Application of Furan as a Diene: Preparation of Condensed 1,3-Oxazines by Retro-Diels–Alder Reactions

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(Di-*exo*-3-amino-7-oxabicyclo[2.2.1]hept-5-en-2-yl)methanol (**3**) was treated with oxo carboxylic acids [*p*-toluoylpropionic acid, *cis*- or *trans*-(*p*-toluoyl)cyclohexanecarboxylic acid, -benzoic acid or methanobenzocyclooctenecarboxylic acid] to furnish the oxanorbornene-fused pyrrolo[1,3]oxazine **4,** the isoindolo[1,3]oxazines **5** and **6**, and the methanobenzocyclooctenepyrrolo[1,3]oxazine **10**, together with the retro-Diels–Alder products pyrrolooxazinone **7**, oxazinoisoindolones **8** and **9**, and oxazinopyrrolobenzocyclooctene **11**. On reflux in chlorobenzene, furan was released from the oxanorbornene heterocycles **5** and **10** to give the retro-Diels–Alder products. The structures of the new compounds were established by NMR spectroscopy and also (for **6** and **9**) by single-crystal X-ray structure determination.

Introduction

Numerous heteromonocycles and condensed heterocycles have recently been synthesized by cyclization of di-*endo*- and di-*exo*-3-aminobicyclo[2.2.1]hept-5-ene-2-carboxylic acids with difunctional compounds, followed by a *retro*-Diels–Alder (rDA) reaction.[1–3] In the closing step of the procedure, cyclopentadiene (CP) is cleaved off by heating to the melting point or by boiling in an organic solvent (chlorobenzene or toluene), resulting in 1,3-heterocycles as target compounds difficult or impossible to obtain by other routes. The CP-fused parent molecules relatively easily yield exclusively the rDA product when the new ring containing the double bond has a "quasi-aromatic" structure: a pyrimidinedione, thioxopyrimidinone or 1,3-oxazinone unit.

For synthetic applications, empirical observations suggest the use of dienes as embedded adducts in the following sequence of rDA reactivity: furan > pyrrole > benzene > naphthalene > fulvene > CP > anthracene > butadiene.[4] We are therefore currently constructing molecules based on furan instead of CP, with the expectation of removing the diene more easily and thus of obtaining heterocycles other than those with "quasi-aromatic" structures. To date, furan has been incorporated into 7-oxabicyclo[2.2.1]heptane, which is of huge potential as a useful intermediate in the synthesis of compounds with complicated structures,[5] such as in the preparation of the biologically active pamamycin.[6] The furan ring is removable from the adducts at lower temperatures, splitting off more easily than CP,[7] and has also been used as a trapping agent for active alkenes.[8]

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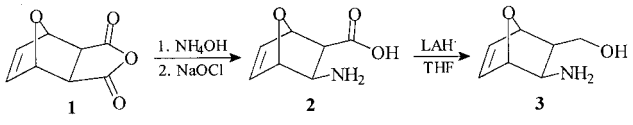
Results and Discussion

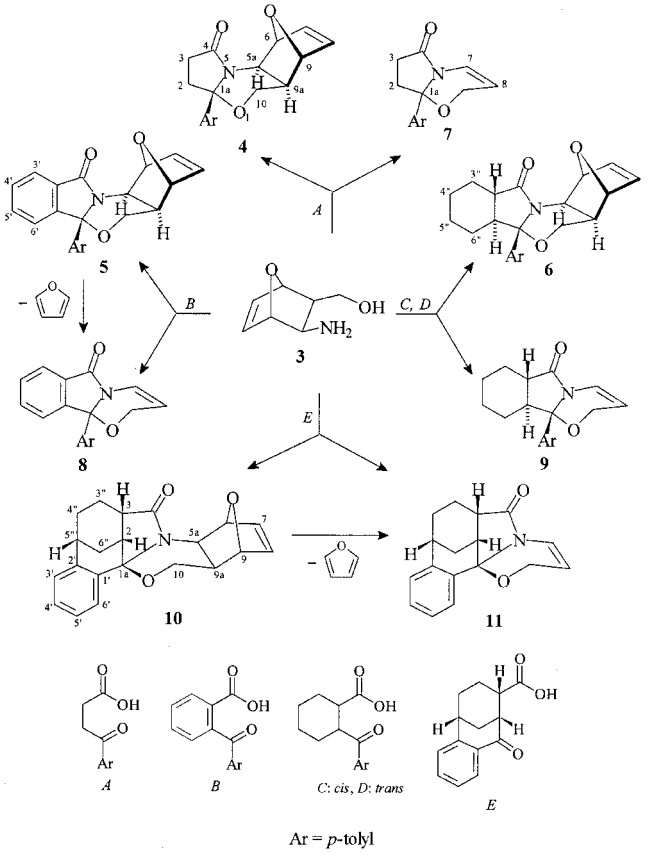
Di-*exo*-7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride[9,10] (**1**) was prepared from furan and maleic anhydride by Diels–Alder addition. After ammonolysis of **1**, the amide was transformed by Hoffmann degradation through treatment with hypochlorite into di-*exo*-3-amino-7-oxabicyclo[2.2.1]hept-5-ene-2-carboxylic acid (**2**) (obtained by another route in the literature,[11] but with no m.p. given), which, on reduction with $LiAlH_4$, yielded the corresponding (3-amino-7-oxabicyclo[2.2.1]hept-5-en-2-yl)-methanol (**3**) (Scheme 1).



Scheme 1

On boiling in toluene with 3-(*p*-toluoyl)propionic acid (*A*), 2-(*p*-toluoyl)benzoic acid (*B*) or *cis*- (*C*) or *trans*- (*D*) 2-(*p*-toluoyl)cyclohexane-1-carboxylic acid in the presence of a catalytic amount of *p*TSA, amino alcohol **3** gave the

partly saturated epoxypyrrolo[2,1-*a*][3,1]benzoxazinone **4** or isoindolo[3,1]benzoxazinones **5** and **6** (Scheme 2). These and the rDA products pyrrolo[1,2-*b*][1,3]oxazinone **7**, [1,3]oxazino[2,3-*a*]isoindolone **8** and *trans*-[1,3]oxazino-[2,3-*a*]isoindolone **9** were isolated from the reaction mixture. The two starting stereoisomeric 2-(*p*-toluoyl)cyclohexane-1-carboxylic acids both yielded the same *trans*-condensed derivative **9**, with the *cis*-*p*-toluoylcyclohexanecarboxylic acid (*C*) isomerizing to the *trans* compound (*D*) in the course of the reaction. Compounds **4**−**9** were isolated by column chromatography and their structures were determined by NMR spectroscopy and also (for the parent oxanorbornene compound **6** and the rDA product **9**) by X-ray analysis (Figure 1).



Scheme 2. The atom numbering is different from the numbering in the systematic names

The similar reaction between **3** and 10-oxohexahydromethanobenzocyclooctene-8-carboxylic acid (*E*) gave the heptacyclic **10** and its rDA product **11**. When **5** or **10** was heated at reflux in chlorobenzene for 1 h, **8** or **11** was obtained in good yield through the loss of furan.

The results demonstrate the advantages of the use of furan instead of CP in the retrodiene synthesis. The main advantage is the preparation of heterocycles possessing no oxo group on the newly formed 1,3-oxazine ring. Thus, condensed heterocycles without a "quasi-aromatic" structure could be prepared for the first time by this rDA method. The process involves the incorporation of the oxazine-fused heterocycles onto the furan diene, followed by cleavage of the carrier part in the closing thermolytic step. The use of furan extends the scope of the rDA reaction, because the formation of the new hetero ring requires the presence of neither an oxo nor a thioxo group to ensure the electron demand and conjugation and to permit incorporation of the heterocycles, as in the case of CP. The easy loss of furan promotes the formation of the new hetero ring. This rDA process does not require drastic thermal conditions or special instruments such as in flash vacuum pyrolysis, and the heterocycles can be obtained in good yields on a preparative scale.

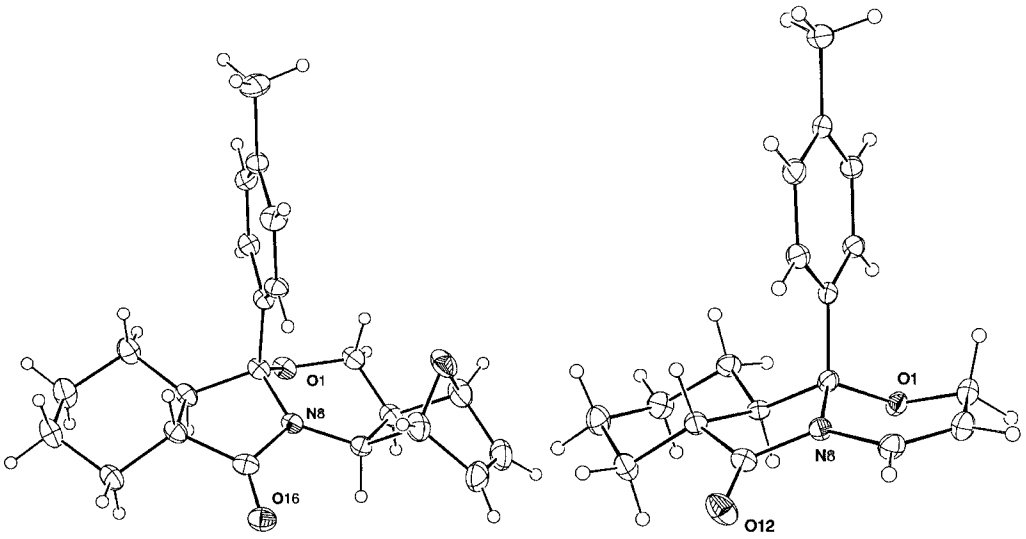
Structure

The structures of compounds **2** and **4**−**11** were confirmed by their IR and ^{1}H and ^{13}C NMR spectroscopic data; these are given in Tables 1 and 2. In the Tables and in the text of this part, the numbering of pyrrolobenzoxazine **4** (Scheme 2) is used for all compounds. The C atoms of the condensed benzene (**5**, **8**, **10** and **11**) and the cyclohexane rings (**6** and **9**−**11**) are numbered C-3′−6′ (**5** and **8**) or C-1′−6′ (**10** and **11**) and C-3′′−6′′, respectively (see Scheme 2).

As a consequence of the $-I$ effect of the C=C double bond on the N (imide-like structure),[12] the amide-I frequency of the rDA products **7**−**9** is higher by 6−21 cm^{-1}.

In **4**−**6** and **10**, the unaltered di-*exo* structure of the oxanorbornene moiety relative to the oxazine ring is confirmed by the doublet split of the 5a-H (NC*H*) ^{1}H NMR signal, in accordance with our splitting rule:[13,14] because of the ca. 90° dihedral angles, the 5a,6 and 9,9a vicinal H,H couplings do not cause a doublet split of the 5a-H and 9a-H signals for the di-*exo* compounds, whereas these couplings give rise to a readily detectable 2−4 Hz split for the di-*endo* molecules, in which the dihedral angles are ca. 30°. Because of the 5a-H,9a-H interaction, these protons give doublets for the di-*exo* and double doublet signals for the di-*endo* derivatives.

In **4**, a *trans* relationship of the tolyl group and 5a,9a-H relative to the oxazinone ring is probable from the negative result of the DIFFNOE experiment: no NOE was observed between the *ortho*-hydrogen atoms of the tolyl group and 5a,9a-H. This is indirect evidence of the stereostructure in Scheme 2. The analogous structure of **6** follows from the identical ^{1}H and very similar ^{13}C NMR chemical shifts of 5a,9a-H/C-5a,9a and the OCH_2 group. In **6**, the *trans* relationship of the cyclohexane ring to the pyrrolidone is obvious from the double triplet split of the 2,3-H signals, which indicates two *diaxial* couplings for each of these hydrogen atoms. With a preferred chair conformation for the cyclohexane, the very strong shielding of 6′′-H_{ax} (δ = 0.45 ppm) is evidence of the *exo* (*trans* to 5a,9a-H and 2-H) orientation of the tolyl group (anisotropic shielding by the close-lying benzene ring).[15a] X-ray measurements on **6** confirm the presumed stereostructure (Figure 1). Its rDA product **9** has an analogous structure: the *trans*-condensed cyclohexane can be assumed from the double triplet split of



6 **9**

Figure 1. Perspective views of **6** and **9**; thermal ellipsoids have been drawn at a probability level of 30%

Table 1. Characteristic IR frequencies and ^{1}H NMR spectroscopic data for compounds **2** and **4**–**11**

[a][b][c]	Amide-I band	$\gamma C_{Ar}H$ band[g]	CH_3 s (3 H)	2-H	3-H	OCH_2 (2 ×1 H)[d]	5a-H[e]	9a-H[f]	6-H	9-H	7-H	8-H	2′,6′-H	3′,5′-H
				Pyrrolidone ring[h]		6-Membered heterocycle			OCH groups[i]		Olefinic group[k]		*p*-Tolyl group[l]	
2	1555[m]	–	–	–	–	–	3.52	2.68	5.06	5.15	6.40	6.64	–	–
4	1699	820	2.36	2.25,[n] ca. 2.4		3.52, 4.15	3.96	2.07	4.98	4.47	6.53	6.28	7.24	7.19
5	1700	800	2.32	–	–	3.96, 4.03	4.60	2.02	4.79	4.73	6.52	6.36	7.42	7.15
6	1699	823	2.37	1.98	1.91	3.52, 4.15	3.97	2.08	4.92	4.41	6.52	6.26	ca. 7.2 broad	
7	1705	819, 837	2.38	ca. 2.3, ca. 2.4,[o] ca. 2.45		3.86, 4.17	7.02	5.07	–	–	–	–	7.20	7.22
8	1716	827	2.34	–	–	4.23, 4.33	7.19	5.17	–	–	–	–	7.47	7.20
9	1713	822	2.29	1.98	1.80	3.84, 4.06	6.90	4.92	–	–	–	–	7.13	6.90
10	1688	767	–	ca. 2.6		3.68, 4.10	3.78	2.48	7.04	4.70	6.39	6.52	–	–
11	1709	759	–	ca. 2.41[p]	2.49[q]	4.33, 4.45	6.96	5.36	–	–	–	–	–	–

[a] IR In KBr discs [cm^{-1}]. Further IR bands: νNH (**2**): 3600–2250 broad; $\nu_s CO_2^-$ (**2**): 1400; νC–O (oxazine): 1079 (**4**), 1045 (**5**, **8**), 1070 (**6**), 1065 (**7**, **10**), 1060 (**9**), 1015 (**11**); νC–O (oxanorbornene): 1382 (**4**, **6**), 1370 (**5**), 1392 (**10**); $\gamma C_{Ar}H$ (olefinic group, split band for **10**): 703 (**4**–**6**, **9**, **10**), 730 (**7**), 724 (**8**), 720 (**9**, **10**), 710 (**11**); $\gamma C_{Ar}H$ band (*ortho*-disubstituted ring): 760 (**5**, **8**, **11**), 767 (**10**). [b] ^{1}NMR in $CDCl_3$ (**4**–**10**), D_2O (**2**) or [D_6]DMSO (**11**) solution at 500 MHz. Chemical shifts in ppm (δ_{TMS} = 0 ppm), coupling constants in Hz. Further ^{1}H NMR signals: cyclohexane, ca. q* and ca. d* [s*, d*, t* and q*: signals (s, d, t, q) split further to more complex multiplets with coalesced lines], 3"-CH_2: 1.25 and 2.15 (**6**, **9**), 1.15 and 1.9 (**10**), 0.75 and 1.6 (**11**), 4"-CH_2: 1.2 and 1.65 (**6**, **9**), 1.8 (2 H, **10**), 1.45 and 1.7 (**11**), 5"-CH_2: 1.0 and 1.75 (**6**, **9**), 3.05 (m, 1 H, **10**, **11**), 6"-CH_2: 0.45 and 1.85 (**6**, **9**), 1.15 and 1.9 (**10**), 1.85 and ca. 2.1 (**11**), condensed benzene ring, 3′-H, ca. d*: 7.85 (**5**, **8**), 7.15 (**10**, **11**), 4′-H, ca. t*: 7.45 (**5**, **8**), 7.25 (**10**, **11**), 5′-H, ca. t*: 7.5 (**5**, **8**), 7.2 (**10**, **11**), 6′-H, ca. d*: 7.45 (**5**, **10**, **11**), 7.55 (**8**). [c] Assignments were supported by HMQC and HMBC (except for **9**), for **4**, **5**, **10** and **11** also by DIFFNOE and for **6**, **8** and **11** by 2D-COSY experiments. [d] 2 × dd, J = 11.9, 9.8 and 11.9, 8.0 (**4**, **6**), 12.1, 6.0 and 12.1, 5.8 (**5**), td and ddd, J = 16,7, 1.8, 1.8 and 16.7, 3.7, 2.0 (**7**, **8**), d and ddd, J = 16.6 and 16.6, 3.8, 2.0 (**9**), t and dd, J = 11.5, 11.5 and 11.2, 5.8 (**10**), ddd and td, J = 17.7, 3.8, 2.0 and 17.7, 2.0 and 2.0 (**11**). [e] NCH group, d, J = 7.5 (**2**), 8.3 (**4**–**6**), 6.7 (**10**), td, J = 8.3, 2.0 and 2.0 (**7**, **9**, **11**). [f] d, J = 7.5 (**2**), qa, J = 8.3 (**4**), td, J = 8.3, 5.9, 5.9 (**5**), 9.8, 8.1, 8.1 (**6**), ddd, J = 8.4, 3.8, 1.7 (**7**–**9**, **11**). [g] *p*-disubstituted ring, split for **7**. [h] Methylene groups in **4** and **7**, 2–3 m (4 H), methine groups in **6** and **9**–**11** (1 H), 2 × dt, J = 12.2, 12.2, 3.4 and 12.5, 12.5, 3.0 (**6**, **9**). [i] 2 × ca. s* (2 × 1 H), for **6** further split to t's by 1.2 Hz due to long-range couplings. [k] 2 × dd, J (for both dd's) = 5.8, 1.0 (**2**), 5.8, 1.7 ± 0.2 (**4**–**6**, **10**). [l] AA′BB′-type signal, 2 × d* (2 × 2 H), J = 8.1 (**4**, **5**, **8** and **9**). [m] $\nu_{as}CO_2^-$ band (**2**). [n] Intensity: 1 H, the m of the other H of 2-CH_2 overlaps with the 3-CH_2 signals at about 2.4. [o] Intensity: 2H. [p] Hidden by the light isotope signal of the solvent. [q] td, J = 11.1, 7.8, 7.8.

the 2,3-H signals and the similar sums of the ^{13}C NMR shifts[15b] for this ring (203.5 and 201.5 ppm for **6** and **9**, respectively), while the *exo* (*trans* to 2-H) orientation of the tolyl group follows from the 6′′-H shift of δ = 0.48 ppm. The X-ray results are in accordance with the above (Figure 1).

As in **6**, the analogous configuration of C-1a (i.e., the position of the tolyl substituent *trans* to 5a,9a-H) in **5** follows from the similar shifts of 9a-H/C-9a, C-5a and C-10 (Δδ = 0.06/1.6, 1.1 and 0.3 ppm). As negative evidence, no NOE was observed for the tolyl *ortho*-protons and 5a,9a-H in **5**. Because of the different steric positions of 5a-H and

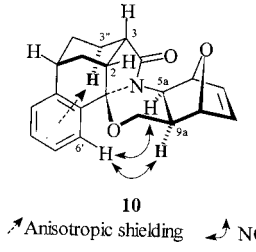
Table 2. ^{13}C NMR chemical shifts for compounds **2** and **4**−**11**

[a][b][c]	C-1a	C-2[d]	C-3[d]	C=O	C-7	C-8	OCH_2	NCH	C-9a	C-6	C-9	C-1′	C-2′6′	C-3′5′	C-4′
	Pyrrolidone ring				Olefinic group		6-Membered heterocycle			OCH groups		*p*-Tolyl group or benzene ring[e]			
2	–	–	–	179.0	135.4	141.9	–	52.9	48.5	84.1	85.1	–	–	–	–
4	93.4	39.4	29.0	176.4	136.1	135.2	65.0	51.5	31.0	83.5	80.3	138.8	126.0	129.6	138.1
5	92.1	149.6	127.9	171.4	136.3	136.7	64.6	51.6	32.9	82.4	81.3	137.2	125.6	129.6	138.1
6	93.9	55.5	43.7	177.2	136.0	135.0	64.9	50.5	31.3	84.0	80.2	134.0	129.2[e]		138.4
7	92.5	36.6	29.3	170.9	120.1	109.5	61.9	–	–	–	–	137.0	125.9	130.1	138.9
8	90.8	147.0	130.43	166.2	121.0	109.8	62.6	–	–	–	–	135.2	126.0	130.35	
9	92.9	52.9	44.6	171.5	119.8	108.2	61.5	–	–	–	–	132.5	127.1	129.4	139.0
10	90.7	38.9	39.8	177.1	135.3	137.5	63.3	53.3	39.9	78.5	78.8	139.3	140.5		
11	85.5	39.7	42.7	173.3	121.4	108.1	60.8	–	–	–	–	139.6	140.0		

[a] In ppm (δ_{TMS} = 0 ppm) at 126 MHz. Solvent: $CDCl_3$ (**4**−**10**), D_2O (**2**) or [D_6]DMSO (**11**). [b] Assignments were supported by DEPT, HMQC and HMBC (except for **9**) measurements. [c] Further lines [numbering: see **4**−**6** and **10** (Scheme 2)]: CH_3: 21.5 (**4**−**9**). Condensed benzene/cyclohexane ring, C-3′/3": 123.9 (**5**), 25.9 (**6** and **9**), 124.6 (**8**), 128.96/21.1 (**10**), 129.5/20.7 (**11**), C-4′/4": 129.7 (**5**), 25.6* (**6** and **9**), 130.1 (**8**), 129.02/31.0 (**10**), 129.7/32.1 (**11**), C-5′/5": 133.4 (**5** and **8**), 25.7* (**6** and **9**), 127.0/34.5 (**10**), 127.8/34.2 (**11**), C-6′/6": 123.2 (**5** and **8**), 27.1 (**6**), 26.8 (**9**), 127.5/26.5 (**10**), 126.4/25.8 (**11**); where * are interchangeable assignments. [d] CH_2 group (**4**, **6**, **7** and **9**−**11**) or substituted carbon atoms (condensed benzene ring, **5** and **8**). [e] Two broad coalesced lines.

the tolyl group, the downfield shift of 5a-H (by 0.63 ppm) is opposite in sign to that expected if the C-1a configuration had changed (*endo*-tolyl group). This is a consequence of the strained benzo-fused skeleton.

Because of the three common C atoms with the condensed pyrrolidone ring, the homotricyclic part of the heptacycle **10** and its rDA derivative **11** is rather rigid and contains the cyclohexane ring in chair form, with 2,3,5′′-H in *cis*,*cis* positions. For steric reasons, the C-1a configuration must be (*R*) for the enantiomer shown; the O atom is thus *cis* with 2,3-H relative to the pyrrolidone ring. Lying above the benzene ring, 3′′-H is strongly shielded (its signal is at δ = 1.15 and 0.72 ppm in **10** and **11**, respectively, shifted upfield in relation to all the other hydrogen signals in these molecules). The oxanorbornene moiety is fused to the other part of the molecule (to the pentacycle in **11**) in such a way that the bridging O lies over the heterobicyclic part of the skeleton, close to 2,3-H (Figure 2).



10

↗Anisotropic shielding ↙ NOE

Figure 2. Stereo structure of **10**; anisotropic shielding and NOE

The strong hindrance between the bridging O and the benzene ring means that the opposite mode of fusion, which would result in an extremely crowded structure, can be ruled out for steric reasons. The oxazine ring of **11** has a boat conformation, with N and the methylene C atom out of the plane of the other four atoms. In the other relatively stable conformation of oxazine (a sofa form with five coplanar atoms and an out-of-plane O), the two ethereal O atoms would come rather close to each other. As evidence of this steric arrangement, besides the geminal coupling of 11.2 Hz, the O-methylene hydrogen atoms have vicinal couplings of 11.8, 5.8 Hz with 9a-H, consistent with the dihedral angles of ca. 170° and ca. 50°. For **10**, the dramatic downfield shift of the 6-H singlet at δ = 7.04 ppm (which appears in the 4.79−4.98 ppm interval in the ^1H NMR spectra of **4**−**6**) is further evidence of this steric structure. This can be explained by the anisotropy of the carbonyl group,[15c] situated close to and coplanar with 6-H in the presumed conformation. In accordance with the above, a strong NOE was observed between 6′-H and 5a,9a-H.

Experimental Section

General Remarks: IR spectra were run in KBr discs with a Bruker IFS-55 FT spectrometer controlled by Opus 3.0 software. The ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ solution in 5-mm tubes at room temp. with a Bruker DRX 500 spectrometer at 500 (^1H) and 126 (^{13}C) MHz, with the deuterium signal of the solvent as the lock and TMS as internal standard. The standard Bruker micro program NOEMULT was used to generate NOE[16] and to obtain DIFFNOE spectra[15d,17] with a selective pre-irradiation time. DEPT spectra[18] were run in a standard manner,[19] with use only of a Θ = 135° pulse to separate the CH/CH_3 and CH_2 lines phased "up" and "down", respectively. The 2D-COSY,[20a,21a] HMQC[20b,21b] and HMBC[22,23] spectra were obtained by use of the standard Bruker pulse programs COSY-45 INV4GSSW and INV4GSLRNDSW, respectively.

Di-*exo*-3-amino-7-oxabicyclo[2.2.1]hept-5-ene-2-carboxylic Acid (2): Di-*exo*-7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride (33.23 g, 0.2 mol) was added in portions at 0 °C to a stirred solution of NH_4OH (6%, 280 mL). At the same temperature, a cooled solution of NaOH (24.40 g, 0.61 mol) in water (110 mL) was added dropwise. After removal of the excess ammonia, the mixture was diluted with water (330 mL), and NaOCl solution (2.04 M, 100 mL) was added dropwise over a period of 1 h, with stirring and cooling. The solution was maintained at 70 °C for 5 min, and was then cooled and adjusted to pH = 2 with HCl (36%). After concen-

tration to dryness in vacuo, the residue was extracted with hot EtOH (5 × 100 mL). The alcoholic solution was concentrated, and the residue was dissolved in water and transferred to a column of Dowex 50 ion-exchange resin (in acid form). The column was washed with water until neutral, and the amino acid **2** was eluted with a mixture of NH_4OH (25%, 600 mL) and water (2400 mL). The residue from the concentrated eluate was dissolved in water, the solution was filtered, and acetone was added until turbidity appeared. Yield: 16.45 g (53%), as a white powder, mp. 194−195 °C (decomp.).

(Di-*exo*-3-amino-7-oxabicyclo[2.2.1]hept-5-en-2-yl)methanol (3): Amino acid **2** (5.0 g, 32 mmol) was added to a stirred suspension of $LiAlH_4$ (3.15 g, 0.083 mol) in dry THF (200 mL) at 0 °C. Stirring was continued at room temperature for 8 h. After standing overnight, the mixture was cooled, and a solution of water (7 mL) in THF (30 mL) was added dropwise. After filtration, the filtrate was concentrated to furnish the crude amino alcohol as a yellow oil (3.45 g, 76%), which was applied in the further reactions.

6,9-Epoxy-3a-*p*-tolyl-2,3,5a,6,9,9a-hexahydro-5*H*-pyrrolo[1,2-*a*]-[3,1]benzoxazin-1-one (4), 1,4-Epoxy-6a-*p*-tolyl-1,4,4a,12a-tetrahydro-5*H*-isoindolo[2,1-*a*][3,1]benzoxazin-11(6a*H*)-one (5), 1,4-Epoxy-6a-*p*-tolyl-1,4,4a,6b,7,8,9,10,10a,12a-decahydro-5*H*-isoindolo[2,1-*a*][3,1]benzoxazin-11(6a*H*)-one (6), 8a-*p*-Tolyl-7,8-dihydro-2*H*-pyrrolo[2,1-*b*][1,3]oxazin-6-one (7), 10b-*p*-Tolyl-2*H*-[1,3]-oxazino[2,3-*a*]isoindol-6(10b*H*)-one (8), 10b-*p*-Tolyl-6a,7,8,9,10,10a-hexahydro-2*H*-[1,3]oxazino[2,3-*a*]isoindol-6(6a*H*)-one (9), 1,4-Epoxy-7,9-ethano-4,4a,7,7a,8,9,15,15a-octahydro-1*H*,6*H*-benzo-[6,7]indolo[1,7a-*a*][3,1]benzoxazin-6-one (10) and 11,13-Ethano-11,11a,12,13-tetrahydro-6*H*,10*H*-benzo[*g*][1,3]oxazino[2,3-*i*]indol-10-one (11). General Procedure: A mixture of amino alcohol **3** (1.41 g, 0.01 mol), oxo acid [(0.01 mol): 3-(*p*-toluoyl)propionic acid (1.92 g) or *cis*- or *trans*-2-(*p*-toluoyl)cyclohexane-1-carboxylic acid (2.46 g) or 2-(*p*-toluoyl)benzoic acid (2.40 g) or 10-oxohexahydro-5,9-methanobenzocyclooctene-8-carboxylic acid[24] (2.30 g)] and *p*TSA (0.05 g) in dry toluene (30 mL) was heated at reflux for 8 h with the application of a Dean−Stark separator. After the solvent had been evaporated, the residue was dissolved in $CHCl_3$ (10 mL), transferred to a silica gel column (Kieselgel 60 Merck, 0.040−0.063 mm) and eluted, first with *n*-hexane/EtOAc (4:1) for the rDA products **7**−**9** and **11**, and then with *n*-hexane/EtOAc (2:1) for **4**−**6** and **10**. The residues of the eluates were crystallized. Data on compounds **4**−**11** are listed in Table 3.

Preparation of Compounds 8 and 11 from 5 and 10: Compound **5** (0.58 g, 1.68 mmol) or **10** (0.42 g, 1.25 mmol) was heated at reflux in dry chlorobenzene (10 mL) for 2 h. The cooled solution was transferred to a silica gel column and eluted with *n*-hexane/EtOAc (4:1) for the rDA products **8** or **11**. Yields are given in Table 3.

Preparation of Compounds 7 and 9 by Direct rDA Reaction: A mixture of amino alcohol **3** (1.41 g, 0.01 mol), oxo acid **A** (1.92 g, 0.01 mol) or **C** (2.46 g, 0.01 mol) and *p*TSA (0.05 g) in dry 1,2-dichlorobenzene (30 mL) was heated at reflux for 2 h. The residue from the concentrated dichlorobenzene solution was dissolved in $CHCl_3$ (2×30 mL), transferred onto an aluminium oxide column (Merck, Aluminium oxide 90, neutral, 0.063−0.200 mm) and eluted with *n*-hexane/EtOAc (4:1) for the rDA products **7** or **9**. Yields and melting points are given in Table 3.

X-ray Crystallographic Study: Crystallographic data were collected at 173 K with a Nonius Kappa CCD area-detector diffractometer, with use of graphite-monochromatized Mo-K_α radiation (λ = 0.71073 Å). The data collection was performed with φ and ω scans. The data were processed with DENZO-SMN v0.93.0.[25] Crystal data for **6**: $C_{22}H_{25}NO_3$, M_r = 351.43, monoclinic, a = 8.7200 (4), b = 8.2127(4), 25.6171(15) Å, β = 93.827(2)°, V = 1830.47(16) Å^3, T = 173 K, space group $P2_1/c$ (no. 14), Z = 4, μ(Mo-K$_\alpha$) = 0.084 mm^{-1}, 3118 unique reflections (R_{int} = 0.067) which were used in calculations. The final $wR(F^2)$ was 0.0144 (all data). Crystal data for **9**: $C_{18}H_{21}NO_2$, M_r = 283.36, triclinic, a = 8.0749 (3), b = 9.7002(4), 9.9297(4) Å, α = 100.160(2), β = 99.861(2), γ = 97.555(2)°, V = 743.71(5) Å^3, T = 173 K, space group $P\bar{1}$ (no. 2), Z = 2, μ(Mo-K$_\alpha$) = 0.090 mm^{-1}, 2611 unique reflections (R_{int} = 0.040) which were used in calculations. The final $wR(F^2)$ was 0.1177 (all data). The structures were solved by direct methods by use of the *SIR92* program,[26] and full-matrix, least-squares refinements on F^2 were performed by use of the *SHELXL-97* program.[27] In both cases all heavy atoms were refined anisotropically. The H atoms were included at the fixed distances with fixed displacement parameters from their host atoms. Figures were drawn with *ORTEP-3 for Windows.*[28] CCDC-235065 (**6**) and -235066 (**9**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: (internat.) + 44-1223-336-033; E-mail: deposit@ccdc.cam.ac.uk].

Table 3. Physical and analytical data for compounds **2**−**11**

Compound	M.p. [°C]	Yield (%)	Formula (mass)	Analysis					
				Found			Calcd.		
				C	H	N	C	H	N
2	194−195[a][b]	53	$C_7H_9NO_3$ (155.15)	54.35	6.02	9.15	54.19	5.85	9.03
4	173−174[c]	25	$C_{18}H_{19}NO_3$ (297.35)	72.96	6.60	4.87	72.71	6.44	4.71
5	126−128[d]	28	$C_{22}H_{19}NO_3$ (345.39)	76.29	5.37	4.19	76.50	5.54.	4.06
6	192−194[c]	27	$C_{22}H_{25}NO_3$ (351.44)	75.31	7.30	3.51	75.19	7.17	3.99
7	77−78[e]	18	$C_{14}H_{15}NO_2$ (229.27)	73.56	6.75	6.23	73.34	6.59	6.11
8	148−150[e]	17 (57)[f]	$C_{18}H_{15}NO_2$ (277.32)	77.74	5.33	4.89	77.96	5.45	5.05
9	139−140[e]	22	$C_{18}H_{21}NO_2$ (283.36)	76.08	7.35	4.80	76.29	7.47	4.94
10	196−198[c]	19	$C_{21}H_{21}NO_3$ (335.40)	75.43	6.48	4.29	75.20	6.31	4.18
11	151−152[e]	21 (64)[g]	$C_{17}H_{17}NO_2$ (267.32)	76.61	6.57	5.39	76.38	6.41	5.24

[a] Crystallization solvent:H_2O/Me_2CO. [b] With decomposition. [c] Crystallization solvent: iPr_2O. [d] Crystallization solvent: Et_2O. [e] Crystallization solvent: Et_2O/*n*-hexane. [f] Obtained from **5**. [g] Obtained from **10**.

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[1] G. Stájer, F. Csende, F. Fülöp, *Curr. Org. Chem.* **2003**, *7*, 1423−1432.
[2] F. Miklós, G. Stájer, P. Sohár, Z. Böcskei, *Synlett* **2000**, 67.
[3] G. Stájer, F. Miklós, P. Sohár, R. Sillanpää, *Eur. J. Org. Chem.* **2001**, 4153−4156.
[4] L. A. Paquette (Ed.), *Organic Reactions*, John Wiley & Sons, New York, **1998**, vol. 52, p. 27.
[5] P. Vogel, J. Cossy, J. Plumet, O. Arjona, *Tetrahedron* **1999**, *55*, 13521−13642.
[6] G. Mandville, R. Bloch, *Eur. J. Org. Chem.* **1999**, 2303−2307.
[7] R. N. Warrener, D. Margetic, G. Sun, *Tetrahedron Lett.* **2001**, *42*, 4263−4265.
[8] O. Diels, K. Alder, *Ber. Dtsch. Chem. Ges.* **1929**, *62*, 554.
[9] T. A. Eggelte, H. De Koning, H. O. Huisman, *Tetrahedron* **1973**, *29*, 2445−2447.
[10] J. T. Manka, A. G. Douglas, P. Kaszynski, A. C. Friedli, *J. Org. Chem.* **2000**, *65*, 5202−5206.
[11] A. Basso, L. Banfi, R. Riva, G. Guanti, *Tetrahedron Lett.* **2004**, *45*, 587−590.
[12] S. Holly, P. Sohár, Theoretical and Technical Introduction to the Series *Absorption Spectra in the Infrared Region* (Eds L. Láng, W. H. Prichard), Akadémiai Kiadó, Budapest, **1975**, pp. 113−115.
[13] P. Sohár, G. Stájer, G. Bernáth, *Org. Magn. Reson.* **1983**, *21*, 512−519.
[14] P. Sohár, I. Pelczer, G. Stájer, G. Bernáth, *Magn. Reson. Chem.* **1987**, *25*, 584−591.
[15] P. Sohár, *Nuclear Magnetic Resonance Spectroscopy*, CRC Press, Boca Raton, FL, **1983**: [15a] vol. 1, pp. 35−40. [15b] vol. 2, p. 165. [15c] vol. 1, pp. 32−33. [15d] vol. 1, pp. 194−196.
[16] J. H. Noggle, R. E. Schirmer, *The Nuclear Overhauser Effect*, Academis Press, New York, **1971**.
[17] J. K. M. Sanders, J. D. Mersch, *Prog. Nucl. Magn. Reson.* **1982**, *15*, 353−400.
[18] D. T. Pegg, D. M. Doddrell, M. R. Bendall, *J. Chem. Phys.* **1982**, *77*, 2745.
[19] M. R. Bendall, D. M. Doddrel, D. T. Pegg, W. E. Hull, *High Resolution Multipulse NMR Spectrum Editing and DEPT*, Bruker, Karlsruhe, **1982**.
[20] R. R. Ernst, G. Bodenhausen, A. Wokaun, *Principles of Nuclear Magnetic Resonance in One and Two Dimensions*, Clarendon Press, Oxford, UK, **1987**: [20a] pp. 400−448. [20b] pp. 471−479.
[21] J. K. M. Sanders, B. K. Hunter, *Modern NMR Spectroscopy − A Guide for Chemistry*, University Press, Oxford, UK, **1987**: [21a] pp. 108−113. [21b] pp. 94−97 and pp. 100−107.
[22] A. Bax, G. Morris, *J. Magn. Reson.* **1981**, *42*, 501−505.
[23] H. Kessler, C. Griesinger, J. Zarboch, H. Loosli, *J. Magn. Reson.* **1984**, *57*, 331−336.
[24] F. Miklós, F. Csende, G. Stájer, P. Sohár, R. Sillanpää, G. Bernáth, J. Szúnyog, *Acta Chem. Scand.* **1998**, *52*, 322−327.
[25] Z. Otwinowski, W. Minor, *Methods in Enzymology*, vol. 276 ("Macromolecular Crystallography, part A") (Eds.: C. W. Carter Jr., R. M. Sweet), Academic Press, New York, **1997**, pp. 307−326.
[26] A. Altomare, M. Cascarano, C. Giacovazzo, A. Guagliardi, M. C. Burla, G. Pilodori, M. Camalli, *J. Appl. Crystallogr.* **1994**, *27*, 435−436.
[27] G. M. Sheldrick, *SHELX-97*, University of Göttingen, Germany, **1997**.
[28] L. J. Farrugia, *J. Appl. Crystallogr.* **1977**, *30*, 565−567.

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