H, 5.58; N, 13.12.

4.2.13. 2-Methoxyethyl 5-[(anilinocarbonyl)amino]-6-methyl-4-oxo-5-azaspiro[2.4]hept-6-ene-7-carboxylate (**3m**)

Spirocompound **3m** was isolated by column chromatography (cyclohexane/ethyl acetate 50:50) in 56% yield as a white solid; mp 166–168 °C; IR (Nujol) ν_{max} 3348, 1693, 1633, 1602, 1551, 1281, 1240, 1147, 1082 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.25–1.31 (m, 2H), 1.75–1.91 (m, 2H), 2.33 (s, 3H), 3.26 (s, 3H), 3.53 (t, J=4.8 Hz, 2H), 4.17 (t, J=4.8 Hz, 2H), 6.97 (t, J=7.6 Hz, 1H), 7.26 (t, J=7.6 Hz, 2H), 7.42 (d, J=7.6 Hz, 2H), 8.84 (s, 1H), 9.32 (br, 1H); ^{13}C NMR (DMSO-d_6) δ 11.8, 17.0, 17.2, 26.9, 58.0, 62.1, 69.8, 103.7, 118.6, 122.4, 128.7, 139.1, 154.0, 154.1, 162.5, 175.9; EIMS m/z (%) 359 (M^+, 16), 284 (6), 240 (66), 182 (36), 164 (100), 148 (12), 136 (22), 119 (23). Anal. Calcd for $C_{18}H_{21}N_3O_5$: C, 60.16; H, 5.89; N, 11.69. Found: C, 60.04; H, 5.99; N, 12.82.

4.2.14. Isopropyl 5-[(anilinocarbonyl)amino]-6-methyl-4-oxo-5-azaspiro[2.4]hept-6-ene-7-carboxylate (**3n**)

Spirocompound **3n** was isolated by column chromatography (cyclohexane/ethyl acetate 60:40) in 60% yield as a white solid; mp 153–155 °C; IR (Nujol) ν_{max} 3302, 1699, 1554, 1409, 1238, 1117, 1066 cm^{-1}; ^1H NMR (DMSO-d_6) δ 1.20 (d, J=6.0 Hz, 6H), 1.20–1.30 (m, 2H), 1.75–1.88 (m, 2H), 2.32 (s, 3H), 4.93 (sept, J=6.0 Hz, 1H), 6.97 (t, J=7.6 Hz, 1H), 7.25 (t, J=7.6 Hz, 2H), 7.42 (d, J=7.6 Hz, 2H), 8.84 (s, 1H), 9.31 (br, 1H); ^{13}C NMR (DMSO-d_6) δ 11.8, 17.0, 17.2, 21.7, 26.9, 66.6, 104.0, 118.6, 122.4, 128.7, 139.1, 153.6, 154.0, 162.1, 175.9; EIMS m/z (%) 343 (M^+, 12), 301 (7), 284 (6), 224 (39), 208 (6), 182 (75), 166 (100), 153 (9), 137 (17), 119 (23), 111 (27). Anal. Calcd for $C_{18}H_{21}N_3O_4$: C, 62.96; H, 6.16; N, 12.24. Found: C, 63.08; H, 6.29; N, 12.07.

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References and notes

1. For selected reviews, see: (a) Heathcock, C. H.; Graham, S. L.; Pirrung, M. C.; Plavac, F.; White, C. T. Spirocyclic Systems. In *The Total Synthesis of Natural Products*; ApSimon, J., Ed.; John Wiley and Sons: New York, NY, 1983; Vol. 5, p 264; (b) Sannigrahi, M. *Tetrahedron* **1999**, *55*, 9007.
2. (a) Primke, H.; Sarin, G. S.; Kohlstruk, S.; Adiwidjaja, G.; de Meijere, A. *Chem. Ber.* **1994**, *127*, 1051; (b) Tokuzaki, K.; Kanemitu, Y.; Yoshimitsu, T.; Nagaoka, H. *Tetrahedron Lett.* **2000**, *41*, 5923; (c) Friese, J. C.; Schäfer, H. J. *Synlett* **2002**, 814; (d) Hashimoto, H.; Jin, T.; Karikomi, M.; Seki, K.; Haga, K.; Uyehara, T. *Tetrahedron Lett.* **2002**, *43*, 3633; (e) Movassaghi, M.; Piizzi, G.; Siegel, D. S.; Piersanti, G. *Angew. Chem., Int. Ed.* **2006**, *45*, 5959; For the synthesis of an illudinoid library, see: (f) Pirrung, M. C.; Liu, H. *Org. Lett.* **2003**, *5*, 1983.
3. Bose, G.; Bracht, K.; Bednarski, P. J.; Lalk, M.; Langer, P. *Bioorg. Med. Chem.* **2006**, *14*, 4694.
4. (a) Bryson, T. A.; Roth, G. A. *Tetrahedron Lett.* **1988**, *29*, 2167; (b) Boger, D. L.; Johnson, D. S. *J. Am. Chem. Soc.* **1990**, *112*, 5832; (c) Tietze, L. F.; Hannemann, R.; Buhr, W.; Lögers, M.; Menningen, P.; Lieb, M.; Starck, D.; Grote, T.; Döring, A.; Schuberth, I. *Angew. Chem., Int. Ed.* **1996**, *35*, 2674; (d) Boger, D. L.; Garbaccio, R. M.; Jin, Q. *J. Org. Chem.* **1997**, *62*, 8875; (e) Boger, D. L.; Boyce, C. W.; Carpaccio, R. M.; Goldberg, J. A. *Chem. Rev.* **1997**, *97*, 787; (f) Tietze, L. F.; Buhr, W.; Looft, J.; Grote, T. *Chem.—Eur. J.* **1998**, *4*, 1554.
5. Limbach, M.; Dalai, S.; Janssen, A.; Es-Sayed, M.; Magull, J.; de Meijere, A. *Eur. J. Org. Chem.* **2005**, 610.
6. Brackmann, F.; Es-Sayed, M.; de Meijere, A. *Eur. J. Org. Chem.* **2005**, 2250.
7. (a) Robertson, D. W.; Krushinski, J. H.; Pollock, G. D.; Wilson, H.; Kauffman, R. F. *J. Med. Chem.* **1987**, *30*, 824; (b) Beckwith, A. L. J.; Storey, J. M. D. *J. Chem. Soc., Chem. Commun.* **1995**, 977; (c) Shanmugam, P.; Vaithiyanathan, V.; Viswambharan, B. *Tetrahedron* **2006**, *62*, 4342; (d) Jiang, T.; Kuhen, K. L.; Wolff, K.; Yin, H.; Bieza, K.; Caldwell, J.; Bursulaya, B.; Tuntland, T.; Zhang, K.; Karanewsky, D.; He, Y. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2109; (e) Jiang, T.; Kuhen, K. L.; Wolff, K.; Yin, H.; Bieza, K.; Caldwell, J.; Bursulaya, B.; Wu, T. Y.-H.; He, Y. *Biorg. Med. Chem. Lett.* **2006**, *16*, 2105.
8. Lerchner, A.; Carreira, E. M. *J. Am. Chem. Soc.* **2002**, *124*, 14826.
9. For reviews on cyclopropane-annelated carbo- and heterocycles, see: (a) de Meijere, A.; Wessjohann, L. *Synlett* **1990**, 20; (b) de Meijere, A.; Kozhushkov, S. I.; Khlebnikov, A. F. *Top. Curr. Chem.* **2000**, *207*, 89.
10. For examples on cyclopropane-annelated carbocycles, see: (a) Langer, P.; Bose, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4033; (b) Bose, G.; Nguyen, V. T. H.; Ullah, E.; Lahiri, S.; Görls, H.; Langer, P. *J. Org. Chem.* **2004**, *69*, 9128; (c) Bose, G.; Langer, P. *Tetrahedron Lett.* **2004**, *45*, 3861; (d) Barbero, A.; Castreño, P.; Pulido, F. J. *J. Am. Chem. Soc.* **2005**, *127*, 8022; (e) Rasool, N.; Rashid, M. A.; Reinke, H.; Fischer, C.; Langer, P. *Tetrahedron* **2008**, *64*, 3246.
11. For examples on cyclopropane-annelated heterocycles, see: (a) Anichini, B.; Goti, A.; Brandi, A.; Kozhushkov, S. I.; de Meijere, A. *Chem. Commun.* **1997**, 261; (b) de Meijere, A.; Von Seebach, M.; Kozhushkov, S. I.; Boese, R.; Blaser, D.; Cicchi, S.; Dimoulas, T.; Brandi, A. *Eur. J. Org. Chem.* **2001**, *20*, 3789; (c) Marti, C.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 11505; (d) Storey, J. M. D.; Ladwa, M. M. *Tetrahedron Lett.* **2006**, *47*, 381; (e) Zheng, X.; Kerr, M. A. *Org. Lett.* **2006**, *8*, 3777; (f) Zanobini, A.; Brandi, A.; de Meijere, A. *Eur. J. Org. Chem.* **2006**, *5*, 1251; (g) Hamaguchi, M.; Nakaishi, M.; Nagai, T.; Nakamura, T.; Abe, M. *J. Am. Chem. Soc.* **2007**, *129*, 12981; (h) Rotzoll, S.; Reinke, H.; Langer, P. *Tetrahedron Lett.* **2008**, *49*, 675; (i) Method, J. L.; Dunstan, T. A.; Mampreian, D. M.; Adams, B.; Altman, M. D. *Tetrahedron Lett.* **2008**, *49*, 1155.
12. Cyclopropanes and related rings: de Meijere, A. *Chem. Rev.* **2003**, *103*, 931.
13. (a) Joule, J. A.; Mills, K. *Heterocyclic chemistry*, 4th ed.; Blackwell: Oxford, 2000; (b) Eicher, T.; Hauptmann, S.; Speicher, A. *The Chemistry of Heterocycles*, 2nd ed.; Wiley-VCH: Weinheim, Germany, 2003; p 97.
14. Effland, R.C.; Klein, J.T. U.S. Patent 4,546,105, 1985; *Chem. Abstr.* **1986**, *104*, 186307.
15. Kulagowski, J.; Janusz, J.; Leeson, P.D. UK Patent 2,265,372, 1993; *Chem. Abstr.* **1993**, *120*, 134504.
16. For a review on 1,2-diaza-1,3-butadienes, see: Attanasi, O. A.; De Crescentini, L.; Filippone, P.; Mantellini, F.; Santeusanio, S. *ARKIVOC* **2002**, *xi*, 274; For recent developments on the chemistry of 1,2-diaza-1,3-butadienes, see: (a) Boeckman, R. K., Jr.; Ge, P.; Reed, J. E. *Org. Lett.* **2001**, *3*, 3651; (b) Rossi, E.; Arcadi, A.; Abbiati, G.; Attanasi, O. A.; De Crescentini, L. *Angew. Chem., Int. Ed.* **2002**, *41*, 1400; (c) Kramp, G. J.; Kim, M.; Gais, H.-J.; Vermeeren, C. *J. Am. Chem. Soc.* **2005**, *127*, 17910; (d) Attanasi, O. A.; De Crescentini, L.; Favi, G.; Filippone, P.; Lillini, S.; Mantellini, F.; Santeusanio, S. *Org. Lett.* **2005**, *7*, 2469; (e) Palacios, F.; Aparicio, D.; López, Y.; de los Santos, J. M. *Tetrahedron* **2005**, *61*, 2815; (f) Yang, H.-T.; Wang, G.-W.; Xu, Y.; Huang, J.-C. *Tetrahedron Lett.* **2006**, *47*, 4129; (g) Attanasi, O. A.; Davoli, P.; Favi, G.; Filippone, P.; Forni, A.; Moscatelli, G.; Prati, F. *Org. Lett.* **2007**, *9*, 3461; (h) Attanasi, O. A.; Favi, G.; Filippone, P.; Perrulli, F. R.; Santeusanio, S. *Org. Lett.* **2009**, *11*, 309.
17. Attanasi, O. A.; Favi, G.; Filippone, P.; Lillini, S.; Mantellini, F.; Spinelli, D.; Stenta, M. *Adv. Synth. Catal.* **2007**, *349*, 207.
18. Attanasi, O. A.; Favi, G.; Filippone, P.; Giorgi, G.; Mantellini, F.; Spinelli, D. *Org. Lett.* **2008**, *10*, 1983.
19. Karapetyan, V.; Mkrtchyan, S.; Schmidt, A.; Attanasi, O. A.; Favi, G.; Mantellini, F.; Villinger, A.; Fischer, C.; Langer, P. *Adv. Synth. Catal.* **2008**, *350*, 1331.
20. For a review on 1,3-bis(silyloxy)-1,3-butadienes, see: Langer, P. *Synthesis* **2002**, 441.
21. For a review on [3+3] cyclizations of 1,3-bis(silyloxy)-1,3-butadienes, see: Feist, H.; Langer, P. *Synthesis* **2007**, 327.
22. (a) Rühlmann, K. *Synthesis* **1971**, 236; (b) Bisel, P.; Breitling, E.; Frahm, A. W. *Eur. J. Org. Chem.* **1998**, 729.
23. (a) Shimada, J.; Hashimoto, K.; Kim, B. H.; Nakamura, E.; Kuwajima, I. *J. Am. Chem. Soc.* **1984**, *106*, 1759; (b) Burnell, D. J.; Wu, Y.-J. *Can. J. Chem.* **1990**, *68*, 804; (c) Sisko, J.; Balog, A.; Curran, D. P. *J. Org. Chem.* **1992**, *57*, 4341; (d) Wu, Y.-J.; Strickland, D. W.; Jenkins, T. J.; Liu, P.-Y.; Burnell, D. J. *Can. J. Chem.* **1993**, *71*, 1311; (e) Jenkins, T. J.; Burnell, D. J. *J. Org. Chem.* **1994**, *59*, 1485; (f) Balog, A.; Curran, D. P. *J. Org. Chem.* **1995**, *60*, 337; (g) Reddy, R. S.; Saravanan, K.; Kumar, P.

Tetrahedron **1998**, *54*, 6553; (h) Crane, S. N.; Burnell, D. J. *J. Org. Chem.* **1998**, *63*, 1352; For Diels–Alder reactions, see: (i) Audenaert, F.; De Keukeleire, D.; Vandewalle, M. *Tetrahedron* **1987**, *43*, 5593.
24. Gao, F.; Burnell, D. J. *J. Org. Chem.* **2006**, *71*, 356.
25. (a) For a review on the use of $Bi(TfO)_3$ see: Gaspard-Iloughmane, H.; Le Roux, C. *Eur. J. Org. Chem.* **2004**, *12*, 2517; (b) For Mukaiyama aldol-type reactions see: Le Roux, C.; Ciliberti, L.; Laurent-Robert, H.; Laporterie, A.; Dubac, J. *Synlett* **1998**, 1249; (c) Kobayashi, S.; Ogino, T.; Shimizu, H.; Ishikawa, S.; Hamada, T.; Manabe, K. *Org. Lett.* **2005**, *7*, 4729; (d) For vinylogous Mukaiyama aldol reaction see: Ollevier, T.; Bouchard, J.-E.; Desyroy, V. *J. Org. Chem.* **2008**, *73*, 331.
26. Perlmutter, P. *Conjugate Addition Reactions in Organic Synthesis*; Pergamon: Oxford, 1992.
27. (a) Narasaka, K.; Soai, K.; Mukaiyama, T. *Chem. Lett.* **1974**, 1223; (b) Narasaka, K.; Soai, K.; Aikawa, Y.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* **1976**, *49*, 779; (c) Saigo, K.; Osaki, M.; Mukaiyama, T. *Chem. Lett.* **1976**, 163; (d) Mukaiyama, T. *Angew. Chem., Int. Ed. Engl.* **1977**, *16*, 817; (e) Mukaiyama, T. *Challenges in Synthetic Organic Chemistry*; Clarendon: Oxford, 1990 (translated by Baldwin, E.).
28. (a) Narasaka, K.; Soai, V.; Mukaiyama, T. *Chem. Lett.* **1974**, 1223; (b) Takenaka, N.; Abell, J. P.; Yamamoto, H. *J. Am. Chem. Soc.* **2007**, *129*, 742 and references cited therein.
29. Hanna, I.; Ricard, L. *Tetrahedron Lett.* **1999**, *40*, 863.
30. Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 121.
31. CCDC-725070 contains all crystallographic details of this publication and is available free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html or can be ordered from the following address: Cambridge Crystallographic Data Centre, 12 Union Road, GB-Cambridge CB21EZ; fax: +44 1223 336 033; or deposit@ccdc.cam.ac.uk).
32. Sommer, S. *Tetrahedron Lett.* **1977**, *18*, 117.
33. (a) Attanasi, O. A.; Filippone, P.; Mei, A.; Santeusanio, S. *Synthesis* **1984**, 671; (b) Attanasi, O. A.; Filippone, P.; Mei, A.; Santeusanio, S. *Synthesis* **1984**, 873.