A Stereospecific '2-Aza-divinylcyclopropane' Rearrangement

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The stereochemical course of the thermal 2-aza-*Cope* rearrangement of the optically pure acyl azide (−)-(1*S*)-**5** was investigated by determination of the absolute configuration of the rearrangement product (1*R*,8*S*)-**9**. The reaction proceeds by a sequence of stereospecific steps from **5** to an equilibrating mixture of *exo*- and *endo*-isocyanates **6** and **7**. The *endo*-isomer **7** undergoes *Cope* rearrangement to the putative intermediate **8**, which is trapped and characterized as the adduct **9b** of butan-1-ol. The absolute configuration of **9b** was determined by its reduction to the amide **20**, and determination of the X-ray structure of the *N*-camphanoylamide **21** derived from camphanic acid of known absolute configuration.

Introduction. – The rearrangement of *cis*-divinylcyclopropanes to cyclohepta-1,3-dienes has found numerous applications in asymmetric synthesis owing to its high level of stereospecificity [1]. The analogous rearrangement of *cis*-2-vinylcyclopropyl isocyanates to 1-azacyclohepta-4,6-dien-2-ones (=1,3-dihydro-2*H*-azepin-2-ones) is much less known [2][3]. We have recently reported that the thermal rearrangement of the optically active acyl azide **1** to the azepinone **4** *via* the isocyanate **2** and the isomeric azepinone **3** was accompanied by partial loss of enantiomeric purity [4] (*Scheme 1*). About 2/3 of the reaction proceeded by the expected concerted mechanism, but the remaining fraction reacted *via* racemization. A plausible mechanism for racemization involving an intermediate biradical was proposed, but experiments to back up this mechanistic hypothesis failed.

We reasoned that inclusion of the vinylcyclopropane moiety in a conformationally blocked system having the correct *endo*-orientation[1]) of the double bond, which is required for the reaction to proceed *via* the expected boat-like transition state, might favor the concerted rearrangement pathway over the hypothetical biradical mechanism. Accordingly, we have investigated the steric course of the first '2-aza-divinylcyclopropane' rearrangement reported in the literature that meets this requirement: In 1959, *Doering* and *Goldstein* investigated the thermal transformation of the isocyanate **6**, which was accessible *via Curtius* rearrangement of the *exo*-azide[1]) **5**, to the bicyclic imine **8** (*Scheme 1*). The imine, in turn, was not isolated, but was trapped and characterized as N,O-acetal **9a** after interception with benzyl alcohol [5]. The configuration of **6** was not determined. The well-established stereochemical course of the *Curtius* rearrangement suggested *exo*-configuration, but the authors recognized that the *endo*-isocyanate **7** could rearrange in what currently would be called a concerted fashion.

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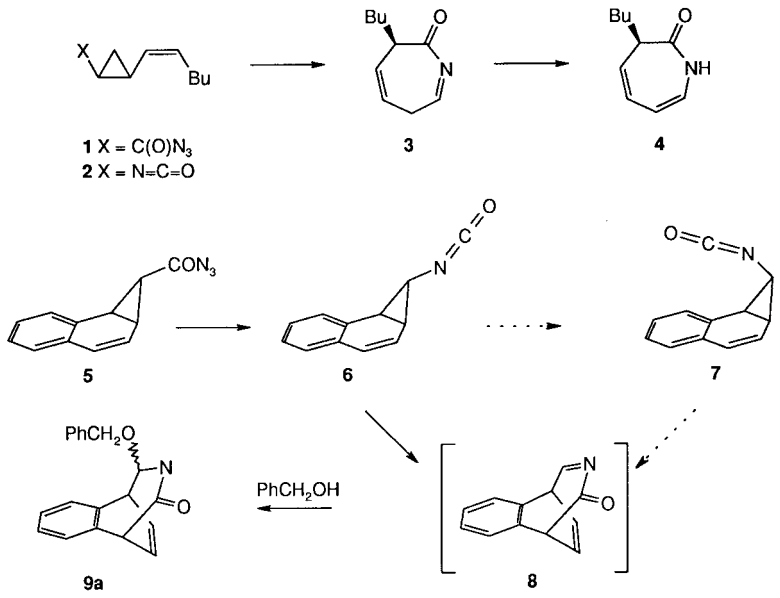
[1]) The descriptors *exo* and *endo* are used to describe the position of the substituent at the cyclopropane moiety relative to the naphthalene moiety.

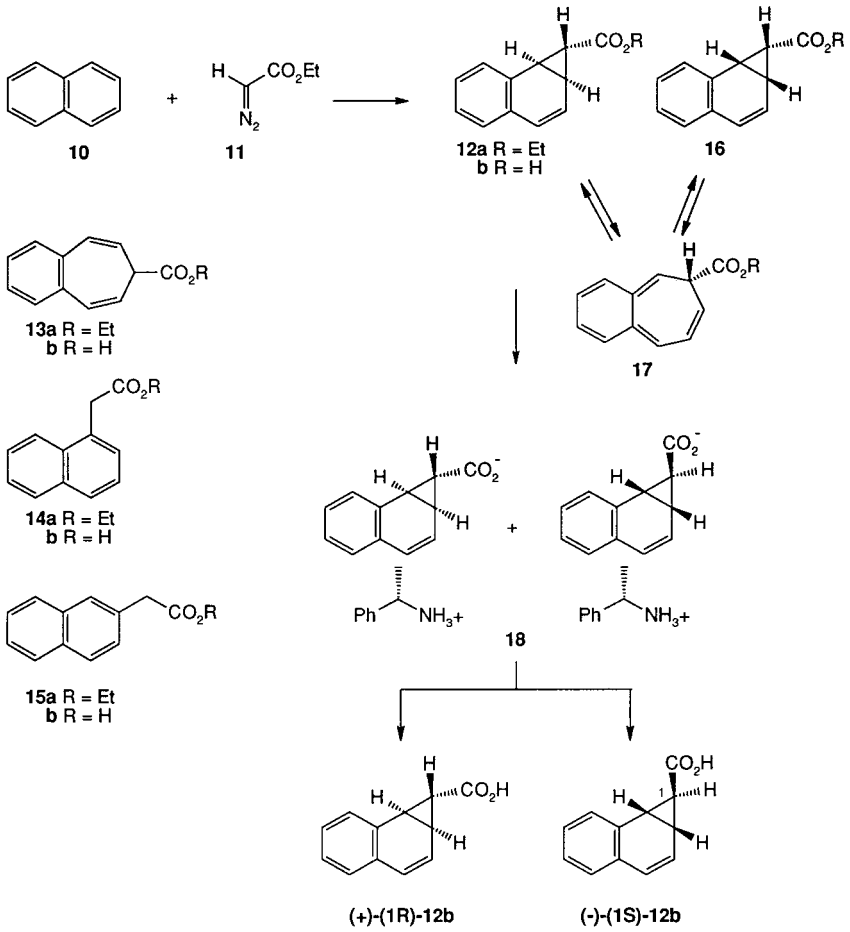
Scheme 1



Results. – *Cyclopropanation of Naphthalene.* The required acyl azide **5** was synthesized by Rh^{II}-catalyzed cyclopropanation of naphthalene (**10**) with ethyl diazoacetate (EDA; **11**). A thermal version of this reaction, involving addition of methyl diazoacetate to **10** at 140° has been described by *Buchner* and *Hediger* already in 1902 [6]. More recently, *Anciaux et al.* reported the addition of butyl diazoacetate to **10** in the presence of $[Rh_2(MeOCH_2COO)_4]$ [7]. These authors already pointed out the influence of the electronegativity of the carboxylate ligands on the product composition of Rh^{II}-catalyzed cyclopropanations of arenes.

We have screened several Rh^{II} catalysts to achieve optimum conversion and selectivity in the cyclopropanation of naphthalene (**10**) with EDA (**11**). Reactions were carried out by adding **11** in CH_2Cl_2 to a five-fold excess of **10** in the same solvent, in the presence of 0.5% of Rh^{II}-catalyst (relative to **11**). In all cases but one, the expected *exo*-norcaradienecarboxylate[1]) **12a** was the main product, and benzocycloheptatrienecarboxylate **13a** and naphthalene-1- and -2-acetates, **14a** and **15a**, respectively, occurred as secondary products in various amounts. As anticipated, the overall yield and product composition of the reaction depended upon the electronegativity of the ligand of the catalyst (*Table 1*). Thus, use of a carboxamidate ligand such as methyl 6-oxopyrrolidine-2-carboxylate (*i.e.* $[Rh_2\{2S)\text{-mepy}\}_4]$) [8] resulted only in formation of carbene dimers, and no norcaradiene derivative **12a** was produced. The carboxylate ligands such as acetate afforded a *ca.* 60–75% overall yield of products, which increased to 94 and 92% with $[Rh_2(CF_3COO)_4]$ [7a] and $[Rh_2(pfb)_4]$ [9] (pfb = perfluorobutanoate), respectively. However, the strongly electron-attracting ligands of these latter catalysts produced higher amounts of secondary products. Finally, $[Rh_2(CF_3COO)_4]$ was selected as catalyst, as a reasonable compromise for the

Scheme 2



synthesis. Since ester **12a** decomposed partially upon chromatography, the crude product was hydrolyzed to the mixture of the corresponding carboxylic acids **12b**–**15b**, from which the desired acid **12b** was separated by bulb-to-bulb distillation and recrystallization.

Table 1. *Cyclopropanation of Naphthalene* (**10**) *with Ethyl Diazoacetate* (**11**) *in the Presence of* Rh^{II}*-Catalysts*

Catalyst	Yield[a])	**12a**	**13a**	**14a**	**15a**
$[Rh_2(O_2CCH_3)_4]$	60	82	7	5	6
$[Rh_2(O_2CCF_3)_4]$	94	75	0	15	10
$[Rh_2(O_2CC_3F_7)_4]$	92	60	0	22	18
$[Rh_2\{(2S)\text{-mepy}\}_4]$	0[b])	–	–	–	–
$[Rh_2\{(S)\text{-tbsp}\}_4]$	73	69	10	14	7
$[Rh_2\{(S)\text{-dosp}\}_4]$	63	68	12	12	8

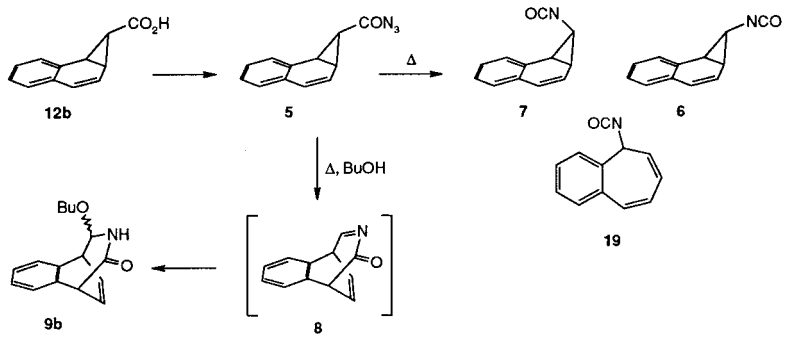
[a]) Crude overall yield. [b]) Carbene-dimer formation.

Exploratory attempts to synthesize the optically active norcaradienecarboxylate **12a** *via* an enantioselective cyclopropanation of **10** in the presence of chiral Rh^{II}-prolinate catalysts such as $[Rh_2\{(S)\text{-tbsp}\}_4]$ or $[Rh_2\{(S)\text{-dosp}\}_4]$ [10] were not successful. These carboxylate catalysts afforded product mixtures comparable to those produced with $[Rh_2(OAc)_4]$, but the norcaradienecarboxylate **12** was racemic.

The cyclopropanation of naphthalene (**10**) with EDA resulted in exclusive formation of the *exo*-norcaradiene **12a**, while a mixture of *exo*- and *endo*-isomers **12a** and **16**, respectively, may be expected *a priori*. It is known, however, that *exo* → *endo* isomerization of **12a** *via* electrocyclization to the cycloheptatriene **17** occurs rapidly, and only **12a** may be observed at room temperature [11]. The *exo*-norcaradiene **12a** may be formed either *via* direct *exo*-cyclopropanation of **10** or *via endo*-cyclopropanation followed by *exo*-isomerization of the initially formed **16**. The product **12a** resulting from these competing pathways may have identical or opposite absolute configurations. In the latter case, it would be impossible to isolate a product of sufficient enantiomer purity by asymmetric cyclopropanation, even if the *exo*- and *endo*-cyclopropanations proceeded with high enantioselectivity. In view of the disappointing results of the first asymmetric cyclopropanation experiments, and in view of these considerations, the enantioselective cyclopropanation of **10** was not further investigated. The enantiomers of the norcaradiene **12** were, therefore, separated by resolution of the diastereoisomeric salt **18** that was obtained upon reaction of **12b** with (+)-α-phenylethylamine according to a literature procedure [12]. The absolute configuration of the *exo*-norcaradienecarboxylic acids **12b** was determined by chemical correlation: the (−)-isomer has (*S*)-configuration at C(1) (named as (1*S*,1a*R*,7b*R*)-1a,7b-dihydro-1*H*-cyclopropa[*a*]naphthalene-1-*exo*-carboxylic acid[1]) ((−)-(1*S*)-**12b**)), and the (+)-enantiomer has (1*R*,1a*S*,7b*S*)-configuration [13]. HPLC Analysis on a chiral column showed that the isolated enantiomers of **12b** had >99% ee.

Rearrangement of **5**. Racemic **12b** was transformed to the acyl azide **5** by treatment with diphenylphosphoryl azide and Et_3N [14] (*Scheme 3*). Heating of **5** in refluxing toluene (15 min) in the absence of an alcohol resulted in formation of a mixture of 3 isocyanates, exhibiting IR absorption at 2264 cm^{-1}, characteristic for the isocyanate group, but the expected rearrangement product **8** could not be detected. The main components (86%) were tentatively identified as *exo*- and *endo*-norcaradienyl isocyanates[1]) **6** and **7**. Their structures were established on the grounds of the

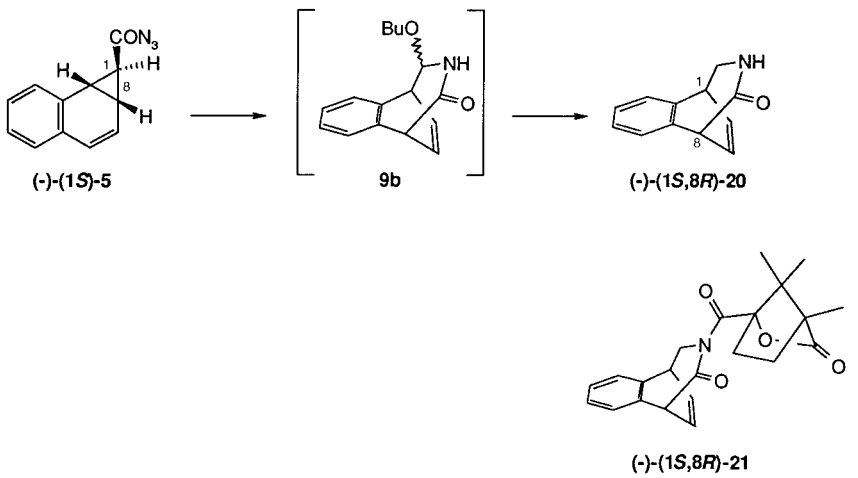
Scheme 3



similarity of the ^{1}H-NMR spectra with those of the corresponding nitriles [15]. The relative configuration at the cyclopropane ring followed from the vicinal coupling constants. The isomer ratio at equilibrium was 35:65 with the *endo*-isomer predominating in accord with the reported *exo*/*endo* 2:3 ratio for the nitrile [15]. The third product was isolated and identified as 1*H*-benzocyclohepten-1-yl isocyanate (**19**; 14%). This product originates probably from a 1,5-shift of **6** or **7** and subsequent cycloreversion. Prolonged heating of **5** resulted in conversion to **19** as the main product. Rearrangement of racemic **5** in the presence of butanol, in turn, afforded a *ca.* 2:1 mixture of stereoisomeric *N*,*O*-acetals **9b** in 65% isolated yield.

This sequence was then repeated with both enantiomers of **12b**. Reduction of **9b** with Et_3SiH/CF_3COOH afforded lactam **20** which is known in the racemic form [16], in 52% yield (relative to **5**) (see *Scheme 4*). HPLC Analysis of the resulting enantiomeric lactams **20** showed that the rearrangement was fully stereospecific. Rearrangement of (−)-(1*S*)-**5** followed by reduction of the intermediate **9b**, which was not isolated, afforded the (−)-enantiomer of lactam **20**. This material was derivatized by reaction with (−)-(1*S*)-camphanoyl chloride in the presence of NaH, and the resulting crystalline *N*-camphanoylamide **21** was subjected to X-ray structure analysis (*Fig.*). Since the absolute configuration of (−)-camphanic acid is known, that of **20** was unambiguously determined to be (1*S*,8*R*).

Scheme 4



Discussion. – According to the proposed mechanism for the '2-aza-divinylcyclopropane' rearrangement, the reaction proceeds through a boat-like transition state. Application of these criteria to (−)-(1*S*)-**5** requires first a *Curtius* rearrangement to (1*S*)-**6** followed by *exo* → *endo* isomerization (*Scheme 5*). *Exo* → *endo* isomerization of (1*S*)-**6** may proceed *via* concerted cycloreversion to the cycloheptatriene (*S*)-**22** followed by electrocyclization to afford (1*S*-**7**). Alternatively, breaking of one of the lateral cyclopropane bonds followed by configurational inversion and ring closure would result in formation of (1*R*)-**7**. Concerted rearrangement of (1*S*)-**7** must afford

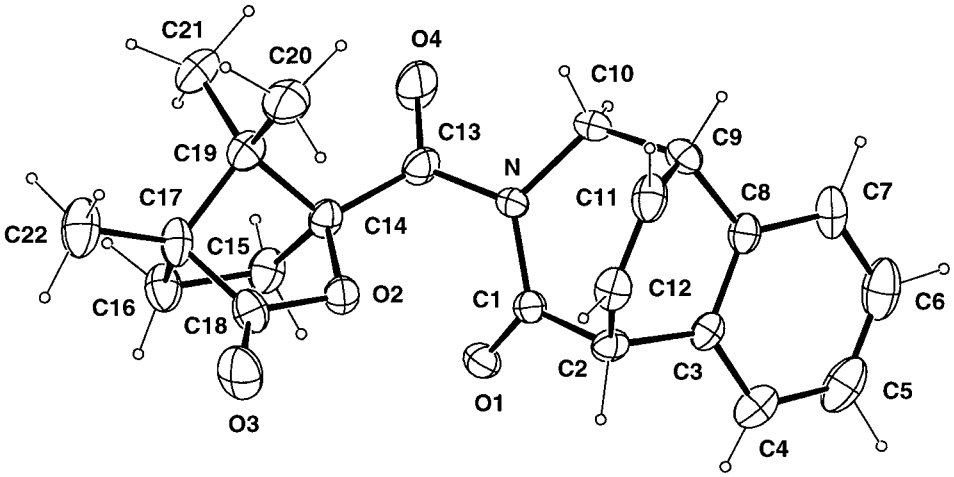
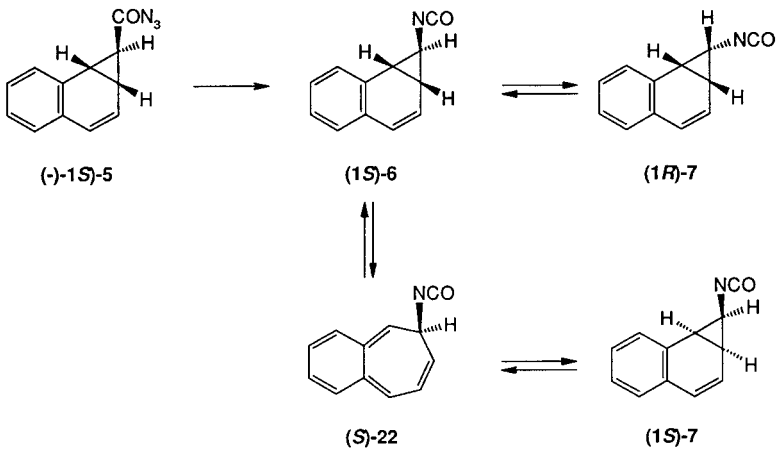


Figure. *Perspective view of the crystal structure of (−)-(1S,8R)-***21**. Ellipsoids are represented with 40% probability; arbitrary atom numbering.

(1*S*,8*R*)-**9b** and, subsequently, (1*S*,8*R*)-**20**. This is indeed observed. Therefore, the rearrangement of **5** to **9b** involves three successive fully stereospecific steps, namely *Curtius* rearrangement followed by electrocyclic *exo* → *endo* isomerization, and *Cope* rearrangement. The competing racemization observed in the case of **2** does not occur with **5**.

Scheme 5



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Experimental Part

General. See [17]. FC = flash chromatography.

*1a,7b-Dihydro-1*H-*cyclopropa[*a*]naphthalene*-1-exo-*carboxylic acid*[1]) (**12b**). To a well-stirred soln. of $[Rh_2(CF_3COO)_4]$ (65.7 mg, 0.10 mmol) and naphthalene (**10**; 12.8 g, 100 mmol) in CH_2Cl_2 (200 ml) was added, within 2 h by syringe pump and at r.t., ethyl diazoacetate (**11**; 2.28 g, 20 mmol) in CH_2Cl_2 (20 ml). After the addition, stirring was continued for 15 min until decomposition of EDA was completed. The soln. was concentrated *in vacuo*. KOH soln. (1M in H_2O/EtOH 15:65; 150 ml) was added, and the soln. containing the ester **12a** was refluxed for 30 min. After evaporation, the slurry was dissolved in Et_2O and H_2O (100 ml each). The aq. phase was washed with Et_2O (3×50 ml) and the org. phase combined and extracted with H_2O (2×50 ml). These aq. layers were further washed with Et_2O (50 ml). Et_2O (100 ml) was added to the combined aq. phases, and the stirred emulsion was acidified to pH 1 with 1M HCl at 0°. The aq. phase was extracted wtih Et_2O (2×50 ml) and the combined Et_2O phase washed with brine (2×50 ml), dried ($MgSO_4$), and evaporated: 3.28 g of **12b** as partly crystallized oil. Bulb-to-bulb distillation of this crude product at 160–190°/$3 \cdot 10^{-2}$ Torr gave a yellowish solid which was recrystallized in HCOOH to give 2.22 g (0.12 mmol, 60%) of a colorless solid containing **12b** and 23% of naphthaleneacetic acids **14b** and **15b**. Acid **12b** was purified by recrystallization from Bu_2O. M.p. 166° ([12] 164–168°). IR (CH_2Cl_2): 3496*w*, 1687*vs*, 1438*m*, 1213*m*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.90 (*t*, *J* = 4.0, 1 H); 2.78 (*ddd*, *J* = 8.5, 4.8, 4.0, 1 H); 3.20 (*dd*, *J* = 8.4, 3.9, 1 H); 6.34 (*dd*, *J* = 9.5, 4.9, 1 H); 6.46 (*d*, *J* = 9.5, 1 H); 7.16–7.20 (*m*, 1 H); 7.24–7.20 (*m*, 2 H); 7.43–7.48 (*m*, 1 H); 11.5 (br. *s*, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 22.8 (*d*); 28.5 (*d*); 31.5 (*d*); 125.5 (*d*); 126.3 (*d*); 127.0 (*d*); 127.8 (*d*); 128.0 (*d*); 128.7 (*d*); 130.7 (*s*); 132.2 (*s*); 182.3 (*s*). MS: 186 (29, M^+), 168 (18), 142 (16), 141 (100), 140 (17), 139 (12), 125 (10), 115 (20).

Enantiomer Separation of **12b**. The separation was effected by fractional recrystallization of the ammonium salts of **12b** (contaminated with **15b**) with (+)-(*R*)- or (−)-(*S*)-α-methylbenzylamine, resp., in EtOH as described in [12]. The diastereoisomers of **18** were decomposed with 1M HCl, and the free acids were extracted with Et_2O.

(+)-(1*R*)-**12b**: M.p. 124–126° ([12]: 126.5–127.5°). $[\alpha]_D^{20} = +120.5$ ($c = 0.97$, acetone) ([12]: $[\alpha]_D = +121.3$ ($c = 1.3$, acetone)).

(−)-(1*S*)-**12b**: M.p. 124–126° ([12]: 126.5–127.5°). $[\alpha]_D^{20} = -119.7$ ($c = 1.0$, acetone) ([12]: $[\alpha_D = -121.6$ ($c = 1.0$, acetone)).

*1a,7b-Dihydro-1*H-*cyclopropa[*a*]naphthalene-1-carbonyl Azide* (**5**). To a soln. of **12b** (559 mg, 3.00 mmol) in toluene (30 ml) at 0°, Et_3N (1.21 g, 12.0 mmol) and diphenylphosphoryl azide (1.65 g, 6.00 mmol) were successively added. After stirring for 30 min at r.t., the mixture was stirred to 0°, and sat. aq. $NaHCO_3$ soln. (10 ml) was added dropwise. The milky mixture was concentrated *in vacuo* to *ca.* 50%, and Et_2O (10 ml) was added. The aq. phase was separated and extracted with Et_2O (2×10 ml) and the combined org. phase dried ($MgSO_4$) and evaporated: 1.18 g of racemic **5**. Yellow oil. Chromatography (SiO_2, petroleum ether/MeCN 98.5:1.5) afforded pure **5** (389 mg, 61%), which was recrystallized from pentane at −18°. M.p. 61–62°. IR (CH_2Cl_2): 2147v*s*, 1690v*s*, 1489*w*, 1397*m*, 1299*m*, 1175*m*, 1097*m*, 916*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.87 (*t*, *J* = 3.7, 1 H); 2.79 (*ddd*, *J* = 8.5, 4.8, 4.0, 1 H); 3.22 (*dd*, *J* = 8.4, 4.0, 1 H); 6.29 (*dd*, *J* = 9.6, 4.9, 1 H); 6.43 (*d*, *J* = 9.4, 1 H); 7.11–7.16 (*m*, 1 H); 7.20–7.27 (*m*, 2 H); 7.39–7.43 (*m*, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 25.6 (*d*); 30.1 (*d*); 33.0 (*d*); 125.4 (*d*); 127.1 (*d*); 127.9 (*d*); 128.1 (*d*); 128.7 (*d*); 128.7 (*d*); 130.7 (*s*); 132.1 (*s*); 181.7 (*s*). MS: 211 (8, M^+), 183 (41), 182 (27), 155 (24), 154 (34), 142 (13), 141 (100), 140 (10), 139 (14), 128 (54), 127 (28), 115 (24). HR-MS: 211.0778 ($C_{12}H_9N_3O^+$; calc. 211.0746), 183.0660 ($C_{12}H_9NO^+$; calc. 183.0684).

(−)-(1S)-**5**: Yield 71%. M.p. 57–59°. $[\alpha]_D^{20} = -61.6$ ($c = 1.0$, $CHCl_3$). HPLC (*Chiracel OD-H*, hexane/i-PrOH 99:1): t_R 23.6 min.

(+)-(1R)-**5**: Yield 84%. M.p. 57–59°. $[\alpha]_D^{20} = +62.8$ ($c = 1.0$, $CHCl_3$). HPLC (*Chiracel OD-H*, hexane/i-PrOH/99:1): t_R 19.7 min.

Rearrangement of Acyl Azide **5** *in the Absence of Alcohol: 1*H-*Benzocyclohepten-1-yl Isocyanate* (**19**). Azide **5** (119 mg, 0.56 mmol) was refluxed in toluene (30 ml) during 15 min. Evaporation at 0°/1 Torr afforded 118 mg of crude product containing 14% of **19**, which was separated by two successive bulb-to bulb distillations (90–110°/$6 \cdot 10^{-2}$ Torr): 6 mg (6%) of pure **19**. IR ($CHCl_3$): 3015*w*, 2962*s*, 2269*s*, 1668*m*, 1261*s*, 1097v*s*. ^{1}H-NMR (400 MHz, C_6D_6): 4.23 (*d*, *J* = 5.3, 1 H); 5.44 (*dd*, *J* = 9.9, 5.3, 1 H); 5.74 (*ddd*, *J* = 10.0, 5.6, 1.4, 1 H); 6.26 (*dd*, *J* = 11.4, 5.6, 1 H); 6.92 (*d*, *J* = 11.4, 1 H); 7.09–7.17 (*m*, 2 H); 7.25–7.29 (*m*, 1 H); 7.42 (*d*, *J* = 7.8, 1 H). ^{13}C-NMR ($CDCl_3$): 56.0 (*d*); 123.3 (*d*); 123.6 (*d*); 126.3 (*d*); 127.6 (*s*); 127.8 (*d*); 128.0 (*d*); 128.2 (*d*); 129.7 (*d*); 132.9 (*s*); 133.9 (*d*); 135.8 (*d*). MS: 183 (71, M^+), 182 (26), 168 (12), 155 (17), 154 (36), 142 (13), 141 (100), 139 (11), 128 (45), 127 (29), 115 (28). HR-MS: 183.0704 ($C_{12}H_9NO^+$; calc. 183.0684).

*Data of 1a,7b-Dihydro-1*H*-cyclopropa[*a*]naphthalen-1-*exo*-yl Isocyanate*[1]) (**6**). ^{1}H-NMR (400 MHz, C_6D_6): 1.68 (*dd*, *J* = 3.0, 2.8, 1 H); 1.76 (*ddd*, *J* = 8.8, 5.3, 2.8, 1 H); 2.25 (*dd*, *J* = 8.8, 3.0, 1 H); 5.75 (*dd*, *J* = 9.8, 5.3, 1 H); 6.07 (*d*, *J* = 9.6, 1 H); 7.05–7.30 (*m*, 4 H). ^{13}C-NMR (100 MHz, C_6D_6): 26.1 (*d*); 29.1 (*d*); 35.5 (*d*); 123.5 (*d*); 125.4 (*d*); arom. and isocyanate C-atoms not attributed.

*Data of 1a,7b-Dihydro-1*H*-cyclopropa[*a*]naphthalen-1-*endo*-yl Isocyanate*[1]) (**7**). ^{1}H-NMR (400 MHz, C_6D_6): 1.70 (*ddd*, *J* = 8.1, 7.8, 5.6, 1 H); 2.15 (*dd*, *J* = 8.1, 7.8, 1 H); 2.60 (*t*, *J* = 7.8, 1 H); 5.71 (*dd*, *J* = 9.7, 5.6, 1 H); 6.58 (*d*, *J* = 9.6, 1 H); 7.05–7.30 (*m*, 4 H). ^{13}C-NMR (100 MHz, C_6D_6): 20.4 (*d*); 23.9 (*d*); 26.5 (*d*); 120.2 (*d*); 129.3 (*d*); arom. and isocyanate C-atoms not attributed.

Rearrangement of Acyl Azide **5** *in the Presence of BuOH: 11-Butoxy-10-azatricyclo[6.3.2.0^{2,7}]trideca-2,4,6,12-tetraen-9-one* (= *4-Butoxy-3,4-dihydro-1,5-etheno-2*H*-3-benzazepin-2-one*; **9b**). A soln. of **5** (1.29 g, 6.12 mmol) and butan-1-ol (4.54 g, 61.2 mmol) in anh. toluene (60 ml) was refluxed for 15 min in an oil bath heated to 140° and then immediately cooled in an ice bath. Evaporation at r.t. afforded 1.45 g (92%) of a yellowish oil consisting mainly of a 40:60 (by NMR) mixture of the 2 stereoisomers of **19b**. The crude mixture was used in the next step without any further purification. Anal. samples of both diastereoisomers were isolated by FC (SiO_2, AcOEt/petroleum ether 6:1 → 3:1): combined yield of **9b**, 65%.

Major isomer: R_f 0.12 (SiO_2, petroleum ether/AcOEt 4:1): colorless solid. IR (C_6D_6): 3382*m*, 2960*m*, 1671v*s*, 1458*m*, 1080*m*. ^{1}H-NMR (400 MHz, C_6D_6): 0.89 (*t*, *J* = 6.4, 3 H); 1.26–1.48 (*m*, 4 H); 3.23 (*dt*, *J* = 8.8, 6.3, 1 H); 3.45 (*dt*, *J* = 8.8, 6.3, 1 H); 3.52–3.53 (*m*, 1 H); 4.39–4.43 (*m*, 2 H); 6.16 (*ddd*, *J* = 8.1, 6.2, 1.3, 1 H); 6.46 (*dddd*, *J* = 8.0, 6.9, 1.8, 1.0, 1 H); 7.02–7.29 (*m*, 4 H); 7.30 (br. *s*, 1 H). ^{13}C-NMR (100 MHz, C_6D_6): 13.7 (*q*); 19.3 (*t*); 31.7 (*t*); 45.4 (*d*); 52.9 (*d*); 67.5 (*t*); 85.3 (*d*); 125.4 (*d*); 126.4 (*d*); 126.5 (*d*); 128.4 (*d*); 129.4 (*d*); 133.2 (*d*); 135.9 (*s*); 138.4 (*s*); 169.5 (*s*). MS: 257 (1, M^+), 183 (45), 182 (17), 155 (10), 154 (21), 149 (32), 142 (25), 141 (92), 129 (24), 128 (100), 127 (20), 115 (16), 77 (11). HR-MS: 257.1396 ($C_{12}H_9N_3O^+$; calc. 257.1416).

Minor isomer: R_f 0.24 (SiO_2, petroleum ether/AcOEt 4:1). Colorless solid. IR: (C_6D_6): 3384*w*, 2959*m*, 1670v*s*, 1459*m*, 1081*m*. ^{1}H-NMR (400 MHz, C_6D_6): 0.95 (*t*, *J* = 7.3, 3 H); 1.32–1.42 (*m*, 2 H); 1.44–1.57 (*m*, 2 H); 3.03 (*dt*, *J* = 8.7, 6.6, 1 H); 3.27 (*dt*, *J* = 8.6, 6.4, 1 H); 3.72–3.75 (*m*, 1 H); 4.21 (*t*, *J* = 3.1, 1 H); 4.40 (*dt*, *J* = 6.5, 1.5, 1 H); 5.85 (br. *s*, 1 H); 6.38 (*ddt*, *J* = 8.0, 6.5, 1.5, 1 H); 6.44 (*ddt*, *J* = 8.0, 6.6, 1.3, 1 H); 7.05–7.21 (*m*, 4 H). ^{13}C-NMR (100 MHz, C_6D_6): 13.7 (*q*); 19.3 (*t*); 31.8 (*t*); 45.6 (*d*); 52.7 (*d*); 67.2 (*t*); 88.0 (*d*); 125.6 (*d*); 126.2 (*d*); 126.7 (*d*); 126.8 (*d*); 130.8 (*d*); 139.1 (*d*); 136.1 (*s*); 139.1 (*s*); 168.1 (*s*). MS: 257 (2, M^+), 183 (41), 182 (17), 155 (9), 154 (21), 142 (28), 141 (95), 129 (33), 128 (100), 127 (20), 115 (16), 77 (10). HR-MS: 257.1426 ($C_{12}H_9N_3O^+$; calc. 257.1416).

10-Azatricyclo[6.3.2.0^{2,7}]trideca-2,4,6,12-tetraen-9-one (= *3,4-Dihydro-1,5-etheno-2*H*-3-benzazepin-2-one*; **20**). The epimer mixture **9b** (424 mg, 1.7 mol) and Et_3SiH (600 mg, 5.16 mmol) were dissolved in CH_2Cl_2 (20 ml). Anh. CF_3COOH (2.0 ml) was added dropwise at r.t. The soln. was stirred for 15 min and then poured into a stirred mixture of ice and aq. sat. $NaHCO_3$ soln. (20 ml). The aq. layer was extracted with CH_2Cl_2 (2 × 20 ml), the combined org. phases were washed with brine and dried ($MgSO_4$). After evaporation, a crude solid (324 mg) was obtained, which was washed with Et_2O (2 × 1.5 ml) to afford **20** (132 mg) as a colorless solid. Workup of the filtrate furnished another 40 mg of **20** (combined yield, 52% rel. to **5**). Recrystallization from CH_2Cl_2/*t*-BuOMe: colorless prisms. M.p. 208–209° ([16]: 209°). IR (CH_2Cl_2): 3394*m*, 1666v*s*, 1484*m*, 1308*m*, 1210*w*, 1101*w*. ^{1}H-NMR (400 MHz, $CDCl_3$): 3.44 (*dt*, *J* = 11.7, 2.6, 1 H); 3.58 (*dt*, *J* = 11.8, 2.5, 1 H); 3.66–3.70 (*m*, 1 H); 4.22 (*dt*, *J* = 6.6, 1.5, 1 H); 5.08 (br. *s*, 1 H); 6.56 (*ddd*, *J* = 8.1, 6.6, 1.5, 1 H); 6.66 (*ddd*, *J* = 8.8, 6.9, 1.0, 1 H); 7.26–7.34 (*m*, 4 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 39.4 (*d*); 49.1 (*t*); 51.5 (*d*); 125.3 (*d*); 125.4 (*d*); 126.7 (*d*); 127.3 (*d*); 131.2 (*d*); 132.0 (*d*); 138.4 (*s*); 138.6 (*s*); 169.0 (*s*). MS: 185 (29, M^+), 142 (60), 141 (62), 129 (62), 128 (100), 127 (15), 115 (19).

(−)-(1*S*,8*R*)-**20**: Yield 64% from (−)-**5**. M.p. 258–260°. $[\alpha]_D^{20} = -5.7$ (*c* = 0.9, $CHCl_3$). HPLC (*Chiracel OD-H*, i-PrOH/hexane 1:1): t_R 11.4 min.

(+)-(1*R*,8*S*)-**20**: Yield 56% from (+)-**5**. M.p. 257–259°. $[\alpha]_D^{20} = +5.8$ (*c* = 1.0, $CHCl_3$). HPLC (*Chiracel OD-H*, i-PrOH/hexane 1:1): t_R 14.8 min.

*(1*S*,8*R*)-10-[(1*S*)-Camphanoyl]-10-azatricyclo[6.3.2.0^{2,7}]trideca-2,4,6,12-tetraen-9-one* (= *(1*S*,5*R*)-3,4-Dihydro-3-{[(1*S*)-3-oxo-4,7,7-trimethyl-2-oxabicyclo[2.2.1]hept-1-yl]carbonyl}-1,5-etheno-2*H*-3-benzazepin-2-one*; **21**). NaH (60% dispersion in oil, 30.0 mg, 0.75 mmol) was repetitively washed with Et_2O (3 × 2.0 ml). After addition of THF (3.0 ml), (−)-**20** (63 mg, 0.34 mmol) in THF (2.0 ml) was added at r.t. to the stirred suspension, which was then refluxed for 15 min. After cooling to r.t., a soln. of (−)-(1*S*)-camphanoyl chloride (186 mg, 0.86 mmol) in THF (1.0 ml) was added. The resulting mixture was stirred for 15 min at r.t. and was then refluxed for an additional 15 min. After cooling to r.t., the mixture was poured onto a well-stirred mixture of ice and aq. sat. $NaHCO_3$ soln. This mixture was concentrated under reduced pressure before H_2O and Et_2O (5.0 ml each) were added. The aq. phase was extracted with Et_2O (2 × 5 ml), the combined org. phase washed with

brine, dried ($MgSO_4$), and evaporated, and the residue (151 mg of crude **20**) submitted to FC: pure **21** (59 mg, 47%). Recrystallization by slow evaporation of a soln. in *t*-BuOMe/CH_2Cl_2 mixture afforded crystals suitable for X-ray analysis. M.p. = 275–277°, $[\alpha]_D^{20} = -272$ ($c = 0.5$, $CHCl_3$). IR (CH_2Cl_2): 2972*m*, 2930*m*, 1786v*s*, 1691*s*, 1468*m*. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.81 (*s*, 3 H); 1.06 (*s*, 3 H); 1.13 (*s*, 3 H); 1.69 (*ddd*, $J = 13.2, 9.0, 4.4$, 1 H); 1.87 (*ddd*, $J = 12.9, 10.5, 5.0$, 1 H); 2.34 (*ddd*, $J = 13.8, 9.0, 5.0$, 1 H); 2.39 (*ddd*, $J = 13.8, 10.4, 4.5$, 1 H); 3.66 (*dd*, $J = 12.2, 4.7$, 1 H); 3.74 (*dd*, $J = 12.2, 1.7$, 1 H); 3.85 (*ddt*, $J = 6.2, 4.9, 1.3$, 1 H); 4.46 (*dd*, $J = 6.3, 1.3$, 1 H); 6.54 (*ddd*, $J = 8.3, 6.7, 1.3$, 1 H); 6.81 (*ddd*, $J = 8.2, 6.6, 0.9$, 1 H); 7.22–7.30 (*m*, 3 H); 7.50 (*d*, $J = 6.9$, 1 H). ^{13}C-NMR (100 MHz): 9.8 (*q*); 16.3 (*q*); 17.6 (*q*); 29.7 (*t*); 32.5 (*t*); 39.7 (*d*); 52.7 (*d*); 52.9 (*t*); 54.5 (*s*); 56.8 (*s*); 94.1 (*s*); 125.2 (*s*); 126.1 (*s*); 127.2 (*s*); 127.9 (*s*); 130.7 (*s*); 132.5 (*s*); 135.6 (*s*); 139.9 (*s*); 172.4 (*s*); 177.2 (*s*); 177.8 (*s*). MS: 337 (7), 339 (28), 142 (58), 141 (98), 137 (55), 136 (10), 129 (18), 128 (100), 109 (13), 97 (11), 83 (47). HR-MS: 337.1659 ($C_{21}H_{23}NO_3^+$; calc. 337.1678).

Crystal-Structure Determination of **21**[2]) (see *Table 2*). Cell dimensions and intensities were measured at 200 K on a *Stoe-STADI4* diffractometer with graphite-monochromated CuK_α radiation (λ 1.5418 Å); ω-2θ scans; two reference reflections measured every 45 min showed no variation. Data were corrected for *Lorentz* and polarization effects and for absorption [18]. The structure was solved by direct methods with MULTAN 87 [19], all other calculations with XTAL [20] programs. H-Atoms were placed in calculated positions and, for the Me groups, refined with restraints on bond lengths and bond angles (free rotation) and blocked in the last cycles.

Table 2. *Summary of Crystal Data, Intensity Measurement, and Structure Refinement for (–)-(1*S*,8*R*)-***21**

Formula	$C_{22}H_{23}NO_4$	$(\sin\theta/\lambda)_{max}$ [Å^{-1}]	0.531
M_r	365.5	Temperature [K]	200
Crystal size	$0.10 \times 0.13 \times 0.54$	No. measured reflc.	4932
Crystal system	Orthorhombic	No. observed reflc.	2099
Space group	$P\,2_12_12_1$	Criterion for observed	$\lvert F_o\rvert > 4\sigma(F_o)$
a [Å]	7.8171(8)	Refinement (on F)	Full-matrix
b [Å]	12.741(1)	No. parameters	288
c [Å]	19.060(2)	Weighting scheme	$\omega = 1/[\sigma^2(F_o) + 0.0005\,(F_o^2)]$
V [Å^3]	1898.3(4)	Max. and average Δ/σ	$0.13 \cdot 10^{-3}$, $0.15 \cdot 10^{-4}$
Z	4	Max. and min. $\Delta\rho$ [e·Å^{-3}]	0.16, –0.24
D_c [gr·cm^{-3}]	1.279	*Flack* parameter x [21]	–0.14(50)
μ(CuK_α) [mm^{-1}]	0.71	S	1.81(4)
T min., max.	0.8307, 0.9383	R, ωR	0.040, 0.046

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[2]) Crystallographic data (excluding structure factors) have been deposited with the *Cambridge Crystallographic Data Base* (deposition No. CCDC-141267). Copies of the data can be obtained free of charge on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: int. +44(1223)336-033; e-mail: deposit@ccdc.cam.ac.uk).

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