48. Diastereoselective Spirocyclization of *C*-(Alkyloxycarbonyl)formimines of 2-Substituted 1*H*-Indole-3-ethanamines (= Tryptamines): Basic Studies

5th Communication on Indoles, Indolenines, and Indolines[1])

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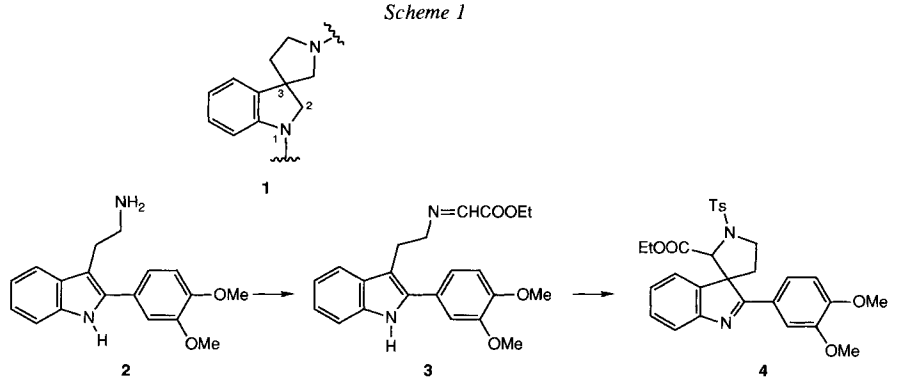
(18.1.90)

C-(Alkoxycarbonyl)formimines of type **15–18** were derived from the 2-substituted tryptamines **2**, **9**, **10**, and **11** and transformed with tosyl chloride into tricyclic 3-spiroindoles of types **19–22** (*Scheme 3*). The influence of the homochiral alkoxy moieties **A–D** on the stereochemical outcome of this reaction was studied. Good-to-excellent diastereoselectivities were observed with the (–)-8-(phenylmenth-3-yl)oxy group (**B**) as homochiral auxiliary. The structures of the tricycles **4**, (2'*R*,3*S*)-**19B**, and (2'*S*,3*R*)-**20C** were established by X-ray analysis, the structures of the others by NOE and CD studies, and by chemical correlation. Possibilities to explain the steric course of the spirocyclizations are discussed.

1. Introduction. – The spirocyclic partial structure **1** with a center of chirality at C(3) is found in many indole alkaloids, *e.g.* in *Strychnos*, *Aspidosperma*, and oxindole alkaloids. Both of possible absolute configurations are observed [2] [3].

In their total synthesis of strychnine, *Woodward* and coworkers prepared compound **4**, which contains the skeleton **1**, by reaction of imine **3** with TsCl in the presence of pyridine [4]. The imine is easily available from the amine **2** and ethyl glyoxalate. *Weissbach* and coworkers provided further examples of such spirocyclizations with TsCl [5]. In all cases, achiral imines were used. Related reactions have been applied in several alkaloid syntheses [2]. Recent publications deal with this type of reaction, making use of other electrophiles than TsCl [6].

Scheme 1

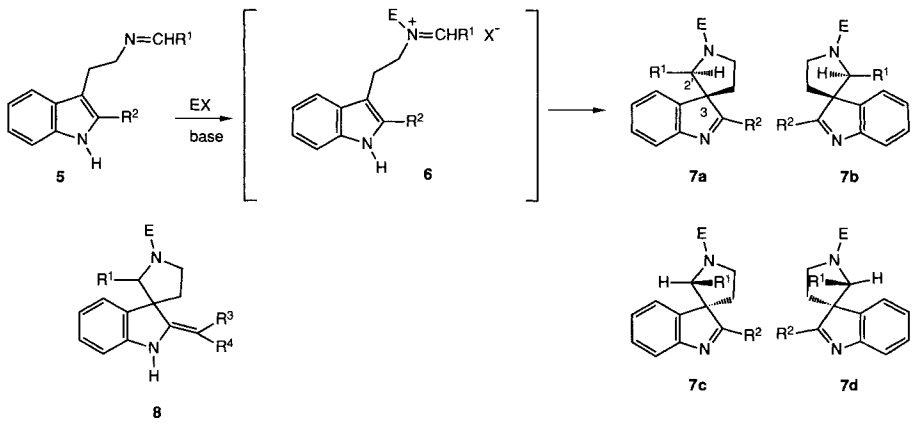


1 **2** **3** **4**

[1]) 4th communication: [1].

Although detailed mechanistic studies are not known, one can assume that these reactions take place *via* *N*-acyliminium ions [7] (see **6** in *Scheme 2*). With achiral or homochiral groups R^1, R^2, and E, in principle, four diastereoisomeric products **7a–d** may be obtained from imine **5** with the electrophile EX. The double bond at C(2) of **7** is endocyclic, but depending on the nature of R^2, it may be exocyclic as in **8**. *Woodward* and coworkers obtained only one racemate **4** from **3** and expressed the view that 'steric factors in the two relevant transition states' might favor the process leading to the isomer corresponding to **7a/7b** in which R^1 and R^2 point to opposite directions. We repeated the transformation **3** → **4** under slightly modified conditions and found only *Woodward*'s compound **4**. NMR control of the crude product as well as of the mother liquor obtained on crystallization of **4** showed no signals of a diastereoisomer of the latter (limit of error *ca.* 2% rel. to **4**). We confirmed the relative configuration of **4** by X-ray analysis (see below).

Scheme 2



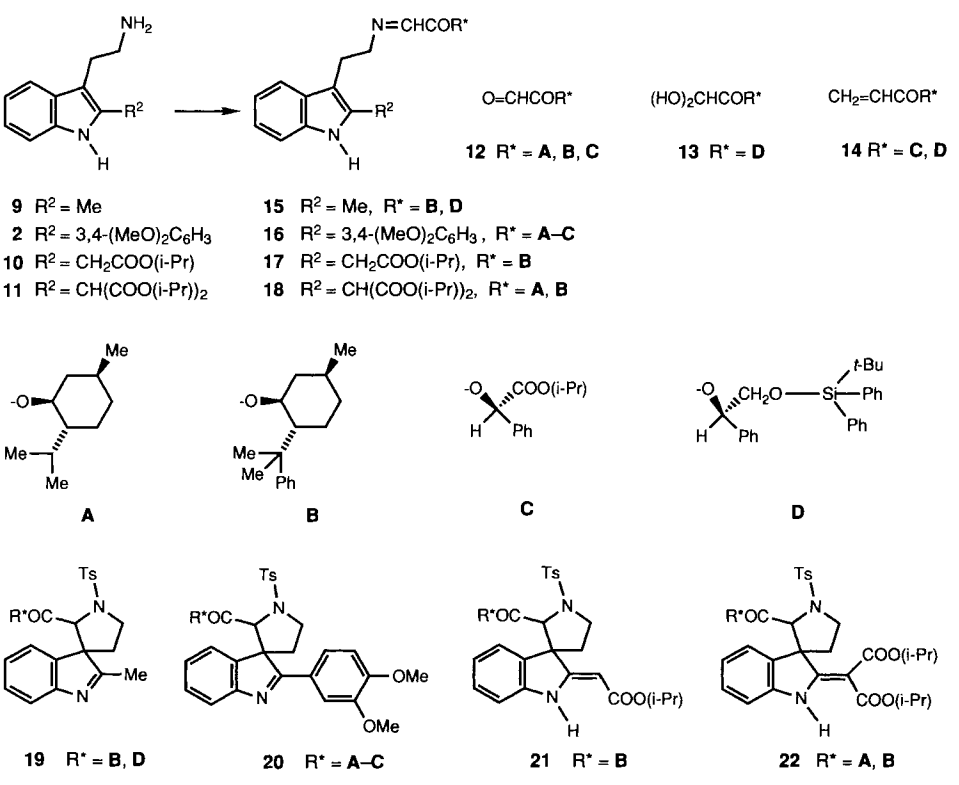
Homochiral compounds of type **7** and **8** could serve as valuable intermediates in enantioselective syntheses not only of *Strychnos* alkaloids, but also of other indole alkaloids which possess the partial structure **1** . Interestingly, no attempts are known to generate such compounds by diastereoselective spirocyclization of simple indole derivatives of type **5**, bearing an inducing chiral group in an appropriate position. We have, therefore, entered into pertinent investigations and report in the following on some of our results.

2. Strategy. – 2.1. *General.* Feasibility and stereochemical outcome of a sequence **5** → **6** → **7** depend on a series of factors, above all on the substituents R^1 and R^2, and the electrophile EX, *i.e.* on their characteristics (size, shape/chirality, electronic properties, functionality-dependent properties). Considering this variety of parameters to which, of course, the reaction conditions (base, solvent, temperature) should be added, we decided to restrict our first studies to a few simple test systems, which should allow to evaluate the principle, particularly with regard to stereoselectivity and applicability in the field of alkaloid synthesis.

2.2. *Position and Characteristics of the Inducing Group.* There are several possibilities to place centers of chirality in the components reacting to **7** in order to steer the configuration at the incipient spiro center (as well as the one at C(2')). Keeping in mind the reaction **3** → **4** and its perfect diastereoselectivity, the most obvious seems to be the one with R^1 = COR*[2]), all the more as plenty of inter- and intramolecular asymmetric cyclizations of α,β-unsaturated esters of chiral alcohols are reported [8]. Accordingly, we decided to study the spirocyclization of imines **5** of homochiral glyoxylates, affording tricycles of type **7** or **8** (R^1 = COR*).

3. Test Systems. – 3.1. *Tryptamine Derivatives* **2** *and* **9–11** (see *Scheme 3*). *Woodward*'s 2-aryltryptamine **2** served as the first test compound to examine the inducing power of various homochiral auxiliaries. Moreover, 2-methyltryptamine (**9**) [9] seemed to be of interest as the simplest suitable compound, but also as a potential alkaloid-building block. It was conveniently obtained *via* the corresponding 3-(2-nitroethenyl)- and 3-(2-nitroethyl)indole (*cf. Exper. Part*) in analogy to the synthesis of **10** and **11** [1]. The latter two were also chosen bearing in mind planned work on alkaloid syntheses. The purpose of the i-Pr group(s) in **10** and **11** was to prevent the exocyclic methylene or methine moiety from reacting (instead of the indole C(3)) with the iminium system (*cf.* **6**).

Scheme 3



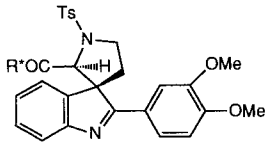
[2]) R* = chiral group of the type RO.

3.2. *Homochiral Auxiliaries* **12** *and* **13**. The glyoxylate **12A** of (–)-menthol (**A**-H) was used in the first exploratory experiments. Because of the notorious inducing power of the (–)-8-(phenylmenth-3-yl)oxy moiety (**B**) [10], glyoxalate **12B** was tested in combination with each of the above-mentioned tryptamines **2** and **9–11**. Both **12A** and **12B** were obtained according to a procedure of *Whitesell* and coworkers [11]. The unknown esters **12C** and **13D**, which were prepared by ozonization of the corresponding acrylates **14C** and **14D**, respectively, were chosen, since their R* can be replaced by OH on catalytic hydrogenation. Ester **14D** was obtained in 79% yield from (*R*)-phenylethylene glycol by regioselective silylation and subsequent acylation with acryloyl chloride.

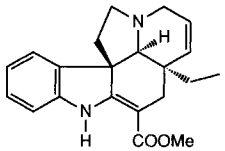
3.3. *Tryptimine Derivatives* **15–18**. Starting from the glyoxylates **12** and **13**, the imines **15–18** were obtained by reaction with the 2-substituted tryptamines **2** and **9–11** in CH_2Cl_2, THF, or benzene in the presence of molecular sieves. Since dehydration of hydrates of high-boiling glyoxylates is a cumbersome process, it was an important finding that the hydrate **13D** could be reacted directly with the tryptamines to the corresponding imines. The reaction was sufficiently fast at temperatures down to –10°. Of the imines, only **16A** was obtained in crystalline form. All other imines were used as crude products for the spirocyclization.

3.4. *Spirocyclization.* CH_2Cl_2 was chosen as solvent to allow the reaction to take place at low temperature. Exploratory studies with the imines **16A** and **16B** gave essentially better diastereoselectivity with 2,4,6-trimethylpyridine than with pyridine as base[3]). Therefore, in further experiments, the former was used. Reaction temperature and time were not optimized.

4. Results. – 4.1. *Spirocyclizations.* In the *Table*, the results of eight spirocyclization experiments with TsCl are compiled. There is no doubt that the steric outcome of the reaction is determined by the chiral groups R*. If the spiro centers C(3) are looked at, it becomes obvious that, in the series of the imines **16**, all groups *R** used favor the formation of tricycles **20** with (3*R*)-configuration. Inspection of the major products shows, not surprisingly, **B** being a much more effective auxiliary group than **A**. With C, only medium diastereoselectivities were observed, but the main product was crystalline.



(2'*S*,3*R*)-**20**



23 (–)-Tabersonine

The imine **15B** afforded, with good diastereoselectivity, the crystalline (2'*R*,3*S*)-tricycle **19B**. In the case of **15D**, a crystalline mixture of diastereoisomers **19D** was obtained. With the imine **17B**, again formation of the (2'*R*,3*S*)-tricycle **21B** is favored, but with poor and variable selectivity. A (3*S*)-spirotricycle **22B** is the main product starting from the imine **18B**. From **18A**, a mixture of two diastereoisomers **22A** was obtained (39% de in favor of the (3*R*)-isomer).

[3]) *Woodward* and coworkers run the reaction **3** → **4** in pyridine at r.t.

4.2. *Structure of Cyclization Products.* For all compounds discussed, correct NMR, IR, and UV spectra were obtained, from the crystalline ones also correct microanalyses. The structure of the very well crystallizing major diastereoisomer (2'*S*,3*R*)-**20C** resulting from the imine **16C** was established by X-ray analysis (see below), *i.e.* it has the same relative configuration as *Woodward*'s compound **4**.

Table. *Results of the Spirocyclizations*

Imine	Temp. [°]	Time [h]	Products	Chemical yield [%]	Configuration of major isomer	% de[a])	Configuration of minor isomer
15B	–90	72	**19B**	57.9	(2'*R*,3*S*)	86.3	?
15D	0	16	**19D**	61	(2'*R*,3*S*)	36.8	(2'*S*,3*R*)
16A	–78	72	**20A**	55	(2'*S*,3*R*)	22.3	(2'*R*,3*S*)
16B	–90	24	**20B**	49.4	(2'*S*,3*R*)	97	?
16C	–80	90	**20C**	44.5	(2'*S*,3*R*)	39.5	?
17B	–80	140	**21B**	56.8	(2'*R*,3*S*)	15.8[b])	(2'*R*,3*R*)
18A	0	6	**22A**[c])	33.2	(2'ξ,3*R*)	39	(2'ξ,3*S*)
18B	–78	120	**22B**[c])	23.8	(2'ξ,3*S*)	66.7	(2'ξ,3*R*)

[a]) Estimated by ^{1}H-NMR (*cf. Exper. Part*).
[b]) Variable.
[c]) The diastereoisomers could not be separated.

For the major diastereoisomers of **20A** and **20B**, (3*R*)-configuration followed from CD correlation with (2'*S*,3*R*)-**20C** (minor isomer of **20A**, (3*S*)-configuration), taking into consideration the long-wavelength range of the spectra (*Fig. 1*). It can be taken for sure that also these compounds possess the same relative configuration as **4.**

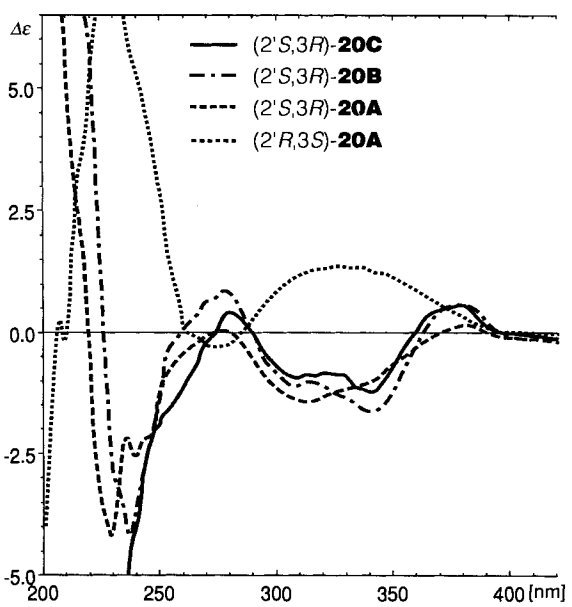


Fig. 1. *CD Spectra of compounds* **20**

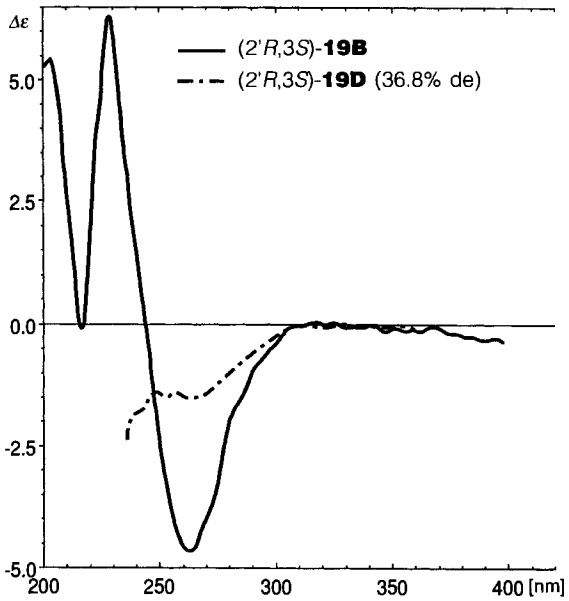


Fig. 2. *CD Spectra of compounds* **19**

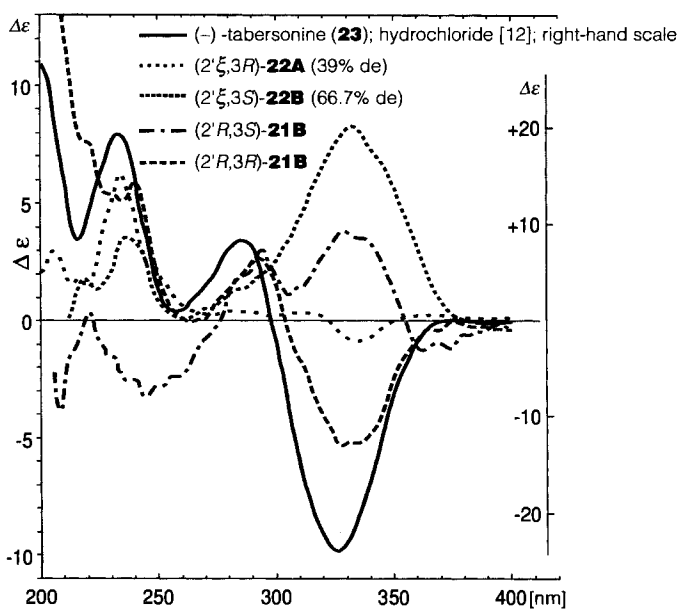


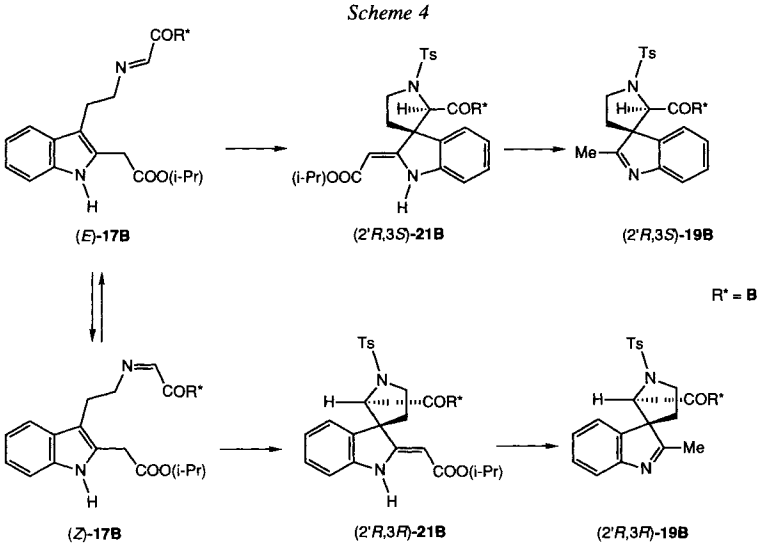
Fig. 3. *CD Spectra of compounds with the chromophor of tabersonine*

The structure of the major diastereoisomer (2'*R*,3*S*)-**19B** derived from imine **15B** was established by X-ray analysis (see below). Its proton at C(2') points to Me–C(2), a fact which found expression also in an NOE experiment (irradiation at *Me*–C(2) signal → increase of *H*–C(2') signal). Both spirotricycles **19D** gave analogous NOE results. Since the mixture of diastereoisomers shows a negative *Cotton* effect at *ca.* 260 nm, like (2'*R*,3*S*)-**19B** (*Fig. 2*), it followed that the major one is (2'*R*,3*S*)-**19D** and the minor one (2'*S*,3*R*)-**19D**.

Of the two spirotricycles from **17B**, the major one is (2'*R*,3*S*)-**21B**, the minor one (2'*R*,3*R*)-**21B**. This was proved by CD comparison with (–)-tabersonine **23** [12] (*Fig. 3*) and by the transformations (2'*R*,3*S*)-**21B** → (2'*R*,3*S*)-**19B** and (2'*R*,3*R*)-**21B** → (2'*R*,3*R*)-**19B**, using HCl/H_2O/EtOH under reflux (*Scheme 4*). Neither of the products epimerized under these conditions. The relative configuration of (2'*R*,3*R*)-**19B** followed from NOE studies: (no *Me*–C(2)/*H*–C(2') interaction, *cf.* above).

The major spirocyclization product obtained from the imine **18A** is a (3*R*)-compound, the one from **18B** a (3*S*)-compound, as follows from CD comparison with (–)-tabersonine (*Fig. 3*). The isomers could not be separated in these cases, and the configurations at C(2') were not established.

Scheme 4



5. Discussion. – The above presented facts clearly show that the reaction of the imines **15**, **16**, and **18** with TsCl is of synthetic value, giving rise to spirotricycles with reasonable-to-excellent control of the absolute configuration at C(2') and C(3). The preferential formation of tricycles with the relative configuration (2'*S**,3*R**) from **3**, **15**, and **16**[4]) and of (2'*S**,3*R**)- as well as (2'*S**,3*S**)-tricycles from **17** and **18** requires an explanation.

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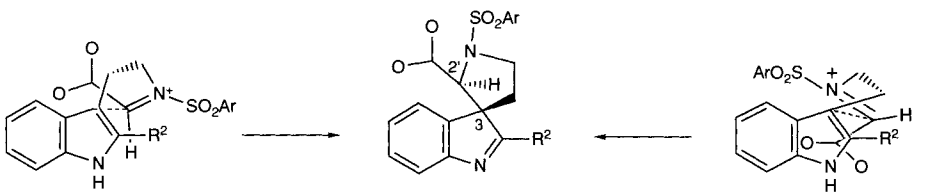
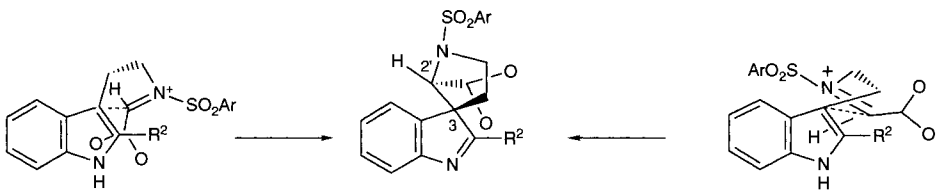
[4]) We will report on additional examples for the preferential formation of (2'*S**,3*R**)-spirotricycles of type **7a**/**7b** in a forthcoming paper.

In *Scheme 5*, the four transition states which, in principle, could afford (3*R*)-tricycles are depicted. (2'*S*,3*R*)-Products may emerge from **24** and **25**, (2'*R*,3*R*)-compounds from **26** or **27**. For the isolable pure imines **3** and **16A** as well as for the imines **15B**, **17B**, and **18B**, formed *in situ* from the components in $CDCl_3$ solution, (*E*)-configuration was proved by NOE (irradation at CH_2N signal → increase of signal N=CH). The other imines very probably also possess (*E*)-configuration (the corresponding *N*-tosyliminium salts have the opposite stereochemical descriptor). Accepting the reasonable assumptions that *a*) the imines are acylated with retention of the configuration (*cf.* [13] [14]), and *b*) the ring closure is kinetically controlled and much faster than (*E*/*Z*)-isomerization of the iminium salts, one has to conclude that the (2'*S**,3*R**)-tricycles are formed *via* **25** (and its mirror image, respectively).

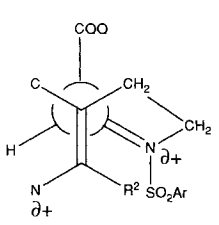
Scheme 5



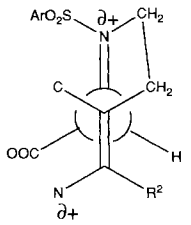
24 *si*-C(3) ◠ *si*-(*E*)-C(2') (2'*S*,3*R*) **25** *si*-C(3) ◠ *si*-(*Z*)-C(2')



26*si*-C(3) ◠ *re*-(*Z*)-C(2') (2'*R*,3*R*) **27***si*-C(3) ◠ *re*-(*E*)-C(2')



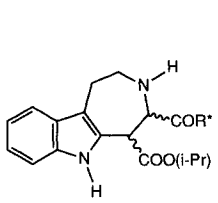
24
26 H and COO interchanged



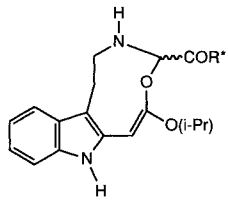
25
27 H and COO interchanged

The stereochemical outcome of the sequence **10** → **17B** → **21B** can be explained by the assumption that (*E*)-**17B** equilibrates with its (*Z*)-isomer. The former leads to (2'*R*,3*S*)-**21B** (*via* a transition state which corresponds to **25**), whereas (*Z*)-**17B** gives rise to (2'*R*,3*R*)-**21B** *via* a transition state of type **27** (*Schemes 4* and *5*). We assume that the (*E*/*Z*)-isomerization is mediated by the enolizable 2-substitutent of **17B**, which plays the role of

an internal nucleophile. This means that a tricyclic intermediate, either **28** or **29**, must be involved. The formation of two isomers of each **22A** and **22B** may be explained analogously.



28 R* = B



29 R* = B

Why are spirocyclizations *via* **25** and **27** favored over those *via* **24** and **26**, respectively? The transition states **25** and **27** with antiperiplanar orientation of the involved indole double bond C(2)=C(3) and the iminium double bond (see *Newman* projections **25** and **27** in *Scheme 5*) correspond to the 'extented transition states' which have been postulated by *Noyori et al.* [15] for certain types of intermolecular aldol reactions and recently by *Denmark* and *Henke* [16] for similar intramolecular aldol reactions. As in those cases, the preference of the antiperiplanar orientations over the synclinal ones (see *Newman* projections **24** and **26**) is due to lower *Coulomb* repulsion of the charged atoms.

Although the observed relative configurations are thus reasonably explained, we think that a mechanistic interpretation of the observed absolute configurations on the basis of the described facts would be premature. However, we whish to draw the attention to two points which might turn out to be essential for the understanding of the results: *a*) the above mentioned connection in the case of compounds **21B** between the relative configuration at C(2') and C(3) and the absolute configuration at C(3), and *b*) the finding that identical chiral groups *R** lead, in the 2-methyl series, to (3*S*)-products, in the 2-(3,4-dimethoxyphenyl) series, however, to (3*R*)-products. Application of auxiliaries which possess less degrees of freedom than **A–D** may allow to find a solution of the problem. Further studies are in progress.

6. X-Ray Structure Analyses. – The stereoscopic drawings of the spirocyclic structures of **4**, (2'*R*,3*S*)-**19B**, and (2'*S*,3*R*)-**20** are given in *Figs. 4–6*[5]).

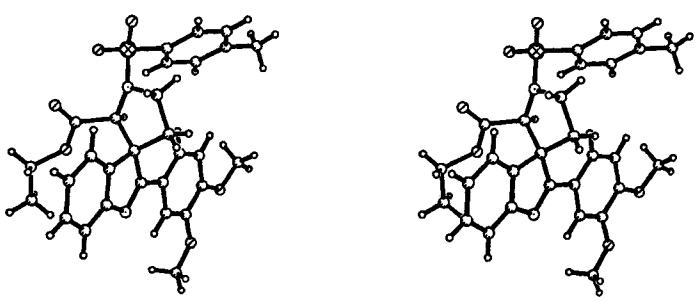


Fig. 4. *Stereoscopic drawing of* **4**

[5]) Coordinates and thermal parameters have been deposited with the *Crystallographic Data Centre*, Cambridge University, University Chemical Lab, Cambridge CB2 1EW, England.

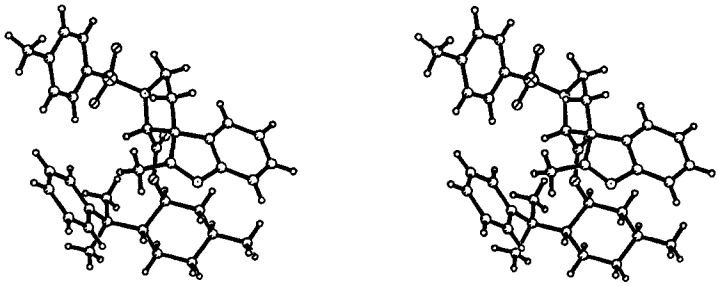


Fig. 5. *Stereoscopic drawing of (2'R,3S)-***19B**

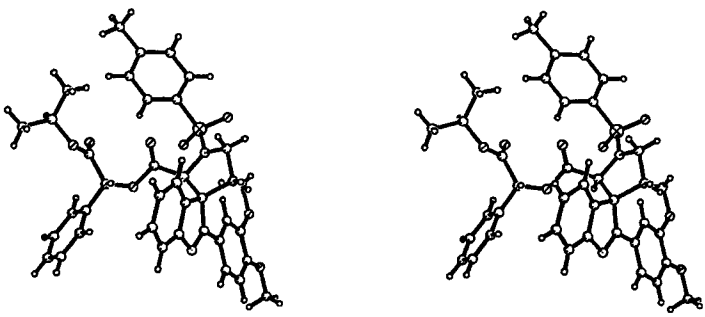


Fig. 6. *Stereoscopic drawing of (2'S,3R)-***20C**

Data for all structures were collected on a *Nicolet-R3m* four-circle diffractometer fitted with a graphite monochromator and the *LT1* cooling apparatus.

Data Collections, Structure Determinations, and Refinements. Compound **4**. $C_{29}H_{30}N_2O_6S \cdot H_2O$ (543.6). $F(000) = 2296$. Orthorhombic, $Pca2_1$; $a = 26.981(10)$, $b = 7.648(3)$, $c = 26.607(8)$ Å; $D = 1.315$ Mg/m³, $Z = 8$; $\mu(\text{MoK}\alpha) = 0.157$ mm^{-1}; absorption effects ignored. Crystal size $0.15 \times 0.4 \times 0.4$ mm³; temp. 183 K; wavelength 0.71069 Å; scan mode ω, scan speed 0.8°/min minimum speed; strong reflections measured up to 10.2°/min, scan width 0.9°; 2θ range 0–50°; peak background ratio 5:1; total data measured, 4951 excluding standards; total observed, 4104; rejection criterion $I > 2.5\sigma(I)$; number of parameters, 693; weights $w = 1/\sigma^2(F) + 0.001\ F^2$. The structure was determined by direct methods using the *Nicolet* SHELXTL PLUS [17] (*MicroVAX II*) system. Refinement proceeded smoothly to convergence at $R = 0.058$ with anisotropic refinement of all non-H-atoms.

*Compound (2'R,3S)-***19B**: $C_{36}H_{42}N_2O_4S \cdot CH_2Cl_2$ (683.7), $F(000) = 1448$. Orthorhombic, $P2_12_12_1$; $a = 7.864(3)$, $b = 12.113(4)$, $c = 36.166(9)$ Å; $D = 1.318$ Mg/m³, $Z = 4$; $\mu(\text{MoK}\alpha) = 0.286$ mm^{-1}; absorption effects ignored. Crystal size $0.35 \times 0.35 \times 0.5$ mm³; temp. 193 K; wavelength 0.71069 Å; scan mode ω; scan speed 1.61°/min; minimum speed; strong reflections measured up to 14.65°/min; scan width 1.1°; 2θ range 0–56°; peak background ratio 5:1; total data measured, 4693 excluding standards; total observed, 4132; rejection criterion $I > 2.5\sigma(I)$; number of parameters, 441; weights $w = 1/\sigma^2(F) + 0.001\ F^2$. Structure determination and refinement as for **4**: $R = 0.041$.

*Compound (2'S3R)-***20C**: $C_{38}H_{38}N_2O_8S$ (682.79); $F(000) = 720$. Monoclinic: $P2_1$; $a = 10.408(2)$, $b = 13.978(4)$, $c = 11.998(2)$ Å; $\beta = 91.31°$; $D = 1.3$ Mg/m³, $Z = 2$; $\mu(\text{MoK}\alpha) = 0.14$ mm^{-1}; absorption effects ignored. Crystal size $0.12 \times 0.25 \times 0.5$ mm³; temp. 267 K; wavelength 0.71069 Å; scan mode ω; scan speed 3.9°/min; minimum speed; strong reflections measured up to 15°/min; scan width 1.9°; 2θ range 0–56°; peak background ratio 5:1; total data measured, 4644 excluding standards; total observed, 2097; rejection criterion $I > 2.5\sigma(I)$; number of parameters, 441; weights $w = 1/\sigma^2(F) + 0.001\ F^2$. The structure was determined by direct methods using the SHELXTL-86 system. Refinement as for **4**: $R = 0.053$.

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Experimental Part

General. See [1]. If not stated otherwise, the molecular sieves used for imine formation were from *Merck* (0.4 nm). Solns. in aprotic solvents were dried with $MgSO_4$ or Na_2SO_4 before evaporation. Flash chromatography (FC) according to [18]. Diastereoselectivities (% de) were estimated by ^{1}H-NMR (250, 270, 300, or 400 MHz; *s* of H–C(2')) of combined chromatographic fractions.

1. *Ethyl (2'*RS,*3*SR*)-2-(3,4-Dimethoxyphenyl)-1'-(4-toluenesulfonyl)spiro[3*H*-indole-3,3'-pyrrolidine]-2'-carboxylate* (**4**). To a stirred soln. of imine **3** [4] (192.0 mg, 0.5 mmol) in CH_2Cl_2 (5 ml) and pyridine (1 ml) at 0°, TsCl (108.4 mg, 0.57 mmol) in CH_2Cl_2 (1 ml) was added dropwise by syringe. After 72 h at 4°, the mixture was shaken with 2N Na_2CO_3. The aq. phase was extracted with CH_2Cl_2 (3 × 5 ml) and the combined org. layer evaporated. The residue was chromatographed with hexane/$CHCl_3$/AcOEt 2:2:1 on silica gel (20 g): 215.2 mg (80.5%) of crude **4**. Crystallization from CH_2Cl_2 gave 112.9 mg (42.2%) of pure substance. M.p. 140–141°. ^{1}H-NMR (250 MHz, $CDCl_3$): 0.57 (*t*, *J* = 7.6, 3 H); 1.91–2.0 (*m*, 1 H); 2.49 (*s*, 3 H); 2.77–2.93 (*m*, 1 H); 3.56 (*q*, *J* = 14.0, 7.6, 2 H); 3.77–3.89 (*m*, 1 H); 3.98 (*s*, 3 H); 4.05 (*s*, 3 H); 4.13–4.23 (*m*, 1 H); 5.32 (*s*, 1 H); 6.88–8.0 (*m*, 11 arom. H).

The residue of the mother liquor, according to ^{1}H-NMR, did not contain any diastereoisomer of **4** (the only signal between 4.5 and 6.8 ppm: 5.33 ppm (*s*), H–C(2') of **4**).

2. *2-Methyl-3*H*-indole-3-ethanamine* (**9**). 2.1. *2-Methyl-3-(2-nitroethenyl)-1*H*-indole.* To a stirred soln. of *N,N*-dimethyl-2-nitroethylenamin (12.08 g, 104 mmol) in CH_2Cl_2 (100 ml), CF_3COOH (20 ml) was added dropwise at 0°, followed by a soln. of 2-methyl-1*H*-indole (*Fluka*; 13.71 g, 105 mmol) in CH_2Cl_2 (60 ml). Stirring was continued at 0° for 2 1/2 h and then at r.t. for 20 h. After cooling to 0°, the precipitate was collected by filtration and recrystallized from AcOEt/CH_2Cl_2 1:1: 16.9 g (80.4%) of 2-methyl-3-(2-nitroethenyl)-1*H*-indole. M.p. 190° ([9]: 197°). Anal. calc. for $C_{11}H_{10}N_2O_2$ (202.21): C 65.34, H 4.98, N 13.85; found: C 65.06, H 4.96, N 13.53.

2.2. *2-Methyl-3-(2-nitroethyl)-1*H*-indole.* A mixture of 2-methyl-3-(2-nitroethenyl)-1*H*-indole (25.94 g, 128 mmol), benzene (500 ml), and tris(triphenylphosphine)rhodium(I) chloride (*Fluka*, 2.6 g) was stirred under H_2 (10 bar) at 50° for 20 h and then filtered and evaporated. The soln. of the residue in CH_2Cl_2 was filtered through silica gel (200 g). The filtrate was evaporated and the residue crystallized from CH_2Cl_2/hexane: 2-methyl-3-(2-nitroethyl)-1*H*-indole (24.7 g, 94.5%). M.p. 85–86°. ^{1}H–NMR (250 MHz, $CDCl_3$): 2.39 (*s*, 3 H); 3.43 (*t*, *J* = 7.4, 2 H); 4.59 (*t*, *J* = 7.4, 2 H); 7.07–7.50 (*m*, 4 arom. H); 7.83 (br. *s*, 1 H). Anal. calc. for $C_{11}H_{12}N_2O_2$ (204.23): C 64.69, H 5.92, N 13.72; found: C 64.68, H 6.06, N 13.63.

2.3. *Compound* **9**. 2-Methyl-3-(2-nitroethyl)-1*H*-indole (414.7 mg, 2.03 mmol) in MeOH (15 ml) was hydrogenated at r.t. over Pd/C (260 mg) for 1/2 h (149 ml of H_2, calc. 148.1 ml). The catalyst was removed by filtration under N_2, the filtrate evaporated, and the residue treated with benzene and again evaporated: crude **9** (346.5 mg, 98.1%), suitable for imine formation .

3. *(1*S,*2*R,*5*S*)-5-Methyl-2-(1-methylethyl)cyclohexyl (*E*)-{{2-[2-(3,4-Dimethoxyphenyl)-1*H*-indol-3-yl]ethyl}imino}acetate* (**16A**). A mixture of **2** (594 mg, 2.0 mmol), **12A** (428.6 mg, 2.02 mmol), and benzene (25 ml) was refluxed for 5 1/2 h. The residue obtained after evaporation was crystallized from Et_2O/hexane 4:1: **16A** (611 mg, 62.3%). M.p. 133–137°. IR (KBr): 1725, 1718, 1513, 1461, 1298, 1248, 1218, 1140, 1025, 743. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.70 (*d*, *J* = 8 , 3 H); 0.84 (*d*, *J* = 7, 3 H); 0.90 (*d*, *J* = 6.5, 3 H); 0.95–2.05 (*m*, 9 H); 3.32 (*t*, *J* = 7.9, 2 H); 3.94 (*s*, 3 H); 3.97 (*s*, 3 H); 4.02 (*t*, *J* = 7.9, 2 H); 4.84 (*m*, 1 H); 6.9–7.7 (*m*, 7 arom. H); 7.49 (*s*, 1 H); 8.03 (*s*, 1 H). Anal. calc. for $C_{30}H_{38}N_2O_4$ (490.64): C 73.44, H 7.81, N 5.71; found: C 73.39, H 7.68, N 5.70.

4. *Imines* **15B**, **17B**, *and* **18B** *in* $CDCl_3$. To a soln. of the corresponding amine **9**, **10**, or **11** (0.2 mmol) in $CDCl_3$ (1.5 ml), **12B** (0.2 mmol) and molecular sieves were added. After stirring for 40 h at r.t., the solns. were used for NMR measurement. ^{1}H-NMR (250 MHz, $CDCl_3$, NOE-relevant signals): **15B**: 3.68 (*t*, *J* = 5.0, 2 H); 6.60 (*s*, 1 H). **17B**: 3.67 (*t*, *J* = 4.6, 2 H); 6.57 (*s*, 1 H). **18B**: 3.68 (*t*, *J* = 5.0, 2 H); 6.60 (*s*, 1 H).

5. *(1S,2R,5S)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl (2'R,3S)-2-Methyl-1'-(4-toluenesulfonyl)-spiro[3H-indole-3,3'-pyrrolidine]-2'-carboxylate* ((2'*R*,3*S*)-**19B**). 5.1. *By Spirocyclization.* A mixture of **9** (425.5 mg, 3 mmol), **12B** (866 mg, 3 mmol), benzene (10 ml), and molecular sieves was stirred at r.t. for 90 h and then filtered. The filtrate was evaporated: crude **15B**. To a stirred soln. of the latter and 2,4,6-trimethylpyridine (0.6 ml) in CH_2Cl_2 (12 ml) at –90°, a soln. of TsCl (575 mg, 3.02 mmol) in CH_2Cl_2 was added by syringe. After 72 h at –90°, the mixture was treated with 2N Na_2CO_3 soln. (15 ml) and warmed to r.t. The aq. phase was extracted with CH_2Cl_2 (3 × 10 ml), and the combined org. phase dried and evaporated. The residue was crystallized from CH_2Cl_2: (2'*R*,3*S*)-**19B** (838.6 mg, 46.6%). M.p. 132–133°. A sample was recrystallized from AcOMe/pentane. M.p. 134–135°. UV (EtOH): 219.5 (4.39), 262 (sh, 3.64). CD (EtOH, 0.86 mM): 263 (–4.64), 229 (6.39), 203 (5.4). IR (KBr):1753, 1581, 1495, 1455, 1330, 1195, 1160. ^{1}H-NMR (250 MHz, $CDCl_3$): 0.52 (*d*, *J* = 8, 3 H); 0.51–1.64 (*m*, *ca.* 8 H); 1.11 (*s*, 3 H); 1.23 (*s*, 3 H); 1.74 (*m*, 1 H); 1.94 (*s*, 3 H); 2.17 (*m*, 1 H); 2.48 (*s*, 3 H); 3.58 (*m*, 1 H); 3.94 (*m*, 1 H); 4.27 (*s*, 1 H); 4.43 (*m*, 1 H); 7.06–7.47 (*m*, 11 arom. H); 8.04 (*ca. d*, 2 arom. H). Anal. calc. for $C_{36}H_{42}N_2O_4S$ (598.80): C 72.21, H 7.07, N 4.68; found: C 71.82, H 7.02, N 4.65.

The mother liquor from the above crystallization was chromatographed with hexane/$CHCl_3$/AcOEt 2:2:1 on silica gel (100 g): 137.2 mg of (2'*R*,3*S*)-**19B** and a mixture containing the same compound, an isomer, and an unknown compound in the ratio 13.3:75.3:11.4 (GC). The isomer was not obtained in pure form. ^{1}H-NMR (250 MHz, $CDCl_3$; characteristic signals): 2.30 (*s*, CH_3–C=N); 2.48 (*s*, 3 H, Ts); 3.6 (*m*, 1 H); 3.9 (*m*, 1 H); 4.19 (*s*, N–CH–CO); 4.53 (*m*, 1 H). The chemical yield of (2'*R*,3*S*)-**19B** was 54.8% and of the isomer 3.1%; de 86.3%.

5.2. *From (2'R,3S)*-**21B**. A mixture of (2'*R*,3*S*)-**21B** (25.1 mg, 0.037 mmol), EtOH (5 ml), and aq. HCl soln. (25%, 2.5 ml) was refluxed for 2 h and then evaporated. The residue was treated with 2N Na_2CO_3 soln. (2.5 ml) and CH_2Cl_2 (5 ml), the aq. phase extracted with CH_2Cl_2 (3 × 5 ml), and the combined org. layer evaporated. The residue was purified by chromatography on a 5-mm silica-gel layer (*Merck*) with hexane/$CHCl_3$/AcOEt 4:2:1. The product was extracted from silica gel with CH_2Cl_2/AcOEt: 14.2 mg (64%) of (2'*R*,3S)-**19B**, identical with the above described compound.

6. *(1S,2R,5S)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl (2'R,3R)-2-Methyl-1'-(4-toluenesulfonyl)spiro[3H-indole-3,3'-pyrrolidine]-2'-carboxylate* ((2'*R*,3*R*)-**19B**). The soln. of (2'*R*,3*R*)-**21B** (95 mg, 0.14 mmol) in EtOH (20 ml) and aq. HCl soln. (25%, 10 ml) were refluxed for 2 h and then evaporated. The residue was treated with 2N Na_2CO_3 soln. (5 ml) and CH_2Cl_2 (5 ml), and the org. layer extracted with CH_2Cl_2 (3 × 5 ml). The combined org. phase was evaporated and the residue chromatographed with hexane/$CHCl_3$/AcOEt 4:2:1 over silica gel (15 g): (2'*R*,3*R*)-**19B** (49.2 mg, 59.3%) as a colorless foam. ^{1}H-NMR (400 MHz, $CDCl_3$): 0.21–0.32 (*m*, 1 H); 0.58–1.7 (*m*, *ca.* 12 H); 0.80 (*d*, *J* = 6.4, 3 H); 1.10 (*s*, 3 H); 1.17 (*s*, 3 H); 1.95–2.05 (*m*, 1 H); 2.17–2.27 (*m*, 1 H); 2.31 (*s*, 3 H); 2.47 (*s*, 3 H); 3.55–3.63 (*m*, 1 H); 3.89–3.97 (*m*, 1 H); 4.19 (*s*, 1 H); 4.48–4.58 (*m*, 1 H); 6.9–8.01 (*m*, 8 arom. H). MS: 598 (1, M^+), 384 (21), 339 (27), 185 (100), 183 (87), 158 (48), 119 (83).

7. *(R)-1-Phenyl-2-{[(tert-butyl)dimethylsilyl]oxy}ethyl 2-Methyl-1'-(4-toluenesulfonyl)spiro[3H-indole-3,3'-pyrrolidine]-2'-carboxylate* (**19D**; mixture of 2 diastereoisomers). To a stirred mixture of **9** (99 mg, 0.59 mmol), CH_2Cl_2 (3.6 ml), and molecular sieves (3 Å; *Fluka*), **13D** (244 mg, 0.54 mmol) in CH_2Cl_2 (6.8 ml) was added by syringe at 0°. After stirring at 0° overnight, a mixture of TsCl (155 mg, 0.81 mmol), 2,4,6-trimethylpyridine (0.215 ml, 1.62 mmol), and CH_2Cl_2 (0.7 ml) was added by syringe. After 16 h at 0°, the mixture was poured into 0.5M citric acid (30 ml). The aq. phase was extracted with CH_2Cl_2 (2 × 30 ml), the combined org. layer evaporated, and the residue submitted to FC (Et_2O/petroleum ether (low-boiling) 3:1): **19D**, colorless foam (245 mg, 61%; mixture of 2 diastereoisomers (36.8% de)). UV (EtOH): 262 (sh, 3.72). CD (EtOH, 1.35 mM): 264 (–1.52), 253 (–1.47), 215 (–5.6). IR ($CHCl_3$): 1750 (br.), 1430, 1350 (br.), 1165, 1115, 825, 816, 705. ^{1}H-NMR (200 MHz, $CDCl_3$)[6]: 0.81* (*s*, 6 H); 0.98 (*s*, 3 H); 1.95–2.16 (*m*, 2 H); 2.20 (*s*, 1 H); 2.29* (*s*, 2 H); 2.39* (*s*, 2 H); 2.43 (*s*, 1 H); 2.82–3.01 (*m*, 1 H); 3.54–4.04 (*m*, 3 H); 4.60* (*s*, 0.67 H); 4.65 (*s*, 0.33 H); 5.33–5.66 (*m*, 1 H); 6.6–7.1 (*m*, 23 arom. H).

8. *(1S,2R,5S)-5-Methyl-2-(1-methylethyl)cyclohexyl (2'S,3R)-2-(3,4-Dimethoxyphenyl)-1'-(4-toluenesulfonyl)spiro[3H-indole-3,3'-pyrrolidine]-2'-carboxylate* ((2'*S*,3*R*)-**20A**) *and (1S,2R,5S)-5-Methyl-2-(1-methylethyl)cyclohexyl (2'R,3S)-2-(3,4-Dimethoxyphenyl)-1'-(4-toluenesulfonyl)spiro[3H-indole-3,3'-pyrrolidine]-2'-carboxylate* ((2'*R*,3*S*)-**20A**). A mixture of **2** (1.186 g, 4 mmol), **12A** (849 mg, 4 mmol), THF

[6]) Separate signals of the major diastereoisomer are marked by *.

(12 ml), and molecular sieves was stirred at r.t. for 20 h, then filtered, and evaporated: crude **16A**. To a stirred soln. of the latter and of 2,4,6-trimethylpyridine (0.8 ml) in CH_2Cl_2 (20 ml) at –78°, a soln. of TsCl (0.842 g, 4.4 mmol) in CH_2Cl_2 (2 ml) was added by syringe within 10 min. After 72 h at –78°, the mixture was treated with 2N Na_2CO_3 (20 ml) and warmed to r.t. The aq. phase was extracted with CH_2Cl_2 (3 × 10 ml), the combined org. phase dried and evaporated, and the residue chromatographed on silica gel (155 g; hexane/$CHCl_3$/AcOEt 4:2:1): (2'*S*,3*R*)-**20A** (808.5 mg, 31.3%; amorphous solid), (2'*R*,3*S*)-**20A** (313.5 mg, 12.2%; amorphous solid), and (2'*S*,3*R*)-**20A**/(2'*R*,3*S*)-**20A** 1:4 (298.3 mg; 11.6%, amorphous solid). Chemical yield for (2'*S*,3*R*)-**20A** 33.7%, for (2'*R*,3*S*,)-**20A** 21.4%; de 22.3%.

*Data of (2'S,3R)-***20A**. UV (EtOH): 201.7 (4.55), 231.6 (4.42), 337.9 (4.22). CD (MeOH, 1.63 mM): 378 (0.17), 310 (–1.4), 238 (–2.5),227 (–4.1), 198 (11.9). IR (KBr): 1748, 1685, 1598, 1509 1461, 1419, 1335, 1270, 1214, 1158, 1097, 1025, 811, 767. ^{1}H-NMR (250 MHz, $CDCl_3$): 0.26–1.69 (*m*, 9 H); 0.61 (*m*, 6 H); 0.76 (*d*, *J* = 8, 3 H); 1.93 (*m*, 1 H); 2.47 (*s*, 3 H); 2.89 (*m*, 1 H); 3.83 (*m*, 1 H); 4.00 (*s*, 3 H); 4.06 (*s*, 3 H); 4.2–4.3 (*m*, 2 H); 5.32 (*s*, 1 H); 6.96–7.94 (*m*, 11 arom. H). MS: 644 (33, M^+), 489 (3), 461 (53), 306 (100), 280 (23), 266 (37), 235 (15), 204 (12), 169 (10), 115 (14), 91 (53), 83 (57), 69 (60), 55 (77), 41 (40).

*Data of (2'R,3S)-***20A**. UV (EtOH): 201.5 (4.57), 230.4 (4.35), 335.2 (4.11) . CD (MeOH, 1.59 mM): 324 (1.39), 274 (–0.29), 243 (sh, 4.4), 226 (8.3), 197 (–6.2). IR (film): 1748, 1599, 1507, 1461, 1418, 1347, 1270, 1161, 1095, 1025. ^{1}H-NMR (250 MHz, $CDCl_3$): 0.13 (*d*, *J* = 8, 3 H); 0.70–1.80 (*m*, 15 H); 1.83 (*m*, 1 H); 2.49 (*s*, 3 H); 2.82 (*m*, 1 H); 3.88 (*m*, 1 H); 3.99 (*s*, 3 H); 4.03 (*s*, 3 H); 4.05–4.21 (*m*, 2 H); 5.21 (*s*, 1 H); 6.80 (*s*, 1 arom. H); 6.88 (*d*, *J* = 8.4, 1 arom. H); 7.06–8.00 (*m*, *ca.* 9 arom. H). MS: identical with that of (2'*S*,3*R*)-**20A** .

9. *(1S,2R,5S)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl (2'S,3R)-2-(3,4-Dimethoxyphenyl)-1'-(4-toluenesulfonyl)spiro[3H-indole-3,3'-pyrrolidine]-2'-carboxylate* ((2'*S*,3*R*)-**20B**). A mixture of **2** (593.5 mg, 2 mmol), **12B** (580.3 mg, 2.01 mmol), and benzene (30 ml) was refluxed (H_2O separator) for 6 h and then evaporated: crude **16B**. To a stirred soln. of the latter and 2,4,6-trimethylpyridine (0.5 ml) in CH_2Cl_2 (10 ml) at –90°, TsCl (500 mg, 2.6 mmol) was added. After 24 h at –90°, the mixture was treated with 2N Na_2CO_3 soln. (5 ml) and warmed to r.t. The aq. phase was extracted with CH_2Cl_2 (3 × 5 ml) and the combined org. phase evaporated. The soln. of the residue in CH_2Cl_2 (10 ml) was extracted with 0.5N HCl. The aq. phase was extracted with CH_2Cl_2 (3 × 5 ml), the combined org. phase washed with sat. $NaHCO_3$ soln. and evaporated, and the residue chromatographed on silica gel (210 g; hexane/$CHCl_3$/AcOEt 4:2:1: pure (2'*S*,3*R*)-**20B** (681.9 mg, 47.3%; colorless, amorphous solid) and a mixture with an isomer (31 mg, *ca.* 2:1); *ca.* 97% de.

*Data of (2'S,3R)-***20B**. UV (EtOH): 200.8 (4.70), 234 (4.39), 339 (4.26). CD (EtOH, 1.4 mM): 376 (0.59), 338 (–1.60), 306 (–1.07), 277 (0.87), 236 (–4.1), 216 (6.6). ^{1}H-NMR (270 MHz, $CDCl_3$): 0.2–1.4 (*m*, *ca.* 7 H); 0.54 (*d*, *J* = 6.0, 3 H); 1.03 (*s*, 6 H); 1.53 (*m*, 1 H); 1.83 (*m*, 1 H); 2.49 (*s*, 3 H); 2.85 (*m*, 1 H); 3.75 (*m*, 1 H); 4.02 (*s*, 3 H); 4.10 (*s*, 3 H); 4.17 (*m*, 1 H); 4.33 (*m*, 1 H); 4.96 (*s*, 1 H); 6.7–8.05 (*m*, 16 arom. H). MS: 721 (22), 720 (38, M^+), 506 (17), 461 (45), 307 (100), 306 (87), 280 (24), 266 (39), 235 (12), 119 (53), 105 (40), 91 (44).

10. *(R)-[(1-Methylethoxy)carbonyl]phenylmethyl (2'S,3R)-2-(3,4-Dimethoxyphenyl)-1'-(4-toluenesulfonyl)-spiro[3H-indole-3,3'-pyrrolidine]-2'-carboxylate* ((2'*S*,3*R*)-**20C**). A mixture of **2** (596 mg, 2.0 mmol), **12C** (500.5 mg, 2.0 mmol), benzene (100 ml), and molecular sieves was stirred at r.t. for 30 h, filtered, and evaporated: crude **16C.** To a stirred soln. of the latter and 2,4,6-trimethylpyridine (0.4 ml) in CH_2Cl_2 (10 ml) at –80°, TsCl (407 mg, 2.1 mmol) in CH_2Cl_2 (2 ml) was added. After 90 h at –80°, the mixture was treated with 2N Na_2CO_3 soln. (5 ml) and warmed to r.t. The aq. phase was extracted with CH_2Cl_2 (3 × 5 ml) and the combined org. phase evaporated. To remove polar impurities, the soln. of the residue in $CHCl_3$/AcOEt 3:1 was filtered through silica gel (70 g), affording 985 mg (72.1%) of crude product which was chromatographed on silica gel (70 g; hexane/$CHCl_3$/AcOEt 3:4:2): pure (2'*S*,3*R*)-**20C** (289.2 mg), a pure isomer (23.8 mg), and mixed fractions containing *ca.* 136 mg of (2'*S*,3*R*)-**20C** and 94 mg of the isomer. Chemical yield for (2'*S*,3*R*)-**20C** 31.1% and for the isomer 13.4%; de 39.5%. (2'*S*,3*R*)-**20C** was crystallized from Et_2O/pentane. M.p. 105–106°. UV (EtOH): 230.6 (4.44), 340.5 (4.25). CD (EtOH, 0.18 mM): 375 (0.57), 337 (–1.20), 306 (–0.91), 278 (0.41), 226 (–7.6), 203 (18.7). ^{1}H-NMR (400 MHz, $CDCl_3$): 1.08 (*d*, *J* = 6.3, 3 H); 1.17 (*d*, *J* = 6.3, 3 H); 1.93 (*m*, 1 H); 2.48 (*s*, 3 H); 2.83 (*m*, 1 H); 3.84 (*m*, 1 H); 3.99 (*s*, 3 H); 4.01 (*s*, 3 H); 4.20 (*m*, 1 H); 4.94 (*s*, 1 H); 4.95 (*m*, 1 H); 5.44 (*s*, 1 H); 6.8–8.0 (*m*, 16 arom. H). Anal. calc. for $C_{38}H_{38}N_2O_8S$ (682.79): C 66.85, H 5.61, N 4.10; found: C 66.64, H 5.76, N 4.12.

The isomer could not be crystallized. ^{1}H-NMR (250 MHz, $CDCl_3$): 1.03 (*d*, *J* = 5, 3 H); 1.10 (*d*, *J* = 5, 3 H); 1.93 (*m*, 1 H); 2.46 (*s*, 3 H); 2.80 (*m*, 1 H); 3.85 (*m*, 1 H); 3.98 (*s*, 3 H); 4.00 (*s*, 3 H); 4.16 (*m*, 1 H); 4.78 (*m*, 1 H); 5.26 (*s*, 1 H); 5.36 (*s*, 1 H); 6.88–7.88 (*m*, 16 arom. H) .

11. *1-Methylethyl {(2'S,3R,Z(?))-2'-{[(1S,2R,5S)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl]-oxycarbonyl}-1'-(4-toluenesulfonyl)spiro[3H-indole-3,3'-pyrrolidin]-2-ylidene}acetate* ((2'*R*,3*S*)-**21B**) *and Isomer* (2'*R*,3*R*)-**21B**. A mixture of crude **10** (2 mmol), **12B** (591.2 mg, 2.05 mmol), CH_2Cl_2 (10 ml), and molecular sieves was stirred at r.t. for 18 h, then filtered and evaporated: crude **17B**. To a stirred soln. of the latter and 2,4,6-trimethylpyridine (0.4 ml) in CH_2Cl_2 (10 ml) at –78°, TsCl (414 mg, 2.17 mmol) in CH_2Cl_2 (*ca.* 1 ml) was added by syringe. After 140 h at –78 to –80°, the mixture was treated with 2N Na_2CO_3 soln. (10 ml) and warmed to r.t. The aq. phase was extracted with CH_2Cl_2 (2 × 5 ml), the combined org. phase extracted with 0.5M citric acid (2 × 5 ml) and evaporated, and the residue chromatographed on silica gel (195 g; hexane/$CHCl_3$/AcOEt 10:1:1): (2'*R*,3*R*)-**21B** (326.7 mg, 23.9%; amorphous solid) and (2'*R*,3*S*)-**21B** (450.4 mg, 32.9%, amorphous solid); de 15.8%.

Data of (2'R,3R)-**21B**. UV (EtOH): 228.7 (4.31), 296.7 (4.12), 328.6 (4.18). CD (EtOH, 1.39 mM): 327 (–5.48), 292 (2.59), 239 (5.81), 206 (14.4). IR (KBr): 3433, 1740, 1688, 1610, 1484, 1219, 1164, 1107. ^{1}H-NMR (250 MHz, $CDCl_3$): 0.5–2.3 (*m*, *ca.* 25 H); 2.48 (*s*, 3 H); 3.58–3.85 (*m*, 2 H); 4.19 (*s*, 1 H); 4.54–4.67 (*m*, 1 H); 4.78 (*s*, 1 H); 4.95 (*sept.*, *J* = 6.2, 1 H); 6.74–7.95 (*m*, *ca.* 13 arom. H); 9.8 (*s*, 1H). MS: 684 (17, M^+), 470 (58), 439 (27), 425 (35), 382 (54), 365 (12), 315 (56), 287 (94), 286 (56), 271 (40), 227 (100).

Data of (2'R,3S)-**21B**. UV (EtOH): 227.7 (4.28), 295.3 (3.99), 326.8 (4.10). CD (EtOH, 1.42 mM): 328 (3.81), 292 (2.91), 245 (–3.23), 207 (–4.0). IR (KBr): 3433, 1745, 1688, 1611, 1454, 1226, 1163, 1107. ^{1}H-NMR (250 MHz, $CDCl_3$): 0.4–1.5 (*m*, 23 H); 1.62–1.76 (*m*, 1 H); 1.90–2.04 (*m*, 2 H); 2.48 (*s*, 3 H); 3.54–3.68 (*m*, 1 H); 3.85–3.96 (*m*, 1 H); 4.12 (*s*, 1 H); 4.38–4.50 (*m*, 1 H); 4.57 (*s*, 1 H); 5.13 (*sept.*, *J* = 6.2, 1 H); 6.69–8.03 (*m*, *ca.* 13 arom. H); 9.74 (*s*, 1 H). MS: 685 (17), 684 (20, M^+), 543 (17), 470 (33), 439 (100), 425 (34), 382 (52), 341 (14), 287 (80), 243 (70), 227 (93).

12. *Bis(1-methylethyl) 2-{(2'ξ,3S)-2'-{[(1S,2R,5S)-5-Methyl-2-(1-methylethyl)cyclohexyl]oxycarbonyl}-1'-(4-toluenesulfonyl)spiro[1H,3H-indole-3,3'-pyrrolidin]-2-ylidene}propanedioate* ((2'ξ,3*R*)-**22A**) *and Minor Isomer (2'ξ,3S)*-**22A**. A mixture of crude **11** (0.54 mmol), **12A** (122.8 mg, 0.56 mmol), CH_2Cl_2 (5 ml), and molecular sieves was stirred at r.t. for 2 ½ h and then filtered. After cooling to 0°, 2,4,6-trimethylpyridine (0,1 ml) and, subsequently, TsCl (112.6 mg, 0.59 mmol) were added under stirring. After 6 h at 0°, the mixture was treated with 2N Na_2CO_3 soln., the aq. phase extracted with CH_2Cl_2 (3 × 5 ml), and the combined org. layer evaporated. The residue was chromatographed on silica gel (24 g; hexane/$CHCl_3$/AcOEt 10:1:1): 124.3 mg (33.2%) of **22A**; colorless foam, mixture of 2 diastereoisomers 80:35. UV (EtOH): 230 (4.37), 295.6 (4.00), 333.9 (4.26). CD (EtOH, 1.76 mM): 366 (0.18), 334 (–0.95), 308 (0.26), 280 (0.30), 233 (6.2). ^{1}H-NMR (400 MHz, $CDCl_3$, characteristic signals only): major isomer: 2.44 (*s*, 3 H); 3.18–3.39 (*m*, 1 H); 3.51–3.61 (*m*, 1 H); 4.20–4.30 (*m*, 1 H); 3.92–4.01 (*m*, 1 H); 5.01–5.2 (*m*, 2 H); 5.37 (*s*, 1 H); minor isomer: 2.46 (*s*, 3 H); 2.96–3.10 (*m*, 1 H); 3.61–3.68 (*m*, 1 H); 3.79–3.86 (*m*, 1 H); 5.18–5.28 (*m*, 2 H); 5.29 (*s*, 1 H). FAB-MS: 695 (50, $[M + 1]^+$), 635 (71), 541 (100), 511 (29), 497 (96).

13. *Bis(1-methylethyl) 2-{(2'ξ,3S)-2'-{[(1S,2R,5S)-5-Methyl-2-(1-methyl-1-phenylethyl)cyclohexyl]-oxycarbonyl}-1'-(4-toluenesulfonyl)spiro[1H,3H-indole-3,3'-pyrrolidin]-2-ylidene}propanedioate* ((2'ξ,3*S*)-**22B**) *and Isomer (2'ξ,3R)*-**22B**. A mixture of crude **11** (2 mmol), **12B** (590 mg, 2.05 mmol), CH_2Cl_2 (5 ml), and molecular sieves was stirred at r.t. for 20 h, then filtered, and evaporated: crude **18B**. To a stirred soln. of the latter and of 2,4,6-trimethylpyridine (0.4 ml) in CH_2Cl_2 (10 ml) at –78°, a soln. of TsCl (426 mg, 2.23 mmol) in CH_2Cl_2 (2 ml) was added by syringe. After 120 h at –78°, 2N Na_2CO_3 soln. (10 ml) was added and the mixture warmed to r.t. The aq. phase was extracted with CH_2Cl_2 (3 × 5 ml), the combined org. phase evaporated, and the residue filtered through silica gel (40 g; hexane/$CHCl_3$/AcOEt 4:2:1). Crude **22B** (481.3 mg, 2 diastereoisomers 5:1), which was further purified by chromatography on silica gel (100 g) with hexane/$CHCl_3$/AcOEt 10:1:1, affording **22B** (367.8 mg, 23.8%, 2 diastereoisomers 5:1). UV (EtOH): 231.4 (4.37), 296.5 (4.00), 336 (4.27). CD (MeOH, 1.51 mM): 331 (8.3), 236 (3.5), 218 (1.28). ^{1}H-NMR (270 MHz, $CDCl_3$, characteristic signals only): major isomer: 2.45 (*s*, 3 H); 3.20–3.34 (*m*, 1 H); 3.51–3.67 (*m*, 1 H); 3.91–4.05 (*m*, 1 H); 4.30–4.46 (*m*, 1 H); 5.13–5.26 (*m*, 2 H); 5.48 (*s*, 1 H); minor isomer: 5.32 (*s*). MS: 616 (28), 615 (49, M^+), 555 (20), 451 (37), 401 (51), 341 (100).

14. *1-Methylethyl (R)-2-(Oxoacetoxy)-2-phenylacetate* (**12C**). 14.1. *1-Methylethyl (R)-2-Hydroxy-2-phenylacetate*. A mixture of (*R*)-2-hydroxy-2-phenylacetic acid (30.6 g, 0.2 mol), i-PrOH (31 ml), TsOH (0.8 g), and benzene (350 ml) was refluxed (H_2O separator) for 7 h, then cooled to r.t., washed with sat. $NaHCO_3$ soln., and evaporated. The residue was triturated with hexane (15 ml), affording a crystalline mass which was collected by filtration and washed with pentane: 1-methylethyl (*R*)-2-hydroxy-2-phenylacetate (33.8 g, 87%). M.p. 39–40°. $[\alpha]_D^{20} = -91.6$ (*c* = 1.00, MeOH). ^{1}H-NMR (250 MHz, $CDCl_3$): 1.13 (*d*, *J* = 6.3, 3 H); 1.28 (*d*, *J* = 6.3, 3 H); 3.4 (br., OH); 5.07 (*sept.*, *J* = 6.3, 1 H); 5.12 (*s*, 1 H); 7.26–7.46 (*m*, 5 arom. H).

14.2. *1-Methylethyl (R)-Acryloyl-2-phenylacetate* (**14C**). To a stirred soln. of the above ester (77.7 g, 0.4 mol), 4-(dimethylamino)pyridine (4.9 g, 40 mmol) and Et_3N (80.9 g, 0.8 mol) in CH_2Cl_2 (400 ml), acryloyl chloride (38 g, 0.42 mol) in CH_2Cl_2 (30 ml) was added dropwise at –10 to –5°. The mixture was then warmed to r.t. After 5 h at r.t., it was poured onto ice H_2O (200 g). The aq. phase was extracted with CH_2Cl_2 (5 × 100 ml). The combined org. phase was evaporated and the residue treated with Et_2O (400 ml) and H_2O (200 ml). The aq. phase was extracted with Et_2O (3 × 150 ml). The combined org. phase was evaporated and the crude product filtered with hexane/Et_2O 5:1 through silica gel (950 g), giving 76.3 g (77%) of **14C**. A sample was further purified by bulb-to-bulb distillation. B.p. *ca.* 105°/0.2 Torr. $[\alpha]_D^{20} = -92.3$ (*c* = 1.00, MeOH). ^{1}H-NMR (250 MHz, $CDCl_3$): 1.22 (*d*, *J* = 6.3, 3 H); 1.27 (*d*, *J* = 6.3, 3 H); 5.05 (*sept.*, *J* = 6.3, 1 H); 5.91–5.95 (*m*, 2 H); 6.45 (*dd*, *J* = 17, 10, 1 H); 6.54 (*dd*, *J* = 17. 1.5, 1 H); 7.36–7.56 (*m* , 5 arom. H). ^{1}H-NMR of **14C** (3 mg) in presence of TAE (= *'(+)-2,2,2-trifluoro-1-(anthryl)ethanol'*; *ca.* 25 mg) gave no indication for the presence of the enantiomer of **14C**. Anal. calc. for $C_{14}H_{16}O_4$ (248.28): C 67.73, H 6.50; found: C 67.91, H 6.69.

14.3. *Compound* **12C.** A soln. of **14C** (4.96 g, 20 mmol) in CH_2Cl_2 (60 ml) and MeOH (40 ml) was ozonized at –78°. A slight excess of O_3 was removed by bubbling N_2 through the mixture. Then, Me_2S (1.6 ml, 21.8 mmol) was added. After 16 h at –78°, the soln. was evaporated at 30°. The soln. of the residue in benzene (25 ml) was washed with sat. aq. NaCl soln. at 10°, dried first with $MgSO_4$ then with molecular sieves, and evaporated at 30°. The residue (6.0 g) was dehydrated by bulb-to-bulb distillation in two portions of 3 g (elimination of H_2O at *ca.* 130°/0.3 Torr). The product (2.98 g) distilled within 25 min between 160°/1.4 Torr and 180°/0.25 Torr contained *ca.* 50% of free aldehyde (^{1}H-NMR). After two additional distillations, 2.5 g (52.4%) of **12C**, containing 90–100% of free aldehyde, were obtained. The substance polymerized quickly at r.t. and should be stored in a deep-freezer. ^{1}H-NMR (270 MHz, $CDCl_3$, signals of the main component only): 1.13 (*d*, *J* = 6.2, 3 H); 1.28 (*d*, *J* = 6.2, 3 H); 5.07 (*sept.*, *J* = 6.2, 1 H); 6.01 (*s*, 1 H); 7.26–7.77 (*m*, 5 arom. H); 9.49 (*s*, 1 H).

15. *(R)-2-{[(*tert*-Butyl)diphenylsilyl]oxy}-1-phenylethyl Dihydroxyacetate* (**13D**). 15.1. *(R)-2-{[(*tert*-Butyl)-diphenylsilyl]oxy}-1-phenylethanol.* To a stirred mixture of (*R*)-1-phenylethane-1,2-diol (4.31 g, 31.2 mmol), imidazole (4.5 g, 66,1 mmol), and DMF (9.0 ml), (*tert*-butyl)diphenylsilyl chloride (8.5 ml, 33.2 mmol) was added dropwise at 0°. Stirring was continued overnight, allowing the temp. to rise to r.t. Then, EtOH (3.0 ml) was added. The mixture was stirred for 1/2 h, poured into H_2O (150 ml), and extracted with Et_2O (2 × 100 ml). The combined org. layer was evaporated and the residue purified by FC with petroleum ether (low-boiling)/ Et_2O 5:1: *(R)-2-{[(*tert*-butyl)diphenylsilyl]oxy}-1-phenylethanol* (**D**-H; 9.56 g, 81.4%), colorless oil. $[\alpha]_D^{20} = -8.5$ (*c* = 0.930, MeOH). IR ($CHCl_3$): 3700, 1430, 1195, 1115, 1063, 902, 860, 825, 703. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.07 (*s*, 9 H); 3.02 (*d*, *J* = 2.5, 1 H); 3.65 (*dd*, *J* = 12, 8, 1 H); 3.76 (*dd*, *J* = 12, 6, 1 H); 4.75–4.85 (*m*, 1 H); 7.2–7.78 (*m*, 15 arom. H). The signal at 3.02 disappears on addition of D_2O. Anal. calc. for $C_{24}H_{28}O_2Si$ (376.58): C 76.55, H 7.49; found: C 76.64, H 7.62.

15.2. *(R)-2-{[(*tert*-Butyl)diphenylsilyl]oxy}-1-phenylethyl Acrylate* (**14D**). To a vigorously stirred mixture of **D**-H (9.56 g, 25.39 mmol), *Hünig*'s base (5.65 ml, 33.0 mmol), 4-(dimethylamino)pyridine (435 mg, 3.56 mmol), and CH_2Cl_2 (29 ml) at –40°, acryloyl chloride (2.68 ml, 32.99 mmol) was added dropwise at a rate to keep the temp. between –40 and –30°. Stirring was continued for 1 h at –35 to –25°. Then, the mixture was poured into H_2O (100 ml). Extraction with CH_2Cl_2 (2 × 50 ml) and Et_2O (50 ml) and evaporation of the combined org. phase afforded crude **14D**, which was purified by FC (petroleum ether (low-boiling)/Et_2O 5:1): colorless oil (10.58 g, 96.7%). $[\alpha]_D^{20} = -16.0$ (*c* = 0.35, $CHCl_3$). IR ($CHCl_3$): 1723, 1430, 1410, 1225, 1195, 1115, 702. ^{1}H-NMR (200 MHz, $CDCl_3$): 1.1 (*s*, 9 H); 3.80 (*dd*, *J* = 12, 4.5, 1 H); 3.96 (*dd*, *J* = 12, 7, 1 H); 5.85 (*dd*, *J* = 10.3, 1.7 , 1 H); 6.00 (*dd*, *J* = 7, 4.5, 1 H); 6.18 (*dd*, *J* = 17.3, 10.2, 1 H); 6.45 (*dd*, *J* = 17.3, 1.8, 1 H); 7.21–7.64 (*m*, 15 arom. H). CI-MS: 360 (20), 359 (100), 235 (17). Anal. calc. for $C_{27}H_{30}O_3Si$ (430.62): C 75.31, H 7.02; found: C 75.57, H 7.07.

15.3. *Compound* **13D**. Through a soln. of **14D** (10.51 g, 22.4 mmol) in CH_2Cl_2 (58 ml) and MeOH (37 ml), O_3 was bubbled at –78°, until a blue color persisted. After removing the excess of O_3 by flushing with N_2, Me_2S (9.0 ml, 122.7 mmol) was added. The mixture was left at –20° overnight, then evaporated to 1/4 of its volume, poured into H_2O (150 ml), and extracted twice with CH_2Cl_2 (80 and 20 ml) and Et_2O (80 ml), and the combined org. layer evaporated. The residue was purified by FC with Et_2O/petroleum ether (low boiling) 2:1. After complete removal of the solvents, finally at 70°/0.001 Torr, pure **13D** (9.89 g, 89.9%) was obtained as a colorless, highly viscous oil. $[\alpha]_D^{20} = -27.4$ (*c* = 1.00, $CHCl_3$). IR ($CHCl_3$): 1758, 1743, 1416, 1288, 1210 (br.), 1117, 703. ^{1}H-NMR (200 MHz, (D_6)DMSO + D_2O): 0.95 (*ca. s*, 9 H); 3.66–4.01 (*m*, 2 H); 5.20 (*s*, 1 H); 5.78–5.92 (*m*, 1 H); 7.28–7.78 (*m*, 15 arom. H).

REFERENCES

[1] S. Mahboobi, K. Bernauer, *Helv. Chim. Acta* **1988**, *71*, 2034.

[2] J.E. Saxton, Ed., 'The Monoterpenoid Indole Alkaloids', Vol. 25 of 'The Chemistry of Heterocyclic Compounds', J. Wiley and Sons, New York, 1983.

[3] M. V. Kisakürek, A. J. M. Leeuwenberg, M. Hesse, in 'Alkaloids, Chemical and Biological Perspectives', Ed. S .W. Pelletier, J. Wiley and Sons, New York, 1983, Vol. 1.

[4] R. B. Woodward, M. P . Cava, W. D. Ollis, A. Hunger, H. U. Daeniker, K. Schenker, *Tetrahedron* **1963**, *19*, 247.

[5] J. A. Weissbach, E. Macko, N. J. De Sanctis, M. P. Cava, B. Douglas, *J. Med. Chem.* **1964**, *7*, 735.

[6] a) A. H. Jackson, P. V. R . Shannon, D. J. Wilkins, *Tetrahedron Lett.* **1987**, *28*, 4901; b) A. H. Jackson, B. Naidoo, A. E. Smith, A. S. Bailey, M. H. Vandrevala, *J. Chem. Soc., Chem. Commun.* **1978**, *779* .

[7] H. Hiemstra, W. N. Speckamp, in 'The Alkaloids', Ed. A. Brossi, Academic Press, New York, 1988, Vol. 32, p. 271.

[8] a) L. A. Paquette, in 'Asymmetric Synthesis', Ed. J. D. Morrison, Academic Press, New York, 1984, Vol. 3, p. 455; b) W. Oppolzer, *Angew. Chem.* **1984**, *96*, 840.

[9] A. H. Jackson, A. E. Smith, *J. Chem. Soc.* **1964**, 5510.

[10] E. J. Corey, H. E. Ensley, *J. Am. Chem. Soc.* **1975**, *97*, 6908.

[11] J. K. Whitesell, A. Bhattacharya, C. M. Buchanan, H. H. Chen, D. Deyo, D. James, C.-L. Liu, M. A. Minton, *Tetrahedron* **1986**, *42*, 2993.

[12] a) W. Klyne, R. J. Swan, B. W. Bycroft, D. Schumann, H. Schmid, *Helv. Chim. Acta* **1965**, *48*, 443; b) N. Kunesch, Y. Rolland, J. Poisson, P. L. Majumber, R. Majumber, A. Chatterjee, V. C. Agwada, J. Naranjo, M. Hesse, H. Schmid, *Helv. Chim. Acta* **1977**, *60*, 2854.

[13] G. E. Keck, E. J. Enholm, *J. Org. Chem.* **1985**, *50*, 146.

[14] L. F. Tietze, M. Bratz, *Synthesis* **1989**, 439.

[15] R. Noyori, I. Nishida, J. Sakata, *J. Am. Chem. Soc.* **1981,** *103*, 2106..

[16] S. E. Denmark, B. R. Henke, *J. Am. Chem. Soc.* **1989,** *111*, 8032.

[17] G. M. Sheldrick, University of Göttingen, SHELXTL 3.0 (1981).

[18] W.C. Still, M. Kahn, A. Mitra, *J. Org. Chem.* **1978**, *43*, 2923.