7. Asymmetric *Diels-Alder* Cycloadditions with Chiral Carbamoyl Dienophiles

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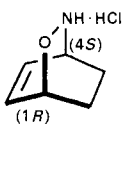
(30.X.91)

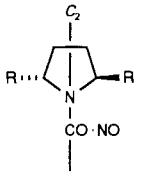
Chiral acylnitroso dienophiles **14**, which were obtained from L-proline and from D-mandelic acid, reacted with cyclohexa-1,3-diene to give the expected diastereoisomers **15** and **16** (*Scheme 2* and *Table 1*). The *d.e.* values for these *Diels-Alder* reactions were moderate; they are related to the molecular stiffness of the dienophiles. The absolute configuration of the major cycloadducts was interpreted in terms of HOMO/LUMO interactions, the approach being *'endo'* and the acylnitroso dienophiles reacting from their s-*cis*-conformation.

Introduction. Hetero-*Diels-Alder* cycloadditions with nitroso dienophiles have been the subject of increasing interest during the last two decades [1], especially also because of the stereospecific *cis* attachement of the potential alcohol and amino functionalities at the termini of the conjugated diene [2] [3]. This methodology was used by us for the total synthesis of aminosugar derivatives [4] and by *Kresze* and coworkers for the synthesis of aminoconduritols and of aminoinositols [5] [6].

In a few cases, *Diels-Alder* cycloadditions with chiral nitroso dienophiles led to excellent asymmetric induction, *e.g.* with α-chloronitroso derivatives of epiandrosterone [7] and of D-mannose [8]. Initially, the results obtained on addition of the latter to cyclohexa-1,3-diene were not interpreted correctly in terms of absolute configuration [8]; in the mean time, the absolute configuration of the addition product was corrected as indicated in *Formula* **1** (dextrorotatory product) [9] [6].



(+)-**1**



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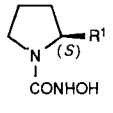
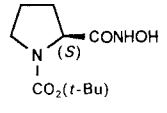


3a $R^1 = CH_2OH$
b $R^1 = CH_2OMe$
c $R^1 = CH_2NHPh$
d $R^1 = CO_2Me$



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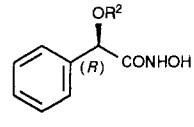


5a $R^2 = H$
b $R^2 = Me$

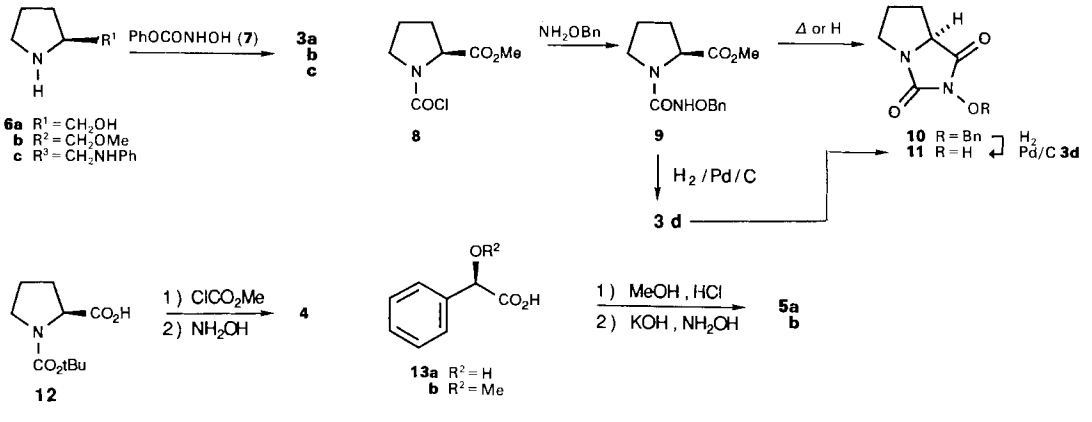
Acylnitroso dienophiles RCO–N=O are extremely reactive and had to be prepared *in situ* by oxidation of the corresponding hydroxamic acids in the presence of the conjugated diene partners [10]. Excellent asymmetric inductions (*d.e. ca.* 98%) were achieved in cycloadditions with *N*-nitrosocarbonyl derivatives of C_2 symmetrical pyrrolidines **2** [11]

[12], with some drawbacks, though: *i*) the preparation of these pyrrolidines **2** required lengthy procedures; *ii*) the chiral inductors could not be removed easily from their *Diels-Alder* cycloadducts.

We describe herein some results we obtained with acylnitroso derivatives of L-proline ((*S*)-configuration) and of D-mandelic acid ((*R*)-configuration) when reacted with cyclohexa-1,3-diene[1]). These acylnitroso derivatives were generated *in situ* from the corresponding hydroxamic acids **3** and **4** and **5**, respectively. During our investigations, two studies were published as preliminary communications which pertain also to asymmetric *Diels-Alder* cycloadditions with chiral acylnitroso dienophiles (mandelic-acid derivatives) [14] [15].

Chiral Hydroxamic Acids. – The preparation of the L-proline-derived *N*-carbohydroxamic acis **3a–d** by the classical approach, *i.e.* from the corresponding carbamoyl chloride and NH_2OH [4b] [16], was unsatisfactory. Therefore, L-prolinol (**6a**), its methyl ether **6b**, and the aniline derivative **6c** were reacted with phenyl *N*-hydroxycarbamate (**7**) in pyridine, to give the corresponding hydroxamic acids **3a–c**, respectively (*Scheme 1*). Compound **7** was obtained from NH_2OH and phenyl carbonate or, even better, phenyl chloroformate [17].

Scheme 1



Hydroxamic acid **3d** of methyl prolinate was synthesized in excellent yield from carbamoyl chloride **8** and *O*-benzylhydroxylamine *via* **9** which was hydrogenolysed. Compounds **9** and **3d** cyclized easily under mild conditions to the corresponding hydantoines **10** and **11** (reaction time and temperature had to be controlled carefully). Hydantoine **11** was the major product when carbamoyl chloride **8** was reacted with NH_2OH; it was also formed on hydrogenolysis of the benzyloxy derivative **10**.

C-Carbohydroxamic acid **4** was obtained by reaction of the mixed anhydride of *N*-[(*tert*-butoxy)carbonyl]-L-proline (**12**) with NH_2OH.

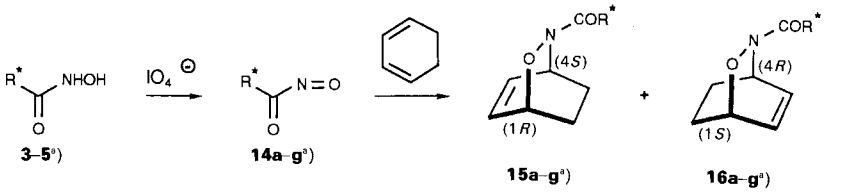
Hydroxamic acid **5a** was prepared in a straightforward manner from NH_2OH and the methyl ester of D-mandelic acid (**13a**) according to [18]. The preparation of methyl ether **5b** from **13b** had already been described [4b]. It should be noticed that the physical

[1]) For a preliminary communication, see [13].

properties of acid **5a** having the (*R*)-configuration are quite different from those described by *Kirby* and *Nazeer* for the (*S*)-enantiomer [14] (see *Exper. Part*).

Asymmetric *Diels-Alder* Cycloadditions. – Oxidation of the chiral hydroxamic acids **3**–**5** in $CHCl_3$ or MeOH with $(Pr_4N)IO_4$ in the presence of equimolar amounts of cyclohexa-1,3-diene led instantaneously to the corresponding acylnitroso dienophiles **14** which underwent *Diels-Alder* cycloaddition to the two expected diastereoisomeric adducts **15** and **16** (*Scheme 2*). The mixtures **15a**/**16a**, **15b**/**16b**, **15c**/**16c**, and **15e**/**16e** were separated.

Scheme 2



3–**5**[a]) **14a**–**g**[a]) **15a**–**g**[a]) **16a**–**g**[a])

a) For R*, see *Table 1*.

All diastereoisomers **15** have the (1*R*,4*S*)-configuration in their tricyclic moiety. The following methods were used to determine the relative amounts of the diastereoisomers **15** and **16**: *i*) ^{1}H-NMR spectroscopy in benzene (this solvent permits excellent differentiation of the olefinic H-atoms), *ii*) ^{13}C-NMR spectroscopy, *iii*) HPLC, and *iv*) prep. TLC when the R_f values were sufficiently different (see *Table 1*). We found that the ^{13}C-NMR spectra yielded the most reliable results since two sets of a large number of peaks (pair of diastereoisomers) could be compared for which the chemical environment is very similar. Comparison of the HPLC integration aeras (see *Table 1*) of the diastereoisomers **15** and **16** must be handled with great care; precise calibration for each isomer is mandatory which requires preliminary isolation and purification. Indeed, the *response factors* of **15a** and **16a**, *e.g.*, were quite different, one being twice as large as the other one.

Asymmetric induction proved to be moderate to poor with the above described chiral acylnitroso dienophiles. The best *d.e.* values were observed with the dienophiles **14a**–**d** obtained from the L-proline derivatives **3a**–**d** (*d.e.* 68% with **14b**; *Table 1*): their molecular stiffness, due to a certain degree of inhibition of free rotation at the N–CO–N=O functionality, led to higher *d.e.* values. Intramolecular H-bonding in **14f** (D-mandelic-acid series) responsible for structural rigidness, also led to a higher *d.e.* value. When the CON=O moiety can freely rotate with respect to the remainder of the molecule, *e.g.* in the case of *C*-(nitrosocarbonyl) compounds **14e**, **g**, the *d.e.* values were poor.

Similar results were recently observed with the nitroso derivatives **14f** and **14g** in the mandelic-acid series [14]. *Procter* and coworkers described some higher *d.e.* values with the nitroso derivative **14f** of **5a** (*d.e.* 68%) when the reaction was performed at lower temperature [15]. Lowering the reaction temperature did indeed increase the *d.e.* values: At r.t., **14b** produced a *d.e.* value of 68%, whereas at −70°, *d.e.* increased to 76% (*Table 1*).

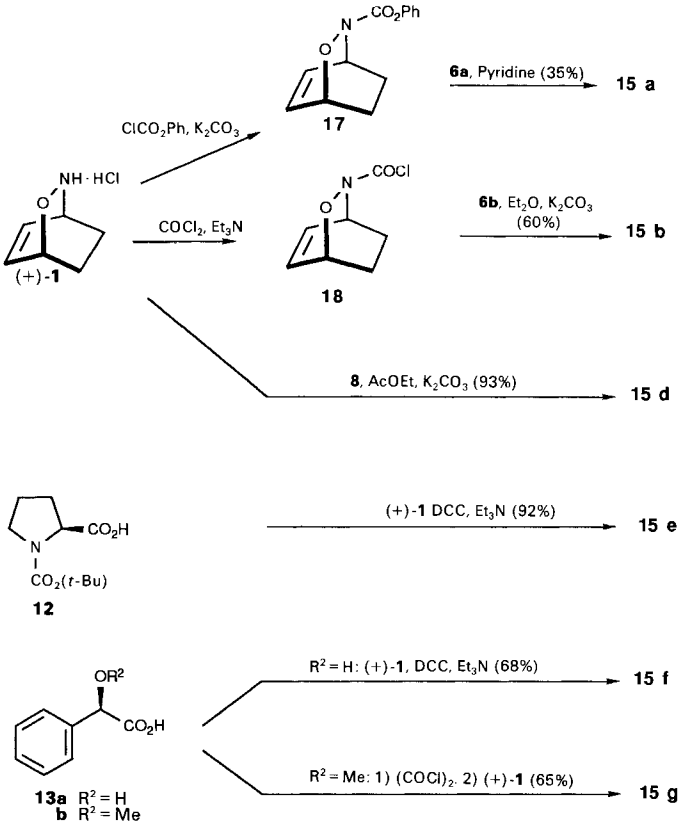
Absolute Configuration of the Cycloadducts. – The absolute configuration of the cycloadducts was determined by a series of independent syntheses. Reaction of the

Table 1. Diels-Alder *Cycloadditions of Acylnitroso Dienophiles* **14a–g** (obtained from the corresponding hydroxamic acids) *and Cyclohexa-1,3-diene*

Hydroxamic acid	Conditions	Adducts	R*	Overall yield [%]	Ratio **15**/**16**				*d.e.*
					^{1}H-NMR	^{13}C-NMR	HPLC	Isolation	
3a (→**14a**)	$CHCl_3$/MeOH, r.t.	**15a**/**16a**	2-($OHCH_2$)C_4H_7N	89	74:26	76:24	76:24[a])	76:24	52
b (→**14b**)	$CHCl_3$, r.t.	**15b**/**16b**	2-($MeOCH_2$)C_4H_7N	83	85:15	84:16	73:27[b])	85:15	68
b (→**14b**)	$CHCl_3$, −70°	**15b**/**16b**	2-($MeOCH_2$)C_4H_7N	–	88:12	–	–	89:11	76
c (→**14c**)	$CHCl_3$/MeOH. r.t.	**15c**/**16c**	2-($PhNHCH_2$)C_4H_7N	79	80:20	82:18	–	80:20	64
d (→**14d**)	$CHCl_3$, r.t.	**15d**/**16d**	2-(MeOOC)C_4H_7N	86	80:20	77:23	–	–	54
4 (→**14e**)	$CHCl_3$, r.t.	**15e**/**16e**	1-(*t*-BuOOC)C_4N_7N	81	60:40	60:40	63:37[c])	–	20
5a (→**14f**)	$CHCl_3$, r.t.	**15f**/**16f**	PhCH(OH)	67	31:69	29:71	–	–	42
a (→**14f**)	$CHCl_3$, 0°	**15f**/**16f**	PhCH(OH)	–	24:76	–	–	–	52
b (→**14g**)	$CHCl_3$, r.t.	**15g**/**16g**	PhCH(OMe)	67	41:59	42:58	–	–	16

[a]) With calibration; column *Spherisorb*; MeOH/H_2O 1:1.
[b]) Without calibration; column *Lichrospher*; MeOH/H_2O 6:4.
[c]) Without calibration; column *Spherisorb*; MeOH/MeCN/H_2O 40:6:54.

Scheme 3



known chiral alkoxyamine (+)-**1** [8] with the appropriate optically active asymmetric inductors, *i.e.* L-proline or D-mandelic-acid derivatives, led to the compounds **15** having the (1*R*,4*S*)-configuration in the bicyclic moiety (*Scheme 3*). Thus, (+)-**1** reacted with phenyl chloroformate in the presence of K_2CO_3 (→ **17**) and then with prolinol (**6a**) in pyridine to a compound which was identical with adduct **15a**. Compound **15b** was obtained by reaction of (+)-**1** with phosgene in the presence of Et_3N (→ **18** [19]), followed by reaction with **6b** in the presence of K_2CO_3. Acylation of (+)-**1** with carbamoyl chloride **8** gave **15d**; stereoisomer **16d** was formed as a minor product (*ca.* 8%) in this experiment, probably as a result of partial epimerization of **8**. Compound **15e** was obtained by direct coupling of (+)-**1** with *N*-[(*tert*-butoxy)carbonyl]-L-proline (**12**) the dehydrating agent being dicyclohexylcarbodiimide (DCC). Identification of all these chiral coupling products with the major cycloadducts **15** was performed by ^1H- and ^{13}C-NMR spectroscopy and in some cases by comparison of their optical rotations and their melting points (see *Table 2*).

Product **15f** was obtained by direct coupling of (+)-**1** with mandelic acid **13a** in the presence of DCC, according to [20], and compound **15g** resulted from coupling of (+)-**1** with the acyl chloride of **13b**. These two 'coupling' products – having the (*R*)-configura-

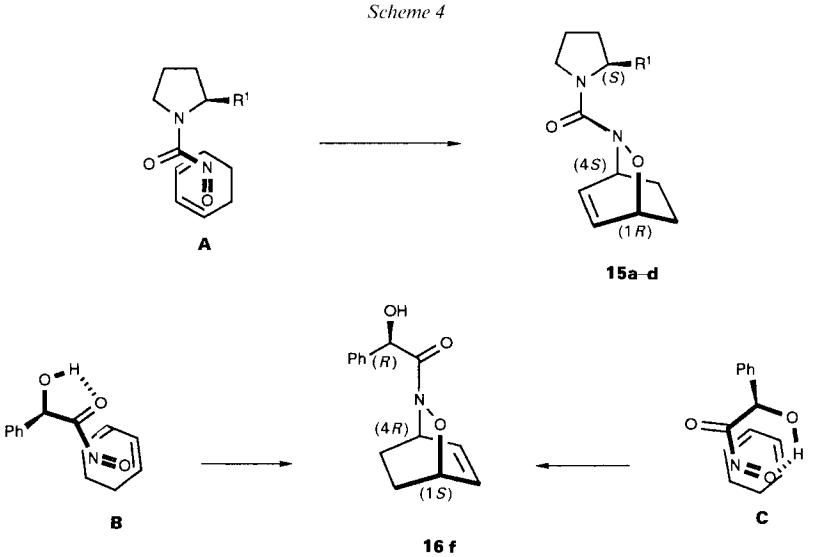
Table 2. *Physical Data of the Adducts* **15a–g** *and* **16a–g**

Series	Adducts of the *Diels-Alder* reaction				Independently synthesized **15**	
	15		**16**		M.p.	$[\alpha]_D$ ($CHCl_3$)
	M.p.	$[\alpha]_D$ ($CHCl_3$)	M.p.	$[\alpha]_D$ ($CHCl_3$)		
a	80–83°	+2.4 (c=0.8)	122–123°	−125 (c=0.6)	76–77°	+3.0 (c=1.0)
b	liq.	−29 (c=1.0)	liq.	−123.4 (c=0.5)	liq.	−27.4 (c=0.7)
c	115–116°	−6 (c=0.8)	132–133°	−46 (c=0.6)	–	–
d	–	–	–	–	liq.	+18 (c=0.7)
e	114–116°	−65 (c=0.7)	159–161°	+18 (c=0.5)	112–114°	−65 (c=1.0)
f	–		90–91°	+33 (c=1.0)	liq.	−33 (c=1.0)
g	–	–	–	–	103–104°	−48.8 (c=1.0)

tion in the mandelic-acid moiety and the (1*R*,4*S*)-configuration in the bicyclic moiety – are identical with the *minor* cycloadducts **15f** and **15g** which were obtained by asymmetric *Diels-Alder* cycloaddition. The absolute configuration of (+)-**1** having been controversial for some time [9], opposite configurations were attributed to these adducts [14] [15].

Mechanistic Interpretation. – The absolute configuration of the major *Diels-Alder* adducts being now firmly established, a stereochemical course can be postulated for their formation. The cycloadducts obtained from the *N*-(nitrosocarbonyl) dienophiles in the L-proline series are urea derivatives with a planar topology, for which two pairs of rotamers should be considered: *a*) the two planar rotamers having s-*trans*- and s-*cis*-conformation at the N(1)–CO bond, the s-*cis*-rotamer (N=O *cis* to the asymmetric C(2) centre) playing obviously the dominant role during the asymmetric cycloaddition step, and *b*) the s-*trans*- and the s-*cis*-rotamers relative to the CO–NO moiety. An assumed '*endo*' approach from the least hindered side during the *Diels-Alder* cycloaddition leads to

Scheme 4



a well-defined transition state in which the acylnitroso moiety is in its s-*cis*-conformation (see **A**, *Scheme 4*). Similar conclusions were reached by *Waldmann* and *Dräger* for some homo-*Diels-Alder* cycloadditions [21] as well as by *Gouverneur* and *Ghosez* [11] and by us [12] [13] for similar hetero-*Diels-Alder* cycloadditions.

In the mandelic acid series, there is a high degree of free rotation around the σ bond which connects the phenyl moiety to the chiral (*R*)-configurated C-atom and around the σ bond which connects the chiral inductor to the acylnitroso moiety. Due to the stiffness of the molecular framework of **14f** (intramolecular H-bond), two transition states **B** and **C** can be postulated (*'endo'*-approach assumed), both of which lead to cycloadduct **16f** as the major product (*Scheme 4*). **B** exhibits a H-bond between OH–C(2) and the carbonyl function which requires s-*cis*-conformation, and **C** shows a H-bond between OH–C(2) and the nitroso function which requires s-*trans*-conformation.

Transition state **B** is similar to the one described for L-proline. Such a transition state was already postulated by *Masamune* for some homo-*Diels-Alder* reactions [22]. Transition state **C** was postulated by *Kirby* and *Nazeer* [14] as well as by *Procter* and coworkers who based their assumption on quantum-chemical considerations [15] [23]. Furthermore, an interpretation for the diastereoselectivity in the *O*-methylmandelic-acid series was proposed [15] [23].

The absolute configuration of the major adducts **15a–d** and **16f** can tentatively be explained in terms of FMO theory. In the transition state the MO interactions appear to be strongest when both the diene and the acylnitroso dienophile (a heterodiene) are in their s-*cis*-conformation. The interaction between the HOMO of cyclohexadiene and the LUMO of the acylnitroso diene in such a transition state comprises two bonding interactions (*Diels-Alder* cycloaddition) and two secondary orbital interactions. The reasoning may also be reversed: since there are two bonding interactions and two secondary orbital interactions, cyclohexadiene and the dienophile must both be in their s-*cis*-conformation.

Experimental Part

General. Flash chromatography (FC): silica gel (*Merck 60*, 230–400 mesh).TLC: Al roll silica gel (*Merck 60 F_{254}*). HPLC: *Spectra-Physics SP 3500 B* liquid chromatograph with spectrophotometric detector *SP 770*; column *Spherisorb Brownlee C_{18}* or *Lichrospher Merck C_{18e}*. M.p.: *Kofler* hot bench or *Büchi SMP 20* apparatus; corrected. $[\alpha]_D$: *Perkin-Elmer-PE-241* polarimeter. IR spectra (cm^{-1}): *Perkin-Elmer 157 G*. ^1H- and ^{13}C-NMR spectra: *Varian T-60*, *Bruker WP-80-DS*, *AC-F-250* and *VM-400* apparatus using double-irradiation techniques; tetramethylsilane (TMS; ^1H-NMR) and $CDCl_3$ or C_6D_6 (δ = 77.0 and 128.0, resp., rel. to TMS; ^{13}C-NMR) as internal references; δ in ppm and *J* in Hz. High resolution (HR)MS: *MAT-311* spectrometer; measured at the University of Rennes. Microanalyses were carried out by the Service Central de Microanalyses of the CNRS, F-69390 Vernaison.

Starting Materials. (–)-D-Mandelic acid, *O*-benzylhydroxylamine, methyl chloroformate, phenyl chloroformate, cyclohexa-1,3-diene, L-Boc-proline (**12**), tetrapropylammonium periodate were purchased from *Fluka*. Methyl *N*-(chlorocarbonyl)-L-prolinate (**8**) was purchased from *Aldrich*, phenyl carbonate from *Schering-Kahlbaum*, (2*S*)-2-(Anilinomethyl)pyrrolidine (**6c**) and (2*S*)-2-(Methoxymethyl)pyrrolidine (**6b**) from *Merck-Schuchardt*, $NH_2OH \cdot HCl$ and K_2CO_3 from *Prolabo*. Methyl D-mandelate was prepared by reaction of mandelic acid with 10% HCl in MeOH. L-Prolinol (**6a**) was prepared according to [24]. Et_3N was distilled and then kept under Ar in the presence of 4 Å molecular sieves. The usual solvents were freshly distilled. The chlorinated ones were kept over Na_2CO_3. Bicyclic hydroxylamine (+)-**1** was prepared according to [8] [12].

(–)-(R)-2-Methoxy-2-phenylacetohydroxamic acid (**5b**) was prepared according to [4b]. Colourless crystals (68%). M.p. 143–144°. $[\alpha]_D^{24} = -71$ (MeOH, $c = 0.5$), $[\alpha]_D^{24} = -58.5$ (acetone, $c = 0.6$); [4b]: m.p. 137–139°; $[\alpha]_D^{23} = -63$ (acetone, $c = 0.66$).

*(−)-(S)-2-(Hydroxymethyl)pyrrolidine-*N*-carbohydroxamic Acid* (**3a**). To a stirred soln. of **6a** (1.15 g, 11 mmol) in pyridine (12 ml) was added hydroxamic acid **7** (1.7 g, 11 mmol). After 16 h at 30° under Ar, the soln. was evaporated and the residue purified by FC (AcOEt/MeOH 8:2): **3a** (0.92 g, 51%). Colourless crystals. M.p. 144–145° (AcOEt/i-PrOH 1:1). $[\alpha]_D^{20} = -78$ (MeOH, $c = 1.5$). IR (KBr): 3400, 3220, 1645, 1530, 1400, 1355, 1075, 1050, 1035, 1010, 875, 865, 775. ^{1}H-NMR (60 MHz, $CDCl_3/CD_3OD$ 9:1): 4.40 (br. *s*, NHOH, OH); 3.90 (*m*, H–C(2)); 3.43 (*m*, CH_2–C(2), 2 H–C(5)); 1.83 (*m*, 2 H–C(3), 2 H–C(4)). Anal. calc. for $C_6H_{12}N_2O_3$ (160.17): C 44.99, H 7.55, N 17.49; found: C 44.9, H 7.5, N 17.7.

*(−)-(S)-2-(Methoxymethyl)pyrrolidine-*N*-carbohydroxamic Acid* (**3b**). To a stirred soln. of **6b** (0.417 g, 3.6 mmol) in pyridine (5 ml) was added **7** (0.593 g, 3.9 mmol, 1.1 equiv.). After 16 h under Ar at r.t., the soln. was evaporated and the phenol distilled off at 40°/0.5 Torr. The crude residue was washed with AcOEt or with Et_2O and the washing soln. separated by FC (AcOEt): **3b** (0.461 g, 72%). Colourless crystals. M.p. 91–92° (AcOEt). $[\alpha]_D^{20} = -92.6$ (MeOH, $c = 1.0$). IR (KBr): 3220, 2940, 2895, 1658, 1460, 1380, 1355, 1090, 767, 656. ^{1}H-NMR (60 MHz, $CDCl_3$): 8.25, 7.15 (2*s*, NHOH); 3.95 (*m*, H–C(2)); 3.38 (*s*, MeO); 3.2–3.6 (*m*, CH_2–C(2), 2 H–C(5)); 2.0–1.6 (*m*, 2 H–C(3), 2 H–C(4)). Anal. calc. for $C_7H_{14}N_2O_3$ (174.20): C 48.26, H 8.10, N 16.08; found: C 48.2, H 8.0, N 16.1.

*(−)-(S)-2-(Anilinomethyl)pyrrolidine-*N*-carbohydroxamic Acid* (**3c**). To a stirred soln. of **6c** (276 mg, 1.56 mmol) in pyridine (3 ml) was added **7** (390 mg, 2.55 mmol, 1.6 equiv.). After 16 h at 30° under Ar, pyridine was evaporated and the residue purified by FC (AcOEt): **3c** (310 mg, 85%). Colourless crystals. M.p. 123–124° (AcOEt). $[\alpha]_D^{20} = -37$ ($CHCl_3$, $c = 2.1$). IR (KBr): 3330, 3210, 2960, 2910, 1665, 1600, 1500, 1415, 1250, 760, 700. ^{1}H-NMR (60 MHz, $CDCl_3$): 7.15 (*m*, 3 arom. H); 6.69 (*m*, 2 H_o); 4.16 (*m*, H–C(2)); 3.27 (*m*, 2 H–C(5), CH_2–C(2)); 1.95 (*m*, 2 H–C(3), 2 H–C(4)). Anal. calc. for $C_{12}H_{17}N_3O_2$ (235.28): C 61.25, H 7.28, N 17.86; found: C 61.4, H 7.4, N 18.0.

*Methyl-1-[(Hydroxyamino)carbonyl]-*L*-prolinate* (**3d**). A stirred soln. of **9** (2 g, 7.2 mmol) in AcOEt (160 ml) was submitted to hydrogenolysis over 5% Pd/C (0.30 g) at 1 atm overnight. After separation of the catalyst by centrifugation, the solvent was evaporated and the crude residue washed with Et_2O: **3d** (1.27 g, 94%). Colourless crystals. M.p. 120° (Me_2CO_3). $[\alpha]_D^{20} = -8.4$ ($CHCl_3$, $c = 0.4$). IR (KBr): 3360, 3170, 1720, 1665, 1645, 1460, 1435, 1390, 1375, 1230, 1210. ^{1}H-NMR (80 MHz, $CDCl_3$): 6.25 (br. *s*, NHOH); 4.48 (*t*, $J = 5.6$, H–C(2)); 3.75 (*s*, MeO); 3.46 (*t*, $J = 6.2$, 2 H–C(5)); 2.10 (*m*, 2 H–C(3), 2 H–C(4)). Anal. calc. for $C_7H_{12}N_2O_4$ (188.18): C 44.68, H 6.43, N 14.88; found: C 44.5, H 6.5, N 15.1.

*(−)-(S)-*tert*-Butyl 2-[(Hydroxyamino)carbonyl]pyrrolidine-1-carboxylate* (**4**). To a stirred soln. of **12** (1.02 g, 4.7 mmol) and Et_3N (0.655 ml, 4.7 mmol, 1 equiv.) in CCl_4 (5 mol) at 0° under Ar was added dropwise methyl chloroformate (0.360 ml, 4.7 mmol, 1 equiv.). After 16 h at r.t., the mixture was filtered, the solid material washed with CCl_4, and the combined org. soln. evaporated. The resulting mixed anhydride was dissolved under Ar in AcOEt (18 ml) and H_2O (0.45 ml) to which $NH_2OH \cdot HCl$ (0.409 g, 5.88 mmol, 1.25 equiv.) and K_2CO_3 (0.72 g, 5.21 mmol, 1.1 equiv.) were added. After 16 h at 25°, the mixture was filtered and the solid residue washed several times with hot AcOEt. The combined org. layer was evaporated and the solid residue washed with i-Pr_2O: **4** (0.794 g, 73%). M.p. 167–168° (AcOEt). Colourless crystals. $[\alpha]_D^{17} = -51$ (MeOH, $c = 0.9$). IR (KBr): 3210, 3030, 2980, 2910, 1665, 1545, 1415, 1370, 1160, 1130, 1050. ^{1}H-NMR (60 MHz, $CDCl_3$): 6.80 (br. *s*, NHOH); 4.20 (*m*, H–C(2)); 3.40 (*m*, 2 H–C(5)); 2.25–1.75 (*m*, 2 H–C(3), 2 H–C(4)); 1.46 (*s*, *t*-Bu). Anal. calc. for $C_{10}H_{18}N_2O_4$ (230.26): C 52.16, H 7.88, N 12.17; found: C 52.3, H 8.0, N 12.1.

(−)-(R)-2-Hydroxy-2-phenylacetohydroxamic Acid (**5a**). To a stirred soln. of $NH_2OH \cdot HCl$ (0.70 g, 10 mmol, 2 equiv.) in MeOH (5 ml) kept at r.t. under Ar was added a soln. of KOH (0.92 g, 16.4 mmol, 3.4 equiv.) in MeOH (2.5 ml). To this mixture cooled to 0° was added methyl D-mandelate (0.80 g, 4.84 mmol). After filtration of the precipitate, the soln. was kept at 30° overnight and evaporated to 30% of its initial volume. H_2O (7 ml) and conc. HCl soln. were added to pH 6. The resulting soln. was extracted with AcOEt (6 times) and the combined org. soln. washed with brine, dried ($MgSO_4$), and evaporated: **5a** (0.435 g, 53%). Colourless crystals. M.p. 157–158° (dec., AcOEt; [14]: m.p. 137–138° for the (+)-(*S*)-isomer). $[\alpha]_D^{20} = -46$ (MeOH, $c = 0.6$) ([14]: $[\alpha]_D^{20} = -164$ (H_2O, $c = 2.5$) for the (+)-(*S*)-isomer!). IR (KBr): 3420, 3190, 2860, 1660, 1570, 1455, 1350, 1030, 970, 745, 700, 620. ^{1}H-NMR (60 MHz, $CDCl_3/CD_3OD$): 7.36 (*m*, Ph); 5.07 (*s*, H–C(2)); 4.26 (br. *s*, OH, NHOH). Anal. calc. for $C_8H_9NO_3$ (167.16): C 57.48, H 5.43, N 8.38; found: C 57.5, H 5.5, N 8.5.

Phenyl N*-Hydroxycarbamate* (**7**). a) To a stirred mixture of $NH_2OH \cdot HCl$ (0.63 g, 9 mmol, 1.4 equiv.) and K_2CO_3 (1.06 g, 7.7 mmol, 1.2 equiv.) in Et_2O (6 ml) and H_2O (0.1 ml) kept at 0° under Ar was added dropwise phenyl chloroformate (0.8 ml, 1.0 g, 6.4 mmol). After 16 h at r.t., the mixture was filtered, the org. soln. evaporated, and the crystalline residue **7** (0.9 g, 90%) washed with benzene.

b) To a stirred soln. of phenyl carbonate (8.2 g, 40 mmol) in MeOH (30 ml) at r.t. under Ar were added $NH_2OH \cdot HCl$ (3.5 g, 50 mmol, 1.25 equiv.) and K_2CO_3 (3.5 g, 25 mmol, 1.25 equiv.). After 1 night, the mixture was

neutralized with conc. HCl soln. (0.8 ml) and filtered, the org. soln. evaporated, and the phenol distilled at 45°/0.5 Torr. The solid residue was washed with C_6H_6: **7** (3.63 g, 62%). Colourless dimorphous crystals. M.p. 105–107° (C_6H_6; [17]: m.p. 105–107°). IR (KBr, form I): 3400, 3240, 1700, 1525, 1480, 1270, 1200, 1095, 1020, 790, 685. IR (KBr, form II): 3280, 1680, 1510, 1480, 1285, 1205, 1160, 1100, 790, 710, 685. ^{1}H-NMR (60 MHz, $CDCl_3$): 8.33 (*s*, NH); 7.20 (*m*, Ph); 3.40 (br. *s*, OH).

(–)-(S)-Methyl 1-{[(Benzyloxy)amino]carbonyl}pyrrolidine-2-carboxylate (**9**). To a stirred soln. of **8** (0.93 g, 4.8 mmol) in AcOEt (10 ml) were added at r.t. under Ar $NH_2OBn \cdot HCl$ (0.86 g, 5.4 mmol, 1.1 equiv.), K_2CO_3 (0.715 g, 5.2 mmol, 1.08 equiv.), and H_2O (0.2 ml). This mixture was left at 60° for 40 h and then filtered, the precipitate washed with AcOEt and CH_2Cl_2, the combined org. layer evaporated, and the crystalline residue washed with cyclohexane: **9** (1.23 g, 91%). M.p. 123–124° (AcOEt/cyclohexane 2:1). $[\alpha]_D^{20} = -63$ ($CHCl_3$, $c = 1.3$). IR (KBr): 3230, 2980, 2960, 1735, 1650, 1500, 1385, 1365, 1200, 1170, 1025, 745, 700. ^{1}H-NMR (80 MHz, $CDCl_3$): 7.39 (*m*, C_6H_5); 4.87 (*s*, $PhCH_2$); 4.44 (*t*, $J = 5.4$, H–C(2)); 3.71 (*s*, MeO); 3.41 (*dt*, $J = 1.0, 6.2$, 2 H–C(5)); 2.0 (*m*, 2 H–C(3), 2 H–C(4)). Anal. calc. for $C_{14}H_{18}N_2O_4$ (278.31): C 60.42, H 6.52, N 10.07; found: C 60.3, H 6.6, N 10.3.

(5S)-3-(Benzyloxy)-1,3-diazabicyclo[3.3.0]octane-2,4-dione (**10**). When left to stand over 40 h at 60° or on column chromatography, **9** cyclized quantitatively to **10**. Colourless crystals. M.p. 99–100° (i-PrOH). $[\alpha]_D^{20} = -79$ ($CHCl_3$, $c = 0.5$). IR (KBr): 2960, 2900, 1785, 1715, 1405, 1310, 1235, 1175, 965, 940, 915, 740, 700. ^{1}H-NMR (80 MHz, $CDCl_3$): 7.38 (*m*, Ph); 5.14 (*s*, $PhCH_2$); 3.93 (*dd*, $J = 7.6, 8.9$, H–C(5)); 3.59 (*dt*, $J = 11.1, 7.1, 7.2$, H_a–C(8)); 3.23 (*m*, $J = 11.3, 5.5, 6.8$, H_b–C(8)); 2.45–1.35 (*m*, 2 H–C(6), 2 H–C(7)). ^{13}C-NMR (20.1 MHz, $CDCl_3$): 168.2 (*s*, C(4)); 156.3 (*s*, C(2)); 133.1 (*s*, C_{ipso}); 129.7 (*d*, $J = 162$, C_o); 129.0 (*d*, $J = 162$, C_p); 128.1 (*d*, $J = 161$, C_m); 78.6 (*t*, $J = 150$, $PhCH_2O$); 60.4 (*d*, $J = 152$, C(5)); 45.3 (*t*, $J = 145$, C(8)); 27.0 (*t*, $J = 136$, C(6)); 25.9 (*t*, $J = 134$, C(7)). Anal. calc. for $C_{13}H_{14}N_2O_3$ (246.27): C 63.40, H 5.73, N 11.38; found: C 63.4, H 5.8, N 11.5.

(5S)-3-Hydroxy-1,3-diazabicyclo[3.3.0]octane-2,4-dione (**11**). a) A stirred soln. of **10** (0.50 g, 2 mmol) in AcOEt (30 ml) containing 5% Pd/C (84 mg) was put under H_2 (1 atm) for 4 h at 30°. Centrifugation and rinsing of the catalyst with $AcOEt/CH_2Cl_2$ gave **11** (0.312 g, 98%). Colourless crystals.

b) Reaction of **8** with $NH_2OH \cdot HCl$ and K_2CO_3, followed by addition of HCl/MeOH, gave **11** quantitatively. M.p. 117–118° (AcOEt/cyclohexane). $[\alpha]_D^{20} = -9.6$ ($CHCl_3$, $c = 0.4$). ^{1}H-NMR (80 MHz, $CDCl_3$): 5.85 (br. *s*, NOH); 4.09 (*t*, $J = 8.2$, H–C(5)); 3.58 (*dt*, $J = 7.2, 7.6, 11.2$, H_a–C(8)); 3.29 (*ddd*, $J = 4.8, 6.9, 11.2$, H_b–C(8)); 2.50–1.60 (*m*, 2 H–C(6), 2 H–C(7)). ^{13}C-NMR (20.1 MHz, $CDCl_3$): 170 (*s*, C(4)); 158.1 (*s*, C(2)); 60.8 (*d*, $J = 152$, C(5)); 45.3 (*t*, $J = 145$, C(8)); 26.4 (*t*, $J = 136$, C(6) or C(7)); 26.3 (*t*, $J = 134$, C(7) or C(6)). Anal. calc. for $C_6H_8N_2O_3$ (156.14): C 46.15, H 5.16, N 17.94; found: C 46.1, H 5.2, N 18.0.

General. Procedure for the Diels-Alder *Cycloaddition with Cyclohexa-1,3-diene.* To a stirred soln. of cyclohexa-1,3-diene and $(Pr_4N)IO_4$ (0.33 mmol per mol of diene) in $CHCl_3$ (1–3 ml per mmol) containing *ca.* 10 beads of 4 Å molecular sieves was added portionwise within 30–45 min the hydroxamic acid; if necessary, some MeOH was added. After 1 h at r.t., the mixture was diluted with Et_2O and washed with 1M $NaHCO_3$ (1 ml) containing some Na_2SO_3 until decoloration and with brine. The aq. phase was extracted several times with Et_2O and the combined Et_2O soln. dried ($MgSO_4$) and evaporated.

(1R,4S)-3-[(2S)-2-(Hydroxymethyl)pyrrolidine-1-carbonyl]-2-oxa-3-azabicyclo[2.2.2]oct-5-ene (**15a**) *and Its (1S,4R)-Diastereoisomer* **16a.** From cyclohexa-1,3-diene (0.142 ml, 1.5 mmol), $(Pr_4N)IO_4$ (0.188 g, 0.5 mmol), and **3a** (0.237 g, 1.5 mmol) in $CHCl_3$ (3 ml) and MeOH (1 ml). The oily residue (0.315 g, 89%) was separated by FC (AcOEt): **15a** and **16a**.

Major Adduct **15a**: Colourless crystals (147 mg, 42%). M.p. 80–83° ($AcOEt/(i\text{-}Pr)_2O$ 1:6). $[\alpha]_D^{20} = +2.4$ ($CHCl_3$, $c = 0.8$). IR (KBr): 3370, 2960, 1650, 1620, 1415, 1370, 1205, 1090, 1058, 920, 768, 710. ^{1}H-NMR (400 MHz, C_6D_6): *Tables 3* and *4*. ^{1}H-NMR (250 MHz, $CDCl_3$): 6.63 (*ddd*, H–C(5)); 6.52 (*ddd*, H–C(6)); 4.63 (*m*, H–C(1), H–C(4)); 4.21 (*m*, OH); 4.10 (*m*, H–C(2′)); 3.75 (*m*, H_a–C(5′)); 3.61 (*m*, $H_2C(\alpha)$); 3.43 (*m*, H_b–C(5′)); 2.16 (*m*, H_a–C(7), H_a–C(8)); 1.96 (*m*, H_a–C(3′), H_b–C(4′)); 1.78 (*m*, H_b–C(3′), H_b–C(4′)); 1.50 (*m*, H_b–C(7), H_b–C(8)). ^{13}C-NMR (20.1 MHz, $CDCl_3$): *Table 5*. Anal. calc. for $C_{12}H_{18}N_2O_3$ (238.29): C 60.48, H 7.61, N 11.76; found: C 60.2, H 7.6, N 11.8.

Minor Adduct **16a**: Colourless crystals (49 mg, 14%). M.p. 122–123° ($AcOEt/(i\text{-}Pr)_2O$). $[\alpha]_D^{20} = -125$ ($CHCl_3$, $c = 0.6$). IR (KBr): 3430, 2980, 2940, 2890, 1620, 1420, 1390, 1375, 1195, 1050, 900, 880, 835, 778, 710. ^{1}H-NMR (400 MHz, C_6D_6): *Tables 3* and *4*. ^{13}C-NMR (20.1 MHz, $CDCl_3$): *Table 5*. Anal. calc. for $C_{12}H_{18}N_2O_3$ (238.29): C 60.48, H 7.61, N 11.76; found: C 60.2, H 7.6, N 11.9.

(1R,4S)-3-[(2S)-2-(Methoxymethyl)pyrrolidine-1-carbonyl]-2-oxa-3-azabicyclo[2.2.2]oct-5-ene (**15b**) *and Its (1S,4R)-Diastereoisomer* **16b**. From cyclohexa-1,3-diene (37 µl, 0.39 mmol), $(Pr_4N)IO_4$ (60 mg, 0.16 mmol), and **3b** (67 mg, 0.38 mmol) in $CHCl_3$ (1 ml). The crude oily residue (117 mg) was separated by prep. TLC (AcOEt): **15b** and **16b.**

Major Adduct **15b**: Colourless oil (60 mg, 62%). $[\alpha]_D^{20} = -29$ ($CHCl_3$, $c = 1.0$). IR (CCl_4): 2970, 2940, 2890, 1640, 1405, 1365, 1195, 1110, 900, 875, 700. ^{1}H-NMR (250 MHz, C_6D_6): *Tables 3* and *4*. ^{1}H-NMR (80 MHz, $CDCl_3$): 6.56 (*m*, H–C(5), H–C(6)); 4.61 (*m*, H–C(1), H–C(4)); 4.13 (*m*, H–C(2′)); 3.51 (*dd*, H_a–C(α)); 3.50 (*m*, 2 H–C(5′)); 3.34 (*s*, MeO); 3.29 (*dd*, H_b–C(α)); 2.30–1.10 (*m*, 2 H–C(7), 2 H–C(8), 2 H–C(3′), 2 H–C(4′)); ^{13}C-NMR (20.1 MHz, $CDCl_3$): *Table 5*. MS: 252 (5), 235 (3), 142 (69), 114 (22), 82 (53), 80 (26), 79 (51), 77 (22), 71 (20), 70 (100), 68 (17), 67 (45). HR-MS: 252.1489 ($C_{13}H_{20}N_2O_3$, M^+, calc. 252.14738).

Minor Adduct **16b**: Colourless oil (11 mg, 11%). $[\alpha]_D^{20} = -123.4$ ($CHCl_3$, $c = 0.5$). IR (CCl_4): 2970, 2940, 2890, 1645, 1410, 1375, 1120, 880. ^{1}H-NMR (80 MHz, C_6D_6): *Tables 3* and *4*. ^{1}H-NMR (80 MHz, $CDCl_3$): 6.67 (*ddd*, H–C(5)); 6.47 (*ddd*, H–C(6)); 4.72 (*m*, H–C(4)); 4.56 (*m*, H–C(1)); 4.18 (*m*, H–C(2′)); 3.53 (*m*, 2 H, H–C(5′)); 3.50 (*dd*, H_a–C(α)); 3.33 (*s*, MeO); 3.28 (*dd*, H_b–C(α)); 2.20 1.20 (*m*, 2 H–C(7), 2 H–C(8), 2 H–C(3′), 2 H–C(4′)). ^{13}C-NMR (20.1 MHz, $CDCl_3$): *Table 5*. MS: 252 (13), 142 (100), 129 (28), 114 (34), 110 (18), 82 (88), 80 (23), 79 (37), 70 (64), 69 (13), 68 (16), 67 (28). HR-MS: 252.1477 ($C_{13}H_{20}N_2O_3$, M^+, calc. 252.14738).

(1R,4S)-3-[(2S)-2-(Anilinomethyl)pyrrolidine-1-carbonyl]-2-oxa-3-azabicyclo[2.2.2]oct-5-ene (**15c**) *and Its (1S,4R)-Diastereoisomer* **16c**. From Cyclohexa-1,3-diene (0.102 ml, 1.07 mmol), $(Pr_4N)IO_4$ (0.146 g, 0.39 mmol), and **3c** (0.253 g, 1.07 mmol) in $CHCl_3$ (3 ml) and MeOH (1 ml). The mixture was separated by prep. TLC (AcOEt/cyclohexane 4:6): **15c** and **16c**.

Major Adduct **15c**: Colourless crystals (0.222 g, 65%). M.p. 115–116° (AcOEt/(i-Pr)$_2$O 1:4). $[\alpha]_D^{20} = -6$ ($CHCl_3$, $c = 0.8$). IR (KBr): 3370, 2960, 2940, 2900, 1660, 1600, 1520, 1390, 1365, 1325, 1210, 915, 750, 695. ^{1}H-NMR (400 MHz, C_6D_6): *Tables 3* and *4*. ^{13}C-NMR (20.1 MHz, $CDCl_3$): *Table 5*. Anal. calc. for $C_{18}H_{23}N_3O_2$ (313.40): C 69.98, H 7.40, N 13.41; found: C 69.0, H 7.4, N 13.3.

Minor Adduct **16c**: Colourless crystals (46 mg, 14%). M.p. 132–133° (AcOEt/(i-Pr)$_2$O 1:2.5). $[\alpha]_D^{20} = -46$ ($CHCl_3$, $c = 0.6$). IR (KBr): 3360, 3060, 2970, 2940, 1635, 1605, 1520, 1500, 1485, 1415, 1370, 1315, 880, 760, 695. ^{1}H-NMR (400 MHz, C_6D_6): *Tables 3* and *4*. ^{13}C-NMR (20.1 MHz, $CDCl_3$): *Table 5*. Anal. calc. for $C_{18}H_{23}N_3O_2$ (313.40): C 68.98, H 7.40, N 13.41; found: C 69.1, H 7.5, N 13.5.

(1R,4S)-3-[(2S)-2-(Methoxycarbonyl)pyrrolidine-1-carbonyl]-2-oxa-3-azabicyclo[2.2.2]oct-5-ene (**15**) *and Its (1S,4R)-Diastereoisomer* **16d**. From cyclohexa-1,3-diene (0.250 ml, 2.6 mmol). $(Pr_4N)IO_4$ (0.335 g, 0.9 mmol), and **3d** (0.497 g, 2.6 mmol) in $CHCl_3$ (3 ml). The mixture was purified but not separated by FC (AcOEt/cyclohexane 8:2) leading to an oily mixture (86%) of the major **15d** and the minor **16d**. $[\alpha]_D^{20} = -7$ ($CHCl_3$, $c = 0.7$). IR (CCl_4): 2970, 2940, 2890, 1750, 1650, 1405, 1365, 1195, 1165, 875. ^{1}H-NMR (250 MHz, C_6D_6): *Tables 3* and *4*. ^{1}H-NMR (80 MHz, $CDCl_3$, **15d**): 6.69 (*m*, H–C(5)); 6.45 (*m*, H–C(6)); 4.78 (*m*, H–C(4)); 4.46 (*m*, H–C(1), H–C(2′)); 3.70 (*s*, CO_2Me); 3.61 (*m*, 2 H–C(5′)); 2.34–1.16 (*m*, 2 H–C(7), 2 H–C(8), 2 H–C(3′), 2 H–C(4′)). ^{13}C-NMR (20.1 MHz, $CDCl_3$): *Table 5*. MS: 266 (17), 156 (15), 129 (37), 128 (100), 80 (17), 79 (34), 77 (12), 70 (25), 68 (11). HR-MS: 266.1269 ($C_{13}H_{18}N_2O_4$, M^+, calc. 266.12665).

*(1R,4S)-3-{(2S)-1-[(*tert*-Butoxy)carbonyl]pyrrolidine-2-carbonyl}-2-oxa-3-azabicyclo[2.2.2]oct-5-ene* (**15e**) *and Its (1S,4R)-Diastereoisomer* **16e**. From cyclohexa-1,3-diene (0.165 ml, 1.72 mmol), $(Pr_4N)IO_4$ (0.23 g, 0.61 mmol), and **4** (0.397 g, 1.72 mmol) in $CHCl_3$ (4 ml). The colourless solid residue was purified by FC (0.431 g, 81%) and separated on a *Jobin-Yvon* steel column filled with silicic acid (AcOEt/MeOH 99:1) under N_2 pressure (4 atm): **15e** and **16e**.

Major Adduct **15e**: Colourless crystals. M.p. 114–116° ((i-Pr)$_2$O). $[\alpha]_D^{20} = -65$ ($CHCl_3$, $c = 0.7$). IR (KBr): 2980, 2950, 2880, 1695, 1660, 1620, 1405, 1370, 1170, 1135, 1085, 962, 915, 702. ^{1}H-NMR (400 MHz, CD_2Cl_2): *Tables 3* and *4*. ^{13}C-NMR (20.1 MHz, $CDCl_3$): *Table 5*. Anal. calc. for $C_{16}H_{24}N_2O_4$ (308.38): C 62.31, H 7.85, N 9.09; found: C 62.0, H 7.9, N 9.1.

Minor Adduct **16e**: Colourless crystals. M.p. 159–161° (AcOEt/(i-Pr)$_2$O 1:3). $[\alpha]_D^{20} = +18$ ($CHCl_3$, $c = 0.5$). IR (KBr): 2990, 2970, 2940, 2890, 1690, 1645, 1405, 1370, 1180, 1170, 1130, 1085, 965, 915, 775, 720. ^{1}H-NMR (400 MHz, CD_2Cl_2): *Tables 3* and *4*. ^{13}C-NMR (20.1 MHz, $CDCl_3$): *Table 5*. Anal. calc. for $C_{16}H_{24}N_2O_4$ (308.38): C 62.31, H 7.85, N 9.09; found: C 62.3, H 8.0, N 9.2.

(1R,4S)-3-[(2R)-2-Hydroxy-2-phenylacetyl]-2-oxa-3-azabicyclo[2.2.2]oct-5-ene (**15f**) *and Its (1S,4R)-Diastereoisomer* **16f**. From cyclohexa-1,3-diene (0.135 ml, 1.42 mmol), $(Pr_4N)IO_4$ (0.182 g, 0.4 mmol), and **5a** (0.237 g, 1.42 mmol) in $CHCl_3$ (3 ml). The yellowish solid residue was purified by prep. TLC (AcOEt) without separation of the two adducts: 0.232 g, 67%. The major adduct was obtained pure by fractional crystallization ((i-Pr)$_2$O).

Major Adduct **15f**: Colourless crystals. M.p. 90–91° ((i-Pr)$_2$O). $[\alpha]_D^{24} = +33$ ($CHCl_3$, $c = 1.0$). IR (KBr): 3420, 3060, 2980, 2940, 1630, 1610, 1390, 1360, 1275, 1190, 1170, 1090, 1065, 1045, 950, 900, 865, 835, 720, 700. ^{1}H-NMR (400 MHz, C_6D_6): *Tables 3* and *4*. ^{1}H-NMR (250 MHz, $CDCl_3$): 7.33 (*m*, 2 arom. H); 7.25 (*m*, 3 arom. H); 6.41 (*ddd*, H–C(5)); 6.02 (*m*, H–C(6)); 5.28 (*d*, H–C(2′)); 5.19 (*m*, H–C(4)); 4.56 (*m*, H–C(1)); 4.15 (*d*, OH–C(2′));

Table 3. *^{1}H-NMR Spectral Data of Adducts* **15a–g** *and* **16a–g** *in C_6D_6.* δ in ppm, internal standard TMS or C_6D_6 ($\delta(C_6D_5H) = 7.16$ ppm)[a]).

	H–C(1)	H–C(4)	H–C(5)	H–C(6)	H_a–C(7),H_a–C(8)	H_b–C(7),H_b–C(8)	H–C(2′)	CH_2(3′),CH_2(4′)	H_a–C(5′),H_b–C(5′)	H_a–C(α)	H_b–C(α)	Other data
15a	4.14	4.63	6.47	6.08	1.88 2.00	0.94 1.07	4.06	1.15–1.45	3.72 3.30	3.64 3.56	4.21 (OH)	343 K, 400 MHz
16a	4.12	4.71	6.52	6.05	1.87	0.91 1.15	4.20	1.10–1.50	3.68 3.34	3.65 3.65	3.57 (OH)	343 K, 400 MHz
15b	4.17	4.75	6.52	6.12	1.91 2.06	0.96 1.11	4.28	1.35–1.85	3.73 3.40	3.64 3.37	3.17 (MeO)	338 K, 400 MHz
16b	4.14	4.83	6.64	6.09	1.85	~ 1.0	4.42	1.10–1.75	3.64 3.54	3.61 3.36	3.14 (MeO)	303 K, 80 MHz
15c	4.14	4.69	6.46	6.11	1.89 2.10	0.95 1.08	4.27	1.30–1.50	3.71 3.30	3.32 2.87	6.68 (H_o); 7.17 (H_m) 6.72 (H_p); 4.33 (NH)	343 K, 400 MHz
16c	4.12	4.78	6.59	6.04	1.89	0.92 1.14	4.40	1.10–1.60	3.65 3.45	3.19 2.98	6.65 (H_o); 7.17 (H_m) 6.72 (H_p); 4.40 (NH)	343 K, 400 MHz
15d	4.11	4.81	6.54	6.07	1.89	0.91 1.06	4.52	1.25–1.75	3.67 3.62	– –	3.40 (CO_2Me)	323 K, 250 MHz
16d	4.17	4.78	6.53	6.11	n.d.	n.d.	4.69	n.d.	n.d.	– –	3.39 (CO_2Me)	323 K, 250 MHz
15e[b])	4.73	5.14 5.10	6.61 6.60	6.51 6.49	*ca.* 2.1 *ca.* 2.2	1.46 1.41	4.44 4.45	1.60–2.10	3.40	3.30 3.29	1.39 (*t*-Bu) 1.35 (*t*-Bu)	278 K, 400 MHz
16e[c])	4.74	5.14	6.61	6.47 6.54	2.01 2.14	1.47 1.77	4.33 4.37	1.70–2.20	3.40	3.29 –	1.38 (*t*-Bu) 1.30 (*t*-Bu)	278 K, 400 MHz
15f	3.84	4.97	5.95	5.71	1.10 1.37	0.5–0.7	5.42	–	–	– –	7.55 (H_o); *ca.* 7.1 (H_m, H_p); 4.71 (OH)	303 K, 250 MHz
16f	3.72	4.93	5.69	5.32	1.54	0.5–0.7	5.54	–	–	– –	7.40 (H_o); *ca.* 7.1 (H_m,H_p); 4.69 (OH)	303 K, 250 MHz
15g	4.09	5.08	6.16	5.92	1.42 1.55	0.72 0.80	5.19	–	–	– –	7.71 (H_o); *ca.* 7.1 (H_m, H_p); 3.33 (MeO)	343 K, 400 MHz
16g	4.00	5.04	5.90	5.55	1.78	0.80 0.91	5.21	–	–	– –	7.57 (H_o); *ca.* 7.1 (H_m, H_p); 3.36 (MeO)	343 K, 400 MHz

[a]) Primed numbers refer to the proline or mandelic moiety, C(α) is *C*–C(2′). [b]) In CD_2Cl_2; 2 rotamers in ratio 1:1. [c]) In CD_2Cl_2; 2 rotamers in ratio 7 (upper line); 3 (lower line).

Table 4. *^{1}H-NMR Coupling Constants* J [Hz] *of Adducts* **15a–g** *and* **16a–g** *in* C_6D_6

	J(1,5)	J(1,6)	J(1,7a)	J(1,7b)	J(4,5)	J(4,6)	J(4,8a)	J(4,8b)	J(5,6)	J(2′,3′)	J(2′,αa)	J(2′,αb)	J(αa,αb)	J(4′,5′a)	J(4′,5′b)	J(5′a,5′b)
15a	1.7	5.7	3.8	1.7	5.9	1.7	3.0	3.0	8.2	7.5 4.4	7.1	3.6	10.8	7.2 7.2	5.7 7.3	11.3
16a	1.6	5.8	4.0	1.4	5.4	1.8	2.9	2.9	8.3	n.d.	n.d.	n.d.	n.d.	n.d.	6.6 9.8	11.5
15b	1.6	5.8	3.9	1.6	5.9	1.7	3.1	3.2	8.2	7.0 3.0	3.4	7.5	9.2	n.d.	n.d.	n.d.
16b	1.6	5.8	4.1	1.5	5.6	1.8	2.8	2.8	8.3	6.7 6.7	3.5	6.8	9.3	n.d.	n.d.	n.d.
15c[a])	1.5	5.8	3.8	1.5	6.0	1.7	3.4	3.2	8.2	3.7 7.0	5.9	6.4	12.4	7.1 7.1	5.3 6.7	11.2
16c	1.5	5.8	3.9	1.5	5.7	1.8	2.9	2.9	8.3	7.1 7.1	6.4	5.4	12.2	4.0 7.3	6.9 8.6	11.5
15d[b])	1.6	5.8	4.1	1.5	5.8	1.7	3.0	3.0	8.4	2.9 7.7	–	–	–	n.d.	n.d.	n.d.
16d	1.5	5.6	4.0	1.5	5.8	1.7	3.0	3.0	8.3	6.5 7.9	–	–	–	n.d.	n.d.	n.d.
15e	1.7	5.8	n.d.	n.d.	6.2	1.7	n.d.	n.d.	8.1	8.5 3.5	–		–	7.2 5.0	7.2 7.2	10.3
16e	1.8	5.7	n.d.	n.d.	6.3	1.6	n.d.	n.d.	8.2	8.7 3.4	–		–	7.5 5.0	7.5 7.5	10.4
15f	1.6	5.6	3.7	1.8	6.1	1.7	3.6	2.2	8.2	7.2[c])	–		–	–	–	–
16f	1.6	5.5	3.7	1.6	6.1	1.7	2.8[d])		8.2	7.4[c])	–		–	–	–	–
15g	1.7	5.6	3.7	1.7	6.2	1.7	3.2	2.8	8.2	–	–		–	–	–	–
16g	1.6	5.6	3.8	1.6	6.1	1.7	2.8[d])		8.1	–	–		–	–	–	–

[a]) J(7a,7b) = 12.7, J(7a,8a) = 9.3, J(7a,8b) = 3.7, J(7b,8a) = 3.4, J(7b,8b) = 11.8, J(8a,8b) = 12.7 Hz. [b]) J(7a,7b) = 12.9, J(7a,8a) = 9.4, J(7a,8b) = 3.8, J(7b,8a) = 3.4, J(7b,8b) = 12.2, J(8a,8b) = 12.7 Hz. [c]) J(2′,OH-2′). [d]) Mean values.

Table 5. *^{13}C-NMR Spectral Data of Adducts* **15a–g** *and* **16a–g** *in $CDCl_3$ at 300 K.* δ in ppm, internal standard $CDCl_3$ ($\delta(CDCl_3) = 77$ ppm)[a]).

	C(1)	C(4)	C(5)	C(6)	C(7)	C(8)	NCO	C(2′)	C(3′)	C(4′)	C(5′)	Other data
15a	70.1 (J = 153)	49.6 (J = 152)	132.8 (J = 170)	131.1 (J = 169)	23.8[b]) (J = 132)	19.8 (J = 133)	163.0	61.0 (J = 143)	27.8 (J = 132)	23.6[c]) (J = 132)	48.5 (J = 143)	66.2 (J = 144, C(α))
16a	70.2	49.8	134.4	130.4	24.4[b])	19.6	164.4	61.0	27.7	24.0[c])	49.2	66.2 (C(α))
15b	69.6 (J = 153)	49.5 (J = 152)	132.8 (J = 170)	130.7 (J = 169)	23.6 (J = 133)	19.6 (J = 133)	161.3	57.2 (J = 143)	27.1 (J = 132)	22.9 (J = 133)	47.7 (J = 143)	72.8 (J = 141, C(α)); 58.2 (J = 140, MeO)
16b	69.7	48.8	134.3	130.1	24.0[b])	19.6	162.2	57.0	27.4	23.9[c])	48.8	72.8 C(α); 58.4 (MeO)
15c	69.8 (J = 156)	50.0 (J = 152)	132.1 (J = 170)	131.1 (J = 169)	23.5[b]) (J = 132)	19.7 (J = 132)	162.3	57.4 (J = 143)	28.3 (J = 132)	23.4[c]) (J = 132)	47.9 (J = 142)	47.5 (J = 136, C(α)); 148.1, 128.7 (J = 158), 116.3 (J = 160), 112.0 (J = 155, arom. C)
16c	70.0	49.1	134.4	130.3	24.2[b])	19.6	163.5	57.1	28.6	24.0[c])	49.1	47.7 (C(α)); 148.2, 128.7, 116.3, 112.0 (arom. C)
15d	70.2 (J = 154)	49.3 (J = 153)	134.2 (J = 170)	130.4 (J = 170)	23.9 (J = 132)	19.4 (J = 134)	161.4	60.1 (J = 152)	29.6 (J = 134)	22.8 (J = 133)	48.1 (J = 144)	173.3 (CO_2); 51.3 (J = 146.5, Me)
16d	70.2	49.2	134.1	130.7	24.2	19.7	161.5	60.0	29.3	23.7	48.6	172.8 (CO_2); 51.4 (Me)
15e[d])	71.1	46.2	132.4	131.0	23.0	20.6	153.6	56.8	29.4	23.0	46.2	171.5 (CO_2); 78.5 (Me_3C); 27.9 (Me)
16e[d])	71.3	46.2	132.2	130.9	23.0	20.6	153.6	57.4	29.4	23.0	46.2	171.3 (CO_2); 78.4 (Me_3C); 27.9 (Me)
15f	71.1	47.2	131.7	131.7	22.1	20.8	170.1	71.6	–	–	–	139.5, 127.9, 127.7, 127.0 (arom. C)
16f	70.9 (J = 153)	47.4 (J = 153)	131.5 (J = 170)	130.8 (J = 170)	23.1 (J = 133)	20.2 (J = 133)	170.8	71.4 (J = 147)	–	–	–	138.0, 127.7, 127.4 (J = 160), 127.2 (J = 160), (arom. C)
15g	71.7	46.8	132.3	131.8	22.6	20.9	169.2	80.6	–	–	–	57.0 (MeO); 136.7, 128.2, 128.0 (arom. C)
16g	71.5 (J = 153)	47.2 (J = 153)	132.3 (J = 170)	130.6 (J = 169)	23.6 (J = 133)	20.4 (J = 133)	170.4	80.6 (J = 145)	–	–	–	57.1 (J = 142, MeO); 135.1, 128.2 (J = 160), 128.0 (J = 160), 128.0 (J = 160), (arom. C)

[a]) Primed atoms refer to the proline or mandelic moiety. C(α) is C–C(2′). [b]) Or C(4′). [c]) Or C(7). [d]) 328 K.

2.17 (*m*, H_a–C(7), H_a–C(8)); 1.36 (*m*, H_b–C(7), H_b–C(8)). ^{13}C-NMR (20.1 MHz, $CDCl_3$): *Table 5*. Anal. calc. for $C_{14}H_{15}NO_3$ (245.28): C 68.55, H 6.16, N 5.71; found: C 68.5, H 6.1, N 5.7.

(1R,4S)-3-[(2R)-2-Methoxy-2-phenylacetyl]-2-oxo-3-azabicyclo[2.2.2]oct-5-ene (**15g**) *and Its (1S,4R)-Diastereoisomer* **16g**. From Cyclohexa-1,3-diene (46 µl, 0.48 mmol), $(Pr_4N)IO_4$ (70 mg, 0.19 mmol), and **5b** (87 mg, 0.48 mmol) in $CHCl_3$ (1.5 ml). Purification of the yellowish solid by prep. TLC (AcOEt) led to **15g**/**16g** (83 mg, 67%). Colourless crystals. M.p. 117–118° ($(i\text{-}Pr)_2O$). $[\alpha]_D^{20} = -4$ ($CHCl_3$, $c = 0.9$) IR (KBr): 2970, 2940, 2820, 1650, 1410, 1365, 1260, 1200, 1165, 1110, 1045, 935, 905, 835, 760, 720, 700. ^{1}H-NMR (400 MHz, C_6D_6): *Tables 3* and *4*. ^{13}C-NMR (20.1 MHz, $CDCl_3$): *Table 5*. Anal. calc. for $C_{15}H_{17}NO_3$ (259.31): C 69.48, H 6.61, N 5.40; found: C 69.7, H 6.5, N 5.4.

15a *from* **17** *and* **6a**. A stirred soln. of phenyl carbamate **17** (203 mg, 0.88 mmol) and **6a** (100 µl, 1 mmol, 1.13 equiv.) in pyridine (1.5 ml) was kept at 35–40° for 10 d. Pyridine was evaporated and the solid residue purified by FC (AcOEt/Et_2O 98:2): **15a** (108 mg, 52%). Colourless crystals. M.p. 76–77° (AcOEt/cyclohexane 2:8). $[\alpha]_D^{20} = +3$ ($CHCl_3$, $c = 1.0$). Spectral data: see above.

15b *from (+)-***1** *and* **6b**. To a stirred soln. of (+)-**1** (187 mg, 1.26 mmol) in CH_2Cl_2 (4 ml) under Ar at r.t. were added Et_3N (211 µl, 1.51 mmol, 1.2 equiv.) and dropwise 0.45M phosgene in toluene (3.4 ml, 1.53 mmol, 1.2 equiv.). After 1 night at r.t., the soln. was evaporated, taken up in CCl_4, filtered, and evaporated and the oily residue dissolved in AcOEt (2 ml). To this stirred soln. were added **6b** (130 µl, 1.05 mmol, 1 equiv.) and K_2CO_3 (100 mg, 0.73 mmol). After 1 night at r.t., the mixture was filtered, the residue washed several times with hot AcOEt, and the soln. evaporated. The residue was purified by FC (AcOEt/cyclohexane 5:5): **15b** (158 mg, 60%). Colourless oil. $[\alpha]_D^{20} = -27.4$ ($CHCl_3$, $c = 0.7$). Spectral data: see above.

15d *from (+)-***1** *and* **8**. To a stirred soln. of **8** (50 µl, 0.34 mmol) in AcOEt (0.5 ml) at r.t. under Ar were added (+)-**1** (58 mg, 0.39 mmol, 1.16 equiv.), K_2CO_3 (51 mg, 0.37 mmol, 1.1 equiv.), and H_2O (10 µl). After 5 h at r.t., the mixture was filtered, the residue washed several times with hot AcOEt, the org. soln. evaporated, and the residue purified by FC (AcOEt): **15d** (83 mg, 93%) which contains *ca.* 8% of **16d**. $[\alpha]_D^{20} = +18$ ($CHCl_3$, $c = 0.7$). IR (CCl_4): 2960, 2940, 2880, 1745, 1645, 1405, 1360, 1190, 1160, 920, 875. Spectral data: see above.

15e *from (+)-***1** *and* **12**. To a stirred soln. of (+)-**1** (60 mg, 0.41 mmol) and Et_3N (53 µl, 0.41 mmol) in CH_2Cl_2 (2 ml) under Ar at r.t. were added **12** (115 mg, 0.53 mmol, 1.3 equiv.) and DCC (97 mg, 0.47 mmol, 1.15 equiv.). After 4 h at r.t., the mixture was filtered, the residue washed several times with CH_2Cl_2, the combined org. soln. evaporated, and the residue purified by prep. TLC (AcOEt): **15e** (115 mg, 92%). Colourless crystals. M.p. 112–114° ($(i\text{-}Pr)_2O$). $[\alpha]_D^{20} = -65$ ($CHCl_3$, $c = 1.0$). IR (KBr): 2960, 2930, 2870, 1685, 1650, 1610, 1390, 1360, 1160, 1120, 1070, 950, 905, 695. ^{1}H-NMR (250 MHz, $CDCl_3$, 318 K; 2 rotamers): 6.62 (*ddd*, H–C(5)); 6.50 (*ddd*, H–C(6)); 5.18 (*m*, H–C(4)); 4.71 (*m*, H–C(1)); 4.62, 4.50 (2 *m*, H–C(2′), 2 rotamers); 3.51, 3.39 (2 *m*, 2 H–C(5′), 2 rotamers); 2.21–1.65 (*m*, 2 H–C(3′), 2 H–C(4′), 2 H–C(7), 2 H–C(8)); 1.46, 1.43 (2*s*, *t*-Bu, 2 rotamers). Anal. calc. for $C_{16}H_{24}N_2O_4$ (308.38): C 62.31, H 7.85, N 9.09; found: C 62.3, H 7.9, N 9.0.

15f *from (+)-***1** *and* **13a**. To a stirred soln. of **13a** (52 mg, 0.34 mmol) in abs. EtOH (0.8 ml) were added sequentially (+)-**1** (50 mg, 0.34 mmol, 1 equiv.), Et_3N (48 µl, 0.35 mmol, 1 equiv.) and a soln. of DCC (74 mg, 0.36 mmol, 1.07 equiv.) in $CHCl_3$ (0.3 ml). After 1 night at r.t. under Ar, the mixture was evaporated, the residue taken up in Et_2O, the resulting suspension filtered, the residue washed with Et_2O and AcOEt, the combined org. soln. evaporated, and the residue purified by FC (AcOEt/cyclohexane 1:1): **15f** (57 mg, 68%). Colourless resin. $[\alpha]_D^{20} = -33$ ($CHCl_3$, $c = 1.0$). Spectral data: see above.

15g *from (+)-***1** *and* **13b**. To a stirred soln. of **13b** (98 mg, 0.59 mmol) in CH_2Cl_2 (2 ml) at r.t. was added 1 drop of DMF and then dropwise oxalyl chloride (56 µl, 0.65 mmol, 1.1 equiv.; immediate reaction). After evaporation, the oily residue was dissolved in AcOEt (5 ml) at r.t. To this stirred soln. were added (+)-**1** (97 mg, 0.66 mmol, 1.1 equiv.), K_2CO_3 (85 mg, 0.62 mmol, 1.04 equiv.), and H_2O (100 µl). After 4 h at r.t., the mixture was filtered, the residue washed several times with hot AcOEt, and the combined org. soln. evaporated. The residue was purified by FC (AcOEt): **15g** (100 mg, 65%). Colourless crystals. M.p. 103–104° ($(i\text{-}Pr)_2O$). $[\alpha]_D^{20} = -48.8$ ($CHCl_3$, $c = 1.0$). IR (KBr): 3050, 2935, 1640, 1410, 1365, 1255, 1185, 1095, 945, 745, 700. ^{1}H-NMR (250 MHz, C_6D_6, 343 K): 7.65 (*d*, 2 H_o); 7.13 (*m*, H_p, 2 H_m); 6.16 (*ddd*, H–C(5)); 5.94 (*ddd*, H–C(6)); 5.14 (*s*, H–C(2′)); 5.05 (*m*, H–C(4)); 4.11 (*m*, H–C(1)); 3.30 (*s*, MeO); 1.49 (*m*, H_a–C(8), H_a–C(7)); 0.78 (*m*, H_b–C(8), H_b–C(7)). Anal. calc. for $C_{15}H_{17}NO_3$ (259.31): C 69.48, H 6.61, N 5.40; found: C 69.5, H 6.6, N 5.3.

(1R,4S)-3-[(Phenyloxy)carbonyl]-2-oxa-3-azabicyclo[2.2.2]oct-5-ene (**17**). To a stirred soln. of (+)-**1** (433 mg, 2.9 mmol) in Et_2O (4.3 ml) at r.t. under Ar were added K_2CO_3 (436 mg, 3.15 mmol, 1.07 equiv.) and benzyl chloroformate (0.4 ml, 3.2 mmol, 1.1 equiv.). After 1 night at r.t., the mixture was filtered, the residue washed several times with hot AcOEt, the combined org. soln. evaporated, and the remaining semi-crystalline residue washed twice with Et_2O: **17** (512 mg, 75%). Colourless crystals. M.p. 130–132° (AcOEt). $[\alpha]_D^{20} = +12.7$ ($CHCl_3$, $c = 1.0$). IR (KBr): 1720, 1590, 1490, 1385, 1195, 1065, 1035, 995, 920, 880, 750, 690. ^{1}H-NMR (250 MHz, $CDCl_3$):

7.33 (*m*, 2 H_m); 7.20 (*m*, H_p); 7.10 (*m*, 2 H_o); 6.70, 6.64 (*m*, H–C(5), H–C(6)); 4.96 (*m*, H–C(4)); 4.85 (*m*, H–C(1)); 2.26 (*m*, H_a–C(7), H_a–C(8)); 1.55 (*m*, H_b–C(7), H_b–C(8)). Anal. calc. for $C_{13}H_{13}NO_3$ (231.25): C 67.52, H 5.67, N 6.06; found: C 67.2, H 5.7, N 6.1.

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