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Chirality transfer in an Ireland–Claisen rearrangement: a new approach toward the *Iboga* alkaloids

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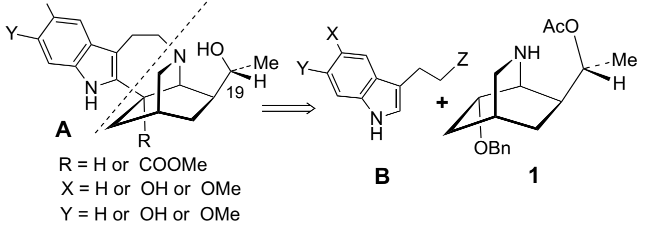
Abstract—The synthesis of the isoquinuclidine core of the *Iboga* alkaloid family is described. This building block contains the entire stereochemical information of the targeted natural products. Starting with (*S*)-4-(hydroxymethyl)-4-butanolide, a derivative available in two steps from L-glutamate, (*S*)-4-benzyloxy-5,5-dimethoxypentanoic acid was obtained in four steps. Mitsunobu esterification with (*S*)-but-3-en-2-ol furnished the inverted ester, which was then subjected to an Ireland–Claisen rearrangement. This crucial step took place with a very satisfactory chirality transfer from the alcohol component to the new carbon backbone of the product. After transformation of the resulting silyl ester function into a hydroxylamino group, the dimethyl acetal moiety was hydrolyzed with 3 M sulfuric acid at 47 °C. Under these conditions, the resulting cyclic nitrone could not be isolated, because it underwent a rapid intramolecular nitrone–olefin [3+2]-cycloaddition reaction to furnish the expected tricyclic isoxazolidine derivative in 67% yield. After chromatographic purification, this product was obtained enantiomerically pure and with a chemical purity of 96%. The targeted isoquinuclidine building block was thus obtained from (*S*)-4-(hydroxymethyl)-4-butanolide in 13 steps with an overall yield of 9.2%, which amounts to an average yield of 83.3% per step.

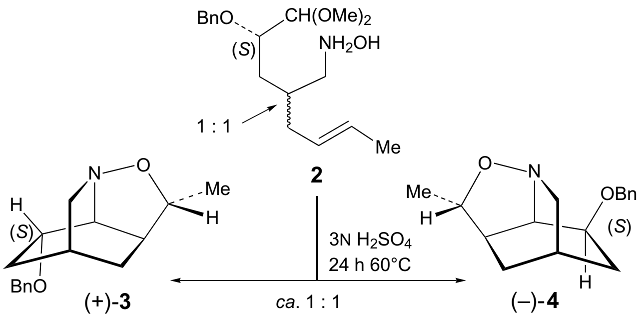
1. Introduction

Recently, we have disclosed a new strategy aimed at the first synthesis of *Iboga* alkaloids being functionalized at C(19).[1,2] Though numerous successful preparations of the structurally more simple representatives of this alkaloid family have already been reported by other research teams, none of our chosen targets, which possess general structure **A** (Scheme 1) have been synthesized to date. Our retrosynthetic plan foresees a scission along the dashed line to yield an appropriately substituted 3-ethylindole unit **B** and the isoquinuclidine building block **1**, which contains the complete stereochemical information of the final products.

While our first approach suffered from low yields and poor reproducibility in certain steps,[1] the second involved an intramolecular [3+2]-cycloaddition of a nitrone, prepared in situ from intermediate **2** by means of acid-promoted hydrolysis (Scheme 2).[2] As compound **2**



Scheme 1. Retrosynthesis of 19-hydroxy-*Iboga* alkaloids.



Scheme 2.

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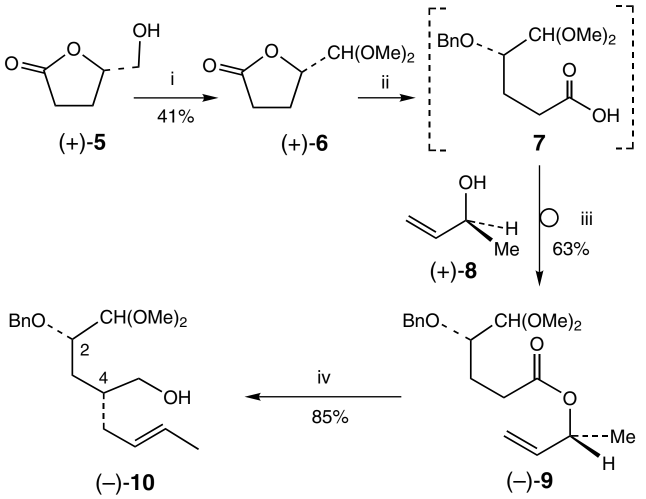
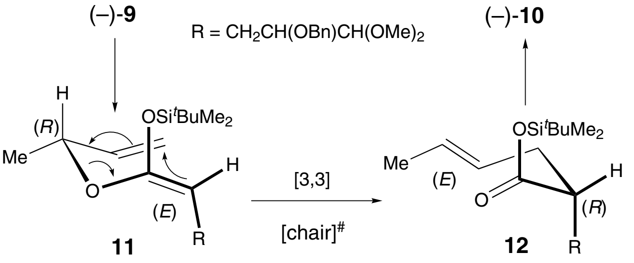
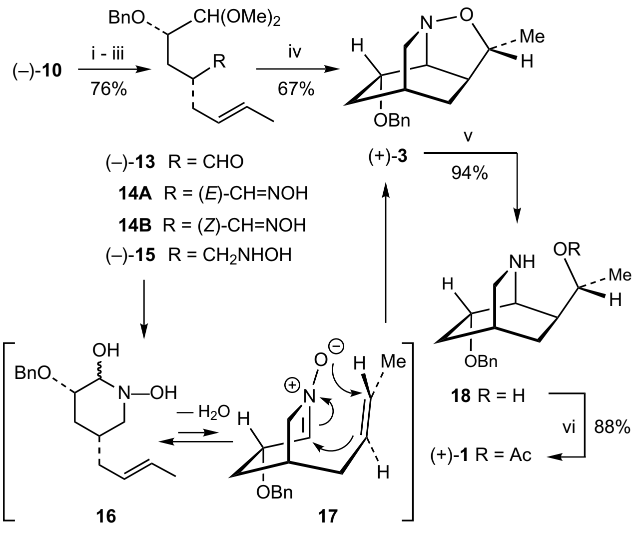


Scheme 3. Reagents and conditions: (i) a. DMSO, (COCl)$_2$, Et$_3$N, CH$_2$Cl$_2$; b. MeOH, AcCl, HC(OMe)$_3$; (ii) a. NaH, H$_2$O, 15-crown-5, benzene, 5 h reflux; b. PhCH$_2$Cl, benzene, 16 h reflux; (iii) (*S*)-but-3-en-2-ol, DIAD, PPh$_3$, THF, 1.5 h, 23 °C; (iv) a. LDA, THF, HMPT, *t*-BuMe$_2$SiCl, 5 h, 65 °C; b. LiAlH$_4$, THF, 16 h, 23 °C.



Scheme 4. Self-immolating 1,4-chirality transfer in the Ireland–Claisen rearrangement 9 → 10.



Scheme 5. Reagents and conditions: (i) a. DMSO, (COCl)$_2$, Et$_3$N, CH$_2$Cl$_2$; (ii) NH$_2$OH·HCl, EtOH, py, 2 h at 23 °C; (iii) NaBH$_3$CN, AcOH/THF, 2.5 h at −10 °C; (iv) 3 N H$_2$SO$_4$, 8.5 h at 47 °C; (v) Zn, AcOH/MeOH, 2 h at 23 °C; (vi) AcCl, MeOH, AcOH, 3 h at 23 °C.

consisted of a 1:1 mixture of two diastereoisomers, roughly equal amounts of (+)-**3** and (−)-**4** were formed, which proved difficult to separate, especially on a larger scale. Herein we report a modified approach that circumvents most of the previously encountered problems. At the same time, the new route shown in Schemes 3–5 is considerably shorter and its overall efficiency therefore better.

2. Results and discussion

The starting material (+)-**5**, which can be readily prepared in two steps with double inversion from L-glutamate,[2,3] was oxidized to the corresponding aldehyde, which was protected in situ as dimethyl acetal derivative (+)-**6** (Scheme 3). The lactone ring was opened with NaOH in benzene in the presence of 15-crown-5 and the resulting alcohol transformed directly into benzyl ether **7** in good overall yield. For the following esterification with but-3-en-2-ol, we did not employ racemic (±)-**8** as in our former approach, but (*S*)-enantiomer (+)-**8**, which was prepared according to Balmer et al.[4] Our sample showed an ee of 85%, as determined by ^{1}H NMR spectroscopy of the derived Mosher ester.[5,6] Mitsunobu's protocol was taken to combine **7** and (+)-**8**, which is known to proceed with virtually complete inversion at the carbinol center.[7] Accordingly, the resulting ester (−)-**9** is expected to possess a de amounting to almost 85%. An Ireland–Claisen rearrangement,[8] followed by in situ reduction with LiAlH$_4$ furnished the primary (*E*)-alcohol (−)-**10** in 85% yield via intermediates **11** and **12**.

The stereochemical outcome of the above Ireland–Claisen rearrangement was of crucial importance for the validity of our modified concept. For a successful chirality transfer[9] from the asymmetric center within the former alcohol component to the new C–C branching point, two prerequisites have to be fulfilled: (i) the formation of the intermediate silyl ketene acetal **11** (Scheme 4) has to be highly stereoselective and (ii) the ensuing transition state must be chair shaped. Whereas the latter condition, which at the same time establishes the (*E*)-configuration of the newly formed C=C double bond, is undoubtedly fulfilled in the case of our acyclic substrate,[10] especially under the mild conditions employed (5–6 h at 65 °C), the stereoselective formation of the (*E*)-silyl ketene acetal **11** in the presence of HMPT[11] could, at best, be hoped for, but not taken for granted.[†] As it turned out, analysis of product **10** and of the compounds derived therefrom gave 76% de, to be compared with the 85% de of the starting ester **9**. This finding demonstrates a very satisfactory chirality transfer within the self-immolative process **9** → **11** → **12** → **10**, which diminished the ratio of the two diastereoisomers from a value of 92.5:7.5 down to 88:12. As we were unable to firmly establish the presumed (4*R*)-configuration of

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[†] In our case, HMPT also had a beneficial effect on the chemical yield of the Ireland–Claisen rearrangement, which increased by some 30% in its presence.

compound **10**, this vital verification had to be postponed till the advent of compounds that were endowed with rigid polycyclic structures, which would subsequently allow an unambiguous assignment of configuration (see below).

Swern oxidation of (−)-**10** led to aldehyde (−)-**13**, which was transformed into a 7:3 mixture of the (*E*)- and (*Z*)-oximes **14A** and **14B**, respectively (Scheme 5). This mixture was reduced with NaBH$_3$CN[12] to give the required hydroxylamine derivative (−)-**15**. To study what happened during the acid-catalyzed hydrolysis of this compound, reaction of (−)-**15** with 1.5 M D$_2$SO$_4$ in D$_2$O was run in an NMR tube and followed spectroscopically (see Fig. 1). As it happened, the two methoxy signals of the starting material disappeared very rapidly and were replaced by a singlet at 3.39 ppm, originating from the liberated methanol. Since no aldehyde signal could be detected during the entire experiment, the first product of hydrolysis most likely is present in the closed form **16**. When the reaction was allowed to proceed at 47 °C, a doublet ($J = 6.5$ Hz) at 1.29 ppm slowly began to show up at the expense of the former olefinic methyl group at 1.65 ppm. This transformation, requiring ca. 6 h for completion, was paralleled by the disappearance of the olefinic hydrogen atoms and by the manifestation of additional signals arising from the expected final product (+)-**3**.[2] As the characteristic doublet at about 7 ppm for H–C(1) of the presumed nitrone intermediate **17** could not be detected at any point during the entire transformation, it would seem that the rate-determining step in the whole sequence is the acid-catalyzed dehydration of **16** to **17**. This process was followed by an expeditious intramolecular cycloaddition reaction, which can take place at temperatures as low as 47 °C. Judging from the integrals of the respective methyl groups, the ratio of the two diastereoisomers (+)-**3** and (−)-**4** was 92:8 in the crude product, as expected, considering the composition of the starting mixture. After chromatography on silica gel, which improved this ratio to a value of 96:4, the yield of purified **3** amounted to 67%.

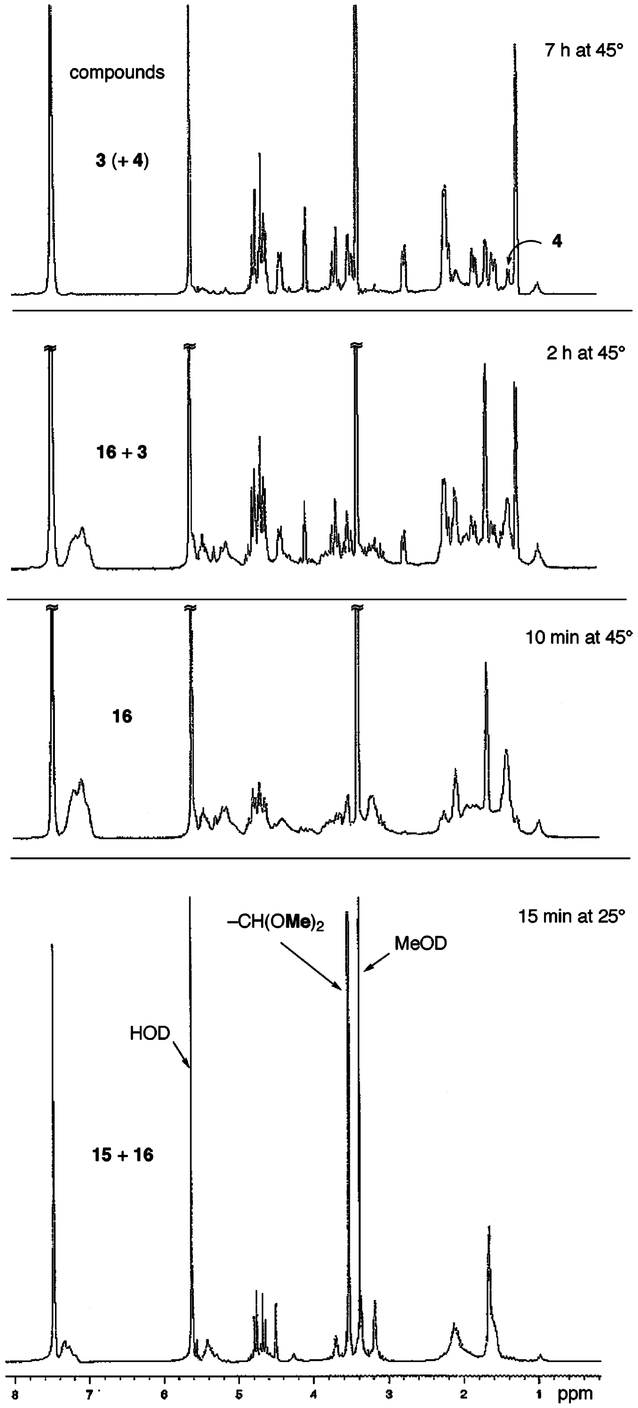

Figure 1. ^{1}H NMR spectra (300 MHz, 3 N D$_2$SO$_4$ in D$_2$O at 47 °C) of the transformation **15** → **3** at the specified time intervals.

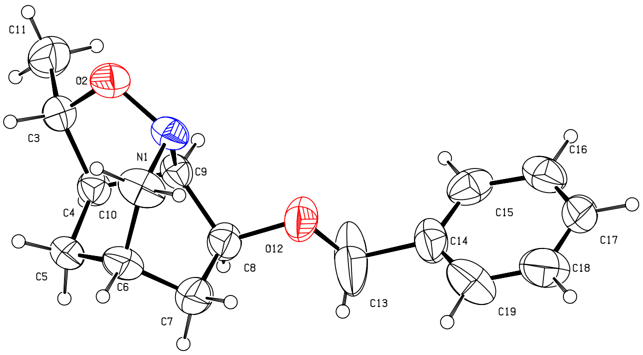

Figure 2. ORTEP view of (+)-**4**. The thermal ellipsoids are scaled at the 30% level.

To confirm the crucial structural assignments of **3** and **4**, which had been deduced earlier by taking recourse to NMR-arguments and to a chemical correlation,[2] an X-ray structure determination of the crystalline minor isomer (−)-**4** was undertaken.[‡] The resulting solution is shown in Fig. 2, and from the drawing it is readily apparent that our original assignments were indeed

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[‡] The authors would like to thank Dr. B. Schweizer, Laboratory for Organic Chemistry, ETH Zürich (Switzerland), for his expeditious X-ray structure determination of this compound. For selected measurements, see Table 1.

Table 1. Selected measurements of (−)-**4** (derived from X-ray data, for numbering system, see Fig. 2)

Bond lengths [Å]	
N(1)–O(2)	1.447(3)
O(2)–C(3)	1.456(5)
C(3)–C(4)	1.515(5)
C(4)–C(5)	1.540(5)
C(5)–C(6)	1.520(4)
C(6)–C(7)	1.506(6)
C(7)–C(8)	1.524(6)
C(8)–C(9)	1.514(4)
C(9)–N(1)	1.467(4)
N(1)–C(10)	1.495(5)
C(6)–C(10)	1.510(5)
C(8)–O(12)	1.445(5)
Bond angles [°]	
N(1)–O(2)–C(3)	108.9(3)
O(2)–C(3)–C(4)	105.4(3)
C(4)–C(3)–C(11)	116.5(3)
O(2)–N(1)–C(10)	108.0(3)
O(2)–N(1)–C(9)	100.9(2)
C(9)–N(1)–C(10)	109.0(3)
N(1)–C(9)–C(8)	112.4(2)
N(1)–C(9)–C(4)	102.1(3)
C(3)–C(4)–C(9)	99.7(3)
C(4)–C(5)–C(6)	108.9(3)
Dihedral angles [°]	
N(1)–O(2)–C(3)–C(4)	−3.8(2)
N(1)–O(2)–C(3)–C(11)	−128.7(4)
N(1)–C(9)–C(8)–O(12)	−68.4(3)
C(3)–O(2)–N(1)–C(9)	31.6(2)
C(5)–C(4)–C(3)–C(11)	−150.7(4)
C(10)–N(1)–C(9)–C(8)	−54.4(3)
C(6)–C(7)–C(8)–O(12)	125.2(3)
C(6)–C(10)–N(1)–C(9)	−4.6(2)
C(3)–C(4)–C(9)–N(1)	43.8(3)
O(2)–N(1)–C(10)–C(6)	104.3(3)
O(12)–C(8)–C(9)–C(4)	176.7(5)
C(6)–C(7)–C(8)–C(9)	3.5(2)

correct. These deductions provided an unambiguous solution for the postponed problem concerning the relative configuration of the acyclic intermediates **10**–**17** in that it is clear that the respective major diastereoisomers possess the absolute and relative configuration displayed in the formulae depicted in Schemes 3–5. Finally, tricyclic isoxazolidine (+)-**3** was readily transformed into the target key intermediate (+)-**1** in good yield through reduction with Zn/AcOH to yield **18**, followed by a chemoselective O-acetylation in an acidic medium (Table 1).

3. Conclusion

A concise asymmetric synthesis of (+)-**1**, a key intermediate in a novel strategic concept toward the *Iboga* alkaloids, has been developed. This compound was prepared in 13 steps from (*S*)-4-(hydroxymethyl)-4-butanolide (+)-**5** with an overall yield of 9.2%, which amounts to an average yield of 83.3% per step. After purification through flash chromatography, cycloaddition product (+)-**3** was obtained in enantiomeric excess, albeit contaminated with 4% of (−)-**4**, the structure of which was secured by X-ray crystallography. This efficient new route to the key aliphatic building block (+)-**1** paves the way for accessing several (19*R*)-hydroxy-*Iboga* alkaloids, which have not been synthesized up to now (Table 2).

4. Experimental part

4.1. General

Mps are uncorrected: Büchi B-540 mp-apparatus, sealed evacuated capillaries. Optical rotations: Perkin–Elmer 241 at 25 °C and 589 nm (Na$_D$). IR spectra: Perkin–Elmer FT-IR 1615, ν_{max} in cm^{-1}. ^{1}H NMR spectra {δ [ppm] from TMS, apparent coupling constants J [Hz]}: 300 MHz: Varian Gemini 300; 400 MHz: Bruker AMX 400. ^{13}C NMR spectra {δ [ppm] from TMS, multiplicities as determined from DEPT spectra}: 75 MHz: Varian Gemini 300; 100 MHz: Bruker AMX 400. Mass spectra {m/z [amu] (% base peak)}: Hitachi–Perkin–Elmer, VG TRIBRID (EI: 70 eV, unless stated otherwise; FAB: in 3-nitrobenzyl alcohol as matrix). High-resolution-MS: Micromass, Autospec-Ultima. The solvents and reagents used for the reactions were of

Table 2. ^{1}H and ^{13}C NMR data of the cyclic compounds **1**, **3**, **4**,[2] and **18** (CDCl$_3$)

^{1}H NMR	3	4	18	1	^{13}C NMR	3	4	18	1
H–C(3)	4.04	4.06	3.84	4.96	C(3)	85.9	85.0	75.4	76.2
H–C(4)	2.28	2.04	2.00	2.17	C(4)	39.6	42.4	35.0	36.6
H_{endo}–C(5)	2.05	1.75	1.83	1.82	C(5)	34.8*	34.5*	29.5	29.4
H_{exo}–C(5)	1.50	1.48	1.60	1.10	C(6)	21.3	22.3	26.0	25.7
H–C(6)	1.66	1.70	1.83	1.73	C(7)	34.4*	33.8*	33.5	33.4
H_{endo}–C(7)	1.87	1.87	1.53	1.53	C(8)	69.8	70.6	71.0	72.0
H_{exo}–C(7)	1.47	1.51	2.10	2.10	C(9)	59.2	59.2	46.1	45.9
H–C(8)	4.12	4.04	3.78	3.86	C(10)	60.8	61.2	45.9	46.8
H–C(9)	3.37	3.55	3.35	2.85	C(11)	20.8	20.8	22.4	21.4
H_A–C(10)	3.17	3.48	2.95*	2.83*	C(13)	70.8	70.0	70.5	70.3
H_B–C(10)	2.94	2.99	2.80*	2.76*					
H_3–C(11)	1.15	1.20	1.22	1.25					
H–C(13)	4.63	4.65	4.52	4.53					
H′–C(13)	4.54	4.59	4.52	4.49					

The numbering system displayed in Fig. 2 was employed; H_B–C(10) is pointing toward the C_2-side chain.

*: Assignments may be interchanged.

reagent grade (Fluka, puriss.) and freshly distilled under N_2 using a solvent recirculation still with the following drying reagents: CH_2Cl_2 from P_2O_5 on silica gel; THF from K/benzophenone; MeOH from Mg; benzene from $LiAlH_4$; Et_3N, pyridine and diisopropylamine from CaH_2. $CHCl_3$ employed as solvent for measuring IR spectra and optical rotations was passed through basic alumina, act. I (ICN Biomedicals), immediately before utilization.

4.2. (*S*)-4-(Dimethoxymethyl)-4-butanolide (+)-6

To a soln of 18.4 mL (214 mmol, 1.2 equiv) of oxalyl chloride (Fluka, purum) in 200 mL of dry CH_2Cl_2 was added at −78 °C under Ar a soln of 33 mL (465 mmol, 2.7 equiv) of DMSO (Fluka, puriss.) in 200 mL of CH_2Cl_2 within 25 min. After stirring for 20 min at −78 °C, a soln of 20.0 g (172 mmol) of (+)-**5**[2] in 200 mL of CH_2Cl_2 was added dropwise within 30 min and stirring continued for another 45 min. Et_3N (100 mL, 718 mmol, 4.2 equiv; Fluka, puriss., dist. from CaH_2) were then added and the cooling bath removed. After reaching 23 °C, the mixture was cooled again to 0 °C. A soln of HCl(g) in MeOH was then added, which had been prepared before by slowly adding 23 mL (324 mmol, 1.9 equiv) of AcCl to 120 mL of MeOH. To the resulting homogeneous soln were added 120 mL of $HC(OMe)_3$ (Fluka, puriss.) and stirring at 23 °C was continued for 8 h. The mixture was washed successively with 400 mL of aq phosphate buffer (1 M, pH 3), 400 mL of satd aq $CuSO_4$ soln, and with 400 mL of satd aq NaCl soln. The aq phases were extracted with 2 × 400 mL of CH_2Cl_2 and the combined org. extracts dried over $MgSO_4$ and evaporated to furnish a dark-brown oil, which was distilled over K_2CO_3 at 80–82 °C/0.2 Torr to yield 11.20 g of (+)-**6** (69.9 mmol, 41%) as a slightly yellow oil. An analytical sample was prepared by FC (silica gel, pentane/Et_2O 1:2 to 1:1). Colorless oil. $C_7H_{12}O_4$ (160.17). $[\alpha]_D = +6.5$ (*c* 3.0, $CHCl_3$). IR ($CHCl_3$): 3006, 2939, 2838, 1778, 1462, 1375, 1346, 1175, 1128, 1073, 980. ^1H NMR (300 MHz, $CDCl_3$): 4.51 (ddd, $J = 7.5$, 5.3, 3.7, 1H), 4.38 (d, $J = 3.7$, 1H), 3.48 (s, 3H), 3.46 (s, 3H), 2.58 (ddd, $J = 17.7$, 9.7, 8.1, 1H), 2.42 (ddd, $J = 17.7$, 10.0, 6.2, 1H), 2.26–2.15 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): 177.6 (s), 105.3 (d), 79.1 (d), 57.3 (q), 56.0 (q), 28.0 (t), 21.9 (t). HR-EI-MS: 129.0551 (100, $M^+ - 31$) [calcd for $C_6H_9O_3$: 129.0552], 115.0378 (20) [calcd for $C_6H_9O_3$: 115.0395], 101.0594 (35) [calcd for $C_5H_9O_2$: 101.0602], 31.0172 (51) [calcd for CH_3O: 31.0184].

4.3. (1*R*)-1-Methylprop-2-enyl (4*S*)-4-(benzyloxy)-5,5-dimethoxy pentanoate (−)-9

To a soln of 5.478 g (34.2 mmol) of (+)-**6** in 200 mL of dry benzene (J.T. Baker) under Ar were added at 23 °C. NaH (5.660 g, 205 mmol, 6 equiv; Fluka, pract. 55–65% in oil, washed three times with *n*-hexane, subsequently shown by titration to contain 87% of NaH) and 0.65 mL (3.3 mmol, 0.1 equiv) of 15-crown-5 (Fluka, purum). Then were slowly added 1.2 mL (66.7 mmol, 2 equiv) of H_2O and the mixture stirred under reflux for 5 h. After cooling the mixture in an ice bath, there were added 5.9 mL (51.2 mmol, 1.5 equiv) of benzyl chloride (Fluka, purum, dist. over P_2O_5) and stirring continued at reflux temperature for 16 h. The mixture was cooled to 0 °C and poured onto 200 mL of 1 M aq phosphate buffer soln with pH = 3. The resulting pH was re-adjusted to 3 by adding concd aq HCl soln, then the mixture extracted three times with *tert*-butyl methyl ether (= MTBE). The extracts were combined, dried over $MgSO_4$, and evaporated to give 10.0 g of a yellow viscous liquid of essentially pure **7**, which was used as such for the next step.

The crude acid **7** was dissolved in 100 mL of anhydrous THF at 23 °C under Ar. Then were added 15.7 g (59.9 mmol, 1.75 equiv) of triphenylphosphine (Fluka, 98.5%), 3.5 mL (40.4 mmol, 1.2 equiv) of (*S*)-3-buten-2-ol[4] ((+)-**8**, 85% ee) and 2.8 g of molecular sieves (Fluka, powder, 4 Å). To the stirred mixture were added slowly 12.3 mL (59.7 mmol, 1.75 equiv) of diisopropyl diazadicarboxylate (= DIAD) (Fluka, 94%) with external cooling in an ice bath. When the addition was completed, stirring was continued at 23 °C for 90 min. Most of the solvent was evaporated under reduced pressure and the residue diluted with 100 mL of MTBE and stored at −20 °C for 16 h after addition of a seeding crystal of triphenylphosphine oxide. The filtrate was washed with 100 mL of H_2O, which was back-extracted with 2 × 100 mL of MTBE. The combined org. extracts were dried over $MgSO_4$ and evaporated. The residue was chromatographed (250 g of silica gel, cyclohexane/AcOEt, gradient ranging from 10:1 to 4:1) to furnish 6.924 g (21.48 mmol, 63% over three steps) of (−)-**9**. Slightly yellow viscous oil. $C_{18}H_{26}O_5$ (322.40). $[\alpha]_D = -21.0$ (*c* 0.12, $CHCl_3$). IR ($CHCl_3$): 3005, 2935, 2835, 1725, 1496, 1454, 1375, 1308, 1261, 1090, 989. ^1H NMR (300 MHz, $CDCl_3$): 7.36–7.24 (m, 5H), 5.82 (ddd, $J = 17.1$, 10.6, 5.9, 1H), 5.34 (quint. t, $J = 6.2$, 1.3, 1H), 5.23 (dt, $J = 17.4$, 1.2, 1H), 5.11 (dt, $J = 10.6$, 1.2, 1H), 4.74 (d, $J = 11.5$, 1H), 4.54 (d, $J = 11.5$, 1H), 4.25 (d, $J = 5.6$, 1H), 3.48 (m, 1H), 3.45 (s, 3H), 3.41 (s, 3H), 2.53–2.34 (m, 2H), 1.99 (dddd $J = 14.3$, 8.4, 7.2, 3.7, 1H), 1.86–1.76 (m, 1H), 1.28 (d, $J = 6.5$, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 172.7 (s), 138.4 (s), 137.7 (d), 128.3 (2×d), 127.9 (2×d), 127.5 (d), 115.6 (t), 106.9 (d), 78.2 (d), 73.2 (t), 70.9 (d), 55.8 (q), 55.0 (q), 30.4 (t), 25.7 (t), 20.0(q). EI-MS: 322 (0.2, M^+), 247 (2), 193 (5), 129 (15), 91 (60), 75 (100).

4.4. (2*S*,4*R*,6*E*)-2-(Benzyloxy)-4-(hydroxymethyl)oct-6-enal dimethyl acetal (−)-10

To a soln of 3.3 mL (23.4 mmol, 1.1 equiv) of diisopropylamine (Fluka, puriss, dist. from CaH_2) in 30 mL of THF were added 14.4 mL (23 mmol, 1.1 equiv) of *n*-Bu–Li (Fluka, 1.6 M in hexane) at −78 °C under Ar. The mixture was warmed to 0 °C for 15 min and then cooled to −78 °C. At the same temperature was added a soln of 6.748 g (20.9 mmol) of **9** in 40 mL of THF. After stirring for 20 min, a soln of 3.248 g (20.9 mmol, 1.0 equiv) of *tert*-butyldimethylsilyl chloride (Merck, 97%) in a mixture of 2.9 mL of HMPT (dist. from NaH) and 40 mL of THF was added dropwise at −78 °C. The cooling bath was replaced by an oil bath adjusted to 65 °C and stirring was continued for 5 h. The mixture was cooled to 23 °C and then added 1.565 g (41.2 mmol, 2 equiv) of $LiAlH_4$ (Fluka, purum) in small portions. After stirring for 16 h at 23 °C, the mixture was poured carefully and slowly into 250 mL of aq phosphate buffer soln (1 M, pH 6) kept at 0 °C. The mixture was filtered through $\text{Celite}_{\text{TM}}$, which was washed thoroughly with 200 mL of MTBE. The water phase was extracted twice with 250 mL of MTBE and the combined org. extracts were dried, evaporated, and chromatographed (130 g of silica gel, cyclohexane/AcOEt 3:1 to 1:1) to yield 5.505 g (17.9 mmol, 85% over two steps) of (−)-**10**. Slightly yellow oil. $C_{18}H_{28}O_4$ (308.42). $[\alpha]_D = -27.3$ (*c* 0.126, $CHCl_3$). IR ($CHCl_3$): 3440, 3005, 2935, 2837, 1454, 1379, 1074, 969. ^1H NMR (400 MHz, $CDCl_3$): 7.36–7.24 (m, 5H), 5.45–5.25 (m, 2H), 4.72 (d, $J = 11.4$, 1H), 4.52 (d, $J = 11.4$, 1H), 4.24 (d, $J = 5.8$, 1H), 3.51 (ddd, $J = 7.9$, 5.8, 3.4, 1H), 3.42 (dd, $J = 11.2$, 4.8 1H), 3.41 (s, 3H), 3.36 (s, 3H), 3.35 (dd, $J = 11.1$, 6.1, 1H), 2.20 (br s, 1H), 2.02–1.96 (m, 1H), 1.91–1.84 (m, 1H), 1.75–1.66 (m, 1H), 1.59 (dm, $J = 5.9$, 3H), 1.58 (ddd, $J = 14.8$, 7.9, 4.0, 1H), 1.50 (ddd, $J = 14.8$, 8.9, 3.4, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 138.3 (s), 129.2 (d), 128.4 (2×d), 128.1 (2×d), 127.8 (d), 126.8 (d), 107.1 (d), 77.5 (d), 73.0 (t), 65.6 (t), 56.0 (q), 55.2 (q), 37.3 (d), 35.7 (t), 32.3 (t), 17.9 (q). EI-MS: 244 (0.6, M^+-64), 233 (0.6), 138 (2), 125 (5), 91 (80), 75 (100). A thorough examination of the ^1H and ^{13}C NMR spectra revealed the presence of 12% of the (2*S*,4*S*)-diastereoisomer.

4.5. (2*R*,4*S*)-(*E*)-4-(Benzyloxy)-2-(but-2-enyl)-5,5-dimethoxypentanal (−)-13

To a soln of 1.8 mL (20.9 mmol, 1.2 equiv) of oxalyl chloride (Fluka, purum) in 30 mL of dry CH_2Cl_2 was added at −78 °C under Ar, a soln of 3.3 mL (46.5 mmol, 2.6 equiv) of DMSO (Fluka, puriss.) in 15 mL of CH_2Cl_2. After stirring for 30 min at −78 °C, a soln of 5.445 g (17.7 mmol) of **10** in 45 mL of CH_2Cl_2 was added dropwise and stirring continued for another 30 min. Then were added 12 mL (86.1 mmol, 5 equiv) of Et_3N (Fluka, puriss., dist. from CaH_2) after which the cooling bath was removed. After reaching 23 °C, the mixture was diluted with 50 mL of CH_2Cl_2 and washed with 200 mL of aq phosphate buffer (1 M, pH 3), 200 mL of satd aq $CuSO_4$ soln and with 200 mL of satd aq NaCl soln. The aq phases were extracted with 2 × 150 mL of CH_2Cl_2 and the combined org. extracts dried over $MgSO_4$ and evaporated to yield 5.361 g of the crude aldehyde **13**, which was used without further purification for the following step. An analytical sample was prepared by FC (silica gel, AcOEt/cyclohexane 1:4). Colorless oil. $C_{18}H_{26}O_4$ (306.40). $[\alpha]_D = -24.2$ (*c* 0.11, $CHCl_3$). IR ($CHCl_3$): 3006, 2936, 2836, 2730, 1721, 1454, 1380, 1078, 968. ^1H NMR (300 MHz, $CDCl_3$): 9.52 (d, $J = 2.2$, 1H), 7.4–7.2 (m, 5H), 5.47 (dqm, $J = 15.3$, 6.2, 1H), 5.33 (m, 1H), 4.69 (d, $J = 11.2$, 1H), 4.47 (d, $J = 11.2$, 1H), 4.23 (d, $J = 5.3$, 1H), 3.48 (ddd, $J = 9.7$, 5.3, 3.1, 1H), 3.44 (s, 3H), 3.41 (s, 3H), 2.52 (m, 1H), 2.36 (m, 1H), 2.10 (m, 1H), 1.95 (ddd, $J = 14.6$, 9.3, 3.1, 1H), 1.70 (ddd, $J = 14.6$, 10.0, 3.4, 1H), 1.63 (dd, $J = 6.2$, 1.3, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 204.8 (s), 138.5 (s), 128.6 (2×d), 128.5 (2×d), 128.1 (d), 127.9 (d), 127.6 (d), 107.1 (d), 76.8 (d), 73.4 (t), 56.2 (q), 55.1 (q), 48.0 (d), 32.5 (t), 29.7(t), 18.1(q). HR-EI-MS: 274.1640 (0.2, M^+-32) [calcd for $C_{17}H_{22}O_3$: 274.1569], 135.0813 (2) [calcd for $C_9H_{11}O$: 135.0810], 113.0601 (25) [calcd for $C_6H_9O_2$: 113.0602], 112.0883 (17) [calcd for $C_7H_{12}O$: 112.0888], 91.0552 (41) [calcd for C_7H_7: 91.0548], 75.0448 (100) [calcd for $C_3H_7O_2$: 75.0446].

4.6. 2:1 Mixture of (2*R*,4*S*)-4-benzyloxy-2-[(*E*)-but-2-enyl]-5,5-dimethoxypentanal (*E*)-oxime 14A and (*Z*)-oxime 14B

To a soln of the above crude aldehyde **13**, prepared from 17.7 mmol of **10**, in 20 mL of dry EtOH (J.T. Baker, 99.9%) and 4 mL of pyridine (Fluka, puriss.) were added 1.84 g (26.5 mmol, 1.5 equiv) of $NH_2OH\cdot HCl$ (Fluka, puriss.). After stirring for 2 h at 23 °C, the mixture was worked up with aq phosphate buffer soln (1 M, pH 3) and MTBE. The crude material was purified by FC (130 g of silica gel, cyclohexane/AcOEt 6:1 to 2:1) to yield 5.415 g (16.9 mmol, 95% over two steps) of **14**. Colorless oil. $C_{18}H_{27}NO_4$ (321.42). IR ($CHCl_3$): 3664, 3586, 3323 (br), 3067, 3006, 2934, 2837, 1496, 1454, 1379, 1322, 1256, 1078, 1028, 968, 917. ^1H NMR (400 MHz, $CDCl_3$): Signals assigned to the major isomer **14A**: 7.71 (br s, 1H), 7.38–7.25 (m, 5H), 7.23 (d, $J = 7.8$, 1H), 5.49–5.31 (m, 2H), 4.72 (d, $J = 11.0$, 1H), 4.55 (d, $J = 11.0$, 1H), 4.207 (d, $J = 5.3$, 1H), 3.48 (m, 1H), 3.44 (s, 3H), 3.404 (s, 3H), 2.63 (m, 1H), 2.20–2.02 (m, 2H), 1.70–1.60 (m, 5H). Signals assigned to the minor isomer **14B**: 8.08 (br s, 1H), 7.38–7.25 (m, 5H), 6.51 (d, $J = 8.3$, 1H), 5.49–5.31 (m, 2H), 4.71 (d, $J = 10.8$, 1H), 4.58 (d, $J = 10.8$, 1H), 4.203 (d, $J = 5.3$, 1H), 3.48 (m, 1H), 3.44 (s, 3H), 3.407 (s, 3H), 2.20–2.07 (m, 3H), 1.70–1.60 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$): Signals assigned to the major isomer **14A**: 155.1 (d), 138.6 (s), 128.30 (2×d), 128.2 (d), 128.1 (2×d), 127.59 (d), 127.57 (d), 107.2 (d), 77.4 (d), 73.5 (t), 55.93 (q), 55.3 (q), 36.9 (t), 36.0 (d), 33.1 (t), 17.9 (q). Signals assigned to the minor isomer **14B** (some signals overlap with the ones of **14A**): 156.0 (d), 138.7 (s), 128.28 (3×d), 127.77 (d), 127.70 (2×d), 127.23 (d), 107.0 (d), 78.2 (d), 73.9 (t), 55.95 (q), 55.3 (q), 36.2 (t), 36.0 (d), 33.2 (t), 17.9 (q). MS (EI): 246 (2) (M^+-75), 91 (48), 75 (100).

4.7. (2*S*,4*R*)-(*E*)-2-Benzyloxy-4-(hydroxylaminomethyl)-oct-6-enal dimethyl acetal (−)-15

To a soln of 5.391 g (16.8 mmol) of **14A** and **14B** in 40 mL of dry THF and 80 mL of AcOH (Scharlau, 100%) were added 1.331 g (20.1 mmol, 1.2 equiv) of $NaBH_3CN$ (Merck, 95%) at −10 °C. The mixture was stirred at −10 °C for 150 min and then poured onto 300 mL of cold (0 °C) aq 2 M NaOH soln The pH was adjusted to 11 by adding solid NaOH in small portions (total: ca. 40 g NaOH). The combined extracts (4 × 150 mL of MTBE) were dried over K_2CO_3 and evaporated. Purification by

FC (130 g of silica gel, cyclohexane/AcOEt 1:1 to neat AcOEt) furnished 4.316 g (13.4 mmol, 80%) of **15** as a colorless oil. $C_{18}H_{29}NO_4$ (323.44). $[\alpha]_D = -21.1$ (*c* 0.1, $CHCl_3$). IR ($CHCl_3$): 3587, 3279 (br), 3006, 2935, 2837, 1731, 1496, 1454, 1378, 1324, 1078 (br), 969, 916. ^1H NMR (300 MHz, $CDCl_3$): 7.4–7.2 (m, 5H), ca. 6–4 (br s, 2H), 5.47–5.32 (m, 2H), 4.76 (d, $J = 11.5$, 1H), 4.57 (d, $J = 11.5$, 1H), 4.23 (d, $J = 5.3$, 1H), 3.56 (ddd, $J = 9.0$, 5.3, 4.1, 1H), 3.46 (s, 3H), 3.42 (s, 3H), 2.80 (d, $J = 5.9$, 2H), 2.09–1.85 (m, 3H), 1.64 (d, $J = 5.0$, 3H), 2.32 (td, $J = 8.1$, 4.1, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): 138.5 (s), 128.8 (d), 128.3 (2×d), 128.0 (2×d), 127.5 (d), 126.9 (d), 107.4 (d), 77.6 (d), 73.1 (t), 57.3 (t), 56.1 (q), 55.5 (q), 36.9 (t), 33.1 (t), 32.20 (d), 18.1 (q). MS (EI): 232 (4) (M^+-91), 216 (6), 200 (7), 184 (7), 124 (9), 91 (82), 75 (100).

4.8. (3*R*,4*S*,6*R*,8*S*)-8-(Benzyloxy)-3-methyl-2-oxa-1-azatricyclo [4.3.1.0^{4,9}]decane (+)-3

A mixture of 4.466 g (13.8 mmol) of (−)-**15** and 150 mL aq 1.5 M H_2SO_4 was warmed to 47 °C (inside temperature) and stirred for 8.5 h under Ar. During this time the starting emulsion turned into a colorless homogeneous solution. The mixture was cooled and poured onto 300 mL of ice-cold aq 2 M NaOH. The mixture was extracted with 4×150 mL of MTBE and the combined organic extracts dried over K_2CO_3. After filtration and evaporation, the residue was chromatographed (70 g of silica gel, cyclohexane/AcOEt 1:1 to pure AcOEt) to yield 2.410 g (9.29 mmol, 67%) of (+)-**3**. Brownish oil, containing 8% of (−)-**4** according to the ^1H NMR spectrum (de = 84%). A second chromatography (same conditions) furnished a product contaminated with only 4% of (−)-**4**. $C_{16}H_{21}NO_2$ (259.35). $[\alpha]_D = +14.0$ (*c* 0.8, $CHCl_3$) for material with 92% de, corrected for the presence of 4% of (−)-**4**:[2] $[\alpha]_D = +15.1$ for chemically and enantiomerically pure (+)-**3**. IR ($CHCl_3$): 3086, 3005, 2940, 2669, 1496, 1454, 1380, 1352, 1097, 1066, 1028, 1002. ^1H NMR (400 MHz, $CDCl_3$): 7.38–7.27 (m, 5H), 4.63 (d, $J = 12.0$, 1H), 4.54 (d, $J = 12.0$, 1H), 4.12 (dt, $J = 9.7$, 3.6, 1H), 4.04 (q, $J = 6.3$, 1H), 3.37 (br t, $J = 3.5$, 1H), 3.17 (ddd, $J = 14.5$, 2.9, 1.2, 1H), 2.94 (dt, $J = 14.5$, 2.9, 1H), 2.28 (br dd, $J = 9.4$, 3.4, 1H), 2.05 (dddd $J = 13.1$, 9.5, 2.9, 1.7, 1H), 1.87 (ddt, $J = 13.1$, 9.7, 3.0, 1H), 1.66 (m, 1H), 1.50 (m, 1H), 1.47 (dq, $J = 13.6$, 3.1, 1H), 1.15 (d, $J = 6.3$, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): 138.4 (s), 128.4 (2×d), 127.64 (d), 127.55 (2×d), 85.9 (d), 70.8 (t), 69.8 (d), 60.8 (t), 59.2 (d), 39.6 (d), 34.8 (t), 34.4 (t), 21.3 (d), 20.8 (q). HR-EI-MS: 259.1573 (15, M^+) [calcd for $C_{16}H_{21}NO_2$: 259.1572], 168.1019 (38) [calcd for $C_9H_{14}NO_2$: 168.1024], 124.0762 (11) [calcd for $C_7H_{10}NO$: 124.0762], 91.0563 (100) [calcd for C_7H_7: 91.0548].

4.9. X-ray crystal-structure determination of (3*S*,4*R*,6*S*,8*S*)-8-(benzyloxy)-3-methyl-2-oxa-1-azatricyclo [4.3.1.0^{4,9}]decane (−)-4

A sample of (−)-**4**[2] was recrystallized twice from AcOEt/cyclohexane. Mp 80–81 °C. A crystal with dimensions 0.3×0.14×0.12 mm was mounted on a Nonius-KappaCCD diffractometer. Data collection and integration were carried out with a Nonius collect suite.[13] The structure was solved by direct methods by using the program SIR92.[14] All calculations were performed by using maXus.[15] The pertinent experimental parameters for the structure determination are listed in Table 3. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 233306. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0)-1223-336033 or e-mail: deposit@ccdc.cam.ac.uk].

Table 3. Crystallographic data of (−)-**4**

Empirical formula	$C_{16}H_{21}NO_2$
Formula weight	259.349
Temperature	298 K
Wavelength	$\lambda = 0.71073$
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
Unit cell dimensions	$a = 9.5166(5)$ Å $\alpha = 90.00°$ $b = 12.2664(6)$ Å $\beta = 90.00°$ $c = 12.3103(7)$ Å $\gamma = 90.00°$
Volume	1437.04 (13) Å^3
Z	4
Density (calculated)	1.199 Mg/m^3
Θ range	0.998–26.733°
Index ranges	$-11 \leq h \leq 12$, $-15 \leq k \leq 15$, $-15 \leq l \leq 15$
Reflections collected	3000
Independent reflections	2982 [$R_{\text{int}} = 0.036$]
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	2982/0/173
R(all)	0.0968
R(gt)	0.0721
wR(ref)	0.2347
wR(gt)	0.2124
S(ref)	1.464
Flack parameter	1 (3)
$\Delta\rho$ (max; min)	0.250 and 0.277 e A^3

4.10. (1*S*,6*S*,7*S*,1′*R*)-6-(Benzyloxy)-7-(1′-hydroxyethyl)-2-azabicyclo[2.2.2]octane 18

To a mixture of 708 mg (2.73 mmol) of (+)-**3** (92% de) in 7 mL of MeOH (J.T. Baker, dist. from Mg) and 28 mL of acetic acid (Scharlau, 100%), stirred at 23 °C, were added 892 mg (13.7 mmol, 5 equiv) of activated Zn dust (Fluka, purum, powder; washed successively with aq 1 M HCl soln, EtOH and Et_2O). After stirring for 2 h, the mixture was filtered through Celite™, evaporated under vacuum at 30 °C and the residue dissolved in 5 mL of MeOH. This soln was poured into 30 mL of cold (0 °C) aq 2 M NaOH soln and extracted four times with 40 mL of MTBE. The combined extracts were dried over K_2CO_3 and evaporated to yield 670 mg (2.56 mmol, 94%) of **18** (92% de). This material was processed to (+)-**1** without additional purification. $C_{16}H_{23}NO_2$ (261.37). IR ($CHCl_3$): 3215 (br), 3000, 2969, 2936, 2865, 1496, 1454, 1422, 1375, 1122, 1075. ^1H NMR (300 MHz, $CDCl_3$): 7.4–7.2 (m, 5H), 4.52 (s, 2H), 4.5 (br s, 2H), 3.84 (qd, $J = 6.5$, 4.0, 1H), 3.78 (ddd, $J = 9.3$, 5.0, 3.4, 1H), 3.35 (dd, $J = 3.4, 0.9$, 1H), 2.95 (dt, $J = 10.3, 2.5$, 1H), 2.80 (dt, $J = 10.3, 2.1$, 1H), 2.10 (dddd $J = 13.4, 9.3, 3.5, 3.0$, 1H), 2.00 (m, 1H), 1.9–1.75 (m, 2H), 1.60 (m, 1H), 1.53 (ddt, $J = 13.4, 5.0, 2.2$, 1H), 1.22 (d, $J = 6.5$, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): 138.3 (s), 128.3 (2×d), 127.5 (3×d), 75.4 (d), 71.0 (d), 70.5 (t), 46.1 (d), 45.9 (t), 35.0 (d), 33.5 (t), 29.5 (t), 26.0 (d), 22.4 (q). HR-EI-MS: 261.1731 (2, M^+) [calcd for $C_{16}H_{23}NO_2$: 261.1729], 246.1513 (18) [calcd for $C_{15}H_{20}NO_2$: 246.1494], 170.1187 (26) [calcd for $C_9H_{16}NO$: 170.1181], 152.1082 (46) [calcd for $C_9H_{14}NO$: 152.1075], 126.0921 (100) [calcd for $C_7H_{12}NO$: 126.0919], 91.0574 (98) [calcd for C_7H_7: 91.0548].

4.11. (1*S*,6*S*,7*S*,1′*R*)-7-(1′-Acetoxyethyl)-6-(benzyloxy)-2-azabicyclo[2.2.2]octane (+)-1

To a stirred soln of 950 μL (13.4 mmol, 5 equiv) of acetyl chloride (Fluka, puriss.) in 4 mL of AcOH (Scharlau, 100%) were added 120 μL (2.96 mmol, 1.2 equiv) of MeOH (Merck, ⩾ 99%) at 23 °C. After stirring for 30 min at 23 °C, the mixture was added to a soln of 670 mg (2.56 mmol) of crude **18** (see above) in 6 mL of AcOH and stirring continued for 3 h. The mixture was poured into 80 mL of ice-cold aq 2 M NaOH and 40 mL of satd aq Na_2CO_3 soln. Extraction with CH_2Cl_2 (3 × 50 mL), drying of the combined extracts over K_2CO_3 and evaporation furnished 682 mg (2.25 mmol, 88%) of (+)-**1** as a slightly yellow oil. $C_{18}H_{25}NO_3$ (303.40). $[\alpha]_D = +62.7$ (*c* 1.2, $CHCl_3$). IR ($CHCl_3$): 3354 (br), 3006, 2969, 2937, 2864, 1720, 1626, 1454, 1373, 1096, 1062, 951. ^{1}H NMR (400 MHz, $CDCl_3$): 7.4–7.3 (m, 5H), 4.96 (dq, $J = 10.1, 6.2$, 1H), 4.53 (d, $J = 11.9$, 1H), 4.49 (d, $J = 11.8$, 1H), 3.86 (ddd, $J = 9.6, 4.5, 3.6$, 1H), 2.85 (br d, $J = 3.4$, 1H), 2.83 (dt, $J = 10.3, 2.5$, 1H), 2.76 (dt, $J = 10.3, 2.3$, 1H), 2.17 (br dddd $J = 12, 9, 6.5, 1.2$, 1H), 2.10 (dddd $J = 13.5, 9.7, 3.8, 2.6$, 1H), 2.04 (s, 3H), 1.82 (dddd $J = 13.1, 11.2, 3.5, 3.0$, 1H), 1.76 (br s, 1H), 1.73 (m, 1H), 1.53 (ddt, $J = 13.5, 4.5, 2.3$, 1H), 1.25 (d, $J = 6.2$, 3H), 1.10 (ddt, $J = 13.1, 6.5, 2.5$, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): 170.9 (s), 138.7 (s), 128.4 (2×d), 127.6 (2×d), 127.5 (d), 76.2 (d), 72.0 (d), 70.3 (t), 46.8 (t), 45.9 (d), 36.6 (d), 33.4 (t), 29.4 (t), 25.7 (d), 21.4 (q), 17.9 (q). HR-EI-MS: 303.1837 (1, M^+) [calcd for $C_{18}H_{25}NO_3$: 303.1834], 244.1596 (19) [calcd for $C_{16}H_{22}NO$: 244.1701],[§] 194.1090 (25) [calcd for $C_{11}H_{16}NO_2$: 194.1181], 153.1026 (14) [calcd for $C_9H_{15}NO$: 153.1154], 152.0993 (100) [calcd for $C_9H_{14}NO$: 152.1075], 108.0780 (11) [calcd for C_7H_8O: 108.0575], 91.0539 (74) [calcd for C_7H_7: 91.0548].

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[§] Judging from the nearby reference peak for $C_5F_9^+$, showing up at $m/z = 230.9731$ instead of 230.9856, there seems to exist a systematic error in this region of the spectrum.