Enantioselective Synthesis of Key Intermediates in a Novel Approach towards the *Iboga*-Alkaloid Family

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Dedicated to Professor *Jack D. Dunitz* on the occasion of his 80th birthday

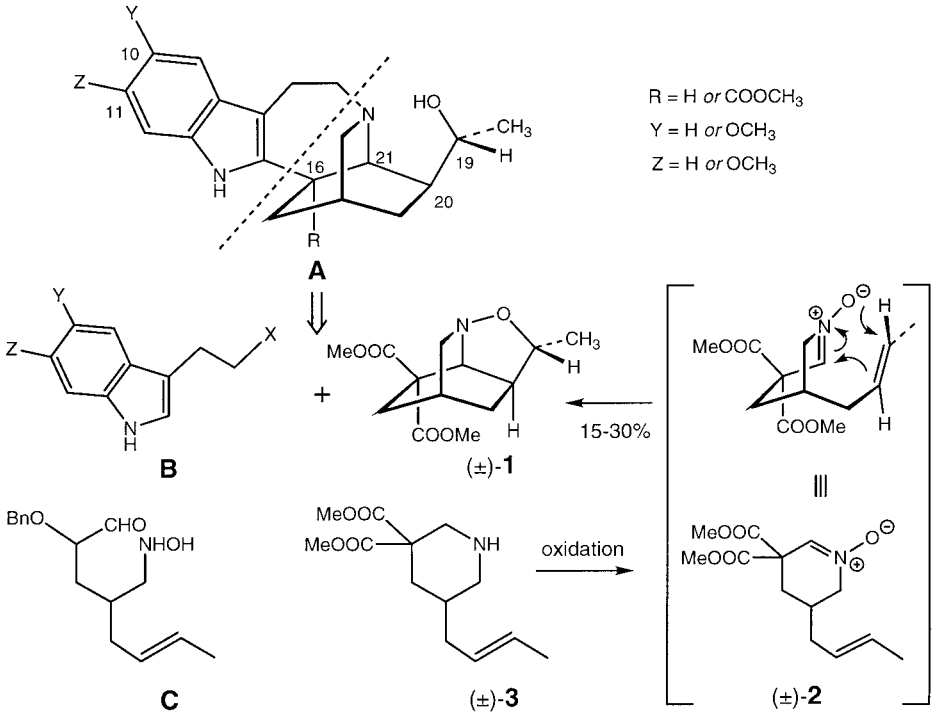
Significant improvements in the realm of a recently disclosed, novel synthetic concept towards the *Iboga* alkaloid family are presented. The key step for the construction of the bicyclic aliphatic core consists of an intramolecular nitrone–olefin 1,3-dipolar cycloaddition reaction of a 1:1 mixture **15**/**16** yielding the two diastereoisomeric tricyclic isoxazolidine derivatives **17** and **18**. The required nitrones were prepared from the readily available (*S*)-hydroxylactone **6** in twelve steps with an overall yield of 15% (average: 83.5% per step). The relative configuration of the minor isomer was deduced unambiguously by single-crystal X-ray analysis of the derived tricyclic carbamate **21**. As four out of five asymmetric centers in the pair **17**/**18** have opposite configuration, destruction of the one possessing the same absolute configuration transforms the original set of diastereoisomers into a pair of enantiomers. We verified this contention by oxidizing the two alcohols **20** and **22** to yield the two antipodal forms of ketone **23**. The absence of significant amounts of by-product and the high reproducibility of the crucial cycloaddition reaction represent marked improvements over our earlier attempts. In addition, the new route, which starts from L-glutamate, should provide access to both naturally occurring antipodal series of the targeted alkaloid class.

1. Introduction. – Recently, we reported some results concerning a new flexible approach to the *Iboga* alkaloid family, a class of natural products of high pharmacological interest (for pertinent references to books and reviews, see [1][2]). The chosen *retro*-synthetic strategy towards these alkaloids, endowed with the general structure **A**, is disclosed in *Scheme 1*. It involves a dissection along the dashed line to give a tryptophyl unit **B** and an aliphatic isoquinuclidine core. In our first approach, the latter was represented by the isoxazolidine derivative (±)-**1** prepared by an intramolecular nitrone–olefin 1,3-dipolar cycloaddition reaction of (±)-**2**, prepared *in situ* from the piperidine derivative (±)-**3**. Apart from (±)-**3** not being as readily available as one might wish, its crucial transformation into (±)-**1** suffered from poor reproducibility and low yields, especially when conversions on a larger scale were attempted [1–3].

Therefore, we decided to investigate an alternative approach to an appropriate nitrone. Instead of the unrewarding amine-oxidation route, a straightforward intramolecular condensation between a hydroxylamine and an aldehyde group was envisaged (see structure **C**). A convenient method to introduce the required primary-hydroxylamine function consists of reduction of the corresponding aldoxime [4]. As the carbonyl group of its precursor and the olefinic C=C bond bear a 1,4-relationship to each other, a *Claisen*-type rearrangement represents an obvious concept

[1]) Taken from the forthcoming Ph.D. thesis of *S. H.*

Scheme 1



to incorporate the unsaturated C_4-side chain. Such a disconnection leads to a chiral 1,2,5-trifunctionalized pentane fragment, a substitution pattern that suggests L-glutamic acid ((+)-**4**) (*Scheme 2*) as a suitable and cheep starting material from the chiral pool.

2. Results and Discussion. – Known methods were applied for the conversion of (+)-**4** to (+)-**6** *via* (+)-**5** [5][2]). The primary OH group of (+)-**6** was protected as trityl ether (→ (+)-**7**) and the lactone opened with NaOH, prepared *in situ* by allowing NaH to react in benzene with the required amount of H_2O. The resulting secondary alcoholate was etherified directly with benzyl bromide (for a similar procedure, see [6]). The resulting acid was esterified with racemic but-3-en-2-ol by using the *Mitsunobu* method [7] to yield **8** as a 1:1 mixture of two optically pure diastereoisomers[3]). The trityl group of ester **8** was selectively removed with $ZnBr_2$ in MeOH/CH_2Cl_2 [8] and the resulting primary-alcohol derivative oxidized by means of *Swern*'s

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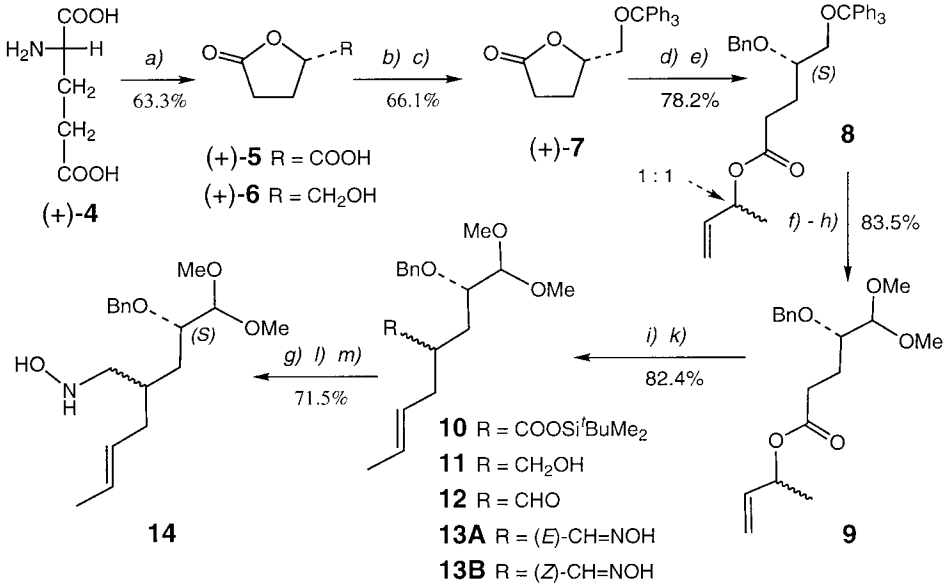
[2]) As some important experimental parameters are lacking in the original procedures, the exact procedure we were following is included in the *Exper. Part.*

[3]) Though this and the subsequent 1:1 mixtures could not be separated in the early stages, this had no deleterious effect on our synthesis as an efficient separation at the level **17**/**18** (*Scheme 3*) subsequently provided the desired building blocks for both naturally occurring antipodal series within this alkaloid class (for a discussion, see below).

Scheme 2



a) $NaNO_2$, HCl. *b*) $BH_3 \cdot SMe_2$, THF. *c*) Ph_3CCl, Et_3N, CH_2Cl_2. *d*) 1. NaH, H_2O, [15]crown-5, benzene; 2. $PhCH_2Br$, benzene. *e*) (±)-But-3-en-2-ol, diisopropyl azodicarboxylate (DIAD), PPh_3, THF. *f*) $ZnBr_2$, MeOH, CH_2Cl_2. *g*) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2. *h*) $HC(OMe)_3$, MeOH, TsOH. *i*) Lithium diisopropylamide, THF, hexamethylphosphorous triamide (HMPT), $^t BuMe_2SiCl$. *k*) $LiAlH_4$, THF. *l*) $NH_2OH \cdot HCl$, MeOH, pyridine. *m*) $NaBH_3CN$, AcOH/THF.

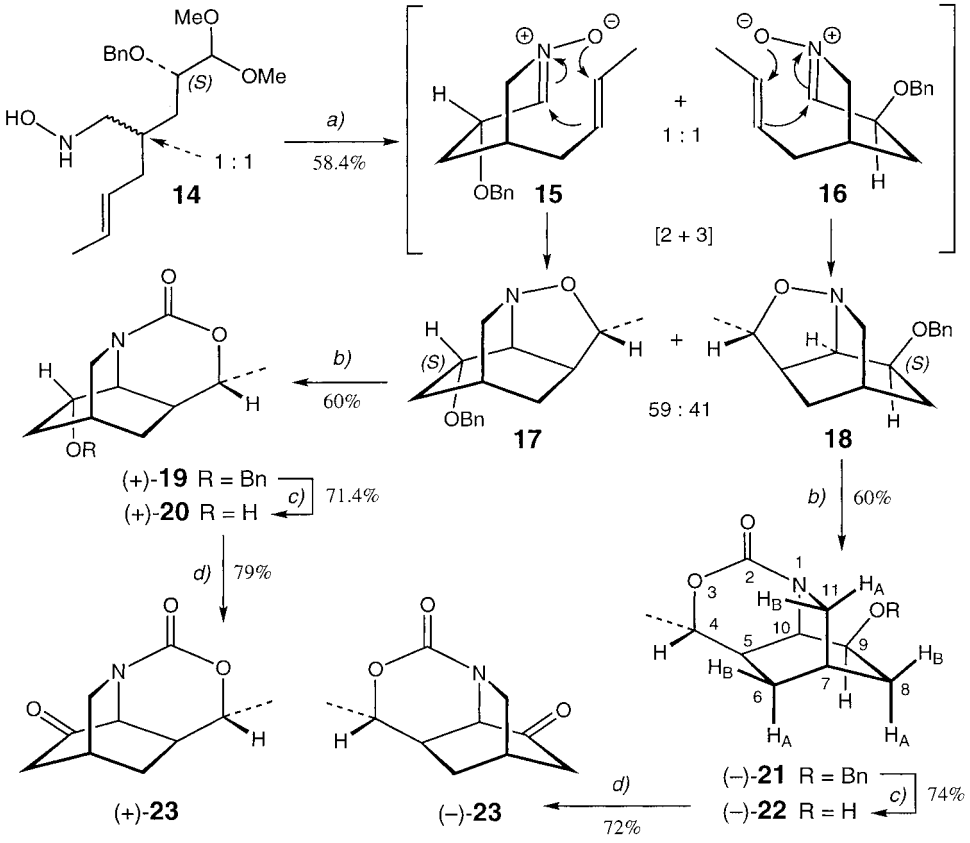
protocol [9]. The ensuing aldehyde was protected as dimethyl acetal **9** (method according to [10]) without previous purification. Application of a slight modification [11] of the original *Ireland–Claisen* rearrangement procedure [12] furnished silyl ester **10**, which was reduced *in situ* to the primary alcohol **11**. This intermedidate, again obtained as a 1:1 mixture of two diastereoisomers, was transformed in straightforward fashion *via* aldehyde **12** into oxime **13**, which was isolated as a 2:1 mixture of (*E*)-isomer **13A** and a (*Z*)-isomer **13B**. This mixture was reduced with $NaBH_3CN$ in THF/AcOH [4] at 0° to yield the rather labile hydroxylamine derivative **14**.

The next reaction sequence proved difficult to follow by TLC and became clear only after extensive experimental work carried out in NMR tubes with deuterated solvents and reagents. As it turned out, the hydrolysis of the dimethyl acetal unit of **14** with 3N D_2SO_4 in D_2O/(D_8)-1,4-dioxane 1:1 at 60° was complete within 30 min[4]). A workup at this time failed to furnish any separable, well-defined products. However, when the reaction was allowed to proceed at 60° for several hours, we noticed the appearance of a *d* ($J = 6.3$ Hz) at 1.29 ppm at the expense of the signal of the former olefinic Me group at 1.65 ppm. This event was paralleled by a considerably slower

[4]) The progress could be followed conveniently by monitoring the appearance of a *s* in the ^{1}H-NMR spectrum at 3.39 ppm (CH_3OD) at the expense of the intensity of the four original MeO signals of **14**, which are situated between 3.55 and 3.50 ppm.

manifestation of an additional *d* ($J = 6.3$ Hz) at 1.40 ppm. After 30 h at 60°, the 2 *d* were of similar intensity, and the broad *s* at 1.65 ppm as well as the olefinic protons of **14** had vanished. The material giving rise to the above signals could be isolated in 58% combined yield by flash chromatography (silica gel) and was shown to consist of a 59 : 41 mixture of the two expected isoxazolidines **17** and **18** (see *Scheme 3*). Seemingly, the *cis*-nitrone **15** reacts faster and more efficiently than the *trans*-nitrone **16**, to give the *endo*-product **17**. Indeed, when, in another run, the reaction was stopped prematurely, a 3 : 1 mixture of **17** and **18** in favor of the former was isolated.

Scheme 3



a) 1.5M H_2SO_4/1,4-dioxane, 24 h at 60°. *b*) 1. Zn, AcOH/MeOH; 2. $(Im)_2CO$, $ClCH_2CH_2Cl$. *c*) H_2, Pd/C, EtOH/AcOH. *d*) DMSO, $(COCl)_2$, Et_3N, CH_2Cl_2.

At first, these cycloaddition products could not be separated, and the mixture was transformed into the cyclic carbamates (+)-**19** and (−)-**21** *via* reductive cleavage of the N−O bond with Zn/AcOH, followed by treatment with 1,1′-carbonylbis[1*H*-imidazole]. The resulting mixture could now be separated by chromatography, and the more-polar isomer was obtained in crystalline form. An X-ray analysis established structure

(−)-**21** for this isomer in which the benzyloxy group occupies the '*exo*' position[5]). From the drawing and the pertinent data revealed in *Fig. 1*, it can be seen that, due to the bridging in the tricyclic system, the N-atom cannot assume the standard sp^2 geometry expected for a urethane derivative. Instead, it can be viewed as the top of a flattened pyramid, positioned *ca.* 0.4 Å above the plane defined by its three bonding partners C(2), C(10), and C(11) (see *Fig. 2*). In addition, the 1,3-oxazin-2-one ring prefers a slightly deformed twist conformation (*Fig. 2,a*). The isoquinuclidine-part system is somewhat deformed and, when examined along the axis C(7)/C(10), it looks like a top view of the lid of a jar being twisted off (see *Fig. 2,b*). This deformation leads to boat forms with dihedral angles that deviate considerably from the idealized values (see bottom of *Fig. 1*). The configuration of (−)-**21** being firmly established, the structures of the remaining compounds were readily deduced, and the NMR data collected are fully consistent with the proposed structures (see *Tables 1* and *2*).

Table 1. *^{1}H-NMR Chemical-Shift Values of Compounds* **1** [2] *and* **17**–**23**. In $CDCl_3$; δ in ppm rel. to $SiMe_4$.

	1[a])	**17**[a])	**18**[a])	**19**	**20**	**21**	**22**	**23**
H−C(4)	4.07	4.04	4.06	4.36	4.45	4.48	4.48	4.57
H−C(5)	2.57	2.28	2.04	2.23	2.33	1.83	1.87	2.25
H_A−C(6)	1.85	2.05	1.75	1.94	2.01	1.84	1.83	2.18
H_B−C(6)	1.52	1.50	1.48	1.18	1.24	1.29	1.28	1.57
H−C(7)	1.78	1.67	1.70	1.86	1.93	2.01	2.02	2.45
H_A−C(8)	2.61	1.87	1.87	2.16	2.27	1.76	1.84	2.45
H_B−C(8)	1.62	1.47	1.51	1.38	1.33	1.86	1.73	2.45
H−C(9)	–	4.12	4.04	4.04	4.43	3.87	4.19	–
H−C(10)	3.72	3.37	3.55	3.23	3.14	3.52	3.35	3.60
H_A−C(11)	3.32	3.17	3.48	3.16	3.25	3.59	3.56	3.95
H_B−C(11)	2.87	2.94	2.99	3.52	3.58	3.66	3.62	3.30
Me−C(4)	1.23	1.15	1.20	1.25	1.36	1.35	1.37	1.40

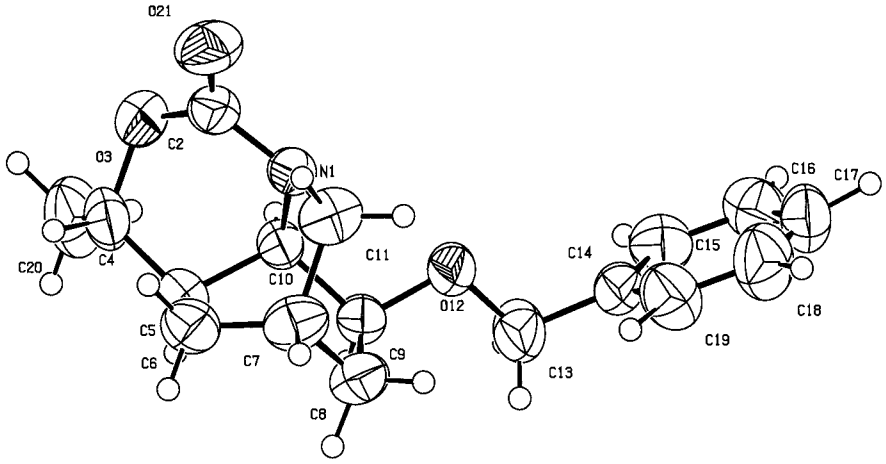
[a]) For convenience, the numbering system fitting the carbamates **19**–**23** was employed for the other compounds as well.

Table 2. *^{13}C-NMR Chemical-Shift Values of Compounds* **1** [2] *and* **17**–**23**. In $CDCl_3$; δ rel. to $SiMe_4$.

	1[a])	**17**[a])	**18**[a])	**19**	**20**	**21**	**22**	**23**
C(2)	–	–	–	163.0	163.2	163.3	163.8	161.4
C(4)	86.2	86.0	85.0	84.9	85.1	84.0	84.5	83.8
C(5)	40.3	39.7	42.4	33.2	32.8	36.4	36.5	37.3
C(6)	34.3[b])	34.8[b])	34.5[b])	30.6	30.8	29.8	29.3	29.0
C(7)	22.0	21.4	22.3	26.0	26.2	26.5	26.6	27.2
C(8)	32.7[b])	34.5[b])	33.8[b])	32.9	34.6	33.1	35.4	43.2
C(9)	51.1	69.8	70.6	71.6	64.6	72.6	66.3	205.7
C(10)	59.2	59.2	59.2	49.3	52.2	48.0	51.3	58.4
C(11)	59.4	60.9	61.2	53.4	53.3	53.5	53.7	55.4
Me−C(4)	20.8	20.8	20.8	20.2	20.2	20.4	20.5	20.4

[a]) For convenience, the numbering system fitting the carbamates **19**–**23** was employed for the other compounds as well. [b]) Assignments may be interchanged.

5) We thank Dr. *B. Schweizer*, Laboratory for Organic Chemistry (ETH Zürich) for his expeditious determination of the X-ray crystal structure.



Selected bond lengths		Selected bond angles		Selected torsion angles	
C(4)–O(3)	1.48 Å	C(2)–O(3)–C(4)	117.8°	C(4)–O(3)–C(2)–O(21)	– 135.4°
O(3)–C(2)	1.36 Å	N(1)–C(2)–O(3)	115.7°	C(10)–N(1)–C(2)–O(21)	177.2°
C(2)–O(21)	1.21 Å	O(3)–C(2)–O(21)	119.8°	C(11)–N(1)–C(2)–O(3)	– 138.0°
C(2)–N(1)	1.37 Å	N(1)–C(2)–O(21)	124.4°	C(11)–N(1)–C(2)–O(21)	45.5°
N(1)–C(10)	1.47 Å	C(2)–N(1)–C(10)	114.9°	O(12)–C(9)–C(10)–N(1)	– 60.5°
N(1)–C(11)	1.49 Å	C(2)–N(1)–C(11)	114.9°	O(12)–C(9)–C(10)–C(5)	– 175.9°
C(4)–C(5)	1.51 Å	C(10)–N(1)–C(11)	111.7°	O(3)–C(4)–C(5)–C(6)	81.8°

Dihedral angles within the 4 aliphatic 6-membered rings

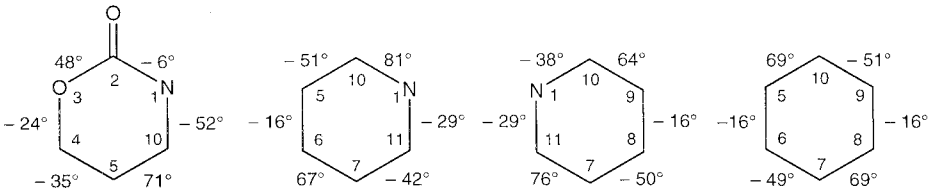


Fig. 1. *ORTEP View of (–)-***21** *and some selected measurements.* Arbitrary atom numbering; the thermal ellipsoids are scaled at the 30% level.

Hydrogenolytic removal of the benzyl groups of (+)-**19** and (–)-**21** furnished the alcohols (+)-**20** and (–)-**22**, respectively. Whereas the absolute configuration at C(9) is the same for both compounds due to their preparation from L-glutamate as the common precursor, the remaining four asymmetric centers all have mutually opposite configurations. To verify this contention, we destroyed the asymmetry at the center C(9) by oxidizing the corresponding OH group of both diastereoisomeric alcohols. Indeed, the two resulting ketones (+)- and (–)-**23** proved to be enantiomers. This

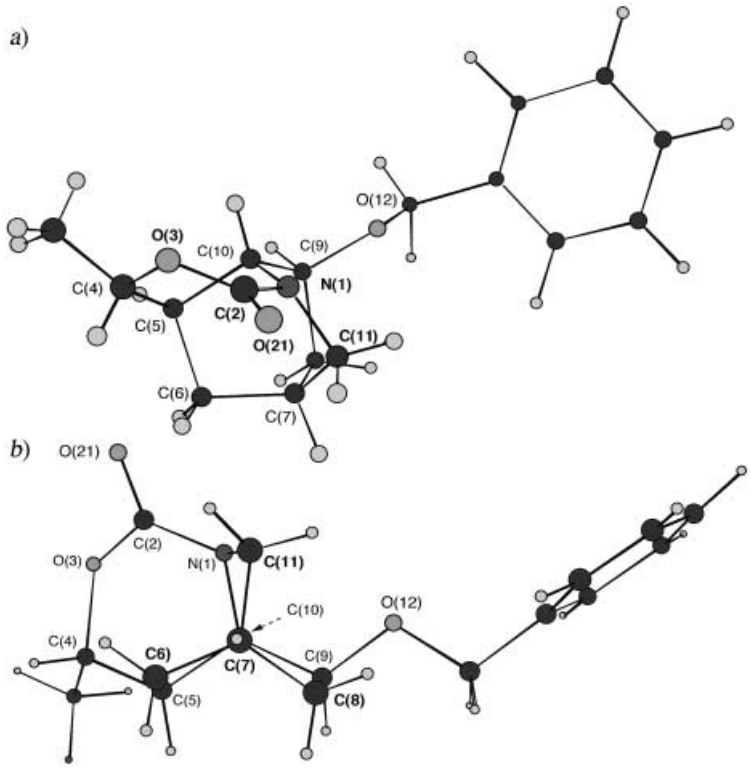


Fig. 2. *Views of (–)-***21** *in* CS Chem3D Pro, *created from imported X-ray data:* a) *conformation of the 1,3-oxazin-2-one ring*; b) *conformation of the isoquinuclidine part system with the two bridgeheads aligned in the* y *direction*

means that both naturally occurring, antipodal series of the *Iboga* alkaloid family should eventually be accessible starting from L-glutamate as the single source from the chiral pool.

Subsequent investigations showed that the mixture **17**/**18** can be at least partly separated by FC. The less-polar, minor isomer **18** was obtained in crystalline state, and it turned out that inoculation of the original mixture with seed crystals of **18** led to crystallization of most of this isomer. Consequently, the mother liquor contained mostly **17**, the more-valuable synthetic precursor, endowed with the absolute configuration shared by most naturally occurring *Iboga* alkaloids [13].

3. Conclusions. – The described new route to an appropriately functionalized, optically pure isoquinuclidine core is by far superior to an earlier attempt as far as reproducibility and overall yield is concerned. The flexible approach chosen should eventually pave the way to numerous representatives of the *Iboga* alkaloid family in both antipodal forms.

We express our gratitude to the *Swiss National Science Foundation* for generous financial support. We also thank our chemical-technician apprentices, Miss *N. Meggiolaro* and Mr. *M. Aschwanden* for their most-valuable contributions to the presented project.

Experimental Part

General. See [14].

(2S)-Tetrahydro-5-oxofuran-2-carboxylic Acid ((+)-**5**). According to [5b]. To a suspension of L-glutamic acid ((+)-**4**; 100 g, 0.68 mol; *Fluka*, *puriss.*) in H_2O (500 ml) was added slowly conc. aq. HCl soln. (140 ml, 1.68 mol; *J. T. Baker*), whereupon a homogeneous soln. resulted. Within 8 h, a soln. of $NaNO_2$ (70 g, 1.02 mol; *Fluka*, *puriss.*) in H_2O (300 ml) was added at 22°. After stirring for 16 h, the mixture was evaporated completely and the residue extracted repeatedly with a total of 1.4 l of hot AcOEt. The hot extracts were filtered, dried ($MgSO_4$), and evaporated. The crude product was recrystallized 3 times from hot benzene/AcOEt 1:1 (60 ml) by adding cyclohexane until the mixture became slightly turbid. The resulting (+)-**5** (56.01 g, 63.3%) was anal. pure. M.p. 72.1–73.2° ([5b]: 71–72°).

(5S)-Tetrahydro-5-(hydroxymethyl)furan-2-one ((+)-**6**). According to [5b]. To a soln. of (+)-**5** (30.96 g, 0.238 mmol) in dry THF (110 ml) was added a soln. of borane-dimethylsulfide complex (27 ml, 0.274 mol; *Fluka*, 95%) in THF (110 ml) within 20 min, under external cooling with ice to keep the temp. in the flask at 15–20°. After stirring for 3 h at 20° with constant monitoring of the temp. and cooling when required, the mixture was cooled to 0° and quenched by adding dry MeOH (180 ml). Most of the solvent was removed by distillation at normal pressure. The residue was diluted with MeOH (180 ml) and the mixture evaporated at 15 Torr. The crude product was distilled at 110°/0.08 Torr: 23.52 g (85.1%) of (+)-**6**. Colorless oil.

(5S)-Tetrahydro-5-[(triphenylmethoxy)methyl]furan-2-one ((+)-**7**). To a soln. of (+)-**6** (16.836 g, 0.145 mol) in dry CH_2Cl_2 (280 ml) were added triphenylmethyl chloride (41.673 g, 0.145 mol; *Fluka*, 97%) and dry Et_3N (36.4 ml, 0.261 mol) while cooling externally with ice. The mixture was stirred at 22° under Ar for 20 h. The resulting violet mixture was extracted twice with sat. aq. $CuSO_4$ soln. (400 ml) and once with sat. aq. NaCl soln. (400 ml), the org. phase dried ($MgSO_4$) and evaporated, and the crude product recrystallized twice from hot AcOEt: 40.37 g (77.7%) of (+)-**7**. Slightly yellow crystals. M.p. 151.1–152°. $[\alpha]_D = +35.8$ ($c = 0.1$, CH_2Cl_2). IR ($CHCl_3$): 3062, 3006, 2948, 2874, 1772, 1597, 1491, 1449, 1178, 1083, 1035, 1001, 950, 901, 632. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.43 (*m*, 6 H); 7.27 (*m*, 9 H); 4.62 (*dddd*, $J = 7.9, 5.8, 4.3, 3.5$, 1 H); 3.41 (*dd*, $J = 10.4, 3.5$, 1 H); 3.15 (*dd*, $J = 10.4, 4.3$, 1 H); 2.66 (*ddd*, $J = 17.8, 10.1, 6.6$, 1 H); 2.49 (*ddd*, $J = 17.7, 10.1, 6.9$, 1 H); 2.21 (*dddd*, $J = 12.8, 10.1, 7.9, 6.6$, 1 H); 2.01 (*dddd*, $J = 12.8, 10.1, 6.9, 5.8$, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 177.4 (*s*); 143.5 (3*s*); 128.6 (6*d*); 127.9 (6*d*); 127.2 (3*d*); 87.0 (*s*); 79.1 (*d*); 65.3 (*t*); 28.4 (*t*); 24.2 (*t*). EI-MS: 358 (11, M^+), 281 (46), 258 (20), 243 (100), 242 (16), 241 (23), 239 (15), 228 (14), 166 (15), 165 (51), 105 (13), 99 (48).

(1R)- and (1S)-1-Methylprop-2-enyl (4S)-4-(Benzyloxy)-5-(triphenylmethoxy)pentanoate (**8**; 1:1 mixture). To a soln. of (+)-**7** (20.0 g, 55.8 mmol) in dry benzene (500 ml; *J. T. Baker*) under Ar were added at 22° NaH (9.374 g, 391 mmol; *Fluka*, *pract.*; 55–65% in oil, washed 3 times with hexane) and [15]crown-5 (1.1 ml, 5.6 mmol; *Fluka*, *purum*). Then H_2O (2.5 ml, 139 mmol) was added dropwise, and the mixture was stirred under reflux for 6 h. After cooling the mixture in an ice bath, benzyl bromide (16.6 ml, 139 mmol; *Fluka*, *purum*) was added, and stirring was continued at reflux temp. for 17 h. The mixture was cooled to 0° and poured onto 1M aq. phosphate buffer soln. of pH 3 (600 ml). The resulting pH was again adjusted to 3 by adding conc. aq. HCl soln., and the mixture was extracted 3 times with ^{t}BuOMe. The combined extract was dried ($MgSO_4$) and evaporated to give 36.08 g of a yellow viscous liquid which was used as such for the next step. This doubly protected dihydroxy acid was dissolved in anh. THF (160 ml) at 22° under Ar. Then were added triphenylphosphine (45.159 g, 167 mmol; *Fluka*, 97%), (±)-but-3-en-2-ol (14.4 ml, 167 mmol; *Acros*, 100%; dest. from Na), and 3-Å molecular sieves (5 g; powder). To the stirred mixture was added slowly diisopropyl azodicarboxylate (= diisopropyl diazenedicarboxylate = DIAD; 34 ml, 167 mmol; *Fluka*, 95%) with external cooling in an ice bath. When the addition was complete, stirring was continued at 23° for 3 h. Most of the solvent was evaporated and the residue diluted with ^{t}BuOMe (240 ml) and stored at 4° for 90 min after addition of a seed crystal of triphenylphosphine oxide. The filtrate was washed with H_2O (440 ml), which was re-extracted twice with ^{t}BuOMe (440 ml), the combined org. extract dried ($MgSO_4$) and evaporated, and the residue chromatographed (silica gel (1 kg), pentane/Et_2O 15:1 → 2:1): 22.73 g (78.2% over 3 steps) of **8**. Slightly yellow, viscous oil. IR ($CHCl_3$): 3088, 3063, 3006, 2933, 2873, 1725, 1491, 1449, 1375, 1348, 1177, 1077, 990, 935, 900, 649, 633. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.46 (*m*, 12 H); 7.32–7.19 (*m*, 28 H); 5.801 (*ddd*, $J = 17.3, 10.5, 5.8$, 1 H); 5.795 (*ddd*, $J = 17.3$,

10.5, 5.9, 1 H); 5.31 (*m*, 2 H); 5.205 (*dt*, *J* = 17.3, 1.3, 1 H); 5.195 (*dt*, *J* = 17.3, 1.3, 1 H); 5.098 (*dt*, *J* = 10.5, 1.3, 1 H); 5.092 (*dt*, *J* = 10.5, 1.3, 1 H); 4.67 (*d*, *J* = 11.5, 2 H); 4.478 (*d*, *J* = 11.6, 1 H); 4.476 (*d*, *J* = 11.6, 1 H); 3.60 (*m*, 2 H); 3.23 (*dd*, *J* = 9.9, 5.5, 2 H); 3.15 (*dd*, *J* = 9.9, 4.5, 2 H); 2.35 (*m*, 4 H); 1.90 (*m*, 4 H); 1.265 (*d*, *J* = 6.5, 3 H); 1.263 (*d*, *J* = 6.5, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 172.73 (2*s*); 144.02 (6*s*); 138.61 (*s*); 137.77 (*s*); 128.71 (12*d*); 128.30 (4*d*); 127.82 (2*d*); 127.80 (4*d*); 127.77 (12*d*); 127.51 (2*d*); 126.96 (6*d*); 115.65 (2*t*); 86.68 (2*s*); 77.33 (2*d*); 72.11 (*t*); 72.10 (*t*); 70.79 (2*d*); 65.64 (2*t*); 30.41 (2*t*); 27.37 (2*t*); 19.90 (*q*); 19.89 (*q*). EI-MS: 333 (4, $[M - 187]^+$), 277 (3), 247 (4), 243 (100), 241 (9), 193 (15), 165 (34), 117 (26), 91 (59).

*(1*R*)- and (1*S*)-1-Methylprop-2-enyl (4*S*)-4-(Benzyloxy)-5,5-dimethoxypentanoate* (**9**; 1:1 mixture). To a soln. of **8** (11.385 g, 21.9 mmol) in dry CH_2Cl_2 (45 ml) was added at 0° 6M $ZnBr_2$ in dry MeOH (36.4 ml, 219 mmol). After stirring for 3 h at 23°, the starting material had disappeared (TLC control: cyclohexane/AcOEt 4:1), and the mixture was poured onto 1M aq. phosphate buffer (350 ml; pH 8). The white precipitate was removed by filtration through *Celite*, which was rinsed several times with a total amount of 150 ml of CH_2Cl_2. The aq. phase was extracted twice with CH_2Cl_2 (2 × 250 ml) and the combined org. extract dried ($MgSO_4$) and evaporated to yield 11.72 g of a slightly yellow oil, which was processed as follows without purification. To a soln. of oxalyl chloride (2.3 ml, 26.8 mmol; *Fluka*, *purum*) in dry CH_2Cl_2 (25 ml) was added at −78° under Ar a soln. of DMSO (4.0 ml, 56.3 mmol; *Fluka*, *puriss.*) in CH_2Cl_2 (15 ml). After stirring for 30 min at −78°, a soln. of the crude intermediate 5-hydroxy derivative in CH_2Cl_2 (100 ml) was added dropwise, and stirring was continued for another 30 min. Then Et_3N (15 ml, 108 mmol; *Fluka*, *puriss.*; dist. from CaH_2) was added, and the cooling bath was removed. After reaching 22°, the mixture was washed with sat. aq. $CuSO_4$ soln. (2 × 250 ml) and sat. aq. NaCl soln. (1 × 250 ml). The aq. phases were extracted with CH_2Cl_2 (2 × 350 ml) and the combined org. extracts dried ($MgSO_4$) and evaporated to yield 11.71 g of an orange oil. To a soln. of this crude aldehyde derivative in dry MeOH (25 ml) and trimethyl orthoformate (25 ml; *Fluka*, *purum*), TsOH · H_2O (104 mg, 0.547 mmol; *Fluka*, *puriss.*) was added, and the mixture was stirred at 23° for 1 h. The mixture was worked up with ^{t}BuOMe and sat. aq. $NaHCO_3$ soln. to furnish 12.68 g of crude **9**. Purification by FC (silica gel, cyclohexane/AcOEt 5:1) yielded 5.885 g (83.5% over 3 steps) of **9**. Colorless oil. IR ($CHCl_3$): 3005, 2935, 2835, 1725, 1496, 1454, 1375, 1308, 1261, 1090, 989. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.35–7.25 (*m*, 10 H); 5.82 (*ddd*, *J* = 17.3, 10.5, 5.9, 2 H); 5.329 (*quint. t*, *J* = 6.5, 1.3, 1 H); 5.326 (*quint. t*, *J* = 6.5, 1.3, 1 H); 5.22 (*dt*, *J* = 17.3, 1.3, 2 H); 5.11 (*dt*, *J* = 10.5, 1.2, 2 H); 4.74 (*d*, *J* = 11.4, 2 H); 4.55 (*d*, *J* = 11.4, 2 H); 4.25 (*d*, *J* = 5.6, 2 H); 3.48 (*ddd*, *J* = 8.9, 5.5, 3.4, 2 H); 3.45 (*s*, 6 H); 3.41 (*s*, 6 H); 2.5–2.4 (*m*, 4 H); 2.0–1.9 (*m*, 2 H); 1.8 (*m*, 2 H); 1.285 (*d*, *J* = 6.5, 3 H); 1.283 (*d*, *J* = 6.5, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 172.81 (2*s*); 138.54 (2*d*); 137.79 (*s*); 137.78 (*s*); 128.31 (4*d*); 127.94 (2*d*); 127.92 (2*d*); 127.59 (2*d*); 115.64 (2*t*); 106.94 (*d*); 106.93 (*d*); 78.26 (*d*); 78.25 (*d*); 73.15 (2*t*); 70.81 (2*d*); 55.67 (2*q*); 54.96 (2*q*); 30.29 (2*t*); 25.57 (2*t*); 19.90 (*q*); 19.88 (*q*). EI-MS: 322 (0.2, M^+), 247 (2), 193 (5), 129 (15), 91 (60), 75 (100).

*(2*S*,4*R*,6*E*)- and (2*S*,4*S*,6*E*)-2-(Benzyloxy)-4-(hydroxymethyl)oct-6-enal Dimethyl Acetal* (**11**; 1:1 mixture). To a soln. of ^{i}Pr$_2$NH (4.9 ml, 34.7 mmol; *Fluka*, *puriss.*) in THF (25 ml) was added 1.6M BuLi in hexane (22 ml, 35.2 mmol; *Fluka*) at −78°. At −78°, a soln. of **9** (10.118 g, 31.4 mmol) in THF (75 ml) was added. After stirring for 20 min, a soln. of (*tert*-butyl)chlorodimethylsilane (4.879 g, 31.5 mmol; *Fluka*, 97%) in hexamethylphosphorous triamide (HMPT; 4.6 ml; dist. from NaH) and THF (75 ml) was added dropwise at −78°. The cooling bath was replaced by an oil bath adjusted to 65°, and stirring was continued for 5.5 h. The mixture was cooled to 23°, and then $LiAlH_4$ (2.380 g, 62.7 mmol; *Fluka*, *purum*) was added in small portions. After stirring for 16 h at 22°, the mixture was poured carefully and slowly onto 1M aq. phosphate buffer soln. of pH 6 (500 ml) kept at 0°. The mixture was filtered through *Celite*, which was washed thoroughly with CH_2Cl_2. The aq. phase was extracted 3 times with CH_2Cl_2, the combined org. extract dried and evaporated, and the residue chromatographed (silica gel (350 g), cyclohexane/AcOEt 3:1 → 1:1): 7.982 g (82.4% over 2 steps) of **11**. Yellowish oil. IR ($CHCl_3$): 3443, 3005, 2935, 2837, 1454, 1379, 1074, 969. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.37–7.25 (*m*, 10 H); 5.48–5.30 (*m*, 4 H); 4.80 (*d*, *J* = 11.3, 1 H); 4.77 (*d*, *J* = 11.4, 1 H); 4.57 (*d*, *J* = 11.4, 1 H); 4.55 (*d*, *J* = 11.3, 1 H); 4.29 (*d*, *J* = 5.8, 1 H); 4.25 (*d*, *J* = 5.3, 1 H); 3.59–3.28 (*m*, 18 H); including *s* (6 H) at 3.41 and *s* (6 H) at 3.46); 2.43 (br. *s*, 1 H); 2.30 (br. *s*, 1 H); 2.07–1.91 (*m*, 4 H); 1.80–1.48 (*m*, 12 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 138.4 (*s*); 138.3 (*s*); 129.3 (*d*); 129.1 (*d*); 128.4 (4*d*); 128.2 (2*d*); 128.1 (2*d*); 127.75 (*d*); 127.73 (*d*); 126.8 (*d*); 126.7 (*d*); 107.4 (*d*); 107.2 (*d*); 78.2 (*d*); 77.5 (*d*); 73.2 (*t*); 73.0 (*t*); 65.9 (*t*); 65.4 (*t*); 55.98 (*q*); 55.91 (*q*); 55.20 (*q*); 55.16 (*q*); 37.8 (*d*); 37.3 (*d*); 35.6 (*t*); 34.7 (*t*); 32.3 (*t*); 32.1 (*t*); 17.9 (2*q*). EI-MS: 258 (0.001, $[M - 50]^+$), 244 (0.5), 233 (0.6), 138 (2), 125 (5), 91 (80), 75 (100), 55 (9).

*(2*R*,4*S*)- and (2*S*,4*S*)-4-(Benzyloxy)-2-[(2*E*)-but-2-enyl]-5,5-dimethoxypentanal (*E*)-Oxime* (**13A**; 1:1 mixture) *and (*Z*)-Oxime* (**13B**; 1:1 mixture) (**13A**/**13B** 2:1). To a soln. of oxalyl chloride (2.7 ml, 31.4 mmol; *Fluka*, *purum*) in dry CH_2Cl_2 (40 ml) was added at −78° under Ar a soln. of DMSO (4.8 ml, 67.6 mmol; *Fluka*, *puriss.*) in CH_2Cl_2 (40 ml). After stirring for 30 min at −78°, a soln. of **11** (7.96 g, 25.8 mmol) in CH_2Cl_2 (70 ml)

was added dropwise, and stirring was continued for another 30 min. Then, Et_3N (18 ml, 127 mmol; *Fluka, puriss.*; dist. from CaH_2) was added, and the cooling bath was removed. After 22° was reached, the mixture was washed with half-sat. aq. $CuSO_4$ soln. (2 × 150 ml) and sat. aq. NaCl soln. (1 × 150 ml). The aq. phases were extracted with CH_2Cl_2 (2 × 150 ml) and the combined org. extracts dried ($MgSO_4$) and evaporated. To a soln. of this crude aldehyde **12** in dry EtOH (32 ml; *J. T. Baker*, 99.9%) and pyridine (6.4 ml; *Fluka, puriss.*), $NH_2OH \cdot HCl$ (2.69 g, 38.7 mmol; *Fluka, puriss.*) was added. After stirring for 1 h at 23°, the mixture was worked up with 1M aq. phosphate buffer (pH 3) and *t*BuOMe. The crude material was purified by FC (silica gel, cyclohexane/AcOEt 6:1 → 2:1): 7.926 g (95.6% over two steps) of **13A**/**13B** 2:1. Colorless oil. IR ($CHCl_3$): 3664, 3586, 3323 (br.), 3067, 3006, 2934, 2837, 1496, 1454, 1379, 1322, 1256, 1078, 1028, 968, 917. ^{1}H-NMR (400 MHz, $CDCl_3$): **13A**: 8.15 (br. *s*, 1 H); 8.08 (br. *s*, 1 H); 7.31 (*d*, *J* = 7.7, 1 H); 7.23 (*d*, *J* = 7.8, 1 H); 3.436 (*s*, 3 H); 3.429 (*s*, 3 H); 3.398 (*s*, 3 H); 3.395 (*s*, 3 H); 2.62 (*m*, 1 H); 2.51 (*m*, 1 H); 1.80–1.71 (*m*, 2 H); **13B**: 8.55 (br. *s*, 1 H); 8.50 (br. *s*, 1 H); 6.58 (*d*, *J* = 7.9, 1 H); 6.51 (*d*, *J* = 8.3, 1 H); 3.438 (*s*, 3 H); 3.429 (*s*, 3 H); 3.401 (*s*, 3 H); 3.393 (*s*, 3 H); **13A**/**13B** first integral for the two (*E*)-epimers, second integral for the two (*Z*)-epimers: 7.39–7.24 (*m*, 10 and 10 H); 5.50–5.27 (*m*, 4 and 4 H); 4.7 (*m*, 2 and 2 H); 4.55 (*m*, 2 and 2 H); 4.52 (*m*, 2 and 2 H); 4.21 (*m*, 2 and 2 H); 3.45 (*m*, 2 and 2 H); 2.09 (*m*, 4 and 6 H); 1.60 (*m*, 8 and 10 H). ^{13}C-NMR (100 MHz, $CDCl_3$): **13A**: 155.66 (*d*); 154.96 (*d*); 138.61 (*s*); 138.44 (*s*); 128.28 (4*d*); 128.18 (2*d*); 128.16 (*d*); 128.12 (2*d*); 127.69 (*d*); 127.60 (*d*); 127.56 (*d*); 127.53 (*d*); 127.51 (*d*); 107.14 (*d*); 107.11 (*d*); 77.69 (*d*); 77.43 (*d*); 73.48 (*t*); 72.76 (*t*); 55.90 (*q*); 55.89 (*q*); 55.43 (*q*); 55.26 (*q*); 37.06 (*d*); 36.90 (*t*); 36.03 (*d*); 35.92 (*t*); 33.09 (*t*); 32.90 (*t*); 17.86 (2*q*); **13B** (some signals overlaping with those of **13A**): 156.21 (*d*); 155.78 (*d*); 138.72 (*s*); 138.47 (*s*); 128.26 (5*d*); 128.18 (3*d*); 128.16 (*d*); 127.77 (*d*); 127.56 (*d*); 127.53 (*d*); 127.33 (*d*); 127.19 (*d*); 107.03 (*d*); 106.92 (*d*); 78.20 (*d*); 78.11 (*d*); 73.84 (*t*); 72.97 (*t*); 55.90 (*q*); 55.89 (*q*); 55.31 (*q*); 55.26 (*q*); 36.16 (*t*); 35.42 (*t*); 33.16 (*t*); 32.72 (*t*); 32.09 (*d*); 31.39 (*d*); 17.86 (2*q*). EI-MS: 246 (2, $[M-75]^+$), 91 (48), 75 (100).

(2S,4R,6E)- and (2S,4S,6E)-2-(Benzyloxy)-4-[(hydroxyamino)methyl]oct-6-enal Dimethyl Acetal (**14**; 1:1 mixture). To a soln. of **13A**/**13B** (2.592 g, 8.06 mmol) in dry THF (14 ml) and AcOH (28 ml; *Scharlau*, 100%) was added $NaBH_3CN$ (608 mg, 9.19 mmol; *Merck*, 95%) at 0°. The mixture was stirred at 0° for 70 min and then poured onto cold aq. 2M NaOH. The pH was adjusted to 9–10 by adding solid NaOH in small portions. The combined extracts (4 × 120 ml of *t*BuOMe) were dried (K_2CO_3) and evaporated. Purification by FC (silica gel (60 g), cyclohexane/AcOEt 1:1 → 1:3) furnished 1.951 g (74.8%) of **14**. Colorless oil. IR ($CHCl_3$): 3587, 3279 (br.), 3006, 2935, 2837, 1731, 1496, 1454, 1378, 1324, 1078 (br.), 969, 916. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.37–7.25 (*m*, 10 H); 6.2–5.6 (br. *s*, 4 H); 5.5–5.3 (*m*, 4 H); 4.78 (*d*, *J* = 11.4, 1 H); 4.76 (*d*, *J* = 11.4, 1 H); 4.57 (*d*, *J* = 11.4, 1 H); 4.55 (*d*, *J* = 11.4, 1 H); 4.23 (*d*, *J* = 5.3, 1 H); 4.22 (*d*, *J* = 5.4, 1 H); 3.6–3.5 (*m*, 2 H); 3.459 (*s*, 3 H); 3.458 (*s*, 3 H); 3.413 (*s*, 3 H); 3.399 (*s*, 3 H); 2.91 (*dd*, *J* = 12.2, 5.4, 1 H); 2.80 (*m*, 2 H); 2.71 (*dd*, *J* = 12.3, 6.9, 1 H); 2.1–1.75 (*m*, 6 H); 1.65–1.45 (*m*, 10 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 138.66 (*s*); 138.54 (*s*); 128.83 (*d*); 128.51 (*d*); 128.30 (2*d*); 128.29 (2*d*); 128.12 (2*d*); 128.00 (2*d*); 127.59 (*d*); 127.54 (*d*); 126.96 (*d*); 126.89 (*d*); 107.55 (*d*); 107.40 (*d*); 77.58 (*d*); 77.49 (*d*); 73.16 (*t*); 73.00 (*t*); 57.92 (*t*); 57.16 (*t*); 55.91 (*q*); 55.90 (*q*); 55.31 (*q*); 54.99 (*q*); 36.68 (*t*); 35.22 (*t*); 32.93 (*t*); 32.84 (*t*); 32.10 (*d*); 31.77 (*d*); 17.92 (*q*); 17.91 (*q*). EI-MS: 232 (4, $[M-91]^+$), 216 (6), 200 (7), 184 (7), 124 (9), 91 (82), 75 (100).

(3R,4S,6R,8S)- and (3S,4R,6S,8S)-8-(Benzyloxy)-3-methyl-2-oxa-1-azatricyclo[4.3.1.0^{4,9}]decane (**17** and **18**, resp.; mixture 59:41). To a soln. of **14** (1.912 g, 5.91 mmol) in 1,4-dioxane (20 ml; *Fluka*, *puriss.*), aq. 1.5M H_2SO_4 (20 ml) was added, and the mixture was stirred at 60° for 24 h. The cold mixture was poured onto aq. 2M NaOH (100 ml) and extracted with CH_2Cl_2 (4 × 70 ml). The combined extracts were dried ($MgSO_4$) and evaporated, and the crude material was submitted to FC (silica gel (50 g, cyclohexane/AcOEt 1:1 → 100% AcOEt): 896 mg (58.4%) of **17**/**18** 59:41. IR ($CHCl_3$): 3068, 3005, 2940, 2669, 1496, 1454, 1380, 1352, 1097, 1066, 1028, 1002. EI-MS: 259 (20, M^+), 214 (28), 168 (40), 124 (24), 108 (32), 107 (25), 91 (100), 79 (34), 77 (21).

From the first fractions of the above FC, a small amount of the less-polar minor **18** could be isolated in pure form as colorless crystals. When the 41:59 mixture was inoculated with a seed crystal and kept at −20° for 3 days, most of this isomer crystallized. This material was recrystallized from hot AcOEt/cyclohexane to give pure **18** (for data, see below). The remaining material consisted of the major isomer **17**, contaminated with *ca.* 21% of **18** (by ^{1}H-NMR). The value of the optical rotation of this sample was corrected accordingly to give an estimate of the rotation of pure **17**.

Data of **17**: More-polar isomer (AcOEt). Colorless oil. $[\alpha]_D = +15.7$ ($c = 0.1$, $CHCl_3$); corrected. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.38–7.25 (*m*, 5 H); 4.63 (*d*, *J* = 12.0, 1 H); 4.54 (*d*, *J* = 12.0, 1 H); 4.12 (*dt*, *J* = 9.5, 3.6, 1 H); 4.04 (*q*, *J* = 6.3, 1 H); 3.37 (br. *t*, *J* = 3.3, 1 H); 3.17 (br. *d*, *J* = 14.3, 1 H); 2.94 (*dt*, *J* = 14.4, 3.1, 1 H); 2.28 (br. *dd*, *J* = 9.5, 3.3, 1 H); 2.05 (*dddd*, *J* = 13.7, 9.5, 2.9, 1.7, 1 H); 1.87 (*ddt*, *J* = 13.1, 9.8, 3.0, 1 H); 1.67 (*m*, 1 H); 1.50 (*m*, 1 H); 1.47 (*dq*, *J* = 13.6, 3.1, 1 H); 1.15 (*d*, *J* = 6.3, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 138.4 (*s*); 128.4

(2*d*); 127.7 (*d*); 127.6 (2*d*); 86.0 (*d*); 70.9 (*t*); 69.8 (*d*); 60.9 (*t*); 59.2 (*d*); 39.7 (*d*); 34.8 (*t*); 34.5 (*t*); 21.4 (*d*); 20.83 (*q*).

Data of **18**: Less-polar isomer (AcOEt). Colorless crystals. M.p. 80.1–80.9°. $[\alpha]_D = -11.3$ ($c = 0.14$, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$): 7.38–7.24 (*m*, 5 H); 4.65 (*d*, *J* = 12.2, 1 H); 4.59 (*d*, *J* = 12.2, 1 H); 4.06 (*q*, *J* = 6.3, 1 H); 4.04 (*ddd*, *J* = 10.0, 3.8, 2.8, 1 H); 3.55 (*t*, *J* = 3.0, 1 H); 3.48 (*ddd*, *J* = 14.4, 2.8, 1.4, 1 H); 2.99 (*dt*, *J* = 14.4, 3.1, 1 H); 2.04 (*dd*, *J* = 9.3, 3.4, 1 H); 1.87 (*ddt*, *J* = 13.2, 10.0, 3.1, 1 H); 1.75 (*dddd*, *J* = 13.3, 9.4, 2.9, 1.5, 1 H); 1.70 (*m*, 1 H); 1.55–1.48 (*m*, 2 H); 1.20 (*d*, *J* = 6.3, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 138.4 (*s*); 128.3 (2*d*); 127.7 (2*d*); 127.5 (*d*); 85.0 (*d*); 70.6 (*d*); 70.0 (*t*); 61.2 (*t*); 59.2 (*d*); 42.4 (*d*); 34.5 (*t*); 33.8 (*t*); 22.3 (*d*); 20.79 (*q*).

*(4*R*,5*S*,7*R*,9*S*)-9-(Benzyloxy)-4-methyl-3-oxa-1-azatricyclo[5.3.1.0^{5,10}]undecan-2-one* ((+)-**19**) *and (4*S*,5*R*,7*S*,9*S*)-9-(Benzyloxy)-4-methyl-3-oxa-1-azatricyclo[5.3.1.0^{5,10}]undecan-2-one* ((−)-**21**). To a mixture **17**/**18** 20 : 80 (133 mg, 0.513 mmol) in MeOH (1 ml; *J. T. Baker*; dist. from Mg) and AcOH (4 ml; *Scharlau*, 100%), activated Zn dust (168 mg; *Fluka, purum*; powder, washed successively with aq. 1M HCl, EtOH, and Et_2O) was added at 23°. After stirring for 3 h, the mixture was filtered through *Celite* and evaporated under vacuum at 30° and the residue dissolved in MeOH (5 ml). This soln. was poured onto cold (0°) aq. 2M NaOH (20 ml) and extracted with CH_2Cl_2 (4 × 15 ml). The combined extracts were dried (K_2CO_3) and evaporated. The yellow residue was dissolved in 1,2-dichloroethane (5 ml; *Riedel-de Häen*, 99.8%; dist. from P_2O_5). After addition of 1,1′-carbonylbis[1*H*-imidazole] (514 mg, 3.17 mmol; *Fluka*, > 97%) at 23°, the mixture was stirred for 24 h at 75° under Ar, poured onto aq. 1M HCl (20 ml), and extracted 3 times with CH_2Cl_2. The combined extract was dried ($MgSO_4$) and evaporated and the residue chromatographed (silica gel (5 g), cyclohexane/AcOEt 1 : 1 → AcOEt): 16 mg (10.9%) of (+)-**19** and 73 mg (49.5%) of (−)-**21**.

*Data of (+)-***19**: Less-polar component. Colorless oil. $[\alpha]_D = +134$ ($c = 0.14$, $CHCl_3$). IR ($CHCl_3$): 3006, 2952, 2868, 1703, 1455, 1384, 1112, 1075, 1020, 888. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.33–7.22 (*m*, 5 H); 4.56 (*d*, *J* = 12.0, 1 H); 4.49 (*d*, *J* = 12.0, 1 H); 4.36 (*q*, *J* = 6.5, 1 H); 4.04 (*ddd*, *J* = 9.4, 6.9, 2.7, 1 H); 3.52 (*dddd*, *J* = 12.1, 4.7, 2.5, 0.9, 1 H); 3.23 (*d*, *J* = 2.7, 1 H); 3.16 (*dd*, *J* = 12.1, 1.8, 1 H); 2.23 (br. *dd*, *J* = 10.0, 6.0, 1 H); 2.16 (*dddd*, *J* = 13.1, 9.2, 5.0, 2.5, 1 H); 1.94 (*dddd*, *J* = 14.2, 10.5, 4.0, 1.9, 1 H); 1.86 (*m*, 1 H); 1.38 (*dddd*, *J* = 13.1, 6.9, 2.5, 1.5, 1 H); 1.25 (*d*, *J* = 6.5, 3 H); 1.18 (*ddt*, *J* = 13.9, 5.9, 2.2, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 163.0 (*s*); 137.9 (*s*); 128.5 (2*d*); 127.9 (*d*); 127.6 (2*d*); 84.9 (*d*); 71.6 (*d*); 71.1 (*t*); 53.4 (*t*); 49.3 (*d*); 33.2 (*d*); 32.9 (*t*); 30.6 (*t*); 26.0 (*d*); 20.2 (*q*). EI-MS: 287 (2, M^+), 243 (2), 242 (3), 212 (11), 152 (55), 137 (31), 136 (25), 131 (11), 122 (10), 91 (100), 81 (18), 65 (12), 55 (19), 41 (13).

*Data of (−)-***21**: More-polar component. Colorless crystals. M.p. 125.4–125.9°. $[\alpha]_D = -121$ ($c = 0.113$, $CHCl_3$). IR ($CHCl_3$): 3006, 2952, 2868, 1698, 1476, 1455, 1384, 1354, 1297, 1267, 1100, 1070, 1013, 970. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.38–7.27 (*m*, 5 H); 4.67 (*d*, *J* = 11.8, 1 H); 4.58 (*d*, *J* = 11.8, 1 H); 4.48 (*q*, *J* = 6.5, 1 H); 3.87 (*ddt*, *J* = 8.3, 4.0, 1.0, 1 H); 3.66 (*dddd*, *J* = 11.0, 4.7, 2.5, 0.7, 1 H); 3.59 (br. *d*, *J* = 11.7, 1 H); 3.52 (*d*, *J* = 3.8, 1 H); 2.0 (*m*, 1 H); 1.9–1.8 (*m*, 3 H); 1.76 (br. *ddt*, *J* = 14.2, 8.3, 2.0, 1 H); 1.35 (*d*, *J* = 6.5, 3 H); 1.29 (*m*, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 163.3 (*s*); 137.9 (*s*); 128.4 (2*d*); 127.7 (*d*); 127.6 (2*d*); 84.0 (*d*); 72.6 (*d*); 70.2 (*t*); 53.5 (*t*); 48.0 (*d*); 36.4 (*d*); 33.1 (*t*); 29.8 (*t*); 26.5 (*d*); 20.4 (*q*). EI-MS: 288 (0.4, $[M+1]^+$), 243 (2), 212 (4), 181 (17), 138 (18), 137 (59), 108 (11), 107 (10), 94 (32), 92 (16), 91 (100), 79 (25), 65 (16), 55 (16), 41 (15).

*(4*R*,5*S*,7*R*,9*S*)-9-Hydroxy-4-methyl-3-oxa-1-azatricyclo[5.3.1.0^{5,10}]undecan-2-one* ((+)-**20**). To a soln. of **19** (100 mg, 0.348 mmol) in EtOH (1 ml) and AcOH (0.1 ml; *Scharlau*, 100%) was added 10% Pd/C (20 mg; *Fluka*, *puriss.*). The mixture was stirred under H_2 at 1 atm for 52 h at 23°. The mixture was filtered through silica gel (0.5 g), the filtrate evaporated, and the residue recrystallized from hot AcOEt/CH_2Cl_2; 49 mg (71.4%) of (+)-**20**. Colorless crystals. M.p. 151–153°. $[\alpha]_D = +245$ ($c = 0.099$, $CHCl_3$). IR ($CHCl_3$): 3401, 3006, 2952, 2867, 1700, 1618, 1480, 1457, 1384, 1299, 1109, 1050, 1016, 960. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.45 (*q*, *J* = 6.5, 1 H); 4.43 (br. *t*, *J* = 8.4, 1 H); 3.58 (*dddd*, *J* = 12.1, 4.7, 2.4, 0.9, 1 H); 3.25 (*dd*, *J* = 12.1, 1.8, 1 H); 3.14 (*d*, *J* = 2.8, 1 H); 2.33 (br. *dd*, *J* = 10.3, 6.5, 1 H); 2.27 (*dddd*, *J* = 13.2, 9.4, 5.1, 2.6, 1 H); 2.27 (br. *s*, 1 H); 2.01 (*dddd*, *J* = 14.2, 10.4, 3.9, 2.0, 1 H); 1.93 (*m*, 1 H); 1.36 (*d*, *J* = 6.5, 3 H); 1.33 (*dddd*, *J* = 13.2, 6.9, 2.5, 2, 1 H); 1.24 (*ddt*, *J* = 14.2, 6.0, 2.1, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 163.2 (*s*); 85.1 (*d*); 64.6 (*d*); 53.3 (*t*); 52.2 (*d*); 34.6 (*t*); 32.8 (*d*); 30.8 (*t*); 26.2 (*d*); 20.2 (*q*). EI-MS: 197 (28, M^+), 154 (16), 153 (78), 152 (38), 138 (25), 136 (100), 124 (20), 110 (15), 109 (29), 108 (61), 96 (31), 95 (36), 94 (27), 82 (73), 80 (35), 71 (37), 70 (82), 69 (37), 68 (91), 67 (90), 58 (24), 55 (36), 43 (31), 41 (33).

*(4*S*,5*R*,7*S*,9*S*)-9-Hydroxy-4-methyl-3-oxa-1-azatricyclo[5.3.1.0^{5,10}]undecan-2-one* ((−)-**22**). As described for (+)-**20**, with **21** (150 mg, 0.522 mmol), EtOH (3 ml; *J. T. Baker*, 99.9%), AcOH (0.3 ml), 10% Pd/C (60 mg) and H_2 for 20 h at 23°: 78 mg (73.8%) of (−)-**22**. Colorless crystals. M.p. 178.4–179.9°. $[\alpha]_D = -319$ ($c = 0.102$, $CHCl_3$). IR ($CHCl_3$): 3412, 3006, 2936, 2867, 1699, 1476, 1456, 1384, 1289, 1112, 1020, 976. ^{1}H-NMR (400 MHz, $CDCl_3$): 4.48 (*q*, *J* = 6.5, 1 H); 4.19 (br. *dt*, *J* = 8.3, 4.1, 1 H); 3.62 (*dddd*, *J* = 11.8, 4.7, 2.5, 0.7, 1 H);

Table 3. *Crystallographic Data of (−)-***21**

Empirical formula	$C_{17}H_{21}NO_3$		Index ranges	$-13 \le h \le 13$, $-16 \le k \le 16$, $-16 \le l \le 16$
M_r	287.359		Reflections collected	4042
Temperature	298 K		Independent reflections	4019 ($R_{int} = 0.026$)
Wavelength	$\lambda = 0.71073$		Refinement method	Full-matrix least-squares on F^2
Crystal system	Orthorhombic		Data, restraints, parameters	4019, 0, 274
Space group	$P2_12_12_1$		R(all)	0.0872
Unit-cell dimensions	$a = 10.1906(3)$ Å	$\alpha = 90.00°$	R(gt)	0.0528
	$b = 11.9127(3)$ Å	$\beta = 90.00°$	wR(ref)	0.1696
	$c = 12.4091(4)$ Å	$\gamma = 90.00°$	wR(gt)	0.1416
Volume	1506.43(8) Å^3		S(ref)	1.071
Z	4		*Flack* parameter	2.0 (15)
Density (calculated)	1.267 Mg/m^3		$\Delta\rho$(max; min)	0.227 and -0.287 e · A^{-3}
θ Range	0.998–29.131°			

3.56 (br. *d*, *J* = 11.7, 1 H); 3.35 (*d*, *J* = 4.0, 1 H); 2.82 (br. *d*, *J* = 3.6, 1 H); 2.02 (*m*, 1 H); 1.9–1.8 (*m*, 3 H); 1.73 (*dm*, *J* = 14.3, 1 H); 1.37 (*d*, *J* = 6.5, 3 H); 1.28 (*m*, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 163.8 (*s*); 84.5 (*d*); 66.3 (*d*); 53.7 (*t*); 51.3 (*d*); 36.5 (*d*); 35.4 (*t*); 29.3 (*t*); 26.6 (*d*); 20.5 (*q*). MS: 197 (64, M^+), 153 (34), 152 (26), 138 (29), 137 (11), 137 (100), 128 (14), 124 (22), 110 (20), 108 (40), 95 (37), 82 (50), 70 (34), 68 (57).

*(4*S*,5*R*,7*S*)-4-Methyl-3-oxa-1-azatricyclo[5.3.1.0^{5,10}]undecane-2,9-dione* ((−)-**23**). To a soln. of oxalyl chloride (38 µl, 0.442 mmol; *Fluka*, *purum*) in dry CH_2Cl_2 (0.5 ml) was added at −78° under Ar a soln. of DMSO (63 µl, 0.886 mmol; *Fluka*, *puriss.*) in CH_2Cl_2 (1 ml). After stirring for 30 min at −78°, a soln. of (−)-**22** (67 mg, 0.34 mmol) in CH_2Cl_2 (2.5 ml) was added dropwise, and stirring was continued for another 30 min. Then, Et_3N (0.24 ml, 1.72 mmol; *Fluka*, *puriss.*; dist. from CaH_2) was added, and the cooling bath was removed. After reaching 22°, the mixture was poured onto aq. 0.1M HCl (25 ml) and extracted with CH_2Cl_2 (3 × 20 ml). The combined extract was dried ($MgSO_4$) and evaporated and the residue purified by chromatography (silica gel (3 g), AcOEt): 48 mg (72.3%) of (−)-**23**. Colorless crystals. M.p. 120.3–120.9°. $[\alpha]_D = -123$ ($c = 0.101$, $CHCl_3$). IR ($CHCl_3$): 2985, 2956, 1739, 1714, 1478, 1456, 1406, 1374, 1103, 1017, 955. ^{1}H-NMR (500 MHz, $CDCl_3$): 4.57 (*q*, *J* = 6.5, 1 H); 3.95 (*ddd*, *J* = 12.5, 4.6, 2.8, 1 H); 3.60 (*s*, 1 H); 3.30 (*dd*, *J* = 12.5, 1.7, 1 H); 2.51–2.41 (*m*, 3 H); 2.25 (br. *dd*, *J* = 10.5, 5.3, 1 H); 2.18 (*dddd*, *J* = 13.8, 10.5, 3.3, 1.8, 1 H); 1.57 (*ddt*, *J* = 13.9, 4.7, 2.1, 1 H); 1.40 (*d*, *J* = 6.5, 3 H). ^{1}H-NMR (400 MHz, C_6D_6): 3.80 (*q*, *J* = 6.5, 1 H); 3.69 (*dddd*, *J* = 12.5, 4.8, 3.1, 0.6, 1 H); 3.35 (*s*, 1 H); 2.68 (*dd*, *J* = 12.5, 1.8, 1 H); 1.70 (*dddd*, *J* = 18.9, 3.3, 2.5, 0.5, 1 H); 1.59 (*dt*, *J* = 18.8, 2.6, 1 H); 1.27 (*m*, 1 H); 1.16 (br. *dd*, *J* = 10.3, 5.4, 1 H); 1.05 (*dddd*, *J* = 14.0, 10.5, 3.6, 1.9, 1 H); 0.72 (*ddt*, *J* = 14.1, 5.5, 2.3, 1 H); 0.71 (*d*, *J* = 6.5, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 205.7 (*s*); 161.4 (*s*); 83.8 (*d*); 58.4 (*d*); 55.4 (*t*); 43.2 (*t*); 37.3 (*d*); 29.0 (*t*); 27.2 (*d*); 20.4 (*q*). EI-MS: 195 (100, M^+), 151 (10), 123 (75), 122 (41), 109 (16), 108 (46), 107 (14), 106 (21), 95 (65), 94 (36), 82 (92), 81 (89), 80 (24), 79 (33), 68 (100), 57 (47), 55 (70), 54 (22), 41 (49).

*(4*R*,5*S*,7*R*)-4-Methyl-3-oxa-1-azatricyclo[5.3.1.0^{5,10}]undecane-2,9-dione* ((+)-**23**). As described for (−)-**23**, with (+)-**20** (28 mg, 0.143 mmol): 22 mg (79.0%) of (+)-**23**. Colorless crystals. M.p. 119.2–120.1°. $[\alpha]_D = +124$ ($c = 0.102$, $CHCl_3$).

X-Ray Crystal-Structure Determination of **21**. Details of the structure determination are listed in *Table 3*. A crystal was mounted on a *Nonius-KappaCCD* diffractometer. Data collection and integration were carried out with a *Nonius* collect suite [15]. The structure was solved by direct methods by using the program SIR92 [16]. The absolute configuration at C(9) was assumed to be (*S*), since it is derived from L-glutamic acid (**4**). All diagrams and calculations were performed by using maXus [17]. ORTEP Drawing according to [18]. Crystallographic data have been deposited with the *Cambridge Crystallographic Data Centre* as deposition no. CCDC 201931.

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