Medium- and Large-ring Heterocyclic Systems by Intramolecular Nitrile Imine Cycloadditions

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A series of hydrazonyl chlorides bearing an alkenyl chain have been synthesised and treated with silver carbonate. The propensity of the so-formed nitrile imine intermediates to undergo intramolecular cycloaddition is markedly dependent on the length and the flexibility of the chain. The latter also affected the regio- and the stereo-chemistry of the intramolecular process. In certain circumstances, tandem intermolecular–intramolecular cycloadditions took place, to produce large-ring heterophanes.

Intramolecular 1,3-dipolar cycloadditions[1-3] are the object of both theoretical interest and synthetic applications in view of the following features: (i) owing to the linkage between the reacting groups, the cycloaddition process gives the simultaneous formation of two annulated (or bridged) rings; (ii) the entropic advantage due to intramolecularity can improve the reactivity of usually poor dipolarophiles such as unactivated alkenes, nitrile groups and aromatic-type unsaturations; (iii) the geometric constraints imposed by the connection between the addends can force a high degree of regio- and stereoselectivity. However, it must be emphasised that the length and the flexibility of the chain joining the reactive groups play a major role in determining the chemical behaviour of functionalised 1,3-dipoles. Significant evidence on this matter is available as concerns carbonyl ylides,[4-6] nitrile oxides,[7,8] sydnones,[9] nitrones[3] and azomethine ylides.[10] We now describe a systematic study dealing with a series of nitrile imines of general formula **3** (Scheme 1).

Results

The desired nitrile imines **3** were thought to be available, as transient species, by base treatment of the corresponding hydrazonyl chlorides **2**. The latter were in turn synthesised starting from isatoic anhydride [3,1-benzoxazine-2,4(1*H*)-dione] and a variety of (homo)allylic alcohols by way of the sequence illustrated in Scheme 1.

Contrary to what is usually observed with hydrazonyl chlorides,[11] compounds **2** were slow to react with triethylamine in boiling toluene; after prolonged heating, degradative processes took place. No improvement was achieved by using either stronger bases {1,4-diazabicyclo[2.2.2]octane (DABCO) and NaH} or a more polar solvent (acetonitrile); in fact, such conditions accelerated the disappearance of the starting hydrazonyl chlorides, but leading to intractable tarry mixtures. However, the treatment of **2** with silver carbonate in acetonitrile at room temperature produced the desired intramolecular cycloadducts **4** in yields ranging from 14 to 61%; one disappointing exception was with the substrate **2c** having a *trans* disubstitution at the ethylenic bond (Table 1).

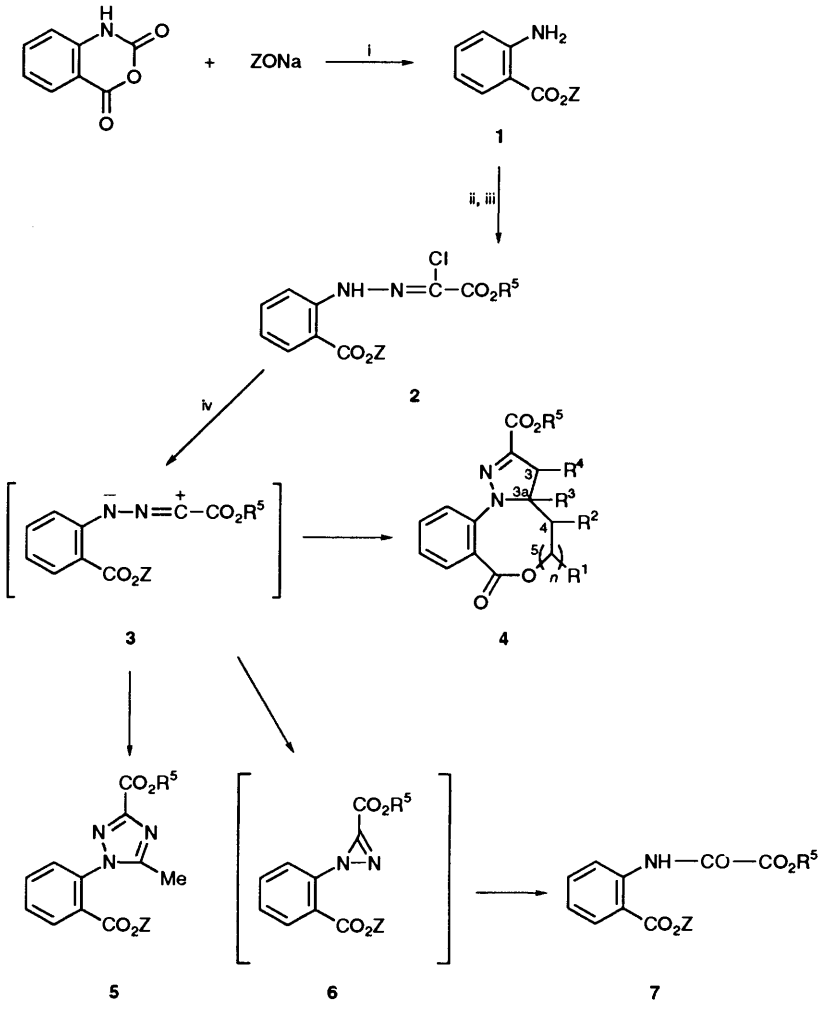
In cases where two stereocentres were present in the product, the stereochemical outcome of the cycloaddition deserved elucidation. The formation of the pyrazolo[1,5-*a*][4,1]benzoxazepines **4d, e** took place in a highly stereoselective manner, leading to a single isomer (within the experimental error limits), whose configuration was inferred to be (3a*R**,4*S**) from NOE measurements (Fig. 1).† However, only a modest diastereoselectivity was operative in the formation of the pyrazolo-[1,5-*a*][5,1]benzoxazocines **4i, j**, which were obtained as both *cis* and *trans* isomers. The two isomeric structures were unequivocally distinguished upon examination of the proton–proton coupling constants, since both literature data[13] and molecular models show that the *trans* constants are much larger than the *cis* ones in eight-membered heterocycles (Fig. 2). On the other hand, the retention of stereochemistry typical of the (4π + 2π)-cycloadditions to alkenes warrants the configuration (3*R**,3a*R**) of the cycloadduct **4h**.

It is to be added that, under the experimental conditions described above, the nitrile imines **3** underwent two side reactions: (i) 1,3-dipolar cycloaddition onto the solvent (acetonitrile), to give the triazole derivatives **5**; (ii) degradative process resulting in the oxalamides **7**.‡ The latter reaction does not have precedent although several rearrangement and fragmentation pathways have been reported for nitrile imines.[11,14] The intermediacy of **6** can be suggested by analogy with the accepted mechanism for the conversion of nitrile oxides to isocyanates.[11]

A further stage of our work was undertaken with the hope of improving the yield of the intramolecular cycloadducts **4**, particularly in cases where $n = 0$. Although this goal was not attained, an interesting pattern of behaviour was brought to light when treating **2a–d** with silver carbonate in dioxane. Under these conditions, we isolated a new kind of product, *i.e.* macrocyclic heterophanes from intermolecular followed by intramolecular cycloaddition (Table 2 and Scheme 2). As concerns the relative configuration of the stereogenic centres of these products, the following considerations can be made.

In the case of **2a**, **2b** and **2e**, we isolated only one macrocyclic product, the ^{1}H NMR signals of which did not show splitting in the presence of the chiral shift reagent [Eu(hfc)$_3$][tris{heptafluoropropylhydroxymethylene-(+)-camphorato}europium(III)]. This evidence speaks in favour of the achiral structures **14a**, **14b** and **15**, respectively. However, compound **2c** furnished two isomeric products from the six conceivable ones (four racemic and two achiral). The simplicity of the ^{1}H NMR spectra, which exhibit only two signals for the hydrogens on the four stereogenic centres, indicates the same configuration at both C-1–C-2 and C-3–C-4. The observed proton–proton coupling constants (2.3 and 2.5 Hz) parallel those reported for the *cis* relationship.[13] Furthermore, the chiral shift reagent

† Vicinal coupling constants (7 Hz) were not diagnostic in these cases, as well precedented for seven-membered heterocyclic rings.[12]
‡ For the sake of recognition, an authentic sample of **7d** was independently prepared by treating **1d** with ethyl chloroglyoxylate.



Entry	n	R^1	R^2	R^3	R^4	R^5
a	0	—	H	H	H	Et
b	0	—	H	Me	H	Me
c	0	—	H	H	Me(*E*)	Et
d	0	—	Me	H	H	Et
e	0	—	Ph	H	H	Me
f	1	H	H	H	H	Me
g	1	H	H	Me	H	Me
h	1	H	H	H	Me(*Z*)	Me
i	1	H	Me	H	H	Me
j	1	Me	H	H	H	Me

Scheme 1 *Reagents and conditions:* i, pyridine, heat; ii, HCl–$NaNO_2$; iii, $MeCOCHClCO_2R^5$; iv, Ag_2CO_3–MeCN, room temp.

Table 1 Treatment of hydrazonyl chlorides **2a–j** with silver carbonate in acetonitrile

Entry	*t*/h	Cycloadduct(s)	Yield (%)[a]	Eluent[b]	Other products (% yield)
a	72	**4a**	18	Et_2O–LP (3:1)	**5a** (11)
b	15	**4b**	14	Et_2O	**5b** (10)
c	24	—	—	Et_2O	**7c** (16)
d	24	(3a*R**,4*S**)-**4d**	28	Et_2O–LP (3:1)	**7d** (12)
e	28	(3a*R**,4*S**)-**4e**	23	Et_2O–LP (3:1)	**5e** (15)
f	28	**4f**	33	$CHCl_3$–AcOEt (9:1)	—
g	16	**4g**	36	$CHCl_3$–AcOEt (4:1)	—
h	170	(3*R**,3a*R**)-**4h**	21	$CHCl_3$–AcOEt (4:1)	—
i	63	(3a*R**,4*R**)-**4i**	23	Et_2O	—
		(3a*R**,4*S**)-**4i**	11		
j	20	(3a*R**,5*S**)-**4j**	42	$CHCl_3$–AcOEt (9:1)	—
		(3a*R**,5*R**)-**4j**	19		

[a] Isolated yield by column chromatography. [b] LP = light petroleum b.p. 40–60 °C.

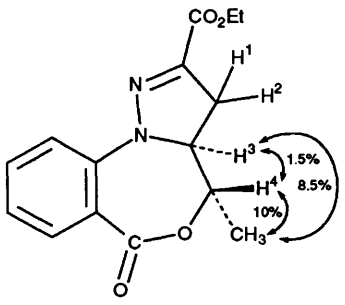
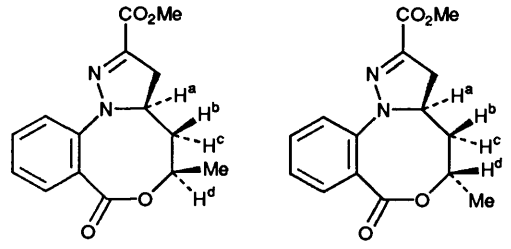


Fig. 1 NOE Measurements for compound **4d**



J_{ab} 10.8 Hz
J_{ac} 2.5 Hz
J_{bd} 10.0 Hz
J_{cd} 2.0 Hz

J_{ab} 11.6 Hz
J_{ac} 3.2 Hz
J_{bd} 3.2 Hz
J_{cd} 11.2 Hz

Fig. 2 Proton–proton coupling constants for the stereoisomeric compounds (3a*R**,5*S**)-**4j** (left) and (3a*R**,5*R**)-**4j** (right)

Table 2 Reaction of hydrazonyl chlorides **2a–d** with silver carbonate in dioxane

Entry	*t*/days	Intramolecular cycloadduct	Yield[a] (%)	Macrocyclic product	Yield[a] (%)
a	12	**4a**	12	**14a**	14
b	14	**4b**	13	**14b**	6
c	17	—	—	**15**	12
d	14	**4d**	11	**16**	4
				17	4

[a] After column chromatography.

[Eu(hfc)$_3$] gave splitting of the NMR signals of the chiral isomer **16**, while such an effect was not observed in the case of the *meso* form **17**.

Discussion

The above results are in line with the view that the effectiveness of the intramolecular cycloadditions is markedly dependent on steric constraints due to the molecular geometry rather than on the electronic properties of the dipolar and dipolarophilic sites. In fact, the nitrile imines studied here are less prone to intramolecular cycloaddition than related substrates leading to pyrazolo[1,5-*a*][1,4]benzoxazines.[15,16] Moreover, the increasing facility of the intramolecular cycloaddition on going from **3a–e** to **3f–j** reflects the larger degree of rotational freedom of the latter substrates with respect to the former ones. The same structural feature can also account for the lack of stereocontrol in the formation of **4i, j** at variance with the stereoselective formation of **4d, e**. Diastereoselection in intramolecular 1,3-dipolar cycloadditions represents a challenging goal which enhances the synthetic value of these reactions. Up to date, systematic studies are available as concerns intramolecular cycloadditions of chiral nitrones and nitrile oxides.[17]

The effect of the basic species used to generate the desired nitrile imines **3** may be rationalised as follows. The apparent inertness of **2** in the presence of triethylamine is not surprising because this base is known to convert hydrazonyl halides into nitrile imines in a reversible fashion.[11] On the other hand, owing to the reluctance of **3** to undergo intramolecular cycloaddition, its irreversible generation (*e.g.* by sodium hydride) can force intermolecular processes leading exclusively to resinous material. The observed effectiveness of silver carbonate in a heterogeneous medium is perhaps the consequence of a very slow generation of the nitrile imines, which mimics high-dilution conditions favouring intramolecular over intermolecular pathways.

As far as the formation of the large-ring products **14–17** is concerned, the step sequence illustrated in Scheme 2 is supported by the actual isolation of **8a** and its conversion into **14a** in the presence of silver carbonate. The intramolecular cycloaddition of the nitrile imines **11–13** has great preparative interest in view of the structural complexity of the resulting macrocyclic heterophanes. Furthermore, this reaction proceeds with a good extent of stereoselection. Although no stereomodel of the transition state can be defined at the present, one may note that the observed products are those stereoisomers having the higher degree of symmetry.

Tandem intermolecular–intramolecular cycloadditions of nitronates[18] and nitrile oxides[7,8] have been previously reported as a route to large-ring heterophanes.

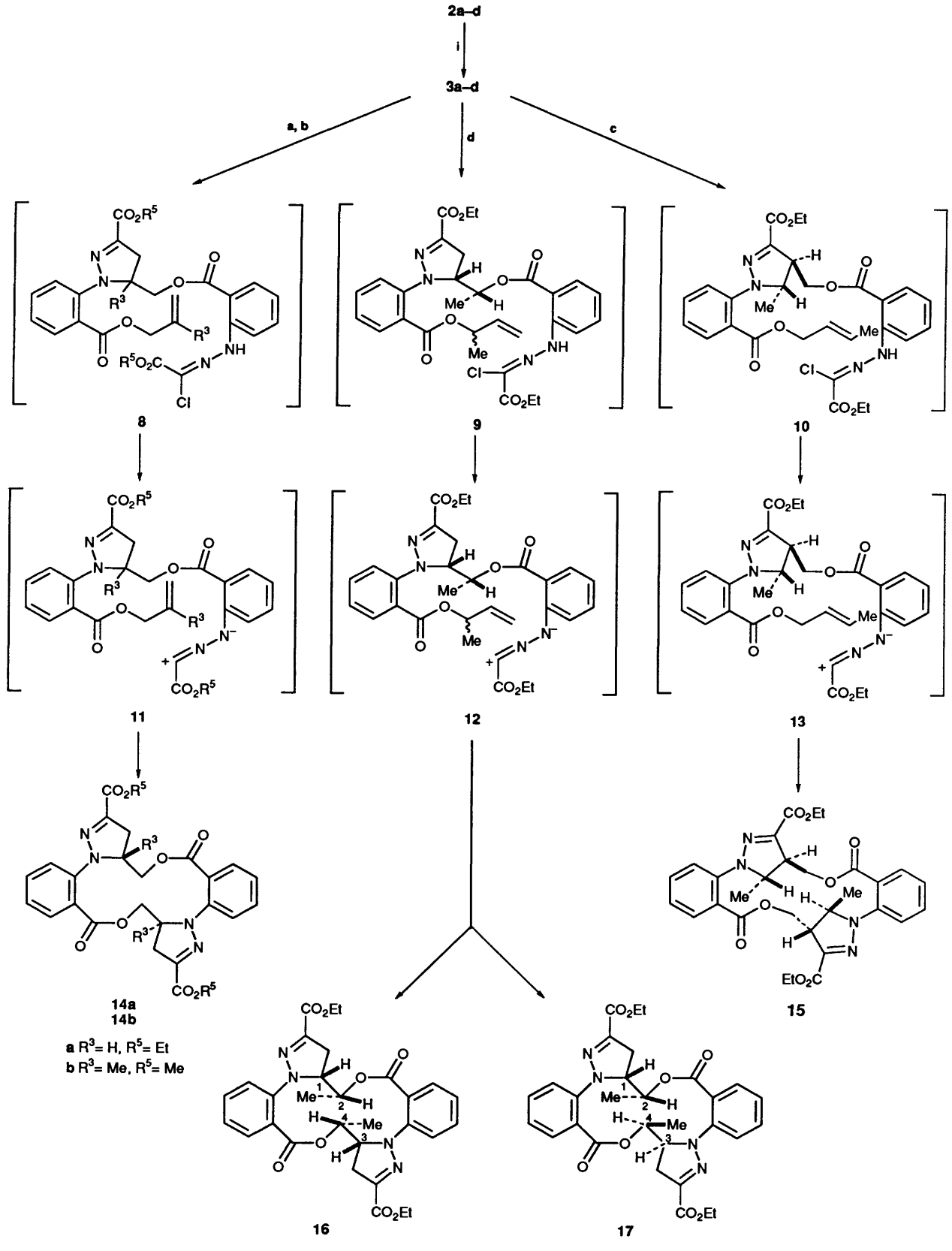
Experimental

M.p.s were determined with a Büchi apparatus and are uncorrected. IR Spectra were recorded with a Perkin-Elmer 298 spectrophotometer. Mass spectra were determined with a VG-70EQ apparatus. NMR Spectra were taken with a Bruker 300 instrument in $CDCl_3$ solutions; chemical shifts are given as ppm from tetramethylsilane. All new compounds gave satisfactory elemental analyses, which are available as Supplementary Material.*

General Procedure for the Preparation of Alkenyl Anthranilates **1**.—A solution of the appropriate alcohol (0.15 mol) in anhydrous benzene (100 cm^3) was treated with sodium hydride (0.16 mol) and then refluxed for 1 h. Isatoic anhydride (0.15 mol) in pyridine (150 cm^3) was added to the reaction mixture and the solution was refluxed for 5 h. The mixture was poured into ice–water (800 cm^3) and extracted with diethyl ether. The organic layer was dried over sodium sulfate and evaporated to dryness. The oily residue was dissolved in anhydrous diethyl ether (100 cm^3) and a solution of hydrogen chloride in diethyl ether (5 mol dm^{-3}; 60 cm^3) was added dropwise under stirring. The solid material was collected by filtration and washed with anhydrous diethyl ether to give the hydrochloride of **1** in 41–56% yield. Physical and spectral data of the products are available as Supplementary Material (*vide infra*).*

General Procedure for the Preparation of Hydrazonyl Chlorides **2**.—A solution of the hydrochloride of **1** (10 mmol) in water (60 cm^3) and methanol (10 cm^3) was treated with hydrochloric acid (10 mol dm^{-3}; 3 cm^3) and then cooled to 0 °C. Sodium nitrite (15 mmol) in water (15 cm^3) was added dropwise to the reaction mixture whilst it was cooled and stirred. After 30 min, the cold mixture was adjusted to pH 5 with sodium acetate and then alkyl 2-chloroacetoacetate (10 mmol) in methanol (15 cm^3) was added whilst it was cooled and vigorously stirred. The mixture was stirred at room temperature

* For details of the supplementary publications scheme, see 'Instructions for Authors,' *J. Chem. Soc., Perkin Trans. 1*, 1994, Issue 1.



Scheme 2 *Reagents and conditions:* i, Ag_2CO_3–dioxane, room temp.

for 6 h and then extracted with diethyl ether. The organic solution was washed with aqueous sodium hydrogen carbonate, dried over sodium sulfate and evaporated. Addition of a small amount of diisopropyl ether and subsequent filtration gave the hydrazonyl chloride **2** in 75–88% yield. Analytically pure samples were obtained by recrystallisation from diisopropyl ether. Physical and spectral data of the products are available as Supplementary Material (*vide infra*).

Table 3 Physical and spectra data of compounds **4**

Compd.	M.p.[a] (°C)	ν_{max} (Nujol)/ cm^{-1}	$\delta_H(CDCl_3)$[b]	m/z (M^+)
4a	174	1720 1700	1.40 (3 H, t, *J* 7), 3.00 (1 H, dd, *J* 18, 10), 3.55 (1 H, dd, *J* 18, 12), 4.3–4.8 (5 H, overlapping), 7.0–8.1 (4 H, m)	274
4b	144	1715 1680	1.38 (3 H, s), 3.12, 3.22 (2 H, AB type, *J* 18), 3.92 (3 H, s), 4.18 (1 H, d, *J* 12), 4.38 (1 H, d, *J* 12), 7.1–8.0 (4 H, m)	274
4d	169	1690	1.40 (3 H, t, *J* 7), 1.55 (3 H, d, *J* 7), 3.05 (1 H, dd, *J* 18, 13), 3.36 (1 H, dd, *J* 18, 12), 4.40 (2 H, q, *J* 7), 4.52 (1 H, ddd, *J* 13, 12, 7), 4.74 (1 H, dq, *J* 7, 7), 6.9–8.1 (4 H, m)	288
4e	231	1745 1720	2.60 (1 H, dd, *J* 18, 13), 2.90 (1 H, dd, *J* 18, 12), 3.80 (3 H, s), 4.85 (1 H, ddd, *J* 13, 12, 7), 5.42 (1 H, d, *J* 7), 6.9–8.1 (9 H, m)	336
4f	289–291	1710	1.9–2.2 (2 H, m),[c] 2.88 (1 H, dd, *J* 18, 4), 3.39 (1 H, dd, *J* 18, 11), 3.86 (3 H, s), 4.2–4.3 (2 H, m), 4.56 (1 H, dddd, *J* 11, 10, 4, 4), 6.9–7.8 (4 H, m)	274
4g	204–206	1720 1705	1.05 (3 H, s), 2.1–2.6 (2 H, m), 2.98 (1 H, d, *J* 18), 3.20 (1 H, d, *J* 18), 3.85 (3 H, s), 4.3–4.4 (2 H, m), 7.2–7.6 (4 H, m)	288
4h	102	1720 1710	1.38 (3 H, d, *J* 7), 1.9–2.2 (2 H, m),[d] 3.72 (1 H, dq, *J* 11, 7), 3.87 (3 H, s), 4.2–4.4 (2 H, m), 4.50 (1 H, ddd, *J* 11, 11, 3), 6.9–7.8 (4 H, m)	288
4i[e]	189–191	1710	1.19 (3 H, d, *J* 7), 1.9–2.1 (1 H, m), 3.03 (1 H, dd, *J* 18, 4), 3.38 (1 H, dd, *J* 18, 11), 3.89 (3 H, s), 4.06 (1 H, d, *J* 12), 4.19 (1 H, ddd, *J* 11, 11, 4), 4.46 (1 H, dd, *J* 12, 3), 6.9–7.9 (4 H, m)	288
4i[f]	184–186	1740 1725	0.80 (3 H, d, *J* 7), 2.2–2.3 (1 H, m), 3.00 (1 H, dd, *J* 18, 4), 3.38 (1 H, dd, *J* 18, 12), 3.85 (3 H, s), 3.9–4.2 (2 H, m), 4.80 (1 H, ddd, *J* 12, 4, 3), 6.9–7.9 (4 H, m)	288
4j[g]	184–186	1725 1710	1.35 (3 H, d, *J* 6), 1.85 (1 H, ddd, *J* 14, 11, 3), 2.00 (1 H, ddd, *J* 14, 11, 3), 2.84 (1 H dd, *J* 18, 4), 3.39 (1 H, dd, *J* 18, 11), 3.90 (3 H, s), 4.5–4.7 (2 H, overlapping), 6.8–7.8 (4 H, m)	288
4j[h]	140–142	1740 1720	1.40 (3 H, d, *J* 6), 1.98 (1 H, ddd, *J* 14, 2.5, 2), 2.23 (1 H, ddd, *J* 14, 11, 10), 2.71 (1 H, dd, *J* 18, 9), 3.45 (1 H, dd, *J* 18, 11), 3.88 (3 H, s), 3.90 (1 H, m), 4.78 (1 H, ddq, *J* 10, 6, 2), 7.1–7.6 (4 H, m)	288

[a] From benzene–diisopropyl ether. [b] *J* Values in Hz. [c] After irradiation of the signals at δ 4.2–4.3: 1.92 (1 H, dd, *J* 14, 10), 2.14 (1 H, dd, *J* 14, 4). [d] After irradiation of the signal at δ 4.2–4.4: 1.94 (1 H, dd, *J* 14, 11), 2.08 (1 H dd, *J* 14, 3). [e] (3a*R**,4*R**)-Isomer. [f] (3a*R**,4*S**)-Isomer. [g] (3a*R**,5*R**)-Isomer. [h] (3a*R**,5*S**)-Isomer.

Table 4 Physical and spectral data of macrocyclic compounds **14–17**

Compd.	M.p.[a] (°C)	ν_{max} (Nujol)/ cm^{-1}	$\delta_H(CDCl_3)$[b]	m/z (M^+)
14a	240	1720	1.25 (6 H, t, *J* 7), 2.90 (2 H, dd, *J* 18, 5), 3.25 (2 H, dd, *J* 18, 12), 4.0–4.1 (6 H, overlapping), 4.6–4.8 (2 H, m), 4.9–5.0 (2 H, m), 6.9–7.6 (8 H, m)	548
14b	265	1720	1.14 (6 H, s), 2.85, 3.25 (4 H, AB type, *J* 17), 3.85 (6 H, s), 4.14, 4.40 (4 H, AB type, *J* 12), 7.0–7.8 (8 H, m)	548
15	270	1730 1710	1.15 (6 H, d, *J* 6.5), 1.32 (6 H, t, *J* 7), 3.38 (2 H, ddd, *J* 5.4, 5.0, 3.2), 4.30 (4 H, q, *J* 7), 4.52 (2 H, dd, *J* 11, 3.2), 4.61 (2 H, dq, *J* 6.5, 5.0), 4.76 (2 H, dd, *J* 11, 5.4), 7.0–7.5 (8 H, m)	576
16	314	1710	1.15 (6 H, d, *J* 6.5), 1.38 (6 H, t, *J* 7), 2.93 (2 H, dd, *J* 18, 5), 3.55 (2 H, dd, *J* 18, 12), 4.35 (4 H, q, *J* 7), 4.93 (2 H, dq, *J* 6.5, 2.5), 5.40 (2 H, ddd, *J* 12, 5, 2.5), 6.8–7.8 (8 H, m)	576
17	285	1720 1700	1.10 (6 H, d, *J* 6.5), 1.25 (6 H, t, *J* 7), 2.85 (2 H, dd, *J* 18, 6), 3.30 (2 H, dd, *J* 18, 12), 4.03 (2 H, q, *J* 7), 4.10 (2 H, q, *J* 7), 4.93 (2 H, ddd, *J* 12, 6, 2.3), 5.18 (2 H, dq, *J* 6.5, 2.3), 7.0–7.7 (8 H, m)	576

[a] From toluene. [b] *J* Values in Hz.

General Procedure for the Treatment of Hydrazonyl Chlorides **2** *with Silver Carbonate in Acetonitrile.*—A solution of hydrazonyl chloride **2** (5 mmol) in dry acetonitrile (100 cm^3) was treated with silver carbonate (10 mmol) and the mixture was stirred at room temperature in the dark for the time indicated in Table 1. The undissolved material was filtered off, the solvent was evaporated, and then the residue was chromatographed on a silica gel column. Eluents, products, and yields are given in Table 1. Physical and spectral data of the intramolecular cycloadducts **4** are collected in Table 3. Physical and spectral data of the side products **5** and **7** are available as Supplementary Material (*vide infra*).

General Procedure for the Reaction of Hydrazonyl Chlorides **2** *with Silver Carbonate in Dioxane.*—A solution of hydrazonyl chloride **2** (5 mmol) in dry dioxane (100 cm^3) was treated with silver carbonate (10 mmol). The mixture was stirred at room temperature in the dark for the time indicated in Table 2 and four portions of silver carbonate were added to it over this period (each 10 mmol). After filtration, the solvent was evaporated and the residue was chromatographed on a silica gel column using diethyl ether–light petroleum (4:1) as eluent. See Tables 2 and 4.

Independent Synthesis of Oxalamide **7a**.—To a solution of amine **1d** (6.2 mmol) and triethylamine (12.4 mmol) in benzene

(50 cm^3), oxalyl chloride (6.2 mmol) was added. After being stirred at room temperature for 1 h, triethylammonium chloride was removed by filtration and the solvent was evaporated under reduced pressure. The residue was recrystallised from diisopropyl ether affording oxalamide **7a** in 85% yield.

Supplementary Material.—[Sup. No. 56984 (5 pp.).] Elemental analyses of new compounds (Table 5), physical and spectral data of products **1** (Table 6), **2** (Table 7), **5** and **7** (Table 8).

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