Towards a New Synthetic Entry into the *Iboga*-Alkaloid Family

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Dedicated to Professor *Albert Eschenmoser* on the occasion of his 75th birthday

A novel retrosynthetic concept is presented that, in principle, allows access to many hitherto not accessible representatives of the *Iboga*-alkaloid family. The flexibility required by this approach is provided through a highly convergent assembly of the target, which allows for a control over the substitution pattern of the indole sub-system, as well as over the relative configuration of the aliphatic core of these alkaloids. The key step for the construction of the latter consists in an intramolecular nitrone-olefin 1,3-dipolar cycloaddition reaction of **26** to yield the crucial tricyclic isoxazolidine derivative **28**.

1. Introduction. – The *Iboga*-alkaloid family presently comprises some sixty structurally closely related monoterpene indole alkaloids (for reviews, see [2]). They occur mainly in the roots and leaves of the tropical West African shrub *Tabernanthe iboga*, which belongs to the botanic family *Apocynaceae* [3]. The *Iboga* alkaloids that have been tested pharmacologically all show interesting activity patterns [4], and dried extracts from the roots of *T. iboga* are used as the ingredients for the *Bwiti* cult, *e.g.*, popular in Gabon. Part of its initiation ritual consists in the consumption of 50–200 g of such an extract, whereupon the novice falls into a deep coma for 2–3 days. During this period, his mind is said to travel in time back to his ancestors [5]. Ibogaine (**1**; *Fig. 1* and *Table 1*) represents the major component of these extracts. It has cytotoxic, anticonvulsant, brachycardic, and hypotensive properties; in addition, it acts as a powerful stimulant of the central nervous system and evokes long-lasting hallucinations [6]. Both ibogaine and its hydrochloride were traded in the USA (*Bogadin*™ and *Endabuse*™, resp.), but had to be withdrawn from the market because they were included in the list of forbidden drugs. There are claims that heroin and cocaine addicts can be cured by a single dose of ibogaine [7]. The corresponding program was patented in the USA under the trade name *Lotsof Procedure*™ [8]; however, this therapy has not been admitted as a clinical method.

Not surprisingly, the pharmacological properties of the *Iboga* alkaloids, combined with their caged structures, have challenged synthetic chemists for quite some time. In 1965, *Büchi* and co-workers were the first to disclose a successful synthesis of two of them, namely of racemic ibogaine ((±)-**1**), and ibogamine ((±)-**2**), as well as of the corresponding unnatural C(20)-epimers [9a]. Several other syntheses followed, but most of them were restricted to the most simple representatives, namely ibogamine (**2**),

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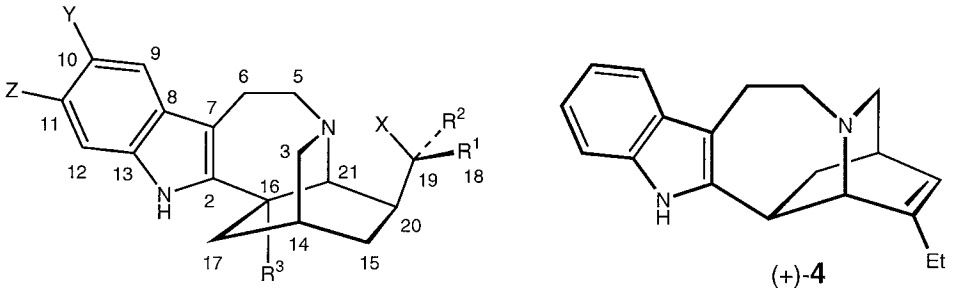


Fig. 1. *General skeleton and biogenetic numbering of the* Iboga *alkaloids and structure of (+)-catharanthine* (**4**)

Table 1. *Some Representative* Iboga *Alkaloids* (the substituents are defined in *Fig. 1*)

Name	Compound	R^1	R^2	R^3	X	Y	Z
Ibogamine	**2**	H	Me	H	H	H	H
Ibogaine	**1**	H	Me	H	H	OMe	H
Tabernanthine	**5**	H	Me	H	H	H	OMe
Ibogaline	**6**	H	Me	H	H	OMe	OMe
19-Hydroxyibogamine	**7**	H	Me	H	OH	H	H
Iboxygaine	**8**	Me	H	H	OH	OMe	H
19-Epiiboxygaine	**9**	H	Me	H	OH	OMe	H
Coronaridine	**3**	H	Me	COOMe	H	H	H
Voacangine	**10**	H	Me	COOMe	H	OMe	H
Isovoacangine	**11**	H	Me	COOMe	H	H	OMe
Conopharyngine	**12**	H	Me	COOMe	H	OMe	OMe
Heyneanine	**13**	Me	H	COOMe	OH	H	H
19-Epiheyneanine	**14**	H	Me	COOMe	OH	H	H
Voacristine	**15**	Me	H	COOMe	OH	OMe	H
19-Epivoacristine	**16**	H	Me	COOMe	OH	OMe	H
Isovoacristine	**17**	Me	H	COOMe	OH	H	OMe

coronaridine (**3**), and catharanthine (**4**) (*Fig. 1*) [9]. In addition, the reported syntheses lack the flexibility required to provide access to the more elaborate representatives, which might display interesting pharmacological profiles, and which conceivably play an important role in the catabolic degradation pathways of **1**, **2**, or **3**.

2. Substitution Patterns within the *Iboga* Alkaloids and Retrosynthesis. – An inspection of the structures of some representative *Iboga* alkaloids (*Table 1*) reveals recurring patterns that should be considered for a generally applicable synthetic approach:

a) The indole part of the structure shows variable oxidation levels. As selective ring-A-oxidation procedures for 2,3-disubstituted indole derivatives are generally not available (presumably apart from microbiological methods), a convergent approach is warranted that incorporates an indole unit or a precursor thereof that is already endowed with the correct substitution pattern in ring A.

b) The C_2 side chain at C(20) is invariably oriented *syn* to the bridgehead N-atom, whereas the relative configuration at C(19) varies, and in some cases it is not even known. A neat solution for these two issues consists in an intramolecular cycloaddition

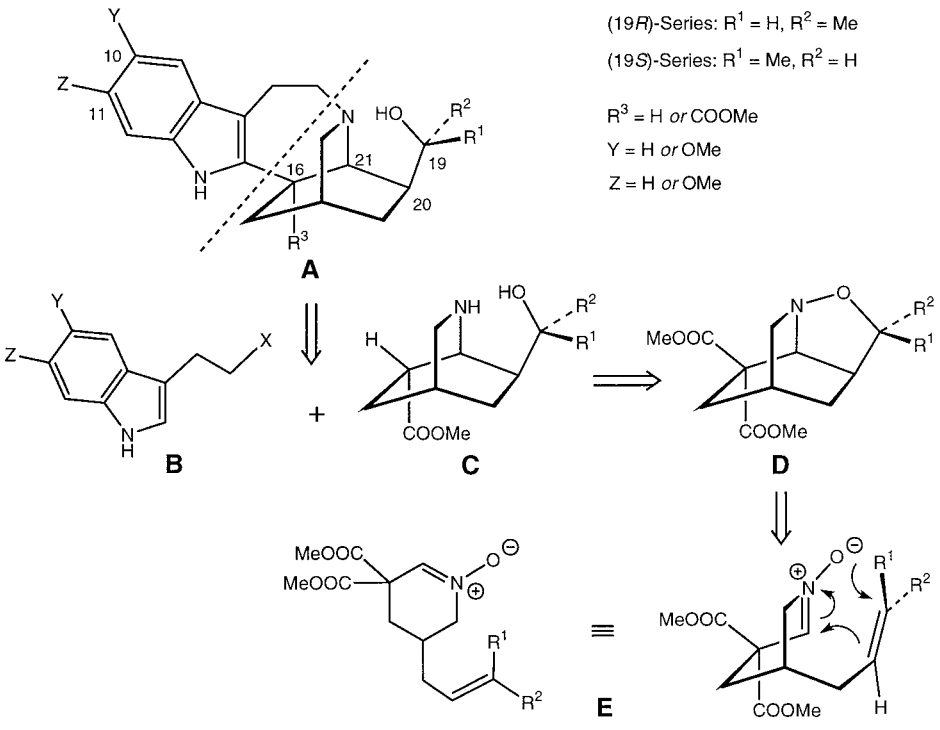
reaction between a nitrone unit and an olefinic C=C bond with defined (*E/Z*)-configuration (see below; *Scheme 1*).

c) As efficient methods are known for passing from the 22-nor series ($R^3 = H$) to the methoxycarbonyl derivatives ($R^3 = COOMe$) and *vice versa* [9], the substitution pattern at C(16) of the envisaged target is of little concern in a retrosynthetic analysis.

d) A peculiar feature of the *Iboga*-alkaloid family is that members of both antipodal series occur in nature [10]. A case at hand is *Catharanthus roseus*, which, during a single growth period, produces both (−)-coronaridine (**3**) and (+)-catharanthine (**4**) (*Fig. 1*) of opposite absolute configuration [11]. An adequate procedure to gain access to both antipodal series would consist in an optical resolution of some advanced intermediate on the route to the aliphatic sub-unit.

A retrosynthetic plan that emerged from the above considerations is shown in *Scheme 1*. Disconnection of the generalized target **A** along the dashed line leads to an appropriately substituted 3-ethylindole building block **B** and to the isoquinuclidine core **C**. The latter should be readily available from the isoxazolidine precursor **D** *via* reductive cleavage of the N−O bond and decarboxylation of the substituted malonate unit. Intermediate **D**, which contains the entire configurational information of target **A**, should be constructed *via* an intramolecular nitrone-olefin [2+3]-cycloaddition reaction of precursor **E**. The *supra-supra* nature of this thermally allowed process assures that the configuration at C(19) relative to the remaining, interdependent

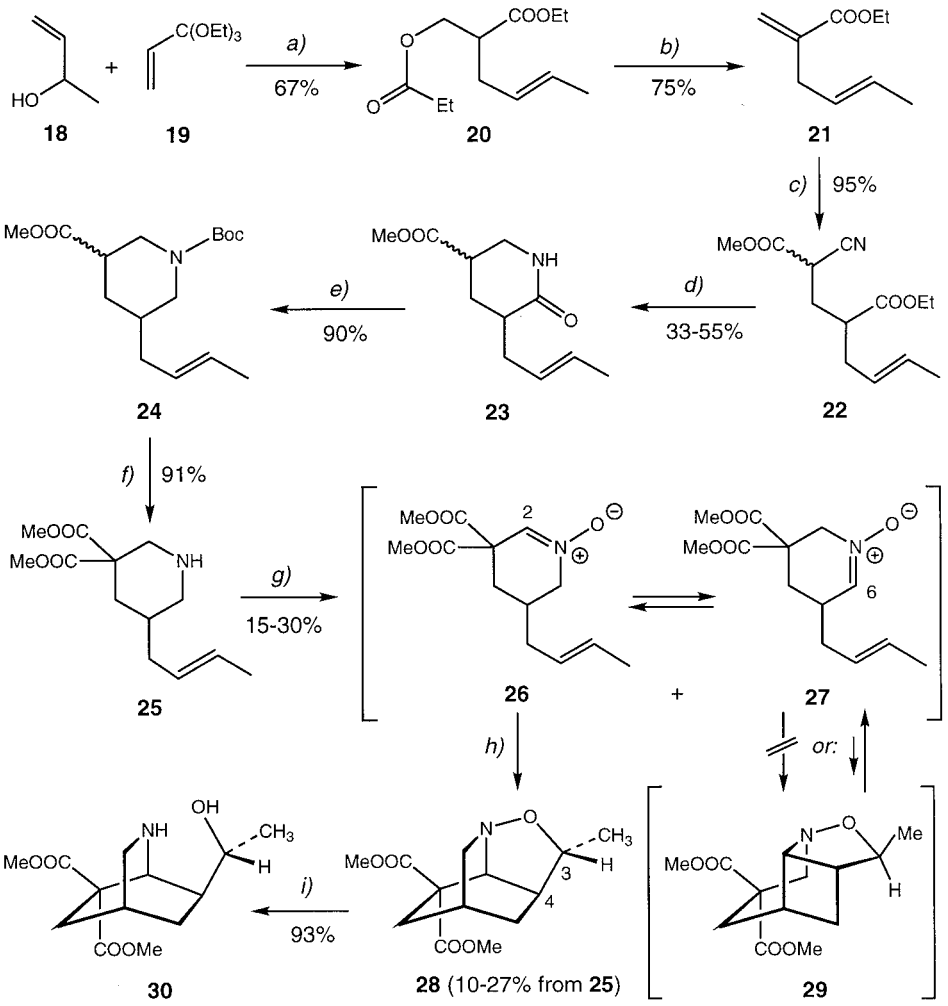
Scheme 1



asymmetric centers of the target **D** can readily be established at an early stage of the synthesis simply by selecting the appropriate geometry of the olefinic C=C bond of **E**.

3. Results and Discussion. – After many unsuccessful attempts to assemble the crucial isoxazolidine **28**, the route shown in *Scheme 2* finally led to the desired target. The *Claisen*-rearrangement modification of the original *Johnson* procedure [12] by *Saucy et al.* [13], applied to but-3-en-2-ol (**18**) and triethyl orthoacrylate (**19**) [14] in the

Scheme 2



a) 1.5 Equiv. EtCOOH, toluene, 19 h reflux. *b*) DBU, benzene, 48 h reflux. *c*) 1. Methyl cyanoacetate, lithium hexamethyldisilazide (LiHMDS), THF, 30 min, 0°; 2. **21**, 25°, 16 h. *d*) $NaBH_4$, $CoCl_2$, (*t*-Bu)$NH_2 \cdot BH_3$, MeOH, 25°. *e*) 1. Me_3OBF_4, CH_2Cl_2, 25°; 2. $NaBH_4$, MeOH, 24 h, 25°; 3. $(Boc)_2O$, Et_3N, CH_2Cl_2, 12 h, 25°. *f*) 1. lithium diisopropylamide (LDA), THF, ClCOOMe, THF, – 70° to 25°, 1 h, 25°; 2. TFA, CH_2Cl_2, 24 h, 25°. *g*) Na_2WO_4, H_2O_2, MeOH, 45 min, 25°. *h*) Toluene, 1 h reflux. *i*) Zn, AcOH/MeOH 4 : 1, 1 h reflux.

presence of 1.5 equiv. of EtCOOH, furnished propionate **20** in 67% yield[2]). The ^{13}C-NMR chemical shift of the olefinic Me group (17.8 ppm) and a coupling constant of 15.1 Hz between the olefinic H-atoms in the ^{1}H-NMR spectrum of **20** are consistent with the expected (*E*)-geometry of the newly formed C=C bond [15]. Treatment of **20** with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in boiling benzene for 2 days furnished *Michael* acceptor **21**, to which the lithium enolate of methyl cyanoacetate was added to give **22** in excellent yield as a 5 : 4 mixture of two diastereoisomers. The formation of a mixture at this step of the synthesis has no deleterious effect on the outcome of the chosen approach, because one of the two stereogenic centers will be destroyed two steps later.

The ensuing chemoselective reduction of the CN group of **22** presented a real challenge, and, of the many procedures tried, only the method of *Ganem* and *Osby* [16] led to acceptable results. Under the employed reaction and workup conditions, the intermediate aminodiester cyclized *in situ* to lactam **23** in 33–55% overall yield. A further chemoselective reduction according to *Borch*'s protocol [17], followed by protection of the resulting secondary amine, furnished the piperidine derivative **24** in excellent yield. The transformation of this intermediate into the substituted dimethyl malonate **25** was uneventful, but the following oxidation to nitrone **26** proved to be a tricky task. Of several procedures recommended for this transformation, such as H_2O_2/SeO_2 (cat.) [18], (*t*-Bu)OOH/$VO(C_5H_7O_2)_2$ [19], O_2/$Cu(OAc)_2$ [20], 2-benzenesulfonyl-3-phenyloxaziridine [21], and H_2O_2/Na_2WO_4 [22], only the last method furnished sizeable amounts (15–30% yield) of the two regioisomeric nitrones **26** and **27**. Their marked instability prevented separation and purification, but their presence is indicated in the ^{1}H- and ^{13}C-NMR spectra of the crude mixture (*s* at 7.3 ppm and *d* at 137.9 ppm for *H*–C(2) and C(2) of **26**, and *d* at 7.2 ppm and *d* at 132.1 ppm for *H*–C(6) and C(6) of **27**, resp.). To avoid dimerization and polymerization, these intermediates were dissolved immediately in toluene, and after 1 h reflux **26** and **27** could no longer be detected in the mixture, and the desired target **28** could be isolated in pure state after chromatographic purification.

The spectroscopic parameters of this compound are fully consistent with the expected structure **28**. The ^{1}H-NMR spectrum is most suggestive, as it lends itself to first-order interpretation (see *Fig. 2* and *Table 2*). The relative configuration at C(3) of this caged molecule is based on the observation that the corresponding methine proton appears as a neat *quadruplet* centred at 4.07 ppm ($J = 6.3$ Hz) due to the presence of the adjacent Me group. The additional vicinal coupling with *H*–C(4) amounts to less than 0.5 Hz, pointing to a dihedral angle of *ca.* 90° between the two H-atoms, which can only be realized if the relative configuration of **28** is (3*R**,4*S**)[3]). The crucial issue whether these two H-atoms are indeed positioned on two *adjacent* C-atoms could be settled by the observation of a coupling constant of 4.1 Hz between *H*–C(3) and *H*–C(4) in the reduced, ring-opened derivative **30**, which is devoid of some of the internal-rotation restrictions imposed by the tricyclic nature of compound **28**.

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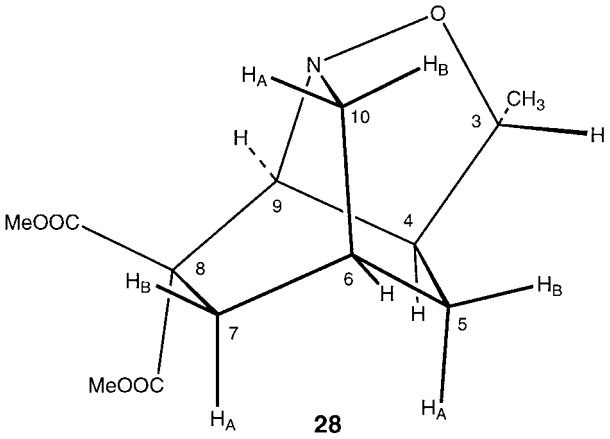
[2]) Utilization of merely catalytic amounts of EtCOOH required much longer reaction times and led to extensive decomposition of the expected product (**20**; OEt in place of O(C=O)Et).

[3]) An inspection of *Dreiding* models and a semi-empirical calculation on the PM3 level predict a dihedral angle of 95° between *H*–C(3) and *H*–C(4) for **28**. The corresponding value for the 3-epi-diastereoisomer was calculated to amount to 38°, which would be expected to lead to a coupling constant of at least 4 Hz between the two H-substituents in question.



Dihedral Angles		^3J [Hz]
H–C(3)/H–C(4)	95°	< 0.5
H–C(4)/H–C(9):	50°	3.3
H–C(4)/H_A–C(5):	17°	9.5
H–C(4)/H_B–C(5):	100°	< 0.5
H_A–C(5)/H–C(6):	68°	1.7
H_B–C(5)H–C(6):	49°	*ca.* 4.5
H–C(6)/H_A–C(7):	56°	2.9
H–C(6)/H_B–C(7):	59°	2.6
H–C(6)/H_A–C(10):	69°	1.3
H–C(6)/H_B–C(10):	50°	2.9

Fig. 2. *Geometry and pertinent dihedral angles of dicarboxylate* **28** *as calculated by PM3, and observed vicinal coupling constants* (^{1}H-NMR, 500 MHz, $CDCl_3$)

Table 2. *Chemical Shifts* (δ in ppm from $SiMe_4$) *and Coupling Constants* [Hz] *Observed in the* ^{1}*H-NMR Spectrum* (500 MHz in $CDCl_3$) *of* **28**

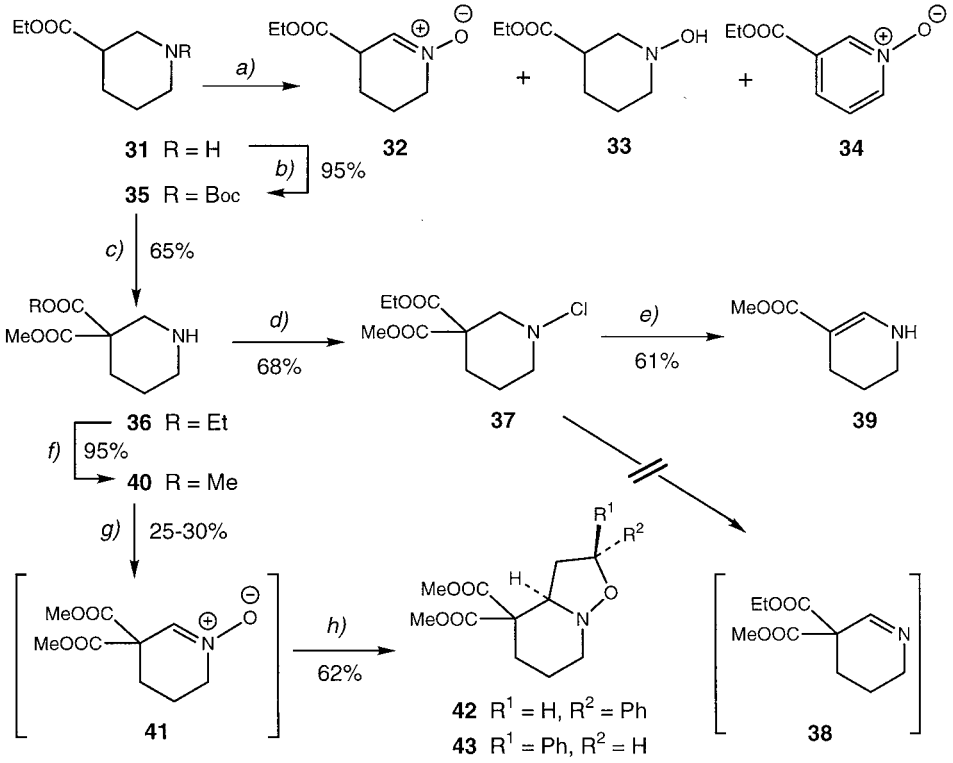
	δ [ppm]	H–C(3)	H–C(4)	H_A–C(5)	H_B–C(5)	H–C(6)	H_A–C(7)	H_B–C(7)	H–C(9)	H_A–C(10)	H_B–C(10)
H–C(3)	4.07	–	< 0.5								
H–C(4)	2.57	< 0.5	–	9.5	< 0.5				3.3		
H_A–C(5)	1.85		9.5	–	13.5	1.7				2.9	
H_B–C(5)	1.52		< 0.5	13.5	–	*ca.* 4.5		2.6			
H–C(6)	1.78			1.7	*ca.* 4.5	–	2.9	2.6		1.3	2.9
H_A–C(7)	2.61					2.9	–	13.9			2.9
H_B–C(7)	1.62				2.6	2.6	13.9	–			
H–C(9)	3.72		3.3						–		
H_A–C(10)	3.32			2.9		1.3				–	14.5
H_B–C(10)	2.87					2.9	2.9			14.5	–

That the yield of **28** from **25** is almost the same as for the process **25** → **26** + **27** can be considered as an indication for a *Behrend* equilibration, which takes place between the regioisomers **26** and **27** under the reaction conditions employed to obtain **28** [23]. At the same time, this observation suggests that the conceivable reaction of **27** to the putative cycloaddition product **29** is either reversible or does not occur at all. Evidently, the isolated product **28** can be considered a thermodynamic sink for the ensemble represented by compounds **26**–**29**.

We had some success in grafting 3-ethylindolyl units onto the crucial intermediate **30** [1], and we hope to reach our goal of a novel synthetic approach to naturally occurring *Iboga* alkaloids in due time.

4. Appendix: Model Studies. – To find the best procedure for the oxidation of **25** to the corresponding nitrones **26** and **27**, commercially available ethyl piperidine-3-carboxylate (**31**; *Scheme 3*) was chosen as a model substrate. However, under a variety of recommended conditions, little if any of the nitrone **32** was produced. Generally, the

Scheme 3



a) For various oxidation procedures, see [1]. *b*) $(Boc)_2O$, Et_3N, CH_2Cl_2, 12 h, 25°. *c*) 1. LDA, THF, ClCOOMe, THF, 1 h, 25°, 2. TFA, CH_2Cl_2, 24 h, 25°. *d*) *N*-Chlorosuccinimide (NCS), CH_2Cl_2, 0°, then 12 h, 25°. *e*) NaOMe, MeOH, 1 h reflux. *f*) NaOMe, MeOH, 3 d, 25°. *g*) Na_2WO_4, H_2O_2, MeOH, 30 min, 25°; *h*) Styrene, toluene, 3 h reflux.

major components of the complex mixtures proved to be *N*-hydroxy derivative **33** and the over-oxidized ethyl nicotinate *N*-oxide (**34**). To avoid the formation of the latter, the model substrate was modified to the readily prepared dicarboxylates **36** and **40**. Under the most favorable oxidation conditions, the corresponding nitrone **41** could be obtained as a single regioisomer in 25–30% yield. This compound reacted with styrene to give the expected [3+2] cycloaddition product as a 6:1 mixture of two diastereoisomers. The major component was obtained in crystalline form, and an X-ray analysis showed it to possess structure **42** (*Fig. 3*)[4]). The constitution and relative configuration of **42** reflect the expected regioselective orientation of the two components in the *exo*-transition state, leading to observed major product, namely that the Ph substituent of the olefin component is positioned next to the O-terminus of the nitrone unit (for precedents, see [24]).

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[4]) We thank Dr. *B. Schweizer*, Laboratory for Organic Chemistry (ETH-Zürich), for the determination of this X-ray crystal structure.

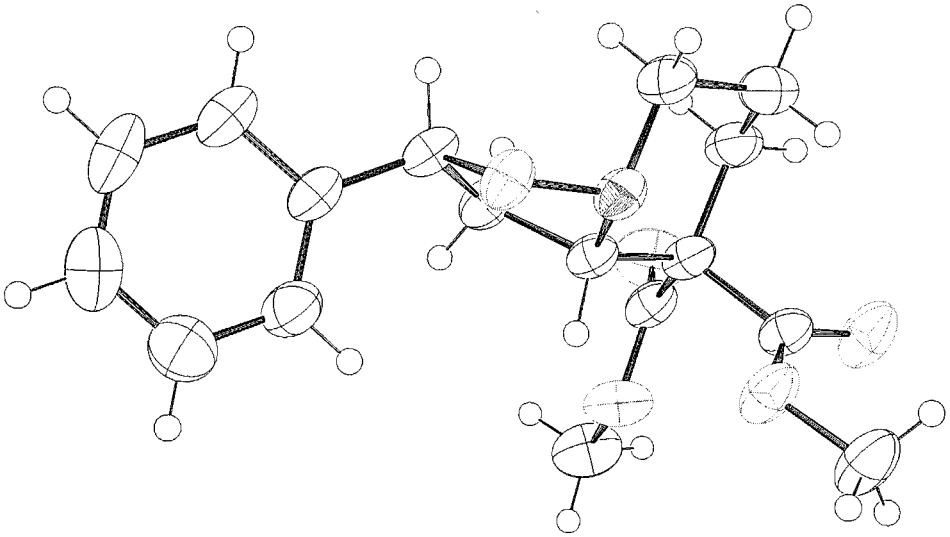

Fig. 3. *ORTEP View of* **42**. Arbitrary atom numbering; the thermal ellipsoids are scaled at the 30% level.

As an alternative to the direct oxidation of **36** to **41**, the route *via* an imine intermediate, **38**, was also investigated. However, all attempts to prepare **38** failed. Treatment of the readily accessible *N*-chloro derivative **37** with base, for instance, led either to no observable reaction or else to the enamino ester **39** under more forcing conditions.

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Experimental Part

General. See [25]. All new chiral compounds were obtained as racemic mixtures.

*Ethyl (*E*)-2-[(Propionyloxy)methyl]hex-4-enoate* (**20**). A mixture of 46.2 g (0.27 mol) of *triethyl orthoacrylate* (**19**) [14], 19.5 g (0.27 mol) of rac-*but-3-en-2-ol* (**18**; *Fluka*, *purum*), and 5.4 g (0.07 mol) of propionic acid (*Fluka*, *puriss.*) in 200 ml of toluene was heated at reflux for 24 h. After 2, 3, 4, and 5 h, additional portions of 6 g (0.08 mol) of propionic acid (total 29.4 g (0.4 mol)) were added. The crude product obtained after workup with Et_2O/sat. aq. $NaHCO_3$ soln. was chromatographed (hexane/Et_2O 10:1) to yield 41.3 g (0.18 mol, 67%) of pure **20**. Colorless oil. IR ($CHCl_3$): 3020, 2980, 2940, 1738, 1727, 1461, 1378, 1350, 1275, 1176, 1082, 1020, 965. ^{1}H-NMR (400 MHz, $CDCl_3$): 5.50 (*dqt*, J = 15.1, 6.3, 1.2, 1 H); 5.35 (*dtq*, J = 15.1, 7.0, 1.6, 1 H); 4.22 (*dd*, J = 11.0, 6.0, 1 H); 4.20 (*dd*, J = 11.0, 7.2, 1 H); 4.16 (*qd*, J = 7.1, 1.0, 1 H); 2.72 (*qd*, J = 7.1, 6.0, 1 H); 2.31 (*q*, J = 7.6, 2 H); 2.37–2.19 (*m*, 2 H); 1.64 (*dq*, J = 6.3, 1.6, 3 H); 1.25 (*t*, J = 7.1, 3 H); 1.12 (*t*, J = 7.6, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 174.1 (*s*); 173.0 (*s*); 128.3 (*d*); 126.5 (*d*); 63.9 (*t*); 60.5 (*t*); 44.9 (*d*); 31.8 (*t*); 27.4 (*t*); 17.8 (*q*); 14.2 (*q*); 9.0 (*q*). MS (EI): 183 (37, $[M-45]^+$), 155 (15), 154 (82), 125 (22), 109 (68), 81 (100), 57 (58), 55 (13).

*Ethyl (*E*)-2-Methylidenehex-4-enoate* (**21**). To a soln. of 41.3 g (0.19 mol) of **20** in 250 ml of benzene were added 33.8 g (0.22 mol) of DBU (*Fluka*, *puriss.*). After 48 h reflux, the mixture was poured on cold sat. aq. NH_4Cl soln. and extracted with Et_2O (3×). The combined org. extracts were dried, evaporated, and chromatographed (hexane/Et_2O 10:1) to yield 21.4 g (0.14 mol, 75%) of **21** with some impurities. Colorless oil. IR ($CHCl_3$): 3010, 2980, 2960, 2930, 1710, 1630, 1447, 1370, 1301, 1265, 1255, 1144, 1026, 969, 951. ^{1}H-NMR (400 MHz, $CDCl_3$): 6.14 (*m*, 1 H); 5.55–5.4 (*m*, 3 H); 4.20 (*q*, J = 7.1, 2 H); 2.98 (*m*, 2 H); 1.68 (*dm*, J = 5.8, 3 H); 1.30 (*t*, J = 7.1, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 167.1 (*s*); 140.1 (*s*); 127.6 (*d*); 124.6 (*d*); 115.6 (*t*); 60.6

(*t*); 34.7 (*t*); 17.9 (*q*); 14.9 (*q*). EI-MS: 154 (38, M^+), 139 (41), 127 (37), 126 (86), 125 (41), 111 (100), 109 (39), 81 (26), 79 (17), 57 (40), 55 (26).

*Methyl (*E*)-2-cyano-4-(ethoxycarbonyl)oct-6-enoate* (**22**). To a soln. of 1.78 g (18 mmol) of methyl cyanoacetate (*Fluka*, *puriss.*) in 35 ml of THF were added 18 ml (18 mmol) of a 1M soln. of lithium hexamethyldisilazide (*Fluka*, *pract.*) in THF at 0°. After stirring at 25° for 30 min, a soln. of 2.31 g (15 mmol) of **21** in 15 ml of THF was added. Stirring at 25° was continued for 16 h. The mixture was poured on cold satd. aq. NH_4Cl-soln. and extracted with ether (3×). The combined org. extracts were dried, evaporated, and chromatographed (hexane/Et_2O 5:1) to yield 3.16 g (12.5 mmol, 83%) of **22** as a 57:43 mixture of two diastereoisomers, which were not separated. Colorless oil. IR ($CHCl_3$): 3030, 2980, 2960, 2940, 2250, 1751, 1726, 1438, 1380, 1265, 1248, 1184, 1029, 968, 910. ^{1}H-NMR (400 MHz, $CDCl_3$): 5.52 (*m*, 1 H); 5.33 (*m*, 1 H); 4.14 (*m*, 2 H); 3.82 (*s*, 1.71 H); 3.81 (*s*, 1.29 H); 3.68 (*dd*, *J* = 10.8, 5.1, 0.57 H): 3.62 (*dd*, *J* = 8.0, 6.8, 0.43 H); 2.69 (*dddd*, *J* = 10.8, 6.9, 6.5, 3.5, 0.57 H); 2.61 (*dtd*, *J* = 8.9, 6.6, 5.5, 0.43 H); 2.4–2.2 (*m*, 3 H); 2.13 (*ddd*, *J* = 14.1, 7.7, 5.5, 0.43 H); 1.99 (*ddd*, *J* = 14.1, 10.8, 3.5, 0.57 H); 1.66 (*dd*, *J* = 6.5, 1.2, 3 H); 1.28 (*t*, *J* = 7.0, 1.71 H); 1.27 (*t*, *J* = 7.0, 1.29 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 173.7 (2*s*); 166.2 (2*s*); 129.0 (2*d*); 126.2 (*d*); 126.1 (*d*); 116.0 (2*s*); 60.9 (2*t*); 53.5 (2*q*); 42.5 (*d*); 42.4 (*d*); 35.7 (*d*); 35.5 (*t*); 35.1 (*d*); 35.0 (*t*); 30.6 (2*t*); 17.8 (2*q*); 14.2 (2*q*). EI-MS: 253 (1, M^+), 209 (28), 181 (11), 180 (100), 179 (37), 176 (53), 153 (61), 148 (31), 141 (15), 140 (20), 138 (41), 121 (26), 120 (37), 101 (18), 81 (71), 79 (17), 57 (11), 55 (12).

*Methyl (*E*)-3-(But-2-enyl)-2-oxopiperidine-5-carboxylate* (**23**). To a soln. of 7.73 g (59.5 mmol) of anh. $CoCl_2$ in 150 ml of MeOH, 7.56 g (200 mmol) of $NaBH_4$ at 0° were added slowly. After 10 min, 8.70 g (100 mmol) of *t*-$BuNH_2 \cdot BH_3$ (*Fluka*, *pract.*) and 12.41 g (49 mmol) of **22** were added. The resulting mixture was stirred at 25° for 16 h and then refluxed for 1 h. The cooled mixture was treated with an excess of sat. aq. NH_4Cl soln. and filtered through *Celite*™. The filtrate was extracted with CH_2Cl_2, and the residue was suspended in 25% aq. NH_3 soln. and stirred for 10 min. Then, the mixture was extracted with CH_2Cl_2. The combined org. extracts were dried ($MgSO_4$) and evaporated. The residue was chromatographed (AcOEt) to give 5.60 g (26.5 mmol, 54%) of **23**, consisting of a 57:43 mixture of two diastereoisomers, which were not separated. Colorless needles. M.p. 67° (hexane). IR ($CHCl_3$): 3410, 3030, 3000, 2950, 2920, 1732, 1659, 1487, 1461, 1437, 1378, 967. ^{1}H-NMR (400 MHz, $CDCl_3$): 6.35 (br. *s*, 1 H); 5.51 (*m*, 1 H); 5.38 (*m*, 1 H); 3.73 (*s*, 1.71 H); 3.72 (*s*, 1.29 H); 3.6–3.4 (*m*, 2 H); 2.82 (*m*, 1 H); 2.54 (*m*, 1 H); 2.44 (*dtd*, *J* = 9.1, 6.7, 4.0, 0.57 H); 2.33 (*m*, 0.43 H); 2.3–2.2 (*m*, 1.86 H); 2.13 (*dddd*, *J* = 14.5, 8.1, 6.5, 0.7, 0.57 H); 1.91 (*dddd*, *J* = 13.8, 7.0, 4.4, 0.8, 0.57 H); 1.66 (*dq*, *J* = 6.3, 1.1, 1.71 H); 1.67 (*dq*, *J* = 6.3, 1.1, 1.29 H). ^{13}C-NMR (100 MHz, $CDCl_3$): signals assigned to the major compound (3,5-*cis*-disubstituted): 174.1 (*s*); 173.1 (*s*); 128.09 (*d*); 127.9 (*d*); 52.2 (*q*); 42.2 (*t*); 35.6 (*d*); 36.4 (*d*); 34.8 (*t*), 27.4 (*t*); 18.0 (*q*); signals assigned to the minor compound (3,5-*trans*-disubstituted): 173.4 (*s*); 172.9 (*s*); 128.13 (*d*); 127.7 (*d*); 52.1 (*q*); 43.6 (*t*); 40.4 (*d*); 39.3 (*d*); 34.2 (*t*), 29.6 (*t*); 18.0 (*q*). EI-MS: 211 (18, M^+), 196 (33), 180 (14), 157 (85), 152 (26), 124 (19), 110 (29), 101 (23), 98 (100), 96 (30), 95 (25), 81 (19), 79 (10), 55 (30).

*Methyl (*E*)-3-(But-2-enyl)-1-(*tert*-butoxycarbonyl)piperidine-5-carboxylate* (**24**). To a soln. of 1.55 g (7.35 mmol) of **23** in 60 ml of CH_2Cl_2 were added 1.63 g (11 mmol) of trimethyloxonium tetrafluoroborate (*Fluka*, *purum*) at 0°. After stirring for 16 h, the solvent was evaporated *in vacuo*, and the residue was dissolved in MeOH. After addition of 0.56 g (14.7 mmol) of $NaBH_4$, the mixture was stirred at 25° for 4 h. The crude product (1.3 g) obtained after workup with Et_2O/sat. aq. $NaHCO_3$ soln. was taken up in 40 ml of CH_2Cl_2. After addition of 0.52 g (8 mmol) of Et_3N and of 1.74 g (8 mmol) of $(Boc)_2O$ (*Fluka*, *purum*), the mixture was stirred at 25° for 18 h. The mixture was poured on cold sat. aq. NH_4Cl soln. and extracted with Et_2O (3×). The combined org. extracts were dried, evaporated, and chromatographed (hexane/AcOEt 5:1) to yield 1.97 g (6.6 mmol, 90%) of **24** as a 57:43 mixture of two diastereoisomers. For the NMR spectra, pure samples of the *cis*- and the *trans*-isomers were separated by chromatography (hexane/AcOEt 5:1) of a small sample of this mixture. Colorless oil. IR ($CHCl_3$): 3030, 3000, 2980, 2950, 2930, 2855, 1730, 1683, 1476, 1462, 1425, 1366, 1267, 1251, 1166, 1149, 966, 882, 857. EI-MS: 241 (32, $[M-56]^+$), 224 (11), 223 (17), 197 (18), 196 (17), 192 (17), 182 (14), 155 (12), 154 (100), 142 (19), 141 (17), 138 (11), 128 (12), 82 (12), 57 (33).

cis-*Isomer* (=(3*RS*,5*SR*)): ^{1}H-NMR (300 MHz, C_6D_6, 70°): 5.3–5.2 (*m*, 2 H); 4.56 (*m*, 1 H); 4.20 (*m*, 1 H); 3.31 (*s*, 3 H); 2.67 (*dd*, *J* = 12.8, 11.8, 1 H); 2.35 (*tt*, *J* = 12.1, 4.0, 1 H); 2.04–1.95 (*m*, 2 H, including 1.99 (*q*, *J* = 12.1, 1 H)); 1.72–1.61 (*m*, 2 H); 1.51 (*m*, 3 H); 1.44 (*s*, 9 H); 1.33–1.22 (*m*, 1 H); 1.03 (*q*, *J* = 12.1, 1 H). ^{13}C-NMR (75 MHz, C_6D_6, 70°): 173.3 (*s*); 153.7 (*s*); 128.5 (*d*); 127.1 (*d*); 79.3 (*s*); 50.9 (*q*); 49.6 (*t*); 46.3 (*t*); 42.1 (*d*); 37.0 (*t*); 35.9 (*d*); 34.3 (*t*); 28.4 (3*q*); 17.6 (*q*).

trans-*Isomer* (=(3*RS*,5*RS*)): ^{1}H-NMR (300 MHz, C_6D_6, 70°): 5.4–5.27 (*m*, 2 H); 3.76 (br. *dd*, 13.1, 6.2, 1 H); 3.46–3.38 (*m*, 2 H); 3.36 (*s*, 3 H); 2.89 (*dd*, *J* = 13.1, 6.8, 1 H); 2.38 (*m*, 1 H); 1.87–1.66 (*m*, 4 H); 1.54 (*m*, 3 H); 1.45 (*s*, 9 H); 1.31–1.23 (*m*, 1 H). ^{13}C-NMR (75 MHz, C_6D_6, 70°): 173.5 (*s*); 153.8 (*s*); 129.2 (*d*); 126.9 (*d*); 79.0 (*s*); 51.0 (*q*); 48.4 (*t*); 45.8 (*t*); 38.6 (*d*); 35.7 (*t*); 33.1 (*d*); 32.0 (*t*); 28.4 (3*q*); 17.7 (*q*).

*Dimethyl (*E*)-3-(But-2-enyl)piperidine-5,5-dicarboxylate* (**25**). To a soln. of 0.42 g (4.2 mmol) of (i-Pr)$_2$NH (*Fluka*, *puriss.*) in 25 ml of THF were added 2.63 ml of an 1.6M soln. of BuLi in hexane. After stirring at 0° for 10 min, the soln. was cooled to −70°; then, a soln. of 0.83 g (2.8 mmol) of **24** in 5 ml of THF was added. The cooling bath was removed, and stirring was continued for 1 h at 25°. The mixture was again cooled to −70°, and 0.256 g (2.8 mmol) of methyl chloroformate (*Fluka*, *puriss.*) were added slowly. The cooling bath was removed, and stirring was continued for 1 h at 25°. The mixture was poured on cold sat. aq. NH_4Cl soln. and extracted with Et_2O (3×). The combined org. extracts were dried, evaporated, and chromatographed (hexane/AcOEt 5:1) to yield 0.91 g of a yellowish oil, which was dissolved in 25 ml of CH_2Cl_2. At 0°, 0.40 g (3.53 mmol) of CF_3COOH were added slowly, and the resulting mixture was stirred at 25° for 24 h. The mixture was worked up with sat. aq. Na_2CO_3 soln. and CH_2Cl_2 to yield 0.959 g (2.56 mmol, 91%) of **25**. Yellow oil. IR ($CHCl_3$): 3340, 3000, 2950, 2920, 2855, 1725, 1453, 1434, 1262, 1150, 1104, 967, 879, 867. ^{1}H-NMR (400 MHz, $CDCl_3$): 5.47–5.30 (*m*, 2 H); 3.78 (*s*, 3 H); 3.70 (*s*, 3 H); 3.01 (*dm*, *J* = 13.1, 1 H); 2.73 (*d*, *J* = 13.2, 1 H); 2.42 (*dq*, *J* = 13.0, 2.4, 1 H); 2.17 (*dd*, *J* = 13.1, 11.1, 1 H); 1.94 (br. *s*, 1 H); 1.86 (*tm*, *J* = 6.6, 1 H); 1.65 (*ddm*, *J* = 6.0, 1.2, 3 H); 1.52 (*dd*, *J* = 13.0, 12.5, 1 H); 1.46–1.38 (*m*, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 171.4 (*s*); 171.2 (*s*); 128.0 (*d*); 127.0 (*d*); 55.0 (*s*); 52.7 (*q*); 52.6 (*q*); 51.4 (*t*); 50.8 (*t*); 37.3 (*t*); 36.1 (*t*); 34.1 (*d*); 17.9 (*q*). HETCOR: 128.0/5.35; 127.0/5.41; 52.7/3.78; 52.6/3.70; 51.4/3.01 and 2.17; 50.8/3.61 and 2.73; 37.3/1.86; 36.1/2.42 and 1.52; 34.1/1.42; 17.9/1.65. EI-MS: 255 (26, M^+), 224 (15), 213 (13), 212 (100), 199 (12), 196 (32), 145 (40), 140 (14), 113 (52), 82 (20).

*Dimethyl (3*RS*,4*SR*,6*RS*)-3-Methyl-2-oxa-1-azatricyclo[4.3.1.0^{4,10}]decane-8,8-dicarboxylate* (**28**). To a soln. of 130 mg (0.5 mmol) of **25** in 10 ml of MeOH was added a soln. of 15 mg (0.05 mmol) of Na_2WO_4 (*Fluka*, *puriss.*) and 170 mg (1.5 mmol) of 30% aq. H_2O_2 soln. (*Fluka*, *puriss.*) at 0°. After stirring for 45 min at 25°, the excess H_2O_2 was destroyed by adding 1 ml of 10% aq. $NaHSO_3$ soln. After addition of 10 ml of toluene, MeOH was removed *in vacuo* (40°, 80 Torr), and the remaining toluene soln. was extracted with aq. 0.5M HCl soln. The aq. phase was extracted once with toluene and with CH_2Cl_2 (3×). The combined org. extracts were dried ($MgSO_4$) and evaporated. A soln. of this material and of 2 mg of *bis*[5-(*tert*-butyl)-4-hydroxy-2-methylphenyl] sulfide (*Aldrich*, *puriss.*) in 20 ml of toluene was refluxed for 1 h, evaporated, and chromatographed (pentane/AcOEt 2:1) to yield 37 mg (0.14 mmol, 27%) of **28.** Yellow oil. IR ($CHCl_3$): 3010, 2950, 2930, 2870, 1734, 1445, 1434, 1380, 1265, 1239, 1178, 1108, 968. ^{1}H-NMR (500 MHz, $CDCl_3$): 4.07 (*q*, *J* = 6.3, 1 H); 3.79 (*s*, 3 H); 3.75 (*s*, 3 H); 3.72 (*d*, *J* = 3.4, 1 H); 3.32 (*ddd*, *J* = 14.5, 2.9, 1.3, 1 H); 2.87 (*dt*, *J* = 14.5, 2.9, 1 H); 2.61 (*dt*, *J* = 13.9, 3.1, 1 H); 2.57 (*dd*, *J* = 9.5, 3.4, 1 H); 1.85 (*dddd*, *J* = 13.5, 9.5, 2.9, 1.7, 1 H); 1.78 (br. *s*, 1 H); 1.62 (*dt*, *J* = 13.9, 2.6, 1 H); 1.52 (br. *dt*, *J* = 13.5, 3.6, 1 H); 1.23 (*d*, *J* = 6.3, 3 H). ^{13}C-NMR (125 MHz, $CDCl_3$): 171.1 (*s*); 170.8 (*s*); 86.2 (*d*); 59.4 (*t*); 59.2 (*d*); 53.5 (*q*); 52.9 (*q*); 51.1 (*s*); 40.3 (*d*); 34.3 (*t*); 32.7 (*t*); 22.0 (*d*); 20.8 (*q*). EI-MS: 269 (61, M^+), 254 (11), 252 (34), 210 (26), 192 (11), 154 (15), 138 (18), 125 (100), 124 (38), 113 (16), 108 (16), 107 (34), 81 (16).

*Dimethyl (3*RS*,4*SR*,6*RS*)-7-(1-Hydroxyethyl)bicyclo[2.2.2]octane-6,6-dicarboxylate* (**30**). Activated Zn powder (*Fluka*, *p.a.*) was washed successively with 2N HCl, EtOH, and Et_2O and was then dried under high vacuum at 25° overnight. To a soln. of 217 mg (0.81 mmol) of **28** in 5 ml of AcOH/MeOH 4:1 were added 310 mg (4.74 mmol) of activated Zn powder. After stirring for 1 h at 60°, the mixture was evaporated under reduced pressure, and the residue was taken up in CH_2Cl_2. The mixture was washed with 15% aq. KOH soln. and extracted twice with CH_2Cl_2. The combined org. extracts were dried ($MgSO_4$), filtered, and evaporated to yield 204 mg (93%) of **30**. An anal. sample was obtained by chromatography on silica (AcOEt/EtOH/$EtNH_2$ 100:10:1). Yellowish oil. IR ($CHCl_3$): 3370, 3040, 3000, 2950, 2870, 1728, 1456, 1385, 1252, 1180, 1146, 1120, 1082, 1030, 925, 908. ^{1}H-NMR (400 MHz, $CDCl_3$): 3.85–3.70 (*m*, 10 H, including 3.78 (*s*, 3 H) and 3.75 (*s*, 3 H)); 2.98 (*dt*, *J* = 10.3, 2.8, 1 H); 2.86 (*dt*, *J* = 10.3, 2.3, 1 H); 2.56 (*dt*, *J* = 14.3, 2.6, 1 H); 2.08 (*ddd*, *J* = 14.3, 3.4, 2.6, 1 H); 1.94 (*m*, 1 H); 1.78 (*dddd*, *J* = 13.5, 11.3, 3.5, 2.6, 1 H); 1.68 (*ddt*, *J* = 13.5, 5.9, 2.6, 1 H); 1.46 (*dddd*, *J* = 11.3, 5.9, 4.0, 1.7, 1 H); 1.23 (*d*, *J* = 6.4, 3 H). ^{1}H-NMR (300 MHz, C_6D_6): 3.90 (*d*, *J* = 1.6, 1 H); 3.81 (*qd*, *J* = 6.2, 4.1, 1 H); 3.44–3.08 (*m*, 8 H, including 3.26 (*s*, 3 H) and 3.25 (*s*, 3 H)); 2.67 (*dt*, *J* = 10.0, 2.8, 1 H); 2.60 (*dt*, *J* = 14.3, 2.5, 1 H); 2.45 (br. *d*, *J* = 10.0, 1 H); 1.96 (*dm*, *J* = 14.3, 1 H); 1.59 (*m*, 1 H); 1.56 (*qm*, *J* = 2.2, 1 H); 1.50 (*m*, 1 H); 1.42 (*dd*, *J* = 5.9, 2.8, 1 H); 1.24 (*d*, *J* = 6.2, 3 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 172.4 (*s*); 170.7 (*s*); 70.7 (*d*); 56.4 (*s*); 53.04 (*q*); 52.99 (*q*); 48.4 (*d*); 45.7 (*t*); 38.3 (*d*); 31.6 (*t*); 28.0 (*t*); 25.3 (*d*); 22.1 (*q*). EI-MS: 271 (41, M^+), 256 (100), 254 (60), 253 (25), 228 (30), 227 (20), 196 (16), 168 (17), 138 (16), 122 (33), 121 (32), 112 (24), 109 (34), 108 (89), 107 (26), 96 (21), 94 (58), 83 (40), 82 (55), 55 (32).

Ethyl Methyl Piperidine-3,3-dicarboxylate (**36**). To a soln. of 1.51 g (15 mmol) of (i-Pr)$_2$NH (*Fluka*, *puriss.*) in 150 ml of THF were added 9.38 ml of a 1.6M soln. of BuLi in hexane. After stirring at 0° for 10 min, the soln. was cooled to −70°; then, a soln. of 2.57 g (10 mmol) of **35** in 20 ml of THF was added. The cooling bath was removed, and stirring was continued for 1 h at 25°. The mixture was again cooled to −70°, and 1.42 g (15 mmol) of methyl chloroformate (*Fluka*, *puriss.*) were added slowly. The cooling bath was removed, and stirring was

continued for 1 h at 25°. The resulting mixture was poured onto a cold sat. aq. NH_4Cl soln. and extracted with Et_2O (3×). The combined org. extracts were dried, evaporated, and chromatographed (hexane/AcOEt 5:1) to yield 2.05 g (6.5 mmol, 65%) of a yellowish oil, which was dissolved in 50 ml of CH_2Cl_2. At 0°, 1.94 g (17 mmol) of CF_3COOH were added slowly, and the resulting mixture was stirred at 25° for 24 h. The mixture was worked up with sat. aq. Na_2CO_3 soln. and CH_2Cl_2 to yield 1.38 g (6.4 mmol, 98%) of **36**. Yellow oil. IR ($CHCl_3$): 3330, 2980, 2950, 2855, 1725, 1453, 1446, 1431, 1368, 1304, 1260, 1149, 1101, 1070, 1038, 1021, 880, 869. ^{1}H-NMR (300 MHz, $CDCl_3$): 4.17 (*q*, *J* = 7.2, 2 H); 3.70 (*d*, *J* = 1.2, 3 H); 3.17 (*s*, 2 H); 2.75 (*t*, *J* = 5.3, 2 H); 2.45 (br. *s*, 1 H); 2.12 (*t*, *J* = 6.1, 2 H); 1.47 (*tt*, *J* = 6.1, 5.3, 2 H); 1.22 (*td*, *J* = 7.2, 1.2, 3 H). ^{13}C-NMR (75 MHz, $CDCl_3$): 171.4 (*s*); 170.8 (*s*); 61.3 (*t*); 54.3 (*s*); 52.4 (*q*); 50.9 (*t*); 45.6 (*t*); 29.8 (*t*); 23.4 (*t*); 14.0 (*q*). EI-MS: 215 (33, M^+), 184 (15), 170 (28), 159 (14), 156 (59), 155 (11), 142 (100), 141 (21), 138 (63), 128 (18), 127 (17), 126 (20), 113 (20), 110 (26), 82 (25).

Ethyl Methyl 1-Chloropiperidine-3,3-dicarboxylate (**37**). To a soln. of 1.00 g (4.6 mmol) of **36** in 50 ml of CH_2Cl_2 were added 0.69 g (5.1 mmol) of *N*-chlorosuccinimide (*Fluka*, *puriss.*), and the resulting mixture was stirred for 12 h at 25°. The precipitate was filtered off and washed with three portions of pentane. The combined filtrate and washings were evaporated to furnish 0.78 g (3.12 mmol, 68%) of **37**. Waxy, low-melting solid. ^{1}H-NMR (200 MHz, $CDCl_3$): 4.21 (*q*, *J* = 7.1, 2 H); 3.76 (*s*, 3 H); 3.58 (br. *s*, 2 H); 3.09 (*d*, *J* = 5.4, 2 H); 1.93–1.83 (*m*, 4 H); 1.26 (*t*, *J* = 7.1, 3 H).

Methyl 2,3-Didehydropiperidine-3-carboxylate (**39**). To a soln. of 160 mg (7 mmol) of Na (*Fluka*, *puriss.*) in 50 ml of MeOH were added 200 mg (0.8 mmol) of **37**. After refluxing for 1 h, the cooled mixture was poured onto sat. aq. NaCl soln. and extracted with CH_2Cl_2 (3×). The combined extracts were dried ($MgSO_4$), evaporated, and chromatographed (pentane/AcOEt 5:1) to yield 104 mg (61%) of **38**. Yellow oil. ^{1}H-NMR (200 MHz, $CDCl_3$): 7.47 (*dq*, *J* = 6.2, 0.8, 1 H); 3.66 (*d*, *J* = 0.8, 3 H); 3.22 (*m*, 2 H); 2.63 (br. *s*, 1 H); 2.33 (*m*, 2 H); 1.81 (*m*, 2 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 169.3 (*s*); 143.0 (*d*); 50.6 (*q*); 40.7 (*t*); 20.9 (*t*); 20.6 (*t*).

Dimethyl Piperidine-3,3-dicarboxylate (**40**). To a soln. of 430 mg (2 mmol) of **36** in 30 ml of MeOH were added 7.4 mg (0.32 mmol) of Na (*Fluka*, *puriss.*). The mixture was stirred at 25° for 3 days and then evaporated to yield 397 mg (1.93 mmol, 97%) of pure **40**. Yellow oil. ^{1}H-NMR (200 MHz, $CDCl_3$): 3.75 (*s*, 6 H); 3.21 (*s*, 2 H); 2.79 (*t*, *J* = 5.3, 2 H); 2.45 (br. *s*, 1 H); 2.16 (*t*, *J* = 6.2, 2 H); 1.73 (br. *s*, 1 H); 1.55–1.45 (*m*, 2 H). ^{13}C-NMR (50 MHz, $CDCl_3$): 170.8 (2*s*); 52.1 (*s*); 50.1 (2*q*); 48.6 (*t*); 43.2 (*t*); 27.5 (*t*); 21.0 (*t*).

*Dimethyl (6*RS*,8*RS*)-8-Phenyl-9-oxa-1-azabicyclononane-5,5-dicarboxylate* (**42**). To a soln. of 354 mg (1.76 mmol) of **40** in 15 ml of MeOH/H_2O 1:1 were added 52 mg (0.17 mmol) of Na_2WO_4 (*Fluka*, *puriss.*) and 239 mg (2.46 mmol) of 30% aq. H_2O_2 soln. (*Fluka*, *puriss.*). After stirring for 45 min at 25°, the excess H_2O_2 was destroyed by adding 1 ml of 10% aq. $NaHSO_3$ soln. After addition of 10 ml of toluene, MeOH was removed *in vacuo* (40°/80 Torr), and the remaining toluene soln. was extracted with aq. 0.5N HCl soln. The aq. phase was extracted with toluene (1×) and CH_2Cl_2 (3×). The combined org. extracts were dried ($MgSO_4$) and evaporated. The residue was chromatographed (CH_2Cl_2/MeOH 15:1) to yield 100 mg (0.44 mmol, 25%) of **41**. To a soln. of this material and 5 mg of bis[5-(tert-butyl)-4-hydroxy-2-methylphenyl] sulfide (*Aldrich*, *puriss.*) in 20 ml of toluene were added 68 mg (0.66 mmol) of styrene (*Fluka*, *puriss.*). After refluxing for 3 h, the mixture was poured onto a sat. aq. NaCl soln. and extracted with 3 portions of Et_2O. The combined org. extracts were dried, evaporated, and chromatographed (pentane/Et_2O 4:1) to yield 100 mg (0.31 mmol, 71%) of a 5:1 mixture of **42**/**43**. Yellow oil.

Data of the Major Isomer **42**: IR ($CHCl_3$): 3030, 2980, 2950, 2855, 1725, 1453, 1444, 1432, 1367, 1304, 1260, 1149, 1101, 1071, 1038, 1020, 881, 868. ^{1}H-NMR (400 MHz, $CDCl_3$): 7.52–7.27 (*m*, 5 H); 4.97 (*dd*, *J* = 8.6, 6.6, 1 H); 3.82 (*s*, 3 H); 3.72 (*s*, 3 H); 3.55 (*dm*, *J* = 7.4, 1 H); 3.22 (*dt*, *J* = 12.1, 9.2, 1 H); 2.96 (*t*, *J* = 8.7, 1 H); 2.63 (*ddd*, *J* = 12.3, 8.6, 3.2, 1 H); 2.60 (*d*, *J* = 11.4, 1 H); 2.38 (*ddd*, *J* = 12.3, 8.0, 6.6, 1 H); 2.19 (*qt*, *J* = 13.6, 4.4, 1 H); 1.86 (*dm*, *J* = 13.9, 1 H); 1.57 (*td*, *J* = 13.3, 5.0, 1 H). ^{13}C-NMR (100 MHz, $CDCl_3$): 170.5 (*s*); 169.1 (*s*); 140.5 (s); 128.5 (2*d*); 127.9 (d); 126.9 (2*d*); 78.3 (*d*); 70.3 (*d*); 57.6 (*s*); 55.3 (*t*); 52.8 (*q*); 52.5 (*q*); 39.2 (*t*); 31.9 (*t*); 22.1 (*t*). EI-MS: 333 (47, M^+), 317 (21), 316 (100), 157 (21), 156 (18), 146 (12), 104 (20), 140 (14), 113 (52), 82 (20).

X-Ray Crystal-Structure Determination of **42**. An open vial containing a soln. of **42** in CH_2Cl_2 was placed in a closed beaker containing hexane. After standing for one week at 25°, the crystals formed were collected and dried at 0.005 Torr/25°. M.p. 127–129°. From a crystal of size 0.3 × 0.2 × 0.15 mm, 2908 reflexions were measured on an *Enraf Nonius CAD-4* diffractometer with CuK_α radiation (graphite monochromator, $\lambda = 1.54$ Å). The structure was solved by the direct method SIR97 [26]. The non-H-atoms were refined anisotropically with SHELXL-97 [27]. The H-atoms were calculated at idealized positions and included in the structure-factor calculation with fixed isotropic displacement parameters. Crystallographic data have been deposited with the *Cambridge Crystallographic Data Centre* as supplementary publication No. CCDC 142152. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK.

Table 3. *Crystallographic Data of* rac-**42**

Empirical formula	$C_{17}H_{21}NO_5$	
Formula weight	319.35	
Temp.	293(2) K	
Wavelength	1.54 Å	
Crystal system	Monoclinic	
Space group	$P21/n$	
Unit cell dimensions	$a = 10.493(2)$ Å	$\alpha = 90^\circ$
	$b = 8.455(5)$ Å	$\beta = 103.57(3)^\circ$
	$c = 18.410(10)$ Å	$\gamma = 90^\circ$
Volume	1587.7(13) Å^3	
Z	4	
Density (calculated)	1.336 Mg/m^3	
Absorption coefficient	0.098 mm^{-1}	
$F(000)$	680	
Crystal size	$0.30 \times 0.20 \times 0.15$ mm	
θ Range	2.05 to 64 deg.	
Index ranges	$0 \leq h \leq 12$, $0 \leq k \leq 9$, $-21 \leq l \leq 20$	
Reflections collected	2908	
Independent reflections	2562 [$R(\text{int}) = 0.0200$]	
Max./min. transmission	0.9854 and 0.9711	
Refinement method	Full-matrix least-squares on F^2	
Data/restraints/parameters	2090/0/208	
Goodness-of-fit on F^2	1.463	
Final R indices [$I > 3 < \Gamma\sigma > \perp (I)$]	$R1 = 0.0473$, $wR2 = 0.1530$	
R indices (all data)	$R1 = 0.0601$, $wR2 = 0.1619$	
$\Delta\rho$ (max; min)	0.169 and -0.304 e · A^{-3}	

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