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An Unprecedented Mode of Ring Opening of Methylenecyclopropane Moieties – Reactions of Methylenecyclopropanecopper Reagents with an Electrophilic Glycine Equivalent

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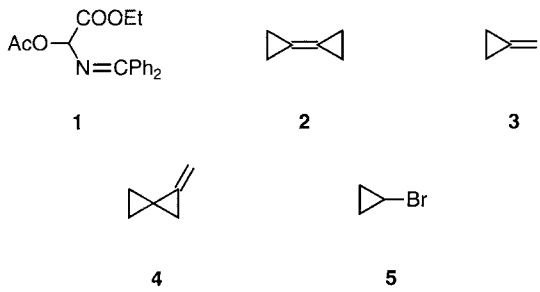
The reactions of ethyl 2-acetoxy-2-diphenylmethyleneaminoacetate (**1**) with organocopper reagents derived from bicyclopropylidene (**2**) and methylenecyclopropane (**3**) are accompanied by an unusual mode of opening of one three-membered ring to give 4-methylene-1,2,3,4-tetrahydropyridine derivatives **8a**, **9** in good yields. The cuprate derived from methylenespiropentane (**4**) reacts with **1** to yield both the normal substitution product **14** (37%) as well as the rearrangement product **15** (34%), while the simple cyclopropylcuprate undergoes substitution to give the protected cyclopropylglycine **16** (75%) without rearrangement. The tetrahydropyridine **8a** shows an interesting tautomerism in solution. The 4-cyclopropylidenetetrahydropyridine **15** undergoes an unusual dehydrodimerization to produce two separable rotamers, C_2-**19** and C_1-**19**, via **18**.

The reactions of an electrophilic glycine cation equivalent – O'Donnells acetate **1** – with heteroatom electrophiles[1], organocopper reagents[2], organometallic species under palladium catalysis[3][4] and aromatic nucleophiles under Lewis acid catalysis[5] offer versatile ways of preparing α-amino acids. In the course of our investigations in the field of α-amino acids containing three-membered rings[6] and methylenecyclopropane fragments[7], we have also examined reactions of **1** with higher-order mixed cuprates of the type $R_2Cu(CN)Li_2$[8] derived from bicyclopropylidene (**2**)[9], methylenecyclopropane (**3**)[10], methylenespiropentane (**4**)[11] and bromocyclopropane (**5**). Higher-order cuprates **6**, **7** derived from **2**, **3**, as well as that from **4**, can readily be produced by direct lithiation of these hydrocarbons[12] followed by reaction with CuCN at −40°C.

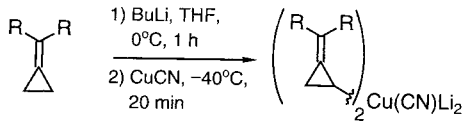
Surprisingly, in the reactions of the cuprates **6**, **7** with **1**, the only detectable products were derivatives of 4-methylene-1,2,3,4-tetrahydropyridine **8a** and **9** (Scheme 1), isolated in 63 and 69% yield, respectively.

The structures of **8a** and **9** were assigned on the basis of their ^{1}H-NMR spectra (see Experimental Section). Thus, H-D exchange was observed for the signals at δ = 6.23 and 6.19, respectively. However, initially no signals of the cyclopropane CH_2 groups could be detected in the ^{13}C-NMR

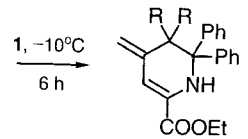


1 **2** **3** **4** **5**

Scheme 1



2 R–R = –$(CH_2)_2$–
3 R,R = H,H
6 R–R = –$(CH_2)_2$–
7 R,R = H,H



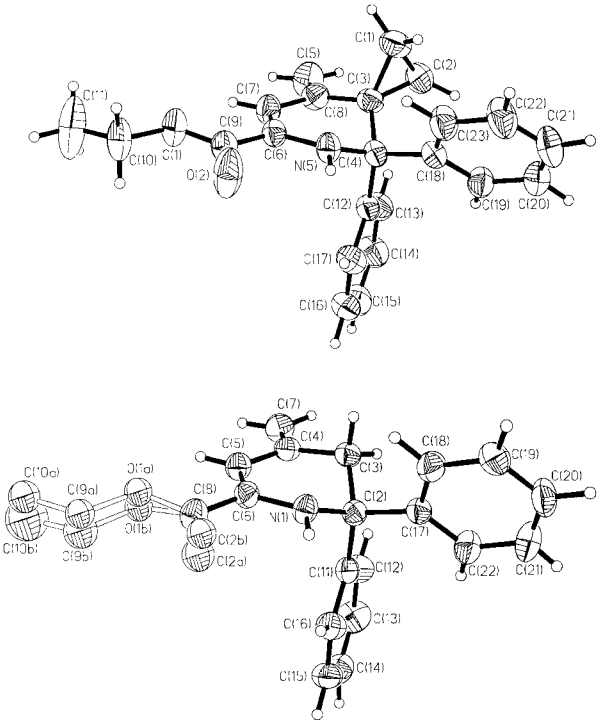
8a R–R = –$(CH_2)_2$– (63%)
9 R,R = H,H (69%)

[◇] Part 41: B. Anichini, A. Goti, A. Brandi, S. I. Kozhushkov, A. de Meijere, *Synlett* **1997**, 25–26. – Part 40: V. Chaplinski, H. Winsel, M. Kordes, A. de Meijere, *Synlett* **1997**, 111–114.

  0947–3440/97/1111–2197 $ 17.50+.50/0

spectrum of **8a** at room temperature under standard conditions, and the signals of the two phenyl groups were very broad in both the ^{1}H- and ^{13}C-NMR spectra. Therefore, the structures of **8a** and **9** were unequivocally established by X-ray crystal structure analyses[13] (Figure 1) after suitable crystals had been obtained by slow evaporation of the solvents from dilute solutions in diethyl ether.

Figure 1. Structures of compounds **8a** (top) and **9** (bottom) in the crystal

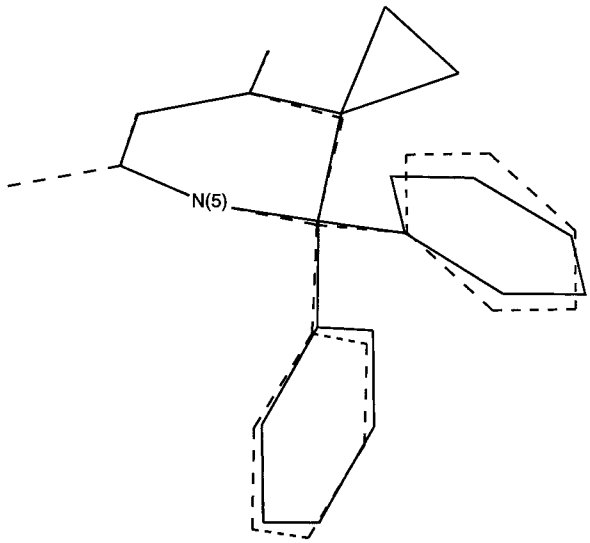


The conformations of molecules **8a** and **9** are remarkably similar; a superposition of these structures (Figure 2) shows that only the orientations of the pseudoequatorial phenyl groups are slightly different. The difference is obviously caused by repulsive intramolecular non-bonding interactions between C(1)/C(23), C(2)/C(19) and C(2)/C(13), as these distances would have to be even shorter than 3.228(5), 3.357(5) and 3.339(5) Å for the phenyl group to be oriented as it is in **9**. The heterocycles in molecules **8a** and **9** adopt a half-chair conformation. According to the Cambridge Crystallographic Data File, no structure analysis of any 4-methylene-1,2,3,4-tetrahydropyridine has yet been carried out, although in all reported structure analyses of 2,3-dihydro-4-pyridinones the molecules also adopt half-chair conformations.

In the crystal, molecules of **8a** and **9** form centrosymmetrical dimers held together by pairs of N–H···O hydrogen bonds. The structural parameters of the hydrogen bonds are also very close: N···O 3.109 Å, N–H 0.85 Å, angle N–H–O 165.6° in **8a** and N···O 3.10 Å, N–H 0.83 Å and N–H–O 168.5° in molecule **9** (mean values for two disordered carbonyl O atoms).

Apparently, steric interactions between the phenyl groups and the adjacent spirocyclopropane ring in **8a** cause a significant increase in the tetrahydropyridine ring inversion barrier, which accounts for the rather unusual NMR spectral features. Signals for the cyclopropane CH_2 groups could eventually be observed in the ^{13}C-NMR spectrum of **8a** recorded at ambient temperature at 62.9 MHz, but only as a broad feature after an overnight spectral accumulation using a concentrated solution. Low- and high-temperature ^{13}C-NMR measurements of **8a** in CD_2Cl_2 and $C_2D_2Cl_4$ solutions indicate a dynamic behavior, with a strong temperature dependence of the cyclopropane and phenyl carbon signals. At 25°C, the cyclopropyl CH_2 and phenyl C signals are close to coalescence, whereas the phenyl CH group signals are above their coalescence temperature. At −25°C and below, the cyclopropyl CH_2 and the C_{quat} fragments are each observed as a set of two narrow signals (see Experimental Section, Table 1). At −51°C, two of the ten phenyl CH signals are at their coalescence temperature; at −80°C as well as at −90°C, a total of nine CH signals can be observed.

Figure 2. Superposition of the structures of compounds **8a** and **9**

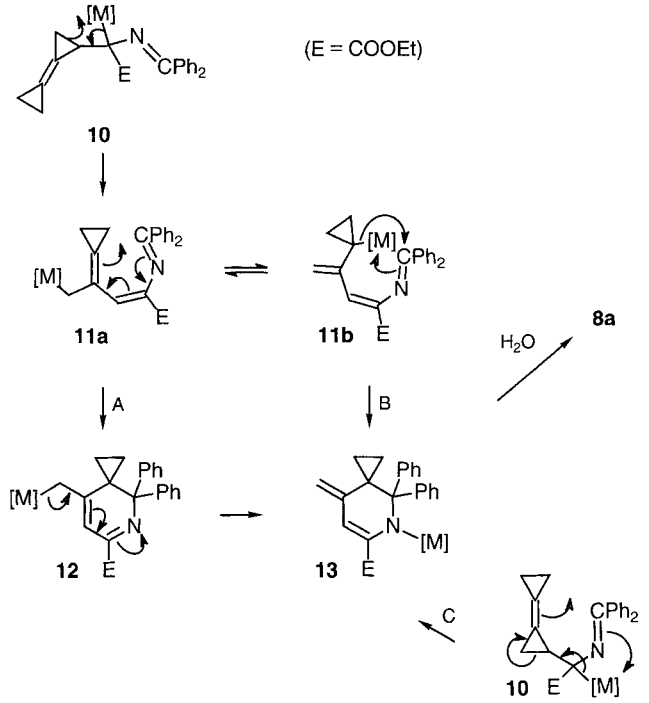


Upon increasing the temperature, fast exchange is apparent for the CH signals, even at +50°C; the signals of the cyclopropyl CH_2 and quaternary carbons sharpen only at +100°C and, after cooling, return to their initial coalesced state. Using the data for the CH_2 and C_{quat} signals obtained at −90°C, values of $k = 1.66 \times 10^3$ and 1.38×10^3 s^{-1} as well as $\Delta G^{+} = 13.1$ and 13.2 kcal mol^{-1}, respectively, were calculated for the corresponding coalescence temperatures according to the commonly used approximation[14].

Possible Mechanism of Rearrangement: Among all the reported reactions of methylenecyclopropane and bicyclopropylidene derivatives, the type of rearrangement observed here is unprecedented. Thus, instead of the previously reported [3 + 2] cycloaddition mode for bicyclopropylidene (**2**) and methylenecyclopropane (**3**) under transition metal catalysis[10], the new reaction can be formally described as a [3 + 3] cycloaddition[15][16]. Mechanistically, the abnormal products **8a** and **9** may be formed via the normal coupling product which, in its metallated form **10**, can undergo a fast

cyclopropylmethyl to but-3-enyl rearrangement[17] (Scheme 2). The cyclization might proceed as a 6π electrocyclization of the intermediate **11a** (path A) or as a Michael addition onto the C=N double bond in the tautomer **11b** (path B). An attractive alternative would be a concerted cyclization and rearrangement of **10** to lead directly to **13**, the metallated form of **8a** (path C).

Scheme 2



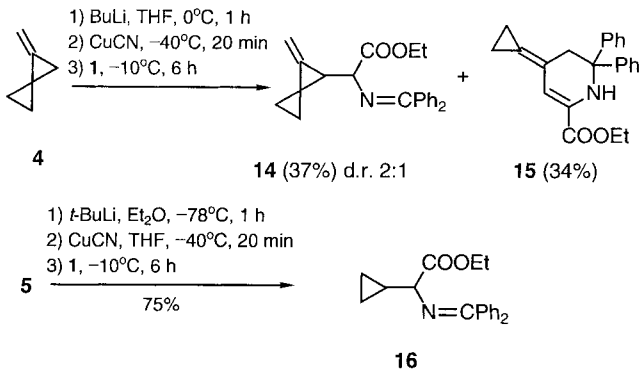
To verify one of these possibilities, the analogous reactions of the mixed cuprates derived from methylenespiropentane (**4**) and bromocyclopropane (**5**) were studied under the same conditions. The coupling product of the cuprate derived from hydrocarbon **4** should be able to form the same intermediate **11b** as that from bicyclopropylidene (**2**), and its transformation along path B should then also give **8a**. However, the sequence of transformations applied to **4** gave the unrearranged coupling product **14** (37% yield) and a rearranged product of yet another structure **15** (34%), which could only have been formed along path A or path C (Scheme 3). The normal coupling product **14** was formed as a mixture of two diastereomers in a ratio of 2:1.

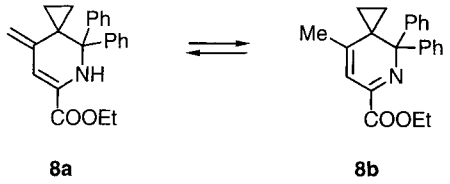
The mixed cuprate prepared from bromocyclopropane **5** yielded only the cyclopropylglycine derivative **16** (75%). This indicates that a methylenecyclopropane moiety is essential for the rearrangement with ring opening to occur. These results are still inconclusive as to whether this ring opening precedes the cyclization (path A) or whether these processes occur simultaneously (path C).

In a preparative sense, these transformations of **4** and **5** provide an access to cyclopropylglycine[18] and (methylenespiropent-2-yl)glycine, although in the latter case the experimental conditions need further optimization.

Tautomerism of Compound **8** *and Dimerization of Compound* **15**: When trying to prepare a pure sample of compound **8a** for an X-ray crystal structure analysis, an interesting phenomenon was observed in that the NMR spectra of pure samples of **8a** always showed signals indicating the presence of **8b**. The proportion of **8b** varied depending on the concentration and the time between the preparation of the NMR sample and the recording of the spectrum. This appears to be a special case of tautomerism, which has not previously been reported.

Scheme 3

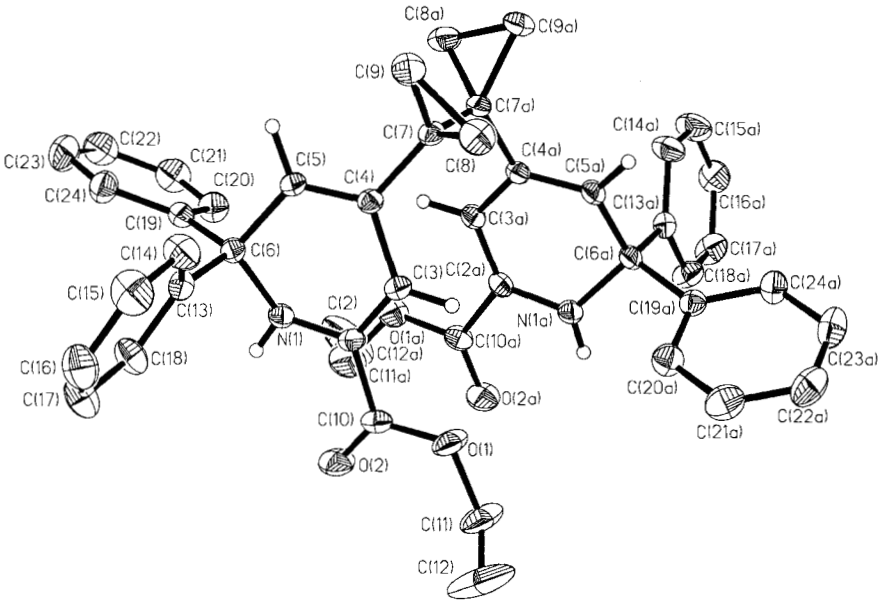




Pure samples of **8a** can be obtained by crystallization through concentration of ethereal solutions by slow evaporation of solvent. However, after any attempt to purify **8a** by column chromatography using various eluent systems, the samples were found to contain varying amounts of **8b**, which could be detected by TLC as well as by NMR. Compound **8b** could be isolated in almost pure form by *rapid* column chromatography (hexane/diethyl ether, 7:3). Both **8a** and **8b** are stable in crystalline form, but easily undergo interconversion in solution, as was demonstrated by NMR measurements of pure samples of **8a** and **8b** dissolved in different solvents (see Experimental Section). With CD_3OD as solvent, no tautomerization could be observed for **8a** at room temperature, which might be due to stabilization of the N–H tautomer by hydrogen bonding to the methanol. When a moderately concentrated solution of pure **8a** in $C_2D_2Cl_4$ was heated to 100°C, the ^{13}C-NMR spectrum indicated that a 1:1 mixture of **8a** and **8b** had been attained. The signals of **8b** showed no temperature dependence, i.e. no dynamic behavior could be observed in **8b** in contrast to **8a**. Compound **9**, in contrast, was found to be completely stable in $CDCl_3$ solution and showed no tautomerism of this kind.

The most surprising observation of all was made for the 4-cyclopropylidene-1,2,3,4-tetrahydropyridine derivative **15**. Upon standing in $CDCl_3$ solution, it did not tautomerize like **8a** (which in this case would be irreversible because of the partial release of strain energy from the methylenecyclo-

Figure 3. Structure of compound C_2-**19** in the crystal

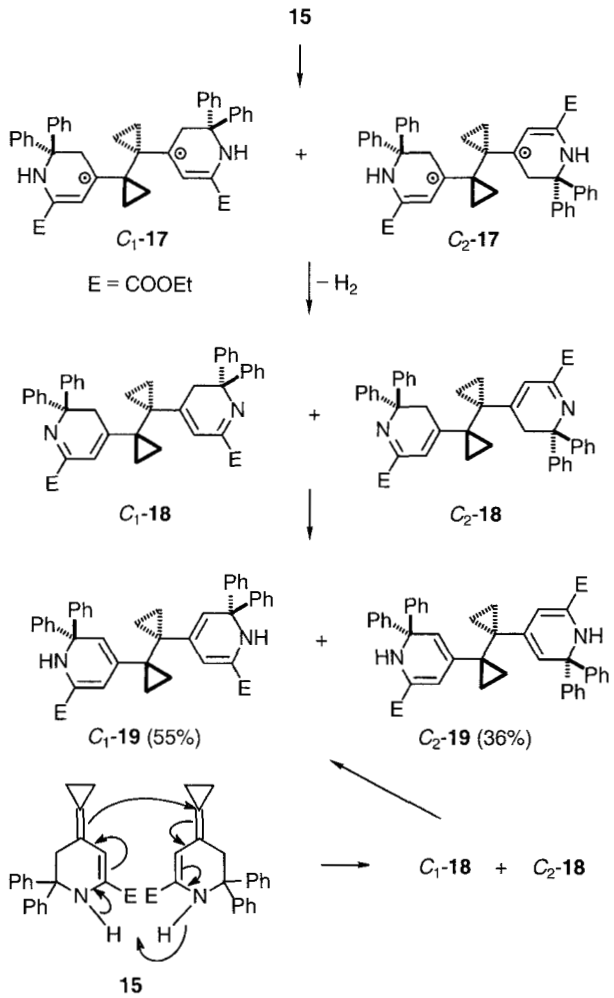


propane fragment[19]), but underwent dimerization with formal loss of a hydrogen molecule to give a 3:2 mixture of two isomeric compounds. These could be separated chromatographically. The ^{1}H- and ^{13}C-NMR spectra of the two compounds were identical in their general appearances and differed only in the chemical shifts of the signals. The minor isomer was crystallized from hexane solution and its structure was established by X-ray crystal structure analysis as that of the C_2-symmetric dehydro dimer C_2-**19** (Figure 3)[13].

In the crystal, the molecules of C_2-**19** are located on a twofold axis passing through the center of the C(7)–C(7a) bond between the two cyclopropyl groups. The bicyclopropyl moiety is in a *synclinal* conformation, which has also been found as the predominating conformer for the unsubstituted hydrocarbon bicyclopropyl in the gas phase[20], and the sole conformation for 1,1′-dimethylbicyclopropyl[21]. The parent bicyclopropyl in the crystal, however, adopts the antiperiplanar conformation[22]. The heterocycles in the molecules C_2-**19** adopt a twist-boat conformation with atoms C(5) 0.26 Å and C(6) 0.66 Å out of the plane defined by N(1), C(2), C(3) and C(4). There are no intermolecular hydrogen bonds or other short intermolecular contacts in the crystal of C_2-**19**. Simple geometrical considerations reveal that the formation of hydrogen bonds is impossible for steric reasons, since the approach of a second molecule of C_2-**19** with the given conformation is effectively blocked both by the pseudoaxial phenyl and by the ethoxycarbonyl group of the second half of the molecule.

In view of the NMR spectroscopic similarities and the identical molecular mass, the second product can only be a diastereomeric rotamer of the minor one, with C_1 symmetry if the conformation in the central bicyclopropyl moiety was *antiperiplanar*. As this is highly unlikely (see above), it must

Scheme 4



have C_s symmetry with a *synclinal* orientation of its bicyclopropyl units, just as in C_2-**19**. The two rotamers C_2-**19** and C_1-**19** cannot interconvert due to an extraordinarily high barrier to rotation[23] about the C(4)–C(7) and C(4a)–C(7a) bonds. The mechanism by which the dimerization of the methylenecyclopropane derivative **15** occurs, can only be speculated on (Scheme 4). Dimerizations of donor-substituted methylenecyclopropanes occurring at room temperature have been observed previously[24][25]. All of these most probably proceed via 1,4-diradical intermediates. In the case of **15**, the first intermediate would probably be the diradical **17**, which by intermolecular loss of H_2 would yield the acyclic dimer **18** rather than a cyclobutane derivative resulting from 1,4-cyclization of **17**. Discrimination between the two diastereomeric rotamers would occur at this stage, i.e. there would be a C_2- and a C_1-symmetric 1,4-diradical, C_2-**17** and C_1-**17**, respectively. An alternative route to **18** would be by a concerted [$_\pi2 + _\pi2 + _\sigma2 + _\pi2 + _\pi2 + _\sigma2$] process[26] with simultaneous loss of H_2. Ultimately, the 3*H*-dihydropyridine moieties in C_2-**18** and C_1-**18** tautomerize to 1*H*-dihydropyridine units, as in the observed products C_2-**19** and C_1-**19**, respectively. Most probably, an analogous intermolecular transformation occurs in the tautomerization of **8a**.

In conclusion, the reactions of organocopper derivatives of methylenecyclopropanes **2**–**4** with **1** provide a synthetic access to a novel family of heterocyclic compounds – methylenetetrahydropyridines – some of which exhibit unusual properties.

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Experimental Section

^{1}H- and ^{13}C-NMR spectra were recorded at 250 (^{1}H) and 62.9 MHz [^{13}C, additional DEPT (Distortionless Enhancement by Polarization Transfer)] on a Bruker AM 250 instrument in $CDCl_3$ solution, $CHCl_3/CDCl_3$ as internal reference, unless otherwise specified; δ in ppm, *J* in Hz. – Low-temperature ^{13}C-NMR was performed at 125 MHz on a Varian INOVA-500 instrument in CD_2Cl_2, $CHDCl_2$ as internal reference. – High-temperature ^{13}C-NMR spectra were obtained at 75.5 MHz on a Varian Unity 300 instrument in $C_2D_2Cl_4$, $C_2HDCl_4/C_2D_2Cl_4$ as internal reference. – FT-IR: Bruker IFS 66, measured as KBr pellets or oils between NaCl plates. – MS (EI) and MS (HR-EI): Finnigan MAT 95 spectrometer (70 eV). – CI-MS: with NH_3. MS (HR-EI): pre-selected ion peak matching at R 10000 to be within ± ⩾ 2 ppm of the exact masses. – Melting points: Büchi 510 capillary melting point apparatus, uncorrected. – TLC: Macherey-Nagel precoated sheets, 0.25 mm Sil G/UV_{254}. – Column chromatography: Merck silica gel, grade 60, 230–400 mesh.

Starting Materials: Anhydrous diethyl ether and THF were obtained by distillation from sodium benzophenone ketyl. Compounds **1**[1], **2**[9] and **4**[11] were prepared according to published procedures. All other chemicals were used as received from commercial sources (Merck, BASF, Bayer, Hoechst, Degussa and Hüls AG). Organic extracts were dried with $MgSO_4$. All reactions were performed under argon.

Table 1. ^{13}C-NMR data for cyclopropyl-CH_2 and phenyl carbon atoms in **8a** at different temperatures

Temperature [°C]	Chemical Shifts (δ)		
	CH_2	C	CH
−90[a]	6.72 12.76	145.74 140.83	130.10 129.11 128.69 127.85 127.06 126.96 126.79 126.66 (2 C) 125.82
−80[a]	6.84 12.82	145.81 140.98	130.20 129.20 128.74 127.92 127.15 127.05 126.86 126.75 (2 C) 125.92
−51[a]	7.16 13.23	146.04 141.42	129.44 128.88 127.28 127.18 127.03 (2 C) 126.95 126.24 127–131 (broad, 2 C)
−25[a]	7.45 13.62	146.27 141.83	129.54 (broad, 4 C) 127.37 (broad, 6 C)
25[b]	9–14 broad	142–144 broad	129.21 (broad, 4 C) 127.98 (broad, 6 C)
50[b]	10.89 broad	143.88 broad	128.65 (2 C) 127.40 (4 C) 126.94 (4 C)
75[b]	10.91 broad	144.04 broad	129.16 (2 C) 128.54 (4 C) 127.34 (4 C)
90[b]	10.94	144.09	129.14 (2 C) 128.64 (4 C) 127.27 (4 C)

[a] In CD_2Cl_2. – [b] In $C_2D_2Cl_4$.

Crystal Structure Determinations: The single-crystal X-ray data for compounds **8a**, **9** and C_2-**19** were collected at room temp. on an Enraf-Nonius CAD-4 diffractometer using graphite-monochromated Mo-K_α radiation and ω/2θ-scan mode. The structures were solved by direct methods (SHELXS-86) and refined anisotropically (non-hydrogen atoms) by the full-matrix least-squares method on F^2 (SHELXL-93). Disordered atoms of the COOEt group in molecule **9** were refined isotropically with fixed s.o.f. = 0.5. The OEt group in molecule C_2-**19** is also probably disordered, but all attempts to split and refine two positions of the group failed. All H atoms, except those of Et groups in molecules **9** and C_2-**19**, were located on the Fourier difference maps and refined isotropically. H atoms of the Et group in molecule C_2-**19** were placed at calculated positions and during the refinement rode on their parent C atoms with $U_H = 1.2\ U_{eq}(C)$. Parameters of crystal data collection and structure refinement are presented in Table 2.

Molecular Structure of **8a**: Selected bond lengths [Å] and angles [°] (for the atom numbering see Figure 1, standard deviations are given in parentheses): C(1)–C(2) 1.490(4), C(1)–C(3) 1.509(3), C(2)–C(3) 1.496(4), C(3)–C(4) 1.551(3), N(5)–C(4) 1.470(3), N(5)–C(6) 1.382(3), C(6)–C(7) 1.345(3), C(7)–C(8) 1.443(3), C(3)–C(8) 1.497(3), C(5)–C(8) 1.334(4), C(6)–C(9) 1.476(3); C(1)–C(2)–C(3) 60.7(2), C(2)–C(1)–C(3) 59.8(2), C(2)–C(3)–C(1) 59.5(2), C(1)–C(3)–C(4) 119.6(2), C(2)–C(3)–C(4) 120.9(2), C(8)–C(3)–C(2) 120.1(2), C(8)–C(3)–C(1) 113.9(2), C(8)–C(3)–C(4) 112.6(2), N(5)–C(4)–C(3) 105.6(2), C(6)–N(5)–C(4) 118.1(2), N(5)–C(4)–C(18) 108.2(2), N(5)–C(4)–C(12) 110.8(2), C(7)–C(6)–N(5) 122.8(2), N(5)–C(6)–C(9) 113.7(2), C(6)–C(7)–C(8) 121.6(2), C(5)–C(8)–C(7) 121.5(3), C(5)–C(8)–C(3) 124.5(3), C(7)–C(8)–C(3) 113.8(2).

Molecular Structure of **9**: Selected bond lengths [Å] and angles [°] (for the atom numbering see Figure 1, standard deviations are given in parentheses). N(1)–C(2) 1.467(3), C(2)–C(3) 1.555(3), C(3)–C(4) 1.508(4), C(4)–C(5) 1.448(4), C(5)–C(6) 1.352(4), N(1)–C(6) 1.379(3), C(4)–C(7) 1.336(4), C(2)–C(17) 1.538(3), C(2)–C(11) 1.539(3), C(6)–C(8) 1.478(4); C(6)–N(1)–C(2) 117.8(2), N(1)–C(2)–C(3) 105.9(2), C(4)–C(3)–C(2) 112.5(2), C(5)–C(4)–C(3) 114.6(2), C(6)–C(5)–C(4) 120.9(2), C(5)–C(6)–N(1) 123.1(2), C(5)–C(6)–C(8) 122.8(2), N(1)–C(6)–C(8) 114.1(2), N(1)–C(2)–C(17) 108.7(2), N(1)–C(2)–C(11) 110.9(2), C(17)–C(2)–C(11) 111.5(2), C(17)–C(2)–C(3) 108.1(2), C(11)–C(2)–C(3) 111.6(2), C(7)–C(4)–C(5) 122.3(3), C(7)–C(4)–C(3) 123.1(3).

Molecular Structure of C_2-**19**: Selected bond lengths [Å] and angles [°] (for the atom numbering see Figure 3, standard deviations are given in parentheses). N(1)–C(2) 1.369(3), C(2)–C(3) 1.342(3), C(3)–C(4) 1.452(3), C(4)–C(5) 1.338(3), C(5)–C(6) 1.522(3), N(1)–C(6) 1.469(3), C(4)–C(7) 1.502(3), C(7)–C(8) 1.504(3), C(8)–C(9) 1.502(4), C(7)–C(9) 1.503(3), C(7)–C(7a) 1.512(4), C(2)–C(10) 1.482(3); C(3)–C(2)–N(1) 121.3(2), C(2)–C(3)–C(4) 118.1(2), C(4)–C(7)–C(9) 116.7(2), C(5)–C(4)–C(3) 118.8(2), C(4)–C(5)–C(6) 122.7(2), N(1)–C(6)–C(5) 105.9(2), C(2)–N(1)–C(6) 119.9(2), N(1)–C(6)–C(13) 109.5(2), N(1)–C(6)–C(19) 107.9(2), C(5)–C(6)–C(19) 108.4(2), C(14)–C(13)–C(6) 123.0(2), N(1)–C(2)–C(10) 113.8(2), C(10)–O(1)–C(11) 117.5(2), O(2)–C(10)–O(1) 124.8(2), C(5)–C(4)–C(7) 121.8(2), C(3)–C(4)–C(7) 119.4(2), C(4)–C(7)–C(8) 116.6(2), C(9)–C(7)–C(8) 59.9(2), C(9)–C(7)–C(7a) 120.1(2), C(4)–C(7)–C(7a) 114.73(14), C(9)–C(8)–C(7) 60.0(2), C(8)–C(9)–C(7) 60.1(2), C(8)–C(7)–C(7a) 117.9(2).

Table 2. Crystal and data collection parameters for compounds **8a**, **9** and C_2-**19**

Compound	**8a**	**9**	C_2-**19**
Formula	$C_{23}H_{23}NO_2$	$C_{21}H_{21}NO_2$	$C_{46}H_{44}N_2O_4$
Molecular mass	345.42	319.39	688.84
Crystal size [mm]	0.33x0.15x0.06	0.45x0.17x0.11	0.45x0.32x0.25
Crystal colour	yellow	yellow	yellow
Space group	*P*–1	*P*–1	*C2/c*
a [Å]	8.413(2)	8.020(2)	10.536(4)
b [Å]	9.247(2)	9.296(2)	10.589(2)
c [Å]	13.758(3)	13.441(3)	18.090(4)
α [°]	77.39(3)	76.83(3)	90.0
β [°]	86.85(3)	81.34(3)	104.86(3)
γ [°]	67.03(3)	64.74(3)	90.0
V [Å^3]	961.4(4)	880.8(4)	3802.2(13)
D [g cm^{-3}]	1.194	1.204	1.203
Z	2	2	4
Temperature [K]	293(2)	293(2)	293(2)
Refl. collected	3527	3714	3466
Refl. independent [$F_o \geq 4\,\sigma(F)$]	3374	3080	3346
R	0.0393	0.0556	0.0486
R_W	0.0829	0.1483	0.1245
μ [mm^{-1}]	0.076	0.077	0.076
Θ range measured [°]	2.45–24.97	2.46–27.90	2.05–24.97
No. of parameters refined	315	278	303

General Procedure (GP1) for the Preparation of Organocopper Derivatives of Types **6**, **7**. – (a) *From* **2**–**4**: BuLi (6.44 ml, 15 mmol of a 2.33 M solution in hexane) and one of the hydrocarbons **2**–**4** (15 mmol) were mixed in THF (40 ml) at −78°C. After stirring at 0°C for 1 h, the solution was cooled to −110°C and CuCN (672 mg, 7.5 mmol) was added in one portion. The mixture was allowed to warm to −40°C and stirred for 20 min. at this temp. until a clear solution had been formed. Subsequently, the reaction mixture was cooled to −78°C once more and cannulated to a dropping funnel precooled to −60°C.

(b) *From* **5**: Cyclopropyl bromide **5** (1.815 g, 1.20 ml, 15 mmol) in Et_2O (30 ml) was treated with *t*BuLi (17.65 ml, 30 mmol of 1.7 M solution in pentane) at −78°C and stirring was continued for an additional 1 h at the indicated temp. The mixture was then diluted with THF (40 ml) and reacted with CuCN (672 mg, 7.5 mmol) under the conditions described above.

General Procedure (GP2) for the Reaction of Organocuprates with Acetate **1**: The organocopper derivative prepared according to GP1 was added to a solution of **1** (1.625 g, 5 mmol) in THF (100 ml) at −10°C over a period of 1 h. The resulting mixture was stirred for 6 h at this temp., quenched at 0°C with saturated NH_4Cl solution, and adjusted to pH = 7–8 with 6 N NH_4OH solution. The aqueous phase was extracted with THF (100 ml). The combined organic phases were dried and concentrated under reduced pressure. The residue was washed with cold (0°C) Et_2O to give **8**, **9** in almost pure form, or purified by column chromatography (50 g of silica gel, column 20 × 3 cm, hexane/Et_2O, 85:15) to give **14**–**16**.

Ethyl 5-Aza-4,4-diphenyl-8-methylenespiro[2.5]oct-6-ene-6-carboxylate (**8a**): From **2** (1.20 g, 1.41 ml, 15 mmol), **8a** (1.090 g, 63%) was obtained according to GP1 and 2, m.p. 156–157.5°C (dec.). – IR (KBr): $\tilde{\nu}$ = 3355 cm^{-1}, 2981, 1705, 1620, 1483, 1446, 1370, 1326, 1257, 1133, 1030, 862, 760, 702. – ^{1}H NMR ($CDCl_3$): δ = 0.61–0.69 (m, 3 H, Cpr), 0.85–1.1 (br. m, 1 H Cpr), 1.30 (t, *J* = 7.2 Hz, 3 H, CH_3), 4.23 (q, *J* = 7.2 Hz, 2 H, OCH_2), 4.76 (s, 1 H, =CH), 4.77 (s, 1 H, =CH), 5.63 (br. s, 1 H, =CH), 6.23 (s, 1 H, NH), 7.22–7.35 (m, 6 H, aromatic H), 7.35–7.50 (m, 4 H, aromatic H). – ^{1}H NMR (C_6D_6): δ = 0.58 (br. s, 1 H, Cpr), 0.74 (br. s, 3 H, Cpr), 0.87 (t, *J* = 7.1 Hz, 3 H, CH_3), 3.91 (q, *J* = 7.1 Hz, 2 H, OCH_2), 4.68 (s, 1 H, =CH), 4.72 (s, 1 H, =CH), 5.91 (br. s, 1 H, =CH), 6.47 (br. s, 1 H, NH), 7.02–7.19 (m, 6 H, aromatic H), 7.35–7.65 (m, 4 H, aromatic H). – ^{1}H NMR ([D_6]DMSO): δ = 0.38 (m, 3 H, Cpr), 1.00 (m, 1 H Cpr), 1.18 (t, *J* = 7.1 Hz, 3 H, CH_3), 4.12 (q, *J* = 7.1 Hz, 2 H, OCH_2), 4.18 (s, 1 H, =CH), 4.21 (s, 1 H, =CH), 5.95 (s, 1 H, =CH), 6.14 (s, 1 H, NH), 7.00–7.50 (m, 10 H, aromatic H). – ^{13}C NMR ($CDCl_3$): δ = 14.14 (CH_3), 9–11 (br. s, 2 CH_2), 61.26, 105.64 (CH_2), 127.16, 127.52 (4 CH), 128.78 (2 CH), 110.10 (CH), 143.90 (2 C), 26.83, 66.20, 132.53, 145.93, 164.85 (C). – ^{13}C NMR (C_6D_6): δ = 13.96 (CH_3), 61.15, 105.40 (CH_2), 127.44, 127.61 (4 CH), 128.38 (2 CH), 110.10 (CH), 27.29 66.20, 133.19, 146.69, 165.08 (C), other signals were not detected. – ^{13}C NMR ([D_6]DMSO): δ = 14.24 (CH_3), 61.18, 105.83 (CH_2), 127.30, 127.42 (4 CH), 128.80 (2 CH), 109.44 (CH), 27.68, 66.02, 132.97, 145.53, 164.11 (C), other signals not found. – MS (EI); *m/z* (%): 372 (20), 346/345 (25/100) [M^+], 316 (15) [$M^+ - C_2H_5$], 268 (40) [$M^+ - C_6H_5$], 242 (10), 215 (5), 194 (65), 165 (20). – MS (HR-EI): 345.1728 ($C_{23}H_{23}NO_2$, calcd. 345.1728).

Ethyl 2,2-Diphenyl-4-methylene-1,2,3,4-tetrahydropyridine-6-carboxylate (**9**): From **3** (0.81 g, 0.95 ml, 15 mmol), **9** (1.106 g, 69%) was obtained according to GP1 and 2, m.p. 161–163°C (dec.). – IR (KBr): $\tilde{\nu}$ = 3363 cm^{-1}, 2978, 1701, 1617, 1482, 1445, 1370, 1309, 1248, 1139, 1044, 874, 764, 699. – ^{1}H NMR: δ = 1.34 (t, *J* = 7.1 Hz, 3 H, CH_3), 3.13 (d, *J* = 0.9 Hz, 2 H, CH_2), 4.27 (q, *J* = 7.1 Hz, 2 H, OCH_2), 4.84 (br. s, 1 H, =CH), 4.96 (br. s, 1 H, =CH), 5.37 (br. s, 1 H, =CH), 6.19 (s, 1 H, NH), 7.18–7.40

(m, 10 H, aromatic H). – ^{13}C NMR: δ = 14.15 (CH_3), 42.70, 61.31, 111.57 (CH_2), 126.94, 128.23 (4 CH), 127.04 (2 CH), 108.24 (CH), 145.31 (2 C), 62.16, 132.96, 138.92, 164.70 (C). – $C_{21}H_{21}NO_2$ (319.4): calcd. C 78.97, H 6.63; found C 79.02, H 6.75.

Ethyl 2-Cyclopropyl-N-(diphenylmethylene)glycinate (**16**): From **5** (1.815 g, 1.20 ml, 15 mmol), **16** (1.149 g, 75%) was obtained according to GP1 and 2 after column chromatography; R_f = 0.29. – ^{1}H NMR: δ = 0.16–0.31 (m, 2 H, Cpr), 0.44–0.54 (m, 2 H, Cpr), 1.27 (t, J = 7.2 Hz, 3 H, CH_3), 1.43–1.57 (m, 1 H, Cpr), 3.53 (d, J = 7.6 Hz, 1 H, CH), 4.19 (q, J = 7.2 Hz, 2 H, OCH_2), 7.14–7.83 (m, 10 H, aromatic H). – ^{13}C NMR: δ = 14.12 (CH_3), 2.25, 2.63, 60.64 (CH_2), 127.89, 127.99, 128.46, 128.73 (2 CH), 14.59, 68.69, 128.33, 130.17 (CH), 136.24, 139.41, 169.95, 172.01 (C). – MS (EI), *m/z* (%): 307 (0.3) [M^+], 235/234 (20/100) [M^+ – COOEt], 165 (15). – MS (HR-EI): 307.1572 ($C_{20}H_{21}NO_2$, calcd. 307.1572). – $C_{20}H_{21}NO_2$ (307.4): calcd. C 78.15, H 6.89; found C 78.70, H 7.05.

Ethyl N-(Diphenylmethylene)-2-(methylenespiropent-2-yl)glycinate (**14**) *and Ethyl 4-Cyclopropylidene-2,2-diphenyl-1,2,3,4-tetrahydropyridine-6-carboxylate* (**15**): From **4** (0.50 g, 6.24 mmol) and **1** (0.51 g, 1.57 mmol), **14** (202 mg, 37%) and **15** (182 mg, 34%) were obtained according to GP1 and 2 after column chromatography. **14**: R_f = 0.23, oil. – IR (film): $\tilde{\nu}$ = 3063 cm^{-1}, 2994, 1735, 1661, 1623, 1599, 1447, 1278, 1180, 1029, 907, 733, 701, 639. – ^{1}H NMR: δ = 0.80–0.95 (m, 2 H, Cpr), 1.0–1.12 (m, 2 H, Cpr), 7.15–7.35 (m, 10 H, aromatic H). Other signals: Major diastereomer: δ = 1.22 (t, J = 7.0 Hz, 3 H, CH_3), 2.44 (d, J = 8.9 Hz, 1 H, CH), 3.80 (d, J = 8.9 Hz, 1 H, CH), 4.09–4.22 (m, 2 H, OCH_2), 5.13 (d, J = 2.0 Hz, 1 H, =CH_2), 5.33 (s, 1 H, =CH_2). Minor diastereomer: δ = 1.25 (t, J = 7.0 Hz, 3 H, CH_3), 2.47 (d, J = 8.6 Hz, 1 H, CH), 3.83 (d, J = 8.6 Hz, 1 H, CH), 4.15–4.30 (m, 2 H, OCH_2), 5.10 (d, J = 2.1 Hz, 1 H, =CH_2), 5.39 (s, 1 H, =CH_2). – ^{13}C NMR: Major diastereomer: δ = 14.03 (CH_3), 8.38, 9.84, 60.80, 99.42 (CH_2), 23.55, 68.38, 129.94, 130.13 (CH), 14.98, 136.01, 137.41, 139.13, 170.14, 171.26 (C). Minor diastereomer: δ = 14.14 (CH_3), 7.68, 10.32, 60.91, 100.08 (CH_2), 24.04, 68.23, 130.19, 132.32 (CH), 15.49, 136.08, 137.83, 139.75, 170.33, 171.50 (C). The signals of two aromatic CH groups appear in the region δ = 127.81–128.81 and are indistinguishable. – MS (CI), *m/z* (%): 362 (18) [M^+ + NH_3], 346 (100) [M^+ + H]. **15**: R_f = 0.46, oil. – ^{1}H NMR: δ = 1.15 (br. s, 4 H, Cpr), 1.30 (t, J = 7.1 Hz, 3 H, CH_3), 3.25 (br. s, 2 H, CH_2), 4.25 (q, J = 7.1 Hz, 2 H, OCH_2), 5.32 (br. s, 1 H, =CH), 6.31 (s, 1 H, NH), 7.22–7.35 (m, 10 H, aromatic H). – ^{13}C NMR: δ = 14.18 (CH_3), 2.13, 2.86, 41.56, 61.13 (CH_2), 127.16, 127.52 (4 CH), 128.78 (2 CH), 108.44 (CH), 143.90 (2 C), 61.81, 121.30, 121.40, 145.90, 165.0 (C).

Ethyl 5-Aza-4,4-diphenyl-8-methylspiro[2.5]oct-5,7-diene-6-carboxylate (**8b**): A solution of pure **8a** (105 mg, 0.3 mmol) in dichloromethane (10 ml) was stirred at room temp. for 8 h and then concentrated. Rapid column chromatography of the residue (50 g of silica gel, column 15 × 3 cm, hexane/Et_2O, 7:3) gave 50 mg (48%) of recovered **8a** (R_f = 0.50) and 48 mg (46%) of **8b**: R_f = 0.28, m.p. 110–113°C. – ^{1}H NMR: δ = 0.58 (br. s, 2 H, Cpr), 0.94 (br. s, 2 H, Cpr), 1.36 (t, J = 7.1 Hz, 3 H, CH_3), 1.85 (d, J = 1.1 Hz, 3 H, CH_3), 4.35 (q, J = 7.1 Hz, 2 H, OCH_2), 6.40 (br. s, 1 H, =CH), 7.15–7.30 (m, 6 H, aromatic H), 7.30–7.45 (m, 4 H, aromatic H). – ^{13}C NMR: δ = 14.18, 19.10 (CH_3), 9.13 (2 CH_2), 61.68 (CH_2), 127.25, 129.28 (4 CH), 126.76 (2 CH), 117.33 (CH), 143.90 (2 C), 23.08, 70.14, 153.42, 156.10, 164.82 (C).

Diethyl Bis[1,6-dihydro-6,6-diphenyl-4-(1',1''-cyclopropyl)-2-pyridinecarboxylate] (**19**): An NMR sample containing **15** (112 mg, 0.32 mmol) in $CDCl_3$ (0.5 ml) was allowed to stand at room temp. for 24 h. It was then concentrated and the residue was purified by column chromatography (40 g of silica gel, column 15 × 3 cm, hexane/Et_2O, 85:15) to give C_1-**19** (62 mg, 55%) and C_2-**19** (40 mg, 36%).

C_2-**19**: R_f = 0.18; m.p. 171–172°C (dec.). – ^{1}H NMR: δ = 0.45–0.68 (m, 8 H, Cpr), 1.23 (t, J = 7.1 Hz, 6 H, CH_3), 4.22 (q, J = 7.1 Hz, 4 H, OCH_2), 4.97 (s, 2 H, =CH), 5.53 (s, 2 H, =CH), 6.07 (s, 2 H, NH), 7.0–7.40 (m, 20 H, aromatic H). – ^{13}C NMR: δ = 14.14 (2 CH_3), 9.84, 27.45, 61.12 (2 CH_2), 126.99, 127.88 (8 CH), 126.61 (4 CH), 104.71, 122.78 (2 CH), 147.84 (4 C), 29.67, 63.77, 130.65, 137.58, 164.29 (2 C).

C_1-**19**: R_f = 0.32, oil. – ^{1}H NMR: δ = 0.45–0.85 (m, 8 H, Cpr), 1.25 (t, J = 7.1 Hz, 6 H, CH_3), 4.25 (q, J = 7.1 Hz, 4 H, OCH_2), 5.01 (s, 2 H, =CH), 5.47 (s, 2 H, =CH), 5.65 (s, 2 H, NH), 7.0–7.35 (m, 20 H, aromatic H). – ^{13}C NMR: δ = 14.19 (2 CH_3), 5.63, 34.60, 61.27 (2 CH_2), 126.97, 128.24 (8 CH), 126.76 (4 CH), 101.21, 119.50 (2 CH), 147.98 (4 C), 26.87, 64.02, 130.04, 137.52, 164.01 (2 C). – MS (EI), *m/z* (%): 689/688 (4/8) [M^+], 613/612/611 (10/45/100) [M^+ – Ph]. – MS (HR-EI): 688.3301 ($C_{46}H_{44}N_2O_4$, calcd. 688.3301).

Compound **18** was never isolated, but was clearly observed in the NMR spectrum of **15** after the sample had been allowed to stand in $CDCl_3$ solution for 1 h at room temp. The sample contained up to 30% of **18**, together with 15% of C_2-**19**. – ^{1}H NMR: δ = 0.65–1.05 (m, 8 H, Cpr), 1.35 (t, J = 7.1 Hz, 6 H, CH_3), 2.79 (br. s, 4 H, CH_2), 4.35 (q, J = 7.1 Hz, 4 H, OCH_2), 6.41 (s, 2 H, = CH), 7.15–7.40 (m, 20 H, aromatic H). – ^{13}C NMR: δ = 14.08 (2 CH_3), 12.46 (4 CH_2), 34.75, 62.12 (2 CH_2), 114.16 (2 CH), 26.70, 65.81, 153.81, 156.55, 164.42 (2 C), aromatic signals could not reliably be assigned.

Interconversions of **8a, b**: Solutions of pure samples of **8a, b** were monitored by NMR. The results are shown in Table 3.

Table 3. Interconversion of compounds **8a,b** in solution

Starting Material	Amount (mg)	Solvent (0.5 ml)	Time after Preparation (h)	Ratio **8a**:**8b**
8a	20	$CDCl_3$	0	3.2:1
8a	20	$CDCl_3$	2	1.9:1
8a	20	$CDCl_3$	8	1.2:1
8b	40	$CDCl_3$	0	1:5.5
8b	40	$CDCl_3$	0.25	1:4.3
8b	40	$CDCl_3$	1.5	1:2.1
8a	20	C_6D_6	0	4.3:1
8a	20	C_6D_6	2	3.5:1
8a	20	[D_6]DMSO	0	6.4:1
8a	20	[D_6]DMSO	2	4.5:1

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[13] Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-100677. Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: int. code +44(1223)336-033, e-mail: deposit@chemcrys.cam.ac.uk].

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