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ISOMERIZATION AND APPLICATION OF AROYLNORBORNENE-CARBOXYLIC ACIDS FOR STEREOSELECTIVE PREPARATION OF HETEROCYCLES

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Abstract – When boiled in acidic or basic solution, *diendo*-3-aroylbicyclo[2.2.1]heptane-2-carboxylic acids (**1** and **1a**) isomerize to *exo*-3-aroylbicyclo[2.2.1]heptane-*endo*-2-carboxylic acids (**2** and **2a)**. Similar *endo* → *exo* and even *exo* → *endo* isomerization of the aroyl group occurred when the Diels-Alder product containing a mixture of 3-*exo*-*p*-toluoylbicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylic acid (**4**) and 3-*endo*-*p*-toluoylbicyclo[2.2.1]hept-5-ene-2-*exo*-carboxylic acid (**5)** was reacted with bifunctional reagents: *o*-aminothiophenol, 3-amino-1-propanol, 1,4-diaminobutane or *diexo*-3-hydroxymethylbicyclo[2.2.1]heptane-2-amine. All the reactions yielded mixtures of norbornene *diendo*- and *diexo*-fused heterocycles (**6**) and (**7, 8** and **10, 9** and **11**, or **12** and **13**), which were separated and whose structures were established by means of IR, ^{1}H- and ^{13}C-NMR spectroscopy, with DIFFNOE, 2D-COSY, DEPT, HMQC and HMBC measurements.

From *diendo*-3-aroylbicyclo[2.2.1]heptane- or -heptene-2-carboxylic acids, we earlier synthesized several heterocyclic compounds and observed that the products formed generally contained the *diendo* structural moiety, *i.e.* the *diendo* configuration of the starting norbornane/ene synthon remained unchanged.[1-3] In a

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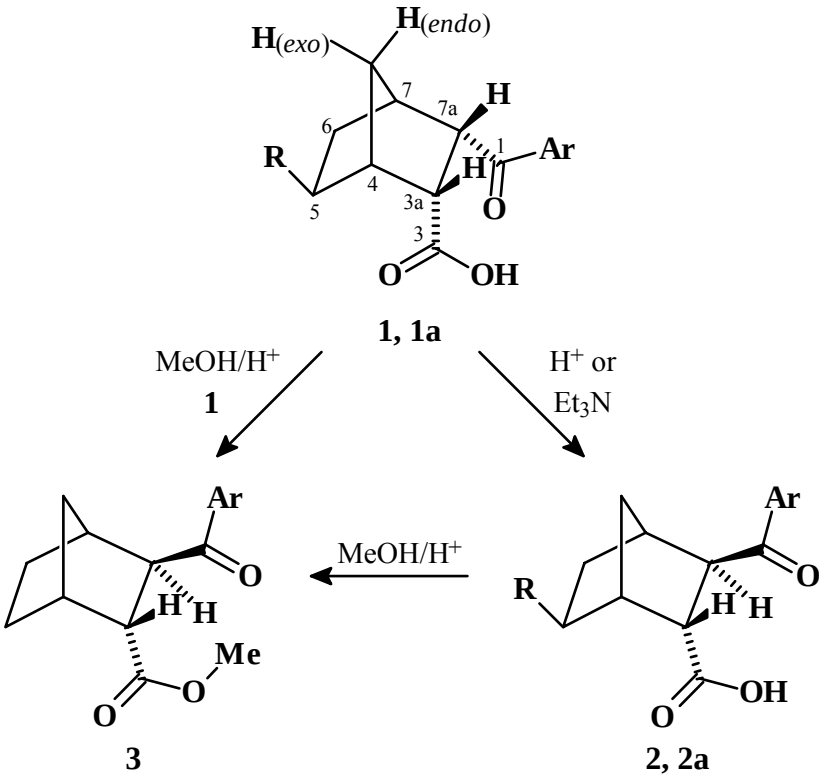
few cases, however, the configuration of the product was *exo–endo*[4] or *diexo*, the latter together with the *diendo*-fused heterocycle, as found in the cyclization of 6-phenyl-3-benzoylnorbornane-2-carboxylic acid (**1a**) with ethylenediamine.[5] These phenomena were of considerable interest; only a few studies have dealt with the similar epimerization of *diendo* norbornane derivatives.[6-8] As isomerization was recently reported in the syntheses of heterocycles from aroylnorbornanecarboxylic acids,[9] we have searched for new examples in order to study this behavior and to exploit it for the stereoselective preparation of new heterocycles.

RESULTS

When refluxed for 2 h in the presence of 2 drops of concentrated HCl or Et_3N in toluene, *diendo*-3-toluoylbicyclo[2.2.1]heptane-2-carboxylic acid (**1**) or its 6-*exo*-phenyl derivative (**1a**) was smoothly transformed to give the corresponding 3-*exo*-aroylbicyclo[2.2.1]heptane-2-*endo*-carboxylic acid (**2** or **2a**) in good yield (Scheme 1). (For comparison of the analogous spectroscopic data, the numbering to be seen in Schemes 1 and 2 have been used in this section on the Scheme and in the Tables.)



1, **2**: R = H, **1a, 2a**: R = Ph

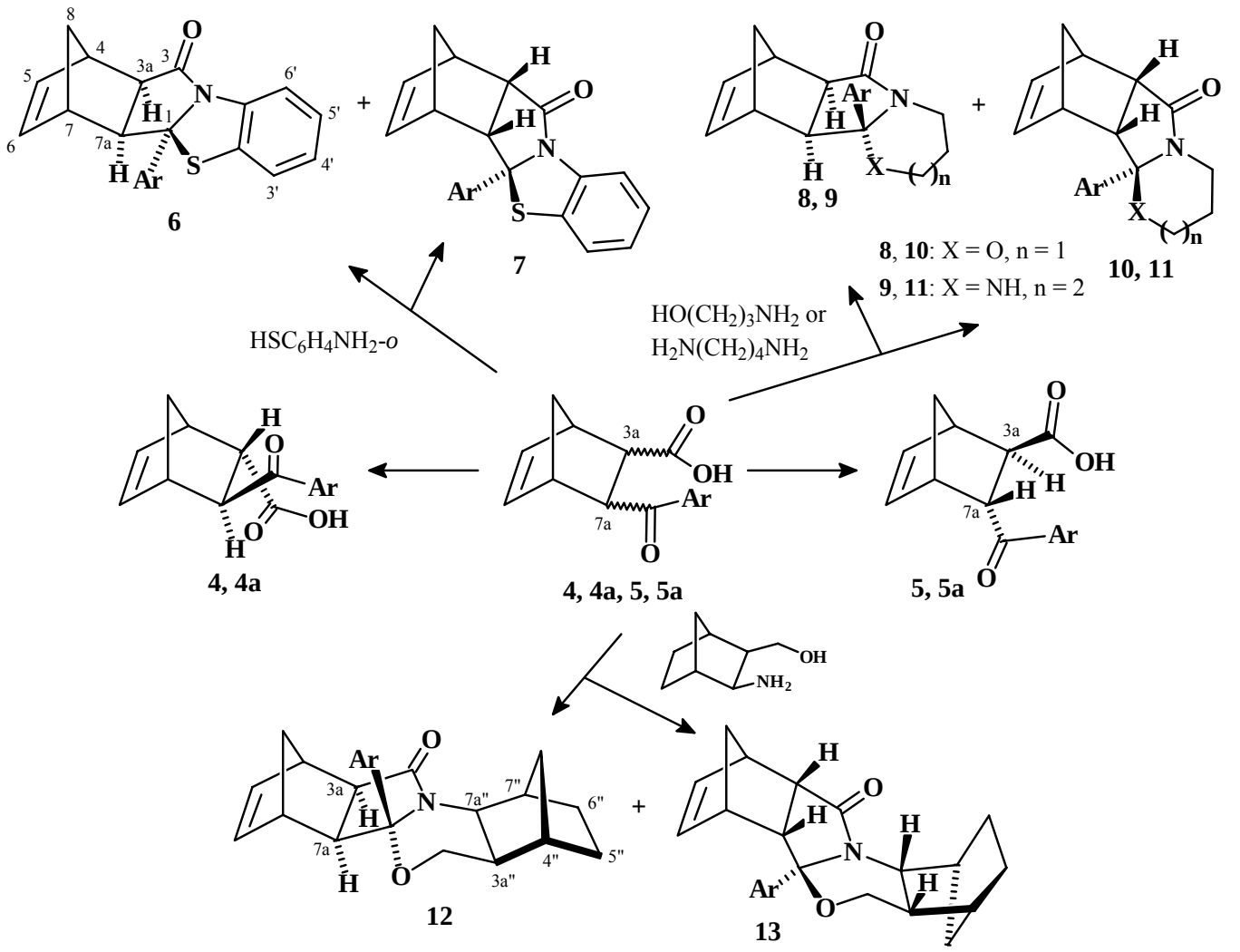
Ar = $C_6H_4CH_3$-*p*

Scheme 1

A similar *endo* → *exo* epimerization takes place in the esterification of **1** to the 3-*exo*-toluoyl derivative (**3**). For analogous cyclohexane derivatives, facile epimerization has frequently been observed, *cis*-aroyl-cyclohexanecarboxylic acids giving *trans* compounds.[10] However, the norbornane skeleton has higher

rigidity, and hence the configuration of the starting compound is generally retained in the product. Thus, few examples of the epimerization of carbons C-2–C-3 are to be found in the literature. Craig described a reversible *diendo* → *diexo* isomerization: when heated above the melting point, *diendo*-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride was transformed to the *diexo* analogue.[6] This change was due to the presence of the double bond in position 4 and was explained by the formation of a tautomeric intermediate (not isolated). In our case, facile enolization can be presumed if basic reagents are used.

To utilize this isomerization for synthetic purposes, a mixture of the isomers of the Diels-Alder adduct of *trans*-toluoylacrylic acid and cyclopentadiene[11,12] (**4**) and (**5**) was applied (Scheme 2). HPLC revealed that the ratio **4** : **5** was 57 : 43. This mixture and that of the phenyl analogues (**4a**) and (**5a**) were separated by column chromatography and the structures were established by means of NMR spectral measurements and, for **4**, also by X-Ray analysis (Figure). The results demonstrated that, in agreement with the literature,[11] **4** and **4a** contain *endo*-carboxyl and *exo*-aroyl, and **5** and **5a** *exo*-carboxyl and *endo*-aroyl groups.



Ar = $C_6H_4CH_3$-*p*, **a**: Ar = Ph

Scheme 2

A mixture of **4** and **5** was reacted with the bifunctional agents *o*-aminothiophenol, 3-amino-1-propanol, 1,4-diaminobutane and *diexo*-3-hydroxymethylbicyclo[2.2.1]hept-5-en-2-amine to afford mixtures of *diexo* and *diendo* isomeric heterocyclic compounds: methanoisoindolobenzthiazoles (**6**) and (**7**), methano[1,3]oxazinoisoindoles (**8**) and **10**, methanodiazepinoisoindoles (**9**) and (**11**)[9] and methanoisoindolomethano[3,1]benzoxazines (**12**) and (**13**). The isomers were separated by column chromatography.

For the products (**9**) and (**11**), HPLC separation showed that the ratio **9** : **11** was 42 : 58. Comparison of this with the ratio of 57 : 43 for **4** : **5** suggests that the aroyl group epimerizes: in these cyclizations, either the *exo* aroyl (**4**) gives the *diendo* (**11**), or the *endo* aroyl (**5**) gives the *diexo* derivative (**9**).

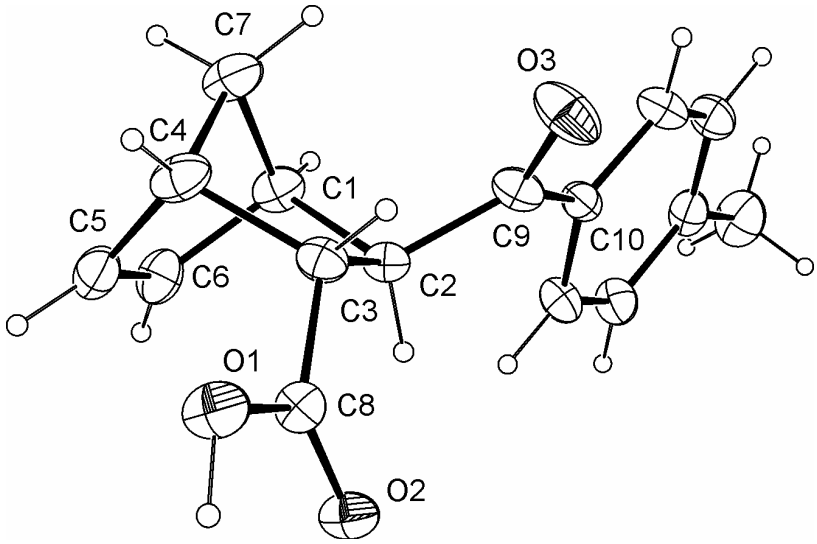


Figure 1

An ORTEP perspective view of compound (**4**). The ellipsoids are drawn at 20% probability

These reactions allow the conclusion that aroylnorbornanecarboxylic acids containing the two vicinal (2,3) functional groups in sterically unfavorable positions for ring closure can be advantageously used for the preparation of condensed heterocycles: on the action of acids or bases and simultaneous heating, the aroyl group epimerizes. The reactions of the readily available *trans*-aroylacrylic acid–cyclopentadiene adduct, containing a mixture of the aroyl group *exo* or *endo* to the *endo* or *exo*-carboxyl group, with bifunctional reagents (amino alcohols, diamines, etc.) provide good possibilities for stereoselective synthesis, but the two (*endo–endo* or *exo–exo*) fused derivatives have to be separated.

STRUCTURE

The constitutions of the new compounds follow straightforwardly from the spectral data (Tables 1 and 2) and only the stereostructures need to be determined. Our 'splitting rule',[13,14] for the H-3a,7a signals in the spectra of heterocycle-3a,7a-fused norbornane/ene derivatives predicts a doublet (*d*) split of the signals of these hydrogens in the *exo* position, and double doublet (*dd*) multiplicity in the event of their *endo* orientation. The doublet split (8-9 Hz) is due to the H-3a,7a-coupling (dihedral angle, $\Theta = 0°$), the

further split to double doublet is the result of the H-7,7a- and H-3a,4-couplings, respectively, which are about 3-4 Hz in *diendo* compounds ($\Theta \approx 30°$) and < 1 Hz in *diexo* analogues ($\Theta \approx 90°$) in accordance to the Karplus relation. For *exo–endo* substituted non-condensed derivatives such as **2-5**, however, this rule is to be modified. The H-3a,7a- (*exo–endo*-) coupling is here significant smaller ($\Theta \approx 110$-$120°$) and, hence a doublet and a triplet multiplicity split by 3-5 Hz is to be expected.

Table 1. Characteristic IR abrorptions and ^{1}H-NMR spectral data[b] for compounds (**2, 2a, 3, 4, 4a, 5, 5a**) and (**6-13**)[c]

Com-pound	νOH/νNH band	νC=O ketone	νC=O band	$\gamma C_{Ar}H$ tolyl	CH_3[d] *s* (3H)	H-3a (1H)[e]	H-4 ~*s* (1H)	H-5 (1H)[f]	H-6 (1H)[f]	H-7 ~*s* (1H)	H-7a (1H)[g]	CH_2(8) 2×*d* (2×1H)[h]		H-2,6 tolyl group[i]	H-3,5 tolyl group[i]
2	3300-2500	1672	1698	857	2.41	~3.65[j]	2.74	~1.5		2.46	~3.65[j]	1.24	1.57	7.89	7.26
2a	3300-2500	1679	1700	820	2.42	3.80	2.90[k]	3.07[l]	1.92[m]	2.59[k]	3.78	1.55		7.93	7.27
3	–	1670	1730	823	2.38	3.55	2.66	1.35[m]	1.57[m]	2.44	3.67	1.19	1.53	7.88	7.28
4	3300-2500	1673	1702	822	2.42	3.73	3.34	6.23	6.42	3.04	3.59	1.42[n]	1.68	7.92	7.27
4a	3300-2500	1674	1696	762	7.58	3.75	3.36	6.24	6.43	3.06	3.62	1.43[n]	1.68	8.02	7.48
5	3300-2500	1669	1699	805	2.42	3.10	3.32	6.32	5.82	3.28	4.27	1.52	1.82	7.90	7.27
5a	3300-2500	1683	1697	763	7.58	3.11	3.30	6.33	5.83	3.33	4.30	1.54	1.82	7.79	7.48
6	–	–	1718	850	2.33	3.15	3.30	6.28	6.16	2.43	3.11	1.26[n]	1.44	~7.6	7.25
7	–	–	1722	831	2.29	3.70	3.32	6.14	5.04	2.88	3.85	1.46	1.51	~7.1	~7.1
8	–	–	1695	820	2.33	2.66	3.11	6.09	5.94	1.77	2.23	1.03	1.28	7.38	7.25
9	3310	–	1666	823	~2.33[j]	2.58	3.14	6.12	6.00	2.07	~2.34[j]	0.97	1.13	7.55	7.23
10	–	–	1695	819		3.31	3.16	5.99	5.33	2.35	2.98	1.27	1.34	7.38	7.20
11	3307 3286	–	1660	821	2.34	3.24	~3.12[j]	5.96	4.77	2.63	~3.12[j]	1.34	1.37	~7.5	~7.1
12	–	–	1693	827	2.39	2.28	3.19	6.15	5.98	2.28	2.67	1.08[n]	1.29	7.38	7.27
						4.14	1.74	1.10[o]	1.45[p]	1.67	2.04	0.72	0.82[n]	7.20	7.12
13	–	–	1692	825	2.40	3.34	3.20	6.10	5.27	2.38	3.09	1.36	1.41	7.16	7.07
						4.03	2.30	1.10[o]	1.45[p]	1.65	1.99	0.76	0.93	7.40	7.23

Further ^{1}H-NMR spectral data, ppm: OCH_3, s (3H): 3.65 (**3**), $CONCH_2$, *dt* and *dd* (*J* = 13.2, 3.6, 5.3): 3.02, 4.10 (**8**), 3.01, 4.02 (**10**), ~*t* and ~*d* (*J* = 13.7): 2.73, 4.02 (**9**), 2.73, 3.97 (**11**); OCH_2/$HNCH_2$, *dt* and *dd*: 3.62 and 3.70 (*J* = 12.0, 3.6, 5.3, **8**), 3.46 and 3.61 (*J* = 12.1, 2.4, 4.6, **10**), ~*t* and ~*d* (*J* = 14.5): 2.46 and 2.98 (**9**), 2.51 and 2.98 (**11**), *dd* and *dd* (**12**): 3.39 (*J* = 12.3, 10.8) and 3.89 (*J* = 12.3, 8.9), *dd* and *t* (**13**): 3.78 (*J* = 12.4, 8.6) and 3.25 (*J* = 11.8); CC**H**$_2$C/(CONCH$_2$)C**H**$_2$: 1.19 and 1.84 (**8**), ~1.5 and ~1.85 (**9**), 1.14 and 1.75 (**10**), 1.48 and ~1.8 (**11**); (O/NHCH$_2$)C**H**$_2$: ~1.1 and ~1.8 (**9**, **11**); Phenyl group (Pos. 5 in **2a**): 7.22 *d* (*J* = *7.4*, 2H), 7.29 *t* (2H) and 7.18 t (1H); Condensed benzene ring (**6** and **7**), 3'-H, d: 7.63 and 7.54, 4'-H, t: 7.17 and 7.12, 5'-H, t: 7.09 and 7.04, 6'-H, d: 7.12 and 7.06. [a]In KBr discs (cm^{-1}); [b]In $CDCl_3$ solution at 500 MHz. Chemical shifts in ppm (δ_{TMS} = 0 ppm); coupling constants in Hz; [c]Assignments were supported by HMQC for **4b**, **5a** and **12** 2D-COSY and for **2, 2a, 3, 4, 4a, 9** and **11** also by DNOE measurements; [d]H-4 (tolyl), *t* (1H) for **4a** and **5a**; [e]Multiplicity, *J* = ~*qa*, 4.8 (**2a**), ~*dt* (**3**), *t*, 4.1 (**4, 4a**), *d*, 4.2 (**5**), 3.2 (**5a**), 7.9 (**8**), 8.5 (**9** and **12,** norbornene), 9.0 (**13,** norbornane), *dd*, 8.2 and 1.1 (**6**), 9.1 and 4.9 (**7** and **10**), 9.1. and ~1 (**12,** norbornane), 9.8 and 4.8 (**13,** norbornene); [f]For norbornenes 2 x *dd* (*J* = 5.5 ± 0.1 and 2.9 ± 0.3), for norbornanes 1-3 m (total intensity: 4H); Coalesced signal (4H) for **2**; [g]Multiplicity, *J* = *t*, 5.6 (**2a**), 4.0 (**5, 5a**), *d*, 5.3 (**3**), 8.2 (**6**), 7.1 (**8**), *dd*, 4.3 and 1.0 (**4, 4a**), 9.3 and 3.8 (**7**), 9.0 and 3.8 (**10**), 9.6 and 4.6 (**11**), 9.8 and 3.9 (**13,** norbornene), *td*, 8.6, 1.3 and 1.3 (**12,** norbornene), *qa*, 9.7 (**12, 13,** norbornane); [h]*J* = 10.0 (**2, 3**), 8.8 (**4, 4a**), 8.5 (**5, 5a, 7**), 9.2 (**6, 8, 9, 12,** norbornane), 8.2 (**10, 11, 13,** norbornene), 10.5 (**12, 13,** norbornane), coalesced for **2a**. δH(*endo*) > δH(*exo*) as proved by NOE's for **2, 2a, 3, 4, 4a** and **9** (reversed for **11**); [i]2 × ~*d* (2 × 2H), *J* = 8.1 ± 0.1. For **4a** and **5a** H-3',5', ~*t* (2H). Due to the hindered rotation of the tolyl group, the H-2,6 and H-3,5 signals are separated (**6-13**), for **6, 7** and **11** also broadened and in cases **7** and **11** coalesced. Further *d*'s at ~6.97 and ~7.1 (**6**), 6.98 and 7.12 (**8**), 6.90 and 7.07 (**9**), 6.92 and 7.06 (**10**), 6.75 (**11**). The counterparts of split signals of **12** and **13** are given in the second row in the Table; [j]Overlapping signals. [k]*d*, *J* = 5.6. [l]*dd* (1H), *J* = 8.6 and 5.8; [m]Intensity 1H. Other signals [m (1H)] of the methylene group for **2a** at 2.15 (Pos. 6) and for **3** at 1.48 (Pos. 5) and 1.62 (Pos.6); [n]Due to W-type long-range couplings, further split by 1.5 0.1 to *qad* (**4, 4a**) or *td* (**6, 12**); [o/p]Intensity 1H/3H.

To determine the *exo* or *endo* position of the substituents in **2a, 3, 4** and **4a** unanimously, DIFFNOE measurements[15a,16] were applied (Table 3). The *exo–endo* arrangement of the 3a,7a substituents is probable from the different splitting patterns (*d* and *t*) and the values of the coupling constants (Table 1), while the *endo* orientation of the 3-carboxyl group in **4** and **4a** is proved by the Overhauser effect (NOE[17]) between one of the bridging methylene-H atoms and H-3a (*cf.* Table 3). The same NOE is also proof of the analogous stereostructure of **3**.

Table 2. ^{13}C-NMR chemical shifts[a] for compounds (**2, 2a**, **3, 4, 4a, 5, 5a**) and (**6-13**)[b,c]

Com-pound	CH_3	C-1	C-3	C-3a	C-4	C-5	C-6	C-7	C-7a	C-8	C-1'	C-2'6'	C-3'5'	C-4'
					norbornane/ene						1-toluoyl/phenyl group			
2	22.0	199.6	179.9	47.6	40.5	25.1	29.8	43.6	51.7	37.8	134.0	129.2	129.7	144.2
2a	22.0	199.4	179.0	48.1	46.8	42.4	38.3	44.1	51.3	35.3	134.0	129.2	129.8	144.4
3	22.0	199.8	174.8	47.7	40.5	25.1	29.7	43.4	51.9	37.8	134.1	129.2	129.6	144.1
4	22.0	199.6	180.2	47.0	46.2	136.4	138.0	49.1	50.4	47.1	134.4	129.1	129.8	144.4
4a	–	200.0	180.1	47.0	46.2	136.4	138.0	49.1	50.6	47.1	136.8	129.0	129.1	133.6
5	22.1	198.6	181.0	46.1	48.4	137.8	134.2	48.6	51.5	48.5	134.6	128.9	129.7	144.3
5a	–	199.0	181.1	46.1	48.3	137.8	134.1	48.6	51.7	48.5	137.1	128.8	129.1	133.5
6	21.5	87.7	178.1	49.9	45.3	139.23	138.4	46.2	53.7	44.0	137.9	~125.1[d]	~128.3[d]	139.20
7	21.5	86.7	178.3	50.4	45.8	134.9	135.8	47.2	53.6	52.0	137.7	~126.3[d]	~128.6[d]	141.1
8	21.6	95.2	178.0	49.9	44.4	138.61	138.57	45.1	53.0	43.5	134.3	127.9	129.1	138.4
9	21.4	84.7	176.7	51.1	44.4	138.9	138.5	46.5	54.4	43.8	137.8	126.0[d]	128.4[d]	138.8
10	21.6	94.3	178.2	49.9	45.0[e]	134.5	135.5	45.1[e]	53.3	52.5	135.3	127.9[d]	128.2[d]	138.4
11	21.4	84.2	176.9	51.6	44.5	134.0	136.6	47.0	54.8	52.5	137.9	~127.7[d]	~127.7[d]	140.4
12[f]	21.6	94.7	180.0 64.5	42.8 39.2	44.2 39.5	138.8 27.5	138.6 30.5	54.0 45.7	49.5 56.5	43.9 35.5	136.2	129.9 127.4	128.4 128.7	138.3
13[f]	21.6	94.2	180.4 64.1	49.9 39.5	44.9 39.3	134.4 27.6	136.3 30.6	45.9 42.9	54.8 56.9	51.3 35.7	138.5	127.6 130.8	127.4 129.4	137.5

[a]In ppm (δ_{TMS} = 0 ppm) at 125.7 MHz. Solvent: $CDCl_3$; [b]Assignments were supported by DEPT, HMQC and for **4**, **4a**, **5, 5a, 6, 12** and **13** also by HMBC measurements; [c]Further lines: OCH_3: 52.1 (**3**); $CONCH_2$: 37.8 (**8**), 41.9 (**9**), 37.9 (**10**) and 42.1 (**11**); OCH_2/$HNCH_2$: 62.7 (**8**), 42.6 (**9**, **11**), 62.3 (**10**), 64.5 (**12**), 64.1 (**13**); C**C**H_2C/(CONCH$_2$)**C**H_2: 25.8 (**8**), 24.7 (**9**), 25.9 (**10**) and 24.9 (**11**); (O/NHCH$_2$)**C**H_2: 33.1 (**9**, **11**); phenyl group (Pos. 5 in **2a**)/condensed benzene ring (**6** and **7**), C–1: 145.6 (**2a**), 133.9 (**6**), 133.3 (**7**); C-2,6/C-2: 127.5 (**2a**), 138.6 (**6**), 138.8 (**7**); C-3,5/C-3: 128.8 (**2a**), 120.6 (**6**), 120.2 (**7**); C-4: 126.3 (**2a**), 125.1 (**6**), 125.7 (**7**); C-5: 127.5 (**6**), 127.3 (**7**); C-6: 123.2 (**6**), 123.3 (**7**); [d]Due to hindered rotation of the aryl group, the C-2,6 and similarly the C-3,5 line pairs are separated (**6, 8, 9, 10, 12** and **13**), for **6** also broadened and for **7** and **11** coalesced. Further lines at ~127.9 and ~129.7 (**6**), 127.6 and 130.7 (**8**), 128.3 and 130.2 (**9**), 129.6 and 130.2 (**10**). The counterparts of the split signal pairs of **12** and **13** are given in the second row; [e]Interchangeable assignments; [f]Data in the first and second rows in columns 4-11 refer to norbornene and norbornane moieties, respectively.

The DIFFNOE measurements confirm the steric closeness of the 5-phenyl and bridging methylene groups (saturation of the signal of the latter group led to an enhanced intensity of the former), and consequently the *exo* position of the 5-phenyl ring in **2a**.

Because of the fully overlapping H-3a,7a signals in **2** and **2a**, the steric arrangements of the 3a,7a-substituents could be not established by NOE. However, the practically identical ^{1}H and ^{13}C chemical

shifts of C-3a,7a and H-3a,7a for **2** and **2a** proved the same stereostructure *i.e. endo*-carboxyl *exo*-aroyl substitution for **2** and **2a**.

In **5** and **5a**, the aroyl and carboxyl substituents must have a different *exo–endo* orientation because of the different multiplicities of the H-3a and H-7a signals (one is *d*, while the other is *t*). On comparison with **4** and **4a**, the reversed positions of these substituents reveal significantly different H-8 shifts (1.42 and 1.68 ppm for the latter; 1.53 and 1.82 ppm for **5** and **5a**). Similarly, the H-3a,7a shifts differ. Because of the α-effect,[15b] which causes a higher downfield shift of the signal of the *endo* aroyl group (relative to the carbonyl in **4** and **4a**), the δH(*exo*) > δH(*endo*) difference in norbornene[13,14,18,19] becomes moderate, while for **5** and **5a**, the aroyl group increases the shift in the *ab ovo* downfield-shifted geminal H-7a signal and, simultaneously, the chemical shift of the upfield-positioned H-3a signal will be increased to a smaller extent by the carbonyl group. Consequently, the shift difference ΔδH-3a,7a is significantly larger in **5** and **5a** (1.17 and 1.19 ppm) than in **4** and **4a** (0.14 and 0.13 ppm).

In the pyrrolidone-fused compounds (**6-13**), mixed (*exo–endo*) annelation to the norbornane/ene moiety is not possible for steric reasons. The *diexo* or *diendo* configurations follow unequivocally from the *d* or *dd* splits of the H-3a,7a signals, in accordance with our splitting rule.[13,14] Thus, in **6, 8, 9** and **12**, the norbornene and the fused hetero ring are *diexo*, while in **7, 10, 11** and **13** they are *diendo*.

In the pairs **6** and **7, 8** and **10**, and **9** and **11**, the C-1 configuration, *i.e.* the position of the aryl group, is to be determined. For **7**, this is straightforward on the basis of the dramatic upfield shift (by 1.12 ppm) of the H-6 signal as compared with that in **6**, due to the anisotropic shielding[15c] of the close-lying tolyl group. This means the *trans* arrangement of H-7a and the tolyl group relative to the pyrrolidone ring.

Table 3. DIFFNOE experiments with compounds (**2a, 3, 4, 4a, 9**) and (**11**)[a]

Saturated signal	Responding signals					
	H-3a	H-4	H-7a	NCH_2[b]	H(*ortho*) (phenyl)	H(*ortho*) (tolyl)
H-5		**2a**			**2a**	
H-7			**2a, 4a**			**2a, 4, 4a**
H-7a				**9, 11**		**4a**
H-8(*endo*)[c]	**3**,[d] **4, 4a**		**3**[c]		**2a**	**9**
ArH(*ortho)*	**3, 4**	**3**				

[a]Interacting pairs showing only trivial effects (NOE between the geminal or vicinal hydrogens) are not included in this Table. Only responses relevant for the stereostructures or dubious assignments are given; [b]One H in both group; [c]For **2a**, *exo* and *endo* H-8 give overlapping signals (*cf.* Table 1) and the response of the H(*ortho*) signal (phenyl) in **2a** is due to an effect with the H-8(*exo*) atom; [d]Inverse experiments were carried out: H-3a was irradiated when the H-8(*endo*) signal responded.

The similarly strong shielding of H-6 in **11** (4.77 ppm) and **10** (5.33 ppm) suggests the analogous stereostructure, and for the former compound this structure was directly confirmed by DIFFNOE measure-

ments: H-7a and the *N*-methylene hydrogens in the diazepine ring were found to be sterically close (on irradiation of one of these signals, an increased intensity was observed for the other one; *cf*. Table 3).

In **9**, NOE between H-8(*endo*) and one of the *ortho*-aryl hydrogens confirms the *trans* orientation of H-7a and the tolyl substituent. The anisotropic shielding of the benzene ring[15c] leads to an upfield shift of the H-8(*endo*) signal (*d*, 1.13 ppm) in **9**, while for **11** the analogous shift is 1.34 ppm. A similar effect was observed, and hence the analogous stereostructure is presumed for **8** [δH-8(*endo*): 1.03 ppm]. The absence of such a strong shielding in **6** suggests a considerable distance between the tolyl and H-8(*endo*) and thus the *cis* arrangement of the former group and H-7a relative to the pyrolidone ring.

Compounds (**12**) and (**13**) have the most complicated structures, including 9 centres of chirality. Discounting the 4 with fixed configurations, 16 diastereomers remain to be considered. On the basis of the splitting rule, the doublet split of the annelational hydrogens H-3a" and H-7a" indicates the *diexo* annelation of the norbornane in both **12** and **13**. For the same reason, the norbornene is *diexo* in **12** (the H-3a,7a signals are *d*'s) and *diendo* in **13** (the above signals are *dd*'s). Thus, for **12** and **13**, among the remaining 4, the true stereostructures have to be selected. The significant upfield shift of the H-6 signal in **13** (5.27 ppm) originates from the anisotropic shielding of the close-lying aromatic ring[15c] and points to the *endo* position of the tolyl group. As concerns the position of the tolyl group and the *diexo*-norbornane relative to the oxazine ring, the spectral data on **13** are practically identical with those of the compound where a phenyl-substituted cyclohexane-fused ring is present instead of norbornene;[20] this confirms that the tolyl group and the bridging methylene in norbornane lie on the same side of the skeleton. This is valid for both **13** and **12**. The most important supporting facts are the shifts of H-3a",7a" (1.99 and 4.03 ppm in **13** and 1.99 and 4.16 ppm for the cyclohexane-fused homologue[20] respectively, while for the isomeric counterpart containing the tolyl and bridging methylene on the opposite side, 2.15 and 3.80 ppm were measured). The practically identical chemical shifts of H-3a,7a in **12** (2.28 and 2.67 ppm) and **8** (2.23 and 2.66 ppm) suggest the close-lying arrangement of the tolyl and bridging methylene group in the norbornene. Hence, the stereostructures given in Scheme 2 were deduced from the spectral data on the new compounds.

It should be noted that the sterically crowded structures of **6-13** lead to hindered rotation of the tolyl group, and in both the ^{1}H- and ^{13}C-NMR spectra the signals of the *ortho* H/C-2,6 and *meta* H/C-3,5-s gave separated or broadened signals.

EXPERIMENTAL

The ^{1}H- and ^{13}C-NMR spectra were recorded in $CDCl_3$ solution in 5 mm tubes at rt, on a Bruker DRX-500 spectrometer at 500.13 (^{1}H) or at 125.76 (^{13}C) MHz, with the deuterium signal of the solvent as the lock and TMS as internal standard. The standard Bruker microprogram NOEMULT to generate NOE[17]

and to get DIFFNOE spectra[15a,16] were used with a selective preirradiation time. DEPT spectra[21] were run in a standard manner,[22] using only a $\Theta = 135°$ pulse to separate the CH/CH_3 and CH_2 lines phased 'up' and 'down', respectively. The 2D-COSY,[23a,24a] HMQC (△ 2D-HSC)[23b,24b] and HMBC (△ COLOC)[25,26] spectra were obtained by using the standard Bruker pulse programs COSY-45, INV4GSSW and INV4GSLRNDSW, respectively. IR spectra were run in KBr discs on a Bruker IFS-55 FT-spectrophotometer controlled by Opus 3.0.

X-Ray data collection and processing

Crystallographic data were collected at room temperature on a Rigaku AFC5S diffractometer with graphite-monochromated MoK_α ($\lambda = 0.71069$ Å) radiation. To collect intensity data, an ω-2θ scan mode at an ω scan speed of 8.0°/min was applied. The weak reflections [$I < 10\sigma(I)$] were rescanned up to two times. All data were corrected for the Lorentz polarization effects. The intensities of the three check reflections showed only statistical fluctuations.

Crystal data for **4** ($C_{16}H_{16}O_3$, $M = 256.29$), monoclinic, $a = 20.645(2)$, $b = 7.965(3)$, $c = 16.941(3)$ Å, $\beta = 91.908(11)°$, $U = 2784.1(11)$ Å^3, $T = 294$ K, space group $C2/c$ (no. 15), $Z = 8$, $\mu(Mo–K_\alpha) = 0.84$ mm^{-1}, 2536 reflections measured, 2464 unique ($R_{int} = 0.026$) which were used in all calculations. The final $wR(F^2)$ was 0.122 (all data).

The structures were solved by direct methods (SIR92)[27] and refined by full-matrix least squares techniques on F^2 (SHELXL-97)[28] The heavy atoms were refined anisotropically. The phenyl and methyl hydrogen atoms were included in calculated positions with fixed isotropic temperature factors (1.2 U_{eq} of the carrying atom) and the rest of hydrogen atoms were refined with isotropic temperature factors. Calculations were performed with teXsan for Windows crystallographic software.[29]

HPLC: An M-600 low-pressure system, equipped with a gradient pump and an M-486 tunable absorbance detector; Millenium software version 2.1 (Waters Chromatography, Milford, MA, USA). An injector with a 20-µl loop from Rheodyne (Cotati, USA). Column: Nova-Pak C_{18}, 150 × 3.9 mm I.D., 4 µm particle size (Waters Chromatography); flow rate, 0.8 ml min^{-1}; r.t.; detection, 254 nm. Eluent: 0.1% aqueous trifluoroacetic acid (pH~2)–MeOH = 40 : 60 (v/v) for **4** and **5**, retention times: 6.55 min (**5**) and 8.27 min (**4**); isomer ratio = 43.2 : 56.8; 1% aqueous triethylammonium acetate (pH~7)–MeOH = 45 : 55 (v/v) for **9** and **11**, retention times, 13.73 min (**11**) and 16.13 min (**9**), isomer ratio = 57.5 : 42.5.

3-*exo*-*p*-Toluoylbicyclo[2.2.1]heptane-2-*endo*-carboxylic acid (2)

A mixture of *diendo*-3-*p*-toluoylbicyclo[2.2.1]heptane-2-carboxylic acid[30] (1.3 g, 5 mmol) and aqueous HCl (36%, 2 drops) or Et_3N (2 drops) in toluene (10 mL) was refluxed for 2 h. After evaporation, the residue was crystallized.

Data on compound (**2**) are listed in Table 4.

6-*exo*-Phenyl-3-*exo*-*p*-toluoylbicyclo[2.2.1]heptane-2-*endo*-carboxylic acid (2a)

A mixture of 6-*exo*-phenyl-3-*endo*-*p*-toluoylbicyclo[2.2.1]heptane-2-*endo*-carboxylic acid[31] (0.84 g, 2.5 mmol) and aqueous HCl (36%, 2 drops) in toluene (10 mL) was refluxed for 3 h. After evaporation, the residue was dissolved in $CHCl_3$ (5 mL) and eluted from a silica gel column (Silica gel 60, Merck, 0.040-0.063 mm) with *n*-hexane–EtOAc (4 : 1).

Methyl 3-*exo*-*p*-toluoylbicyclo[2.2.1]heptane-2-*endo*-carboxylate (3)

A mixture of oxocarboxylic acid (**1**) or (**2**) (1.29 g, 5 mmol) and concentrated H_2SO_4 (0.2 mL) in MeOH (20 mL) was refluxed for 12 h. After evaporation of the solvent, H_2O (30 mL) was added and the mixture was extracted with ether (3×10 mL). After removal of the solvent, the residue was crystallized.

Separation of the mixtures 4 and 5, and 4a and 5a

The product obtained from *trans*-*p*-toluoylacrylic acid with cyclopentadiene[11] (1.0 g) in $CHCl_3$ (10 mL) was separated on a silica gel column with *n*-hexane–acetone–EtOH (90 : 8 : 2) as eluent. First **4** and then **5** appeared. The mixture of **4a** and **5a** was prepared analogously and separated similarly.

8,11-Methano-11b-*p*-tolyl-7a*r*,8*c*,11*c*,11a*c*-tetrahydroisoindolo[2,3-*a*]benzthiazol-7-one (6) and 8,11-methano-11b-*p*-tolyl-7a*r*,8*t*,11*t*,11a*c*-tetrahydroisoindolo[2,3-*a*]benzthiazol-7-one (7)

A mixture of oxocarboxylic acids (**4**) and (**5**)[11,12] (1.28 g, 5 mmol), 2-aminothiophenol (0.63 g, 5 mmol) and *p*-TsOH (0.05 g) in chlorobenzene (10 mL) was refluxed for 10 h. After evaporation, the residue was dissolved in CH_2Cl_2 (5 mL), transferred to a silica gel column (Silica gel 60, Merck 0.040-0.063 mm) and eluted with *n*-hexane–CH_2Cl_2–EtOAc (18 : 1 : 1). First **6** appeared, and then **7** [monitoring by TLC, aluminium sheets, Silica gel 60 F_{254}, benzene–EtOH–petroleum ether (bp 40-60 °C) 4 : 1 : 3, developed in iodine vapour]. The residues of the eluates **6** and **7** were crystallized.

7,10-Methano-10b-*p*-tolyl-2,3,6a*r*,7*c*,10*c*,10a*c*-hexahydro[1,3]oxazino[2,3-*a*]isoindol-6-one (8) and 7,10-methano-10b-*p*-tolyl-2,3,6a*r*,7*t*,10*t*,10a*c*-hexahydro[1,3]oxazino[2,3-*a*]isoindol-6-one (10)

A mixture of oxocarboxylic acids (**4**) and (**5**) (2.56 g, 10 mmol), 3-amino-1-propanol (1.13 g, 15 mmol) and *p*-TsOH (0.05 g) in toluene (15 mL) was refluxed for 10 h. After evaporation, the residue was chromatographed as above; eluents: *n*-hexane–EtOAc (4 : 1) for **8**, and then *n*-hexane–EtOAc (2 : 1) for **10**.

8,11-Methano-11b-*p*-tolyl-2,3,4,5,7a*r*,8*c*,11*c*,11a*c*-octahydro[1,3]diazepino[2,3-*a*]isoindol-7-one (9) and 8,11-methano-11b-*p*-tolyl-2,3,4,5,7a*r*,8*t*,11*t*,11a*c*-octahydro[1,3]diazepino[2,3-*a*]isoindol-7-one (11)

A mixture of oxocarboxylic acids (**4**) and (**5**) (1.28 g, 5 mmol), 1,4-diaminobutane (0.66 g, 7.5 mmol) and *p*-TsOH (0.05 g) in chlorobenzene (10 mL) was refluxed for 8 h. After evaporation, the residue was

dissolved in $CHCl_3$ (10 mL), purified and separated chromatographically as above. Elution with EtOAc–*n*-hexane (1 : 1); first **9** and then **11** appeared.

9,12-Methano-12b-*p*-tolyl-2a*r*,3*c*,4,5,6*c*,6a*c*,8a*c*,9*c*,12*c*,12a*c*-decahydroisoindolo[2,1-*a*]-3,6-methano[3,1]benzoxazin-8-one (12) and 9,12-methano-12b-*p*-tolyl-2a*r*,3*c*,4,5,6*c*,6a*c*,8a*c*,9*t*,12*t*,12a*c*-decahydroisoindolo[2,1-*a*]-3,6-methano[3,1]benzoxazin-8-one (13)

A mixture of oxocarboxylic acids (**4**) and (**5**) (1.28 g, 5 mmol), *diexo*-3-hydroxymethylbicyclo[2.2.1]heptane-2-amine (0.80 g, 5.7 mmol) and *p*-TsOH (0.05 g) in xylene (10 mL) was refluxed for 4 h. After evaporation, the residue was dissolved in CH_2Cl_2 (5 mL) and chromatographed; elution with *n*-hexane–EtOAc–CH_2Cl_2 (18 : 1 : 1) for **12**, and then *n*-hexane–EtOAc (4 : 1) for **13**.

Table 4. Physical and analytical data on compounds (**2-10**)

Compound	mp °C	Yield %	Formula	Analysis					
				Found %			Calcd %		
				C	H	N	C	H	N
2	133-135[a]	81	$C_{16}H_{18}O_3$	74.32	7.08		74.40	7.02	
2a	192-194[b]	77	$C_{22}H_{22}O_3$	78.91	6.75		79.02	6.63	
3	74-75[c]	78	$C_{17}H_{20}O_3$	74.89	7.32		74.97	7.40	
4	125-126[c]		$C_{16}H_{16}O_3$	74.82	6.33		74.98	6.29	
4a	141-142.5[c]		$C_{15}H_{14}O_3$	74.28	5.84		74.36	5.82	
5	127-128[a]		$C_{16}H_{16}O_3$	74.85	6.34		74.98	6.29	
5a	126-127[a]		$C_{15}H_{14}O_3$	74.31	5.80		74.36	5.82	
6	146-148[c]	30	$C_{22}H_{19}NOS$	76.52	5.59	4.01	76.49	5.54	4.05
7	207-208[b]	45	$C_{22}H_{19}NOS$	76.46	5.51	4.02	76.49	5.54	4.05
8	181-183[c]	28	$C_{19}H_{21}NO_2$	77.08	7.18	4.79	77.26	7.17	4.74
9	156-158[b]	35	$C_{20}H_{24}N_2O$	77.81	7.96	9.18	77.89	7.84	9.08
10	148.5-150[c]	21	$C_{19}H_{21}NO_2$	77.32	7.21	4.71	77.26	7.17	4.74
11	164-166[d]	42	$C_{20}H_{24}N_2O$	78.01	7.81	9.12	77.89	7.84	9.08
12	197-198[c]	23	$C_{24}H_{27}NO_2$	79.61	7.48	3.83	79.74	7.53	3.87
13	195-196[c]	34	$C_{24}H_{27}NO_2$	79.82	7.58	3.81	79.74	7.53	3.87

Crystallization solvent: [a]benzene; [b]EtOAc; [c]Et_2O; [d]*i*-Pr_2O.

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