Three-Step Access to the Tricyclic Benzo[*a*]quinolizine Ring System

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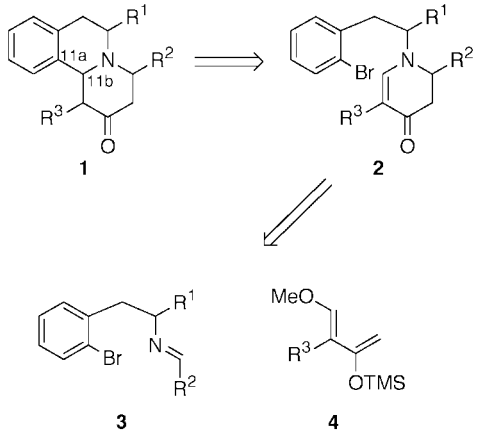
Access to the tricyclic benzo[*a*]quinolizine ring system, which forms the characteristic framework of alkaloids of the berberine and emetine type, is readily obtained by a three-step reaction sequence. This sequence includes the formation of a Schiff base, derived from a 2-bromo-substituted phenylethylamine, and its tandem Mannich/conjugate addition reaction with an electron-rich silyloxy diene forming an intermediate enaminone, which subsequently undergoes a Heck-type cyclization. Highest yields of the tandem Mannich/conjugate addition for aromatic Schiff bases and formaldehyde imines are observed in the presence of $ZnCl_2$ in THF, whereas aromatic imines give the best results in the presence of $EtAlCl_2$ in CH_2Cl_2. The best results for the Heck-type cyclizations are obtained either under heterogeneous conditions in the presence of K_2CO_3/NEt_4Cl at 120 °C in DMF or in refluxing toluene or under homogeneous conditions at 100 °C in DMF in the presence of NEt(*i*-Pr)$_2$. Depending on the substitution pattern of the diene and the steric demand of the base employed in the Heck cyclization, benzo[*a*]quinolizines carrying a double bond in the 11b,1- or 3,4-position or in an exocyclic position are obtained with fair to good results. A mechanistic rationale for this behavior is proposed. If chiral amines, e.g., derived from an amino acid ester, are employed in the three-step reaction sequence, chiral tricyclic benzo[*a*]quinolizines become accessible in a straightforward manner.

Introduction

The tricyclic benzo[*a*]quinolizine ring system forms the characteristic framework of numerous heterocyclic physiologically active compounds. For instance, it is found in alkaloids of the berberine[1] and the emetine type[2] and in psychoactive drugs such as tetrabenazine.[3] In addition, benzo[*a*]quinolizines may bind to the benzodiazepine receptor and mimic the physiological effects typical for benzodiazepine drugs.[4] Although several methods for the construction of these polycyclic heterocycles are known,[5,6] the development of new efficient and short routes to this class of compounds would open up new opportunities for heterocyclic and medicinal chemistry. In an attempt to devise such a method we have drawn from our previous experience in the construction of nitrogen heterocycles.[7,8] In a retrosynthetic analysis, the underlying heterocycle **1** was dissected between C-11a and C-11b (Scheme 1), yielding enaminones **2**, which should be accessible via condensation of imines **3** with electron-rich silyloxy dienes **4**.[8,9] Heck reaction ring closure[10] for the final step

Scheme 1. Retrosynthetic Analysis of the Benzo[*a*]quinolizinone Skeleton



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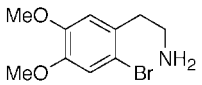
requires a halogen subustituent.[11] A similar approach to such heterocyclic compounds was recently reported by Comins et al.[12]

Results and Discussion

The two amine components, 2-bromohomoveratrylamine **5**[13] and the amino acid ester **6**, were employed for the construction of the desired enaminones.



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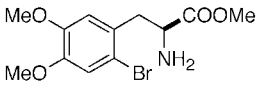
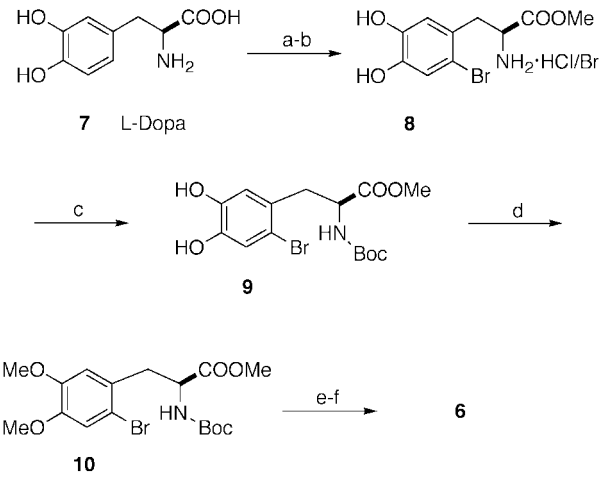


6

Compound **6** was built up from L-Dopa **7** as shown in Scheme 2. Subsequent treatment of the amino acid **7**

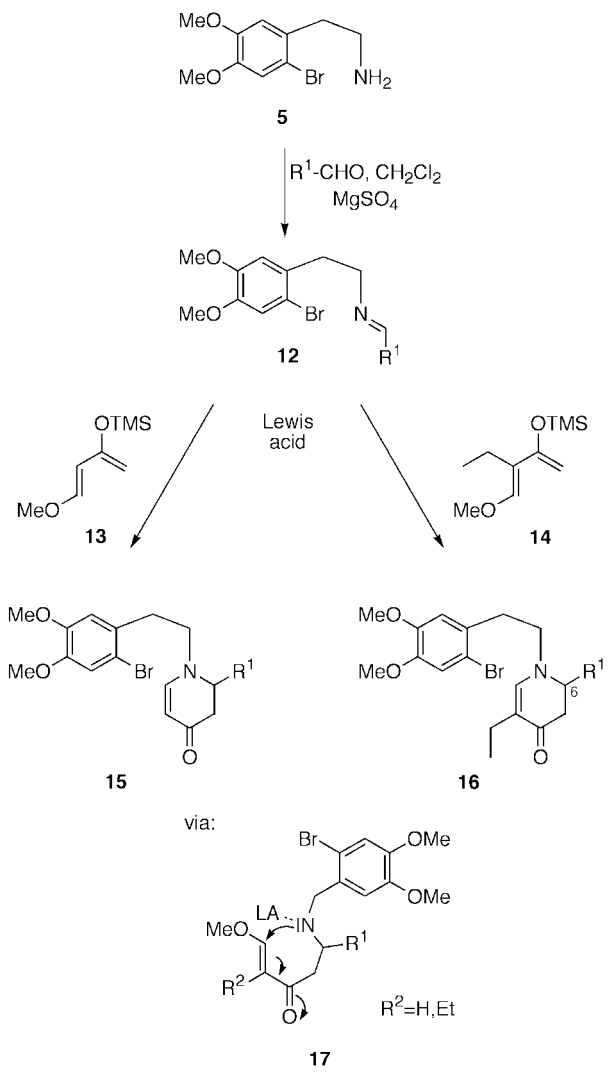
Scheme 2. Synthesis of the Chiral Amino Acid Ester 6[a]



[a] Conditions: (a) Br_2 (1.05 equiv), AcOH, 1.5 h, rt; (b) $SOCl_2$ (10 equiv), MeOH, 0 °C → rt, 15 h; (c) NEt_3 (2.5 equiv), Boc_2O (1.05 equiv), MeOH (degassed), rt, 15 h, 69% (over three steps); (d) CH_2Cl_2 at room temperature, CH_2N_2 (1 M in CH_2Cl_2 at −78 °C, 6 equiv), 2 h, 74%; (e) CF_3COOH, 0 °C, 30 min; (f) H_2O/CH_2Cl_2 3:5, 1 M NaOH to pH 10, 99% (over two steps).

with bromine in acetic acid and $SOCl_2$ in methanol[14] gave rise to the methyl ester **8** as a mixture of the hydrobromide and the hydrochloride. After masking of the amino function as the Boc urethane,[15] the phenolic hydrogens were converted to the methyl ethers by means of diazomethane,[16] which after removal of the Boc group under acidic conditions yielded compound **6**.

Scheme 3. Synthesis of the Enaminones 15 and 16



The homoveratrylamine **5** was converted to the required Schiff bases **12** by treatment with different aldehydes in CH_2Cl_2 in the presence of $MgSO_4$ (Scheme 3). These intermediates were not isolated. After exchange of the solvent, they were immediately subjected to the Lewis acid-mediated reaction with the silyloxy dienes **13**[9b] and **14**.[8d] In the ensuing transformation, the diene first adds to the C=N bond in the sense of a Mannich reaction to give intermediates of type **17**. These then cyclize to the enaminones **15** and **16** via intramolecular conjugate addition of the amine to the vinylogous ester group and subsequent elimination of methanol.[7,8] For aromatic Schiff bases and the formaldehyde imine, the highest yields were obtained if $ZnCl_2$ was used as Lewis acid and THF was employed as solvent (Table 1, entries 1−6 and 10−13). Whereas a slight excess of the diene leads to a markedly increased yield (Table 1, entries 1 and 2), the use of $B(OPh)_3$ in CH_2Cl_2 as solvent as recommended by Yamamoto et al.[17] was not advantageous (Table 1, entry 3). Aliphatic imines gave the best results in the presence of $EtAlCl_2$ in CH_2Cl_2 at −78 °C

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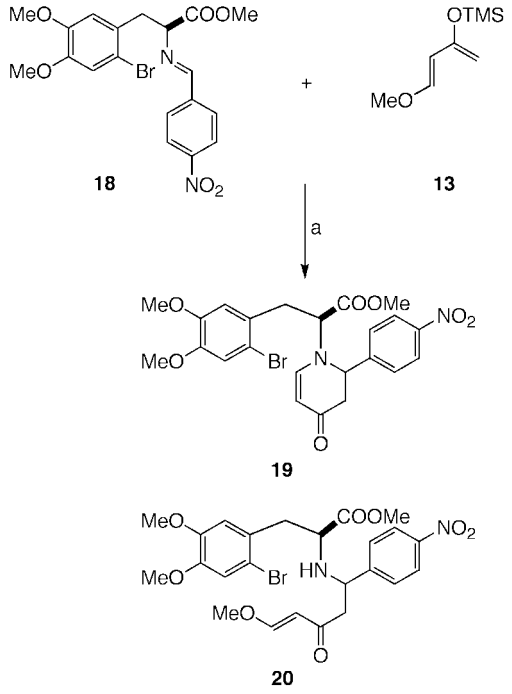
Table 1. Results of the Tandem Mannich/Conjugate Addition Cyclization between the Imines 12 and the Dienes 13 and 14

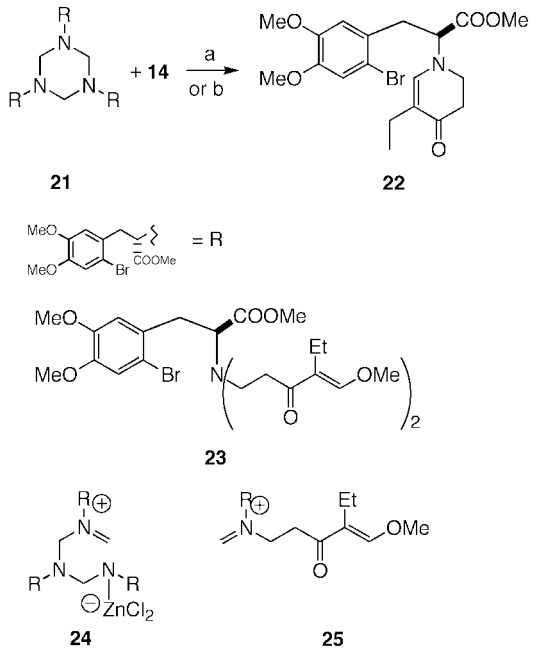
entry	no.	R^1	Lewis acid/equiv/solvent	diene/equiv	*T* (°C)	time (h)	yield (%)
1	**15a**	Ph	$ZnCl_2$/2/THF	**13**/1.0	rt	40	47
2	**15a**	Ph	$ZnCl_2$/2/THF	**13**/1.2	rt	18	58
3	**15a**	Ph	$B(OPh)_3$/1/CH_2Cl_2	**13**/1.25	−78 to rt	5	14
4	**15b**	*p*-OMePh	$ZnCl_2$/2/THF	**13**/1.2	rt	18	66
5	**15c**	*o*-NO_2Ph	$ZnCl_2$/2/THF	**13**/1.2	rt	20	33
6	**15d**	H	$ZnCl_2$/2/THF	**13**/1.2	rt	24	47
7	**15e**	*n*-Pr	$EtAlCl_2$/1/CH_2Cl_2	**13**/1.2	−78 to rt	20	43
8	**15f**	*i*-Pr	$EtAlCl_2$/1/CH_2Cl_2	**13**/1.25	−78 to rt	3	65
9	**15g**	*t*-Bu	$ZnCl_2$/2/THF	**13**/1.2	rt	18	
10	**16a**	Ph	$ZnCl_2$/2/THF	**14**/1.3	rt	20	45
11	**16b**	*p*-NO_2Ph	$ZnCl_2$/2/THF	**14**/1.2	rt	72	77
12	**16c**	*p*-OMePh	$ZnCl_2$/2/THF	**14**/1.2	rt	24	54
13	**16d**	H	$ZnCl_2$/2/THF	**14**/1.2	rt	72	67
14	**16e**	Hep	$ZnCl_2$/2/THF	**14**/1.2	rt	96	22

Scheme 4. Synthesis of the Chiral Enaminone 19[a]



[a] Conditions: (a) $B(OPh)_3$ (1 equiv), diene **13** (1.7 equiv), CH_2Cl_2, −78 °C → rt, 20 h, yielded **19** (28%), **20** (13%).

Scheme 5. Synthesis of the Chiral Enaminone 22[a]



[a] Conditions: (a) THF, $ZnCl_2$ (2 equiv), diene **14** (1.4 equiv), rt, 20 h, yielded **22** (48%), **23** (9%); (b) THF, $ZnCl_2$ (3 equiv), diene **14** (1.2 equiv), rt, 18 h, yielded **22** (34%), **23** (21%).

(Table 1, entries 7 and 8); however, the *tert*-butyl-substituted imine did not react at all (Table 1, entry 9). If the more stable ethyl-substituted diene **14** is used instead of **13**, for aliphatic imines $ZnCl_2$/THF can be used advantageously (Table 1, entry 14).

The reaction of the chiral imine **18** with the diene **13** in the presence of $B(OPh)_3$ as activating Lewis acid yielded the desired enaminone **19** albeit in moderate yield (Scheme 4). However, in addition to **19**, the side product **20** was isolated in a substantial amount. The occurrence of this compound sheds light on the mechanism of the condensation detailed above, since **20** represents the initial adduct resulting from the Mannich reaction prior to ring closure via conjugate addition.[7,18] Similarly, from the condensation of the formaldehyde imine (which is formed in situ from the cyclic trimer **21**) with the diene **14** to give the ethyl-substituted enaminone **22**, substantial amounts of the bis-*N*-alkylated amino acid ester **23** were isolated (Scheme 5). The side product **23** must have been formed via two successive Mannich-type additions, e.g., to iminium intermediates such as **24** and **25**, which may be formed from the cyclic hexahydrotriazine trimer **21** in the presence of the Lewis acid.

Having the desired bromo-substituted enaminones **15**, **16**, and **22** in hand, their cyclization to benzo[*a*]quinolizines under the conditions of the Heck reaction[10] was investigated. To find advantageous conditions for the attempted cyclization, an initial study was carried out. In this study the enaminone **15a** was employed and several reaction parameters were varied (Scheme 6, Table 2). As catalyst system, the $Pd_2(dba)_3 \cdot CHCl_3$[19] complex together with varying amounts of PPh_3 was used. When the reaction mixture was heated to 45 °C, the color changed from deep red to light yellow (exchange of the ligands on Pd), and upon prolonged heating it turned brown accompanied by precipitation of palladium.

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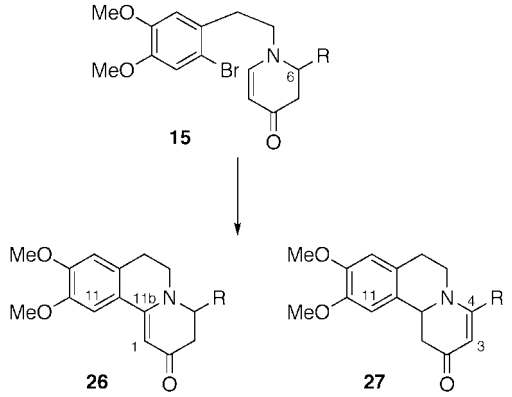
Table 2. Optimization of the Heck-Type Cyclization of the Phenyl-Substituted Enaminone 15a

entry	Pd[a] (mol %)	PPh_3 (mol %)	base/equiv	solvent	additive/equiv	T[b] (°C)	time (h)	**26a** (%)
1	16	42	NEt(*i*-Pr)$_2$/1.8	CH_3CN		80	120	
2	10	20	NEt(*i*-Pr)$_2$/1.8	DMF		150	5	20
3	11	48	NEt(*i*-Pr)$_2$/2.5	DMF		100	6	67
4	10	20	K_2CO_3/1.5	CH_3CN	NEt_4Cl/1	80	24	22[c]
5	10	20	K_2CO_3/1.5	DMF	NEt_4Cl/1	100	3.5	45
6	10	20	K_2CO_3/1.5	DMF	NEt_4Cl/1	120	3	87
7	24	48	NaOH/2	toluene	NEt_4Cl/1.2	120	20	30
8	10	20	NaOH/2	toluene	NEt_4Cl/1.2	120	22	36
9	10	20	DBU/2	toluene	NEt_4Cl/1.2	120	20	25

[a] $Pd_2(dba)_3 \cdot CHCl_3$. [b] Oil bath temperature. [c] 66% of **15a** reisolated.

Scheme 6. Heck-Type Cyclization of 6-Substituted Enaminones 15 To Give Benzo[*a*]quinolizinones 26 and 27



R	15	26/27
Ph	**a**	**a**
p-OMePh	**b**	**b**
o-NO_2-Ph	**c**	**c**
H	**d**	**d**
n-Pr	**e**	**e**
i-Pr	**f**	**f**

The use of NEt(*i*-Pr)$_2$ in CH_3CN was not advantageous; however, changing the solvent to DMF led to formation of the tricyclic enaminone **26a**. At 100 °C and in the presence of 4 equiv of PPh_3 (with respect to Pd), the yield reached 67%, whereas at higher temperatures it was substantially lower (Table 2, entries 1−3). If K_2CO_3 and NEt_4Cl were used in DMF in accord with the heterogeneous system as recommended by Jeffery et al.,[20] the yield could be further increased to 87%, whereas CH_3CN once more gave an inferior result (Table 2, entries 4−6). In this case, 2 equiv of the phosphine ligand are sufficient, presumably because chloride may serve as ligand for Pd(0), as well, thereby stabilizing it. Finally, the use of toluene as solvent was investigated; however, neither in the presence of NaOH/NEt_4Cl or DBU/NEt_4Cl was a satisfactory yield obtained (Table 2, entries 7−9). The best yields were obtained either by running the cyclization in DMF either at 100 °C and in the presence of NEt(*i*-Pr)$_2$ (method A) or at 120 °C in the presence of K_2CO_3/NEt_4Cl (method B), and all further cyclizations were studied using these reaction conditions. Treatment of the enaminones **15** derived from aliphatic and aromatic aldehydes, as well as formaldehyde in the presence of Pd(0) under the conditions of method A or B, yielded the benzo[*a*]quinolizinones **26** in moderate to high yields (Scheme 6, Table 3). In general, under heterogeneous conditions (method B), the yields were higher than under homogeneous conditions (method A).

Table 3. Results of the Heck-Type Cyclizations of 6-Substituted Enaminones 15

entry	R	**15**	method[a]	time (h)	**26** (%)	**27** (%)
1	Ph	**a**	A	6	67	
2	Ph	**a**	B	3	87	
3	*p*-OMePh	**b**	A	20	51	
4	*p*-OMePh	**b**	B	3	76	9
5	*o*-NO_2Ph	**c**	A	25	65	
6	H	**d**	A	15	12	
7	H	**d**	B	6	17	35
8	*n*-Pr	**e**	A	12	9	
9	*n*-Pr	**e**	B	8	26	42
10	*n*-Pr	**e**	C	17	16	30
11	*i*-Pr	**f**	A	6	12	
12	*i*-Pr	**f**	B	20	20	38
13	*i*-Pr	**f**	C	16	30	60

[a] Conditions: (Method A) $Pd_2(dba)_3 \cdot CHCl_3$ (5 mol %), PPh_3 (40 mol %), DMF, NEt(*i*-Pr)$_2$ (2 equiv), 100 °C; (Method B) $Pd_2(dba)_3 \cdot CHCl_3$ (5 mol %), PPh_3 (20 mol %), DMF, K_2CO_3 (1.5 equiv), NEt_4Cl (1−1.2 equiv), 120 °C; (Method C) $Pd_2(dba)_3 \cdot CHCl_3$ (5 mol %), PPh_3 (20 mol %), toluene, K_2CO_3 (10 equiv), NEt_4Cl (1.1 eqiuv), 120 °C.

Unexpectedly, under the heterogeneous conditions the enaminones derived from aliphatic aldehydes and formaldehyde did not only give the expected products **26**, but instead, enaminones **27** carrying the double bond in the 3,4-position were formed (Table 3, entries 4, 7, 9, 10, 12, and 13). This was also observed if toluene was employed as solvent instead of DMF (Table 3, entries 10 and 13). With the exception of the *p*-methoxyphenyl-substituted enaminone (Table 3, entry 4), in the presence of aromatic substituents the formation of these isomers was not observed.

The tricyclic benzo[*a*]quinolizinones **26** and **27** are readily separated by means of flash chromatography and can be identified by characteristic signals in their ^1H NMR spectra. Thus, in the 3,4-unsaturated compounds **27**, H-3 and H-11 are shifted by ca. 0.5 ppm toward higher field as compared to the signals for the analogous H-1 and H-11 of the isomers **26** (Table 4). In **26**, H-1 and H-11 deshield each other, whereas in **27** this is no longer the case. In addition, **27e** was subjected to analysis by means of NOE measurements (Figure 1).[21] Upon irradiation at H-11, a signal enhancement for

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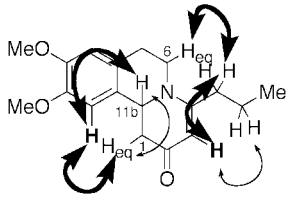
Table 4. Characteristic ^{1}H NMR Chemical Shifts of H-1, H-3, and H-11 in 26 and 27 (δ in ppm)

		26		27	
R		H-1	H-11	H-3	H-11
p-OMePh	**b**	5.72	7.22	5.23	6.65
H	**d**	5.69	7.16	5.06	6.61
n-Pr	**e**	5.56	7.16	5.11	6.62
i-Pr	**f**	5.52	7.17	5.22	6.67



27e

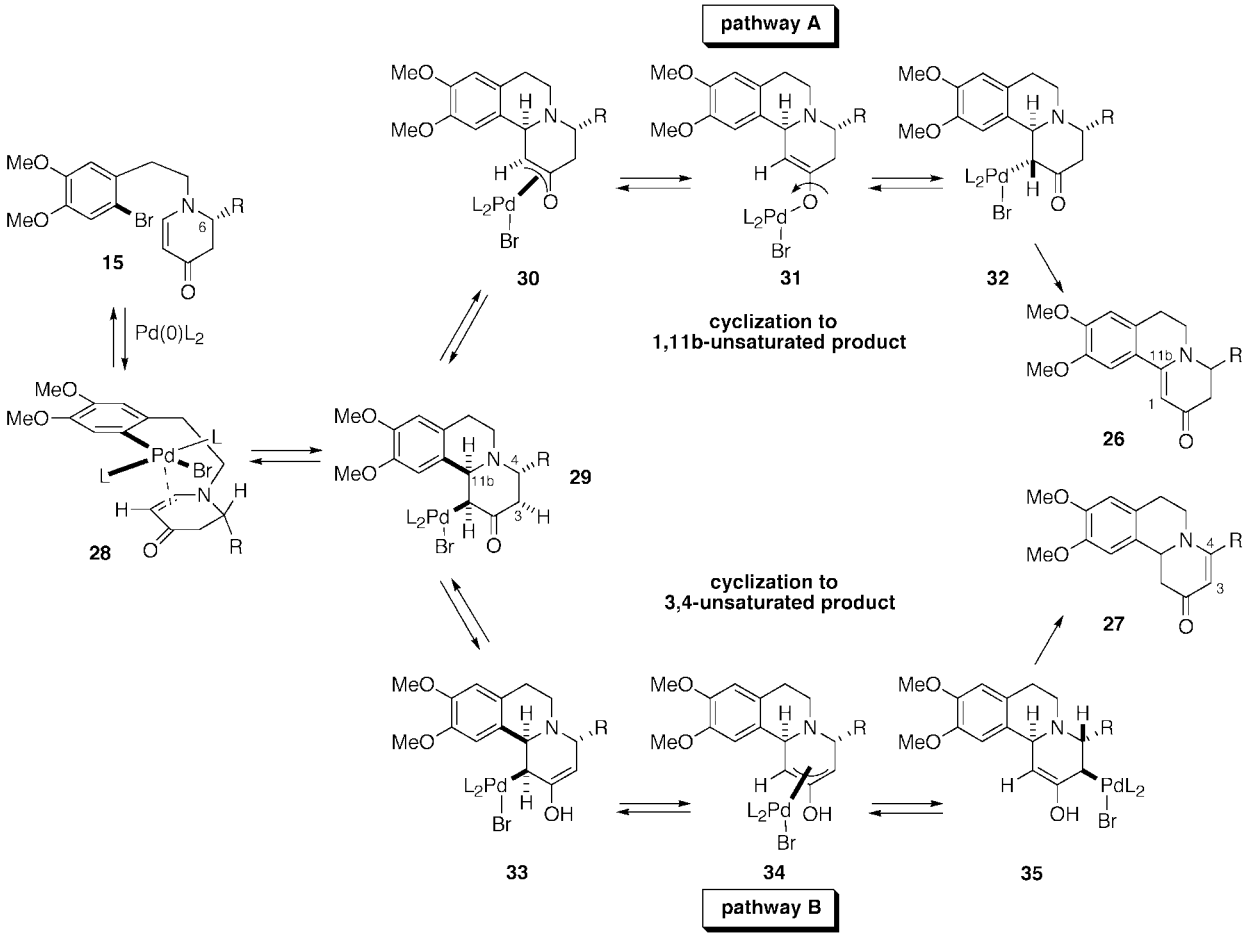
Figure 1. NOE signal enhancements observed for **27e**. Signal amplification: bold = strong, plain = weak.

H-11b and H-1eq was recorded, and similarly it was proven that H-8 is in the vicinity of H-7eq. Most significantly, irradiation at H-3 yielded an enhancement of the signal for the first methylene group of the propyl side chain. In turn, irradiation into the signal characteristic for this CH_2 group proved that it is in the vicinity of H-3 and H-6eq. Thus, the double bond and the propyl side chain lie close to each other; i.e., the double bond must be in the 3,4-position.

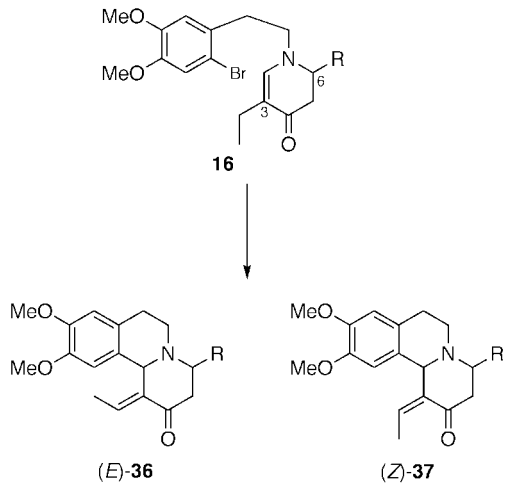
To explain the formation of the isomers **26** and **27**, we propose the mechanistic rationale depicted in Scheme 7. The catalytic cycle starts with the oxidative addition of the aryl bromide **15** to the Pd(0) catalyst to give the intermediate σ-Pd complex **28**, which then undergoes a syn addition to the double bond of the enaminone ring. For steric reasons, C-2 of the aryl ring attacks exclusively C-2 of the enaminone and anti to the substituent R at the 6-position of the enaminone. Consequently, in ring C of **29** the substituents are in a trans orientation, and for the Pd no syn hydrogen is available for subsequent elimination.[22] Intermediate **29** now may undergo two different reactions leading either to **26** or **27**. On the one hand (pathway A), **29** can rearrange to the σ-Pd-enolate **31** via π-oxoallyl complex **30**.[23,24] From **31**, the Pd now can reach the other side of the ring (→ **32**) where a hydrogen is accessible for syn elimination and closure of the catalytic cycle. On the other hand (pathway B), the ketone in **29** can be converted to the enol **33**. This reaction pathway should be accessible in particular if the substituent R is sterically less demanding and if a small base is present. The η^1-σ-allylpalladium intermediate **33** can then isomerize to the η^1-compound **35** by a $\sigma-\pi-\sigma$ 1,3 shift via the η^3-π-complex **34**.[25] In **35**, the Pd now must be syn to the hydrogen at C-4 so that a syn elimination to close the catalytic cycle is possible. Tautomerization of the enol to the carbonyl group finally gives **27**.

If the base employed in the Pd-mediated reaction and the substituent R are sterically demanding, i.e., if EtN-(*i*-Pr)$_2$ is used and R is aromatic, pathway B is not or only hardly accessible to the system and the isomers **26** are formed. If the steric demand of R and the base are lower, i.e., if R is aliphatic or hydrogen and K_2CO_3 is

Scheme 7. Mechanistic Proposal To Rationalize the Formation of the Benzo[*a*]quinolizinones 26 and 27



Scheme 8. Heck-Type Cyclization of 3-Ethyl-Substituted Enaminones 16 To Give the Benzo[*a*]quinolizinones (*E*)-36 and (*Z*)-37



R	16	36/37
Ph	**a**	**a**
p-NO_2Ph	**b**	**b**
p-OMePh	**c**	**c**
H	**d**	**d**
Hep	**e**	**e**

employed, both pathways can be followed and mixtures of **26** and **27** result. These assumptions are supported by force field calculations,[26] which indicate that in **32** the protons at C-3 are not accessible if R is aromatic.

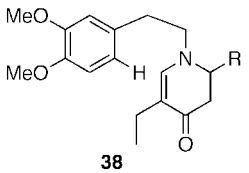
The carbon atoms C-11b, C-1, C-2, and C-3 of the benzo[*a*]quinolizinones built up via the route described above originate from the diene employed. Therefore, the use of dienes carrying additional substituents would give access to further substituted tricyclic compounds in a straightforward manner and without the need to carry out additional transformations after generation of the ring system. Therefore, the Heck-type cyclizations were studied for the ethyl-substituted enaminones **16** (Scheme 8, Table 5). In these cases, the use of K_2CO_3/NEt_4Cl in refluxing toluene in the presence of additional phosphines turned out to be most advantageous. Following the mechanism proposed above (Scheme 7), the initially formed arylpalladium intermediate in these cases also undergoes a syn addition to the double bond of the enaminone. However, due to the presence of the additional ethyl substituent, in the intermediate analogous to **29**, hydrogen atoms are now accessible for elimination of a hydridopalladium species, thus forming an exocyclic double bond. In accord with this process, the benzo[*a*]-quinolizinones **36** and **37** are obtained in moderate yields with the *E*-isomer of the double bond being formed in excess (Table 5). For the phenyl-substituted compound **16a**, the influence of different phosphines on this process was investigated (Table 5, entries 1−3). The best result was obtained if P(*o*-tol)$_3$ was employed; PPh_3 was less advantageous. The use of a sterically more demanding phosphine like BINAP led to a decreased yield and a lower *E*/*Z* ratio. In all cases, compound **38** (R = Ph), which must arise from reduction of the initial σ-Pd complex, was isolated as an undesired side product. In addition, in two cases **39** was isolated as a byproduct. This compound embodies an additional 3,4 double bond (Table 5, entries 2 and 5). The occurrence of the reduction product **38** is in line with observations by Comins et al.[12a] and Branchaud et al.[12b] for related reactions.

Table 5. Results of the Heck-Type Cyclizations of 3-Ethyl-Substituted Enaminones 16[a]

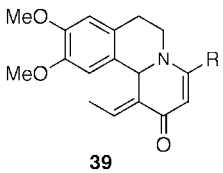
entry	16	R	ligand/mol %	time (h)	yield (%)	36:37	38 (%)
1	**a**	Ph	PPh_3/25	4	53	4:1	30
2	**a**	Ph	P(*o*-tol)$_3$/25[b]	4	60	3:1	18
3	**a**	Ph	(*R*)-BINAP/11	9	36	2.5:1	29
4	**b**	*p*-NO_2Ph	P(*o*-tol)$_3$/25	5	41	3:1	
5	**c**	*p*-OMePh	P(*o*-tol)$_3$/20	3	37[c]	3:1	35
6	**c**	*p*-OMePh	(*R*)-BINAP/11	6.5	53	3:1	24
7	**d**	H	PPh_3/25	6	24	>20:1	
8	**d**	H	P(*o*-tol)$_3$/25	7			30
9	**e**	Hep	(*R*)-BINAP/11	48	40	1:1	5

[a] Conditions: $Pd_2(dba)_3$·$CHCl_3$ (5 mol %), NEt_4Cl (1.1−1.2 equiv), toluene, argon atmosphere, 120 °C oil bath. [b] When 20 mol % ligand is used **39** (15%) can be isolated. [c] 25% of **39** can be isolated.

Enaminones with substituted aromatic groups can be cyclized in yields of ca. 40% (Table 5, entries 4 and 5), using the *o*-tolylphosphine ligand. However, the use of BINAP may be advantageous (Table 5, entry 6). In particular for aliphatic groups "R", this phosphine gives the best result (Table 5, entry 9). If R = H, the use of *o*-tolylphosphine leads only to the formation of the reduction product **38** (R = H); however, in this case, the application of PPh_3 yielded the cyclization product formed as a single regioisomer (Table 5, entries 7 and 8).



38



39

In both compounds **36** and **37**, a new stereocenter is built up; in the presence of the chiral (*R*)-BINAP ligand, asymmetric induction might occur. But unfortunately, in all cases examined the heterocycles **36** and **37** did not display any specific rotation.

The relative stereochemistry of the tricyclic targets **36** and **37** was ascertained by examination of their ^{1}H NMR spectra and additional NOE studies. Thus, due to the influence of the C=O group, the hydrogen substituent of the exocyclic double bond displays a chemical shift of ca. 7 ppm for the *E* isomers **36**, whereas for the *Z* isomers

(22) For examples of trans- or anti-elimination, see: (a) Zhang, Y.; O'Conner, B.; Negishi, E. *J. Org. Chem.* **1988**, *53*, 5590−5592. (b) Amos, P. C.; Whiting, D. A. *J. Chem. Soc., Chem. Commun.* **1987**, 510−511. (c) Chida, N.; Ohtsuka, M.; Ogawa, S. *Tetrahedron Lett.* **1991**, *35*, 4525−4228. (d) Martin, S. F.; Tso, H.-H. *Heterocycles* **1993**, *35*, 85−88. (e) Ahmad-Junan, S. A.; Amos, P. C.; Whiting, D. A. *J. Chem. Soc., Perkin Trans. 1* **1992**, 539−545. (f) Chida, N.; Ohtsuka, M.; Ogawa, S. *J. Org. Chem.* **1993**, *58*, 4441−4447. (g) Hudlicky, T.; Olivo, H. F. *J. Am. Chem. Soc.* **1992**, *114*, 9694−9696. (h) McIntosh, M. C.; Weinreb, S. M. *J. Org. Chem.* **1993**, *58*, 4823−4832 and references therein.

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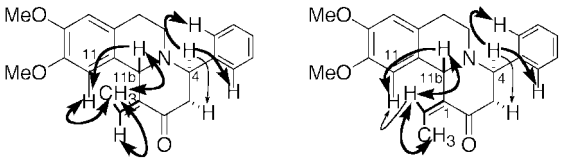
(25) Trost, B. M. *J. Organomet. Chem.* **1986**, *300*, 263−280.

(26) CHEM-3D, release 3.0, CambridgeSoft Corp., Cambridge, MA.

Table 6. Characteristic ^{1}H NMR Chemical Shifts of H-*exo*,*exo*-CH_3 and H-11b in (*E*)-36 and (*Z*)-37 (δ in ppm)

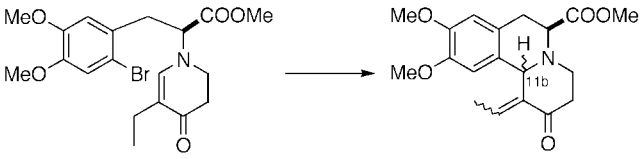
		(*E*)-**37**			(*Z*)-**37**		
R		H-*exo*	*exo*-CH_3	H-11b	H-*exo*	*exo*-CH_3	H-11b
Ph	**a**	7.02	1.94	5.39	5.81	2.06	4.98
p-NO_2Ph	**b**	7.04	1.95	5.41	5.80	2.08	4.98
p-OMePh	**c**	7.01	1.94	5.41	5.80	2.05	4.95
H	**d**	6.99	1.90	5.19			
Hep	**e**	6.99	1.88	5.26	5.39	1.90	4.81



(*E*)-**36** (*Z*)-**37**

Figure 2. NOE signal enhancements observed for (*E*)-**36** and (*Z*)-**37**. Signal amplification: bold = strong, plain = weak.

Scheme 9. Heck-Type Cyclization of Enaminone 22 To Give the Benzo[*a*]quinolizinone 40[a]



22 **40**

[a] Conditions: $Pd_2(dba)_3CHCl_3$ (5 mol %), P(*o*-tol)$_3$ (20 mol %), K_2CO_3 (10 equiv), NEt_4Cl (1.1 equiv), toluene, 120 °C oil bath, 3 h, 32%; ratio of isomers at H-11b, 3:4; *E*:*Z*, 85:15.

37 it appears at 5.4−5.8 ppm (Table 6). For the methyl substituents of the double bond, the effect is opposite but it is less pronounced. In addition, in the *E* isomers **36**, H-11b appears above 5 ppm, whereas in the *Z* isomers the signal is found below 5 ppm. Furthermore, in both isomers an NOE signal enhancement between H-11b and the substituents of the double bond as well as between H-11b and H-11 were detected (Figure 2). H-4 and H-11b, however, do not show an NOE effect. H-4 only displays signal enhancements with H-3 and the side-chain substituents. Consequently, H-11b and H-4 lie on different faces of the tricyclic nitrogen heterocycles, which can be explained by means of the proposed mechanism detailed in Scheme 7.

The reaction sequence described above has the potential to provide access to enantiomerically enriched benzo[*a*]quinolizinones. To this end, the enaminone **22** was subjected to the cyclization reaction. In this case, the heterogeneous reaction conditions employing $Pd_2(dba)_3 \cdot CHCl_3$, P(*o*-tol)$_3$, and K_2CO_3/NEt_4Cl in refluxing toluene as solvent proved to be best. Under these conditions, the desired tricyclic compound **40** was obtained as a mixture of isomers (Scheme 9). This mixture consisted mainly (ca. 85%) of the two isomers with an *E*-configured exocyclic double bond but a different configuration at C-11b (isomer ratio 2:1). In addition, two minor isomers (ca. 15%) with *Z*-double bonds were formed.

Conclusion

The results presented in this paper demonstrate that functionalized benzo[*a*]quinolizidinones can be built up in a three-step reaction, which consists of the formation of an imine, a tandem Mannich/conjugate addition reaction, and a subsequent cyclization by means of a Heck reaction. The desired tricyclic heterocycles are accessible via this very short sequence with fair to good results. This method should be readily amenable to the construction of natural products and analogues thereof and thereby open up new alternatives to the already existing methods.

Experimental Section

General Procedures. The analytical instruments and general experimental techniques used have already been described.[27] The solutions of $ZnCl_2$ and $B(OPh)_3$ were prepared by dissolving the neat Lewis acids in anhydrous THF and CH_2Cl_2. K_2CO_3 was heated for several hours and then stored under argon atmosphere. NEt_4Cl was heated at 120 °C for 24 h at reduced pressure prior to use and stored under argon atmosphere. Methanol and triethylamine (Et_3N) were carefully degassed prior to use by freezing three times under argon atmosphere and warming under reduced pressure.

(*S*)-(2-Bromo-4,5-dihydroxy)phenylalanine Methyl Ester Hydrochloride/Hydrobromide (8).[13] To a solution of L-Dopa **7** (9.86 g, 50 mmol) in acetic acid (250 mL) was added a solution of Br_2 (2.67 mL, 8.39 g, 52.5 mmol) in 50 mL of acetic acid during 1.5 h. The solvent was evaporated in vacuo, and the crude solid was treated with an ice-cold mixture of $SOCl_2$ (20 mL) and methanol (150 mL). The reaction mixture then was allowed to warm to room temperature during 15 h, and the solvent was evaporated in vacuo to give the product as a light yellow amorphous solid (19.12 g, quant) (hydrochloride and hydrobromide), which was used without further purification: ^{1}H NMR (DMSO-d_6, 250 MHz) δ 9.71 (br s, 1H), 9.45 (br s, 1H), 8.77 (br s, 3H), 7.12 (s, 1H), 6.91 (s, 1H), 4.22 (br t, J = 7.2 Hz, 1H), 3.83 (s, 3H), 3.22 (br d, J = 7.2 Hz).

(*S*)-*N*-(*tert*-Butyloxycarbonyl)-2-bromo-4,5-dihydroxyphenylalanine Methyl Ester (9). To a solution of methyl ester **8** (19.12 g, 50 mmol) in degassed methanol (200 mL) was added at room temperature Et_3N (17.4 mL, 125 mmol) followed by a solution of Boc_2O (11.5 g, 52.5 mmol) in methanol (50 mL). The orange red solution was stirred for 12 h, and the solvent was evaporated in vacuo. The residue was purified by flash chromatography on silica gel, employing hexane−acetone (1:1) as eluent to afford 13.6 g (70%) of urethane **9** as a colorless amorphous solid: mp 93−95 °C; silica gel TLC R_f 0.23 (1:1 hexane−acetone); $[\alpha]^{25}_D$ = −13.4 (*c* 1, MeOH); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.02 (s, 1H), 6.85 (br s, 1H), 6.75 (s, 1H), 6.68 (br s, 1H), 5.35 (d, J = 8.6 Hz, 1H), 4.55 (ddd, J = 8.6, 5.5, 8.7 Hz, 1H), 3.74 (s, 3H), 3.14 (dd, J = 5.5, 14.1 Hz, 1H), 2.95 (dd, J = 8.7, 14.1 Hz, 1H), 1.39 (s, 9H). Anal. Calcd for $C_{15}H_{20}BrNO_6$ (390.23): C, 46.17; H, 5.17; N, 3.58. Found: C, 46.51; H, 5.32; N, 3.21.

(*S*)-*N*-(*tert*-Butyloxycarbonyl)-2-bromo-4,5-dimethoxyphenylalanine Methyl Ester (10). To a solution of catechol **9** (2.7 g, 6.92 mmol) in CH_2Cl_2 (60 mL) in an open Erlenmeyer flask was added a 1 M solution of diazomethane in CH_2Cl_2 (40 mL) precooled to −78 °C. After the mixture was stirred for 2 h, acetic acid was added until the yellow color disappeared. The solvent was evaporated in vacuo, the residue was dissolved in toluene (50 mL), and the solvent was evaporated. Purification of the crude residue by flash chromatography (silica gel, 4:1−3:1 hexane−acetone) afforded **10** as colorless viscous oil, which solidified over days upon standing under reduced pressure to give a colorless amorphous solid (2.15 g, 74%): mp 119−121 °C; silica gel TLC R_f 0.12 (4:1 hexane−acetone); $[\alpha]^{25}_D$ = +16.1 (*c* 1, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.00 (s, 1H), 6.70 (s, 1H), 5.09 (d, J = 8.3 Hz, 1H), 4.60 (m, 1H), 3.85 (s, 3H), 3.73 (s, 3H), 3.22 (dd, J = 5.9, 14.0 Hz, 1H), 3.05 (dd, J = 7.9, 14.0 Hz, 1H), 1.39 (s, 9H); ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 172.4, 154.9, 148.5, 148.3, 127.8, 115.4 (CH), 114.9, 113.5 (CH), 79.9, 56.1 (CH_3), 56.0 (CH_3), 53.6 (CH), 52.4 (CH_3), 38.1 (CH_2), 28.3 (3C, CH_3); IR (drift) 1733, 1686,

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1524 cm^{-1}; UV (λ_{max} (ϵ), MeOH) 204 (48 400), 232 (11 250), 284 (4150) nm; MS (85 °C) *m/e* 419 (8), 417 (8), 363, 361 (8), 300, 302 (8), 231 (98), 229 (100), 57 (37). Anal. Calcd for $C_{17}H_{24}BrNO_6$ (418.28): C, 48.82; H, 5.78; N, 3.35. Found: C, 49.10; H, 5.75; N, 3.25.

(*S*)-2-Bromo-4,5-dimethoxyphenylalanine Methyl Ester Hydrotrifluoroacetate (11). A solution of methyl ester **10** (225 mg, 0.54 mmol) in trifluoroacetic acid (5 mL) was stirred at 0 °C for 30 min. The solvent was removed at room temperature under reduced pressure, and the residue was dried in vacuo for 2 d to yield the hydrotrifluoroacetate **11** as a colorless solid (233 mg, 99%): mp 122 °C; $[\alpha]^{25}_D = +10.6$ (*c* 1.18, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.99 (s, 1H), 6.95 (s, 1H), 4.30 (br s, 1H), 3.81 (s, 3H), 3.73 (s, 3H), 3.42 (m, 1H), 3.21 (m, 1H); ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 169.5, 162.0 (q, $^2J_{CF} = 35$ Hz, CF_3C), 149.1, 148.5, 125.1, 116.4 (q, $^1J_{CF} = 291$ Hz, CF_3), 115.7 (CH), 114.7 (CH), 114.5, 56.2 (CH_3), 56.1 (CH_3), 53.4 (CH_3), 52.6 (CH), 36.4 (CH_2); MS (75 °C) *m/e* 319 (0.7), 317 (0.8), 258, 260, 237, 239 (10), 238 (82), 230, 232 (21), 229, 231 (100), 151 (18), 88 (23), 69 (28). Anal. Calcd for $C_{14}H_{17}BrF_3NO_6 \cdot {}^3/_2H_2O$ (432.19): C, 36.62; H, 4.39; N, 3.05. Found: C, 36.94; H, 4.37; N, 2.58.

(*S*)-2-Bromo-4,5-dimethoxyphenylalanine Methyl Ester (6). Hydrotrifluoroacetate **11** (233 mg, 0.54 mmol) was dissolved in a mixture of H_2O (30 mL) and CH_2Cl_2 (50 mL), and the pH was adjusted to 10 with 1 M NaOH at room temperature. After separation of the phases, the aqueous phase was extracted with CH_2Cl_2 (30 mL), the combined organic phases were dried with $MgSO_4$, and the solvent was evaporated in vacuo. The yellowish oil (171 mg, 99%) was immediately used in subsequent reactions without further purification: ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.02 (s, 1H), 6.75 (s, 1H), 3.85 (s, 3H), 3.83 (dd, $J = 5.7$, 8.6 Hz, 1H), 3.72 (s, 3H), 3.18 (dd, $J = 5.7$, 13.7 Hz, 1H), 2.90 (dd, $J = 8.6$, 13.7 Hz, 1H), 1.65 (br s, 2H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 175.3, 148.6, 148.4, 128.8, 115.7 (CH), 114.8, 113.9 (CH), 56.2 (CH_3), 56.1 (CH_3), 54.7 (CH), 52.2 (CH_3), 40.9 (CH_2); MS (75 °C) *m/e* 319 (0.7), 317 (0.8), 258, 260, 237, 239 (10), 238 (82), 230, 232 (21), 229, 231 (100), 151 (18), 88 (23); HRMS *m/e* calcd for $C_{12}H_{16}BrNO_4$ (318.17) 317.0263, found 317.0280.

General Protocol for the Preparation of the Imines 12. To a solution of 1 mmol of the respective amine in of CH_2Cl_2 (20 mL) was added 1 mmol of the corresponding aldehyde and 1 g of $MgSO_4$. The solution was stirred for 12−15 h and filtered through a G4 glass frit, and the solvent was evaporated in vacuo. The resulting imines were directly used in subsequent reactions without further purification.

General Protocol for the Synthesis of the 2,3-Didehydropiperidinones. (1) Using $ZnCl_2$ as Lewis Acid. To a solution of 10 mmol of the respective imine **12** in THF (100 mL) was added under argon a 1 M solution of $ZnCl_2$ in THF (20 mL) followed by 1.3 equiv of the diene **13** (2.4 mL, 13 mmol). The solution was stirred for 20 h at room temperature. After addition of 1 N HCl (20 mL), the organic phase was extracted with saturated $NaHCO_3$ (50 mL), H_2O (50 mL), and brine (50 mL) and was dried with $MgSO_4$. The solvent was removed in vacuo, and the residue was purified by flash chromatography on silica gel with hexane−acetone mixtures as eluents.

(2) Using $B(OPh)_3$ as Lewis Acid. To an ice-cold solution of 5 mmol of the respective imine **12** in CH_2Cl_2 (100 mL) was added 5 g of molecular sieves (4 Å) and 1 equiv of a 1 M solution of $B(OPh)_3$ in CH_2Cl_2 (5 mL). The solution was stirred for 20 min under argon atmosphere, cooled to −78 °C, and 1.25 equiv of diene **13** (1.25 mL, 6.3 mmol) was added. The mixture was stirred for additional 15 h and allowed to warm to room temperature during that time. After filtration over a G3-glass frit, the residue was washed with CH_2Cl_2 (20 mL) and the organic phase extracted with 1 N HCl (50 mL), saturated $NaHCO_3$ (50 mL), H_2O (50 mL), and brine (50 mL). The organic layer was dried with $MgSO_4$, the solvent was evaporated in vacuo, and the residue was purified by flash chromatography with hexane−acetone mixtures as eluents.

(3) Using $EtAlCl_2$ as Lewis Acid. To a solution of 5 mmol of the respective imine **12** in CH_2Cl_2 (60 mL) was added at −78 °C 1.1 equiv of a 1 M solution of $EtAlCl_2$ in hexane (5.5 mL) followed by 1.25 equiv of the diene **13** (1.25 mL, 6.3 mmol). The reaction mixture was stirred for 3 h and allowed to warm to room temperature. After addition of a $NaHCO_3$ solution (30 mL) (half-saturated), the aqueous phase was extracted with CH_2Cl_2 (30 mL). The combined organic phases were extracted with saturated $NaHCO_3$ (50 mL), H_2O (50 mL), and brine (50 mL) and dried with $MgSO_4$, and the solvent was evaporated in vacuo. The residue was purified by flash chromatography with hexane−acetone mixtures as eluents.

According to the procedures described above, the following 2,3-didehydro-4-oxopiperidines were prepared.

***N*-[2-(2-Bromo-4,5-dimethoxyphenyl)ethyl]-2,3-didehydro-4-oxo-6-phenylpiperidine (15a).** Procedure 1: yield 58%; yellowish amorphous solid; mp 102−103 °C; silica gel TLC R_f 0.25 (1:1 hexane−acetone); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.43−7.29 (m, 5H), 7.07 (d, $J = 8.0$ Hz, 1H), 6.97 (s, 1H), 6.49 (s, 1H), 5.02 (d, $J = 8.0$ Hz, 1H), 4.63 (dd, $J = 6.9$, 8.5 Hz, 1H), 3.85 (s, 3H), 3.70 (s, 3H), 3.38−3.26 (m, 2H), 2.92−2.83 (m, 2H), 2.83 (dd, $J = 6.9$, 16.6 Hz, 1H), 2.70 (dd, $J = 8.5$, 16.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 190.2, 153.9 (CH), 148.5, 148.4, 138.6, 129.0 (2C, CH), 128.9, 128.3 (CH), 127.1 (2C, CH), 115.6 (CH), 114.1, 113.3 (CH), 98.6 (CH), 61.5 (CH), 56.1 (CH_3), 56.0 (CH_3), 53.2 (CH_2), 43.8 (CH_2), 35.5 (CH_2); IR (drift) 1637, 1593, 1511 cm^{-1}; UV (λ_{max} (ϵ), MeOH) 202 (50 400), 228.3 (sch, 11 550), 293 (5810), 327 (15 440) nm; MS (130 °C) *m/e* 417 (23), 415 (22), 231, 229 (4), 186 (100), 117 (11), 82 (73); HRMS (130 °C) *m/e* calcd for (M^+) 415.0783, found 415.0798.

***N*-[2-(2-Bromo-4,5-dimethoxyphenyl)ethyl]-2,3-didehydro-4-oxopiperidine (15d).** Procedure 1: yield 47%; yellow oil; silica gel TLC R_f 0.11 (1:1 hexane−acetone); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.03 (s, 1H), 6.88 (d, $J = 7.4$ Hz, 1H), 6.67 (s, 1H), 4.90 (d, $J = 7.4$ Hz, 1H), 3.87 (s, 3H), 3.85 (s, 3H), 3.51 (t, $J = 7.8$ Hz, 2H), 3.45 (t, $J = 7.1$ Hz, 2H), 2.95 (t, $J = 7.1$ Hz, 2H), 2.47 (t, $J = 7.8$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 191.3, 154.0 (CH), 148.6, 148.5, 128.7, 115.7 (CH), 114.1, 113.4 (CH), 98.0 (CH), 56.2 (2C, CH_3), 55.8 (CH_2), 47.3 (CH_2), 35.6 (CH_2), 35.5 (CH_2); MS (140 °C) *m/e* 341 (14), 339 (14), 260 (4), 231, 229 (5), 110 (100), 82 (11); HRMS (105 °C) *m/e* calcd for $C_{15}H_{18}BrNO_3$ (M^+, 340.22) 339.0470, found 339.0456.

***N*-[2-(2-Bromo-4,5-dimethoxyphenyl)ethyl]-2,3-didehydro-4-oxo-6-propylpiperidine (15e).** Procedure 3: yield 43%; brown viscous oil; silica gel TLC R_f 0.22 (1:1 hexane−acetone); major conformational isomer at C-6 (equatorial); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.03 (s, 1H), 6.82 (d, $J = 7.3$ Hz, 1H), 6.69 (s, 1H), 4.85 (d, $J = 7.3$ Hz, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.49−3.39 (m, 3H), 3.07−2.88 (m, 2H), 2.69 (dd, $J = 6.9$, 16.4 Hz, 1H), 2.29 (dd, $J = 2.6$, 16.4 Hz, 1H), 1.75−1.20 (4m, 4H), 0.91 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 190.4, 152.2 (CH), 148.7, 148.5, 128.8, 115.7 (CH), 114.2, 113.6 (CH), 96.8 (CH), 56.6 (CH), 56.2 (CH_3), 56.1 (CH_3), 53.8 (CH_2), 39.5 (CH_2), 36.8 (CH_2), 31.2 (CH_2), 18.8 (CH_2), 14.0 (CH_3); MS (120 °C) *m/e* 383 (13), 381 (13), 340 (2), 338 (2), 302 (4), 244, 242 (10), 231, 229 (15), 164 (42), 152 (100), 151 (32), 110 (45), 86 (23), 84 (37), 82 (27); HRMS (120 °C) *m/e* calcd for $C_{18}H_{24}BrNO_3$ (M^+, 382.29) 381.0939, found 381.0924.

***N*-[2-(2-Bromo-4,5-dimethoxyphenyl)ethyl]-2,3-didehydro-3-ethyl-4-oxo-6-phenylpiperidine (16a).** Procedure 1: yield 45%; red orange viscous oil; silica gel TLC R_f 0.18 (2:1 hexane−acetone); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.37−7.26 (m, 5H), 6.96 (s, 1H), 6.89 (s, 1H), 6.47 (s, 1H), 4.57 (dd, $J = 6.8$, 9.8 Hz, 1H), 3.83 (s, 3H), 3.85 (s, 3H), 3.31−3.16 (m, 2H), 2.88−2.76 (m, 2H), 2.75−2.65 (m, 2H), 2.13 (q, $J = 7.4$ Hz, 2H), 0.97 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 189.6, 151.7 (CH), 148.5, 148.4, 139.0, 129.3, 128.9 (2C, CH), 128.2 (CH), 127.3 (2C, CH), 115.6 (CH), 114.1, 113.4 (CH), 112.4, 62.1 (CH), 56.2 (CH_3), 56.0 (CH_3), 52.9 (CH_2), 44.4 (CH_2), 35.3 (CH_2), 20.3 (CH_2), 14.5 (CH_3); IR (drift) 1640, 1609, 1508 cm^{-1}; UV (λ_{max} (ϵ), MeOH) 192 (46 960), 202 (53 550), 229 (sch, 12 720), 291 (4250), 341 (17 480) nm; MS (115 °C) *m/e* 445 (21), 443 (21), 365 (4), 229 (2), 214 (100), 117 (9), 110 (40); HRMS (115 °C) calcd for (M^+) 443.1096, found 443.1084. Anal. Calcd

for $C_{23}H_{26}BrNO_3$ (444.37): C, 62.17; H, 5.89; N, 3.15. Found: C, 62.14; H, 5.72; N, 2.63.

***N*-[2-(2-Bromo-4,5-dimethoxyphenyl)ethyl]-2,3-didehydro-3-ethyl-4-oxopiperidine (16d).** Procedure 1: yield 64%; yellow viscous oil; silica gel TLC R_f 0.19 (3:2 hexane−acetone); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.03 (s, 1H), 6.72 (s, 1H), 6.68 (s, 1H), 3.87 (s, 3H), 3.84 (s, 3H), 3.46−3.39 (m, 4H), 2.94 (t, J = 7.1 Hz, 2H), 2.45 (t, J = 7.8 Hz, 2H), 2.08 (q, J = 7.5 Hz, 2H), 0.93 (t J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 190.4, 151.8 (CH), 148.6, 148.5, 129.1, 115.7 (CH), 114.2, 113.5 (CH), 111.6, 56.2 (CH_3), 56.1 (CH_3), 55.8 (CH_2), 47.5 (CH), 36.1 (CH_2), 35.4 (CH_2), 20.3 (CH_2), 14.5 (CH_3); IR (drift) 1664, 1591, 1510 cm^{-1}; UV (λ_{max} (ϵ), MeOH) 203 (44 550), 230 (sch, 11 000), 291 (4400), 337 (14 550) nm; MS (90 °C) *m/e* 369 (13), 367 (13), 288 (1), 229 (2), 138 (100), 110 (3); HRMS (100 °C) *m/e* calcd for (M^+) 367.0783, found 367.0769.

***N*-[2-(2-Bromo-4,5-dimethoxyphenyl)ethyl]-2,3-didehydro-3-ethyl-6-heptyl-4-oxopiperidine (16e).** Procedure 1: yield 22%; amber viscous oil; silica gel TLC R_f silica gel TLC R_f 0.15 (4:1 hexane−acetone); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.03 (s, 1H), 6.70 (s, 1H), 6.67 (s, 1H), 3.86 (s, 3H), 3.82 (s, 3H), 3.45−3.35 (m, 3H), 3.02−2.87 (m, 2H), 2.65 (dd, J = 6.7, 16.3 Hz, 1H), 2.30 (dd, J = 3.9, 16.3 Hz, 1H), 2.07 (q, J = 7.4 Hz, 2H), 1.67−1.56 (m, 2H), 1.26 (br s, 10H), 0.93 (t, J = 7.4 Hz, 3H), 0.87 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 189.3, 150.1 (CH), 148.5, 148.4, 129.1, 115.7 (CH), 114.1, 113.7 (CH), 110.0, 56.8 (CH), 56.1 (CH_3), 56.0 (CH_3), 53.6 (CH_2), 39.8 (CH_2), 36.7 (CH_2), 31.7 (CH_2), 29.5 (CH_2), 29.1 (CH_2), 29.0 (CH_2), 25.5 (CH_2), 22.5 (CH_2), 20.1 (CH_2), 14.6 (UH_3), 14.0 (CH_3); IR (drift) 1636, 1601, 1510 cm^{-1}; UV (λ_{max} (ϵ), MeOH) 203 (39 700), 229 (9900), 288 (3600), 343 (11 850) nm; MS (110 °C) *m/e* 467 (16), 465 (16), 387 (4), 368, 366 (4), 244, 242 (14), 236 (100), 231, 229 (9), 164 (6), 138 (39), 126 (16); HRMS (115 °C) *m/e* calcd for $C_{24}H_{36}BrNO_3$ (M^+, 466.46) 465.1879, found 465.1866.

***N*-[(1*S*)-(Carboxymethyl)-2-(2-bromo-4,5-dimethoxyphenyl)ethyl]-2,3-didehydro-6-(4-nitrophenyl)-4-oxopiperidine (19).** Procedure 2: yield 28%; brownish amorphous solid; mp 61−63 °C; silica gel TLC R_f 0.31 (2:1 hexane−acetone); $[\alpha]^{25}_D$ = −28.8 (*c* 1, CH_2Cl_2); dr 89:11; major isomer; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.04 (d, J = 8.8 Hz, 2H), 7.42 (d, J = 8.1 Hz, 1H), 7.07 (d, J = 8.8 Hz, 2H), 6.93 (s, 1H), 6.58 (s, 1H), 5.29 (d, J = 8.1 Hz, 1H), 4.78 (dd, J = 6.0, 10.9 Hz, 1H), 3.93 (dd, J = 5.5, 10.1 Hz, 1H), 3.90 (s, 3H), 3.79 (s, 3H), 3.71 (s, 3H), 3.30 (dd, J = 5.5, 14.3 Hz, 1H), 3.07 (dd, J = 10.1, 14.3 Hz, 1H), 2.71 (dd, J = 5.9, 16.4 Hz, 1H), 2.57 (dd, J = 10.9, 16.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 189.9, 170.5, 150.5 (CH), 149.2, 148.4, 147.8, 145.4, 128.3 (2C, CH), 126.7, 124.2 (2C, CH), 115.5 (CH), 114.8, 114.4 (CH), 101.9 (CH), 63.0 (CH), 61.8 (CH), 56.3 (CH_3), 56.2 (CH_3), 52.8 (CH_3), 43.8 (CH_2), 36.4 (CH_2); MS (150 °C) *m/e* 520 (9), 518 (9), 461, 459 (3), 289 (6), 238 (11), 231 (98), 229 (100), 221 (7), 151 (10), 140 (15), 88 (4); HRMS (150 °C) *m/e* calcd for (M^+) 518.0688, found 518.0668.

As a side reaction product the Mannich adduct **20** was isolated (see the Supporting Information).

***N*-[(1*S*)-(Carboxymethyl)-2-(2-bromo-4,5-dimethoxyphenyl)ethyl]-2,3-didehydro-3-ethyl-4-oxopiperidine (22).** Procedure 1: yield 48%; yellow viscous oil; silica gel TLC R_f 0.12 (2:1 hexane−acetone); $[\alpha]^{25}_D$ = −104.9 (*c* 0.92, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.01 (s, 1H), 6.84 (s, 1H), 6.66 (s, 1H), 4.18 (dd, J = 6.5, 8.9 Hz, 1H), 3.85 (s, 3H), 3.79 (s, 3H), 3.75 (s, 3H), 3.51−3.44 (m, 1H), 3.36−3.29 (m 1H), 3.33 (dd, J = 6.5, 14.1 Hz, 1H), 3.07 (dd, J = 8.9, 14.1 Hz, 1H), 2.41−2.37 (m, 2H), 2.09 (q, J = 7.5 Hz, 2H), 0.94 (t, J = 7.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 191.2, 170.5, 149.9 (CH), 148.9, 148.5, 127.4, 115.7 (CH), 114.4, 114.1 (CH), 113.7, 66.1 (CH), 56.2 (CH_3), 56.1 (CH_3), 52.6 (CH_3), 46.7 (CH_2), 36.5 (CH_2), 36.3 (CH_2), 20.5 (CH_2), 14.5 (CH_3); MS (100 °C) *m/e* 427 (13), 425 (13), 368, 366 (6), 246 (23), 245 (10), 244 (22), 243 (8), 231, 229 (17), 196 (100), 86 (44), 84 (71), 51 (25), 49 (79); HRMS (100 °C) *m/e* calcd for (M^+) 425.0838, found 425.0826. Anal. Calcd for $C_{19}H_{24}BrNO_5 \cdot H_2O$ (426.31): C, 51.36; H, 5.89; N, 3.15. Found: C, 51.55; H, 5.65; N, 2.75.

General Procedure for the Heck-Type Cyclization. (A) Under Homogeneous Conditions. A mixture of 1 mmol of the respective enaminone **15**, 5 mol % of $Pd_2(dba)_3 \cdot CHCl_3$, and 40 mol % of PPh_3 was dried under reduced pressure by carefully heating. After addition of DMF (25 mL) and 2.5 mmol of NEt-*i*-Pr_2 under argon, the resulting solution was stirred at room temperature until the color turned to yellow. After the solution was heated to 100 °C for several hours (see Table 3), the solvent was removed in vacuo and the crude benzo[*a*]quinolizinone was purified by flash chromatography using hexane−acetone mixtures as eluents.

(B) Under Heterogeneous Conditions. A mixture of 1 mmol of the respective enaminone **15**, 5 mol % of $Pd_2(dba)_3 \cdot CHCl_3$, 20 mol % of PPh_3, 1−10 mmol of K_2CO_3, and 1−1.2 mmol NEt_4Cl was dried under reduced pressure by carefully heating. After addition of DMF (25 mL), the resultion solution was stirred at room temperature or at 40 °C until the color turned to yellow and then was heated at 120 °C for several hours (see Table 3). The solvent was removed in vacuo, and the residue was purified by flash chromatography using hexane−acetone mixtures as eluents.

According to the procedures described above, the following 4-substituted benzo[*a*]quinolizinones were prepared.

9,10-Dimethoxy-4-(4-methoxyphenyl)-2-oxo-3,4,6,7-tetrahydrobenzo[*a*]quinolizine (26b). Procedure A: 6 h; yield 51%. Procedure B: 3 h; yield 76%; yellowish amorphous solid; mp 167−170 °C; silica gel TLC R_f 0.17 (1:2 hexane−acetone); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.26 (d, J = 8.7 Hz, 2H), 7.22 (s, 1H), 6.87 (d, J = 8.7 Hz, 2H), 6.67 (s, 1H), 5.72 (s, 1H), 4.69 (t, J = 6.9 Hz, 1H), 3.92, 3.90 and 3.79 (3s, 9H), 3.35−3.22 (m, 2H), 3.02 (dd, J = 7.0, 16.4 Hz, 1H), 2.85 (t, J = 6.8 Hz, 2H), 2.71 (dd, J = 6.8, 16.4 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 190.2, 159.3, 157.0, 151.6, 147.9, 131.7, 129.5, 128.0 (2C, CH), 121.1, 114.3 (2C, CH), 110.2 (CH), 108.7 (CH), 94.8 (CH), 64.2 (CH), 56.0 and 55.3 (3C, CH_3), 46.3 (CH_2), 43.4 (CH_2), 28.6 (CH_2); MS (150 °C) *m/e* 366 (21), 365 (100), 350 (8), 338 (8), 337 (29), 336 (21), 322 (24), 277 (10), 263 (10), 262 (64), 258 (7), 230 (9), 207 (9), 200 (5), 191 (14), 183 (29), 178 (23), 176 (9), 175 (9), 135 (20), 134 (13); HRMS (150 °C) *m/e* calcd for (M^+) 365.1627, found 365.1613. Anal. Calcd for $C_{22}H_{23}NO_4 \cdot {}^1/_3H_2O$ (365.43): C, 71.14; H, 6.42; N, 3.76. Found: C, 71.22; H, 6.41; N, 3.32.

9,10-Dimethoxy-4-(4-methoxyphenyl)-2-oxo-1,6,7,11b-tetrahydrobenzo[*a*]quinolizine (27b). Procedure B: yield 9%; brown oil; silica gel TLC R_f 0.33 (1:2 hexane−acetone); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.34 (d, J = 8.7 Hz, 2H), 6.96 (d, J = 8.7 Hz, 2H), 6.68 (s, 1H), 6.65 (s, 1H), 5.23 (s, 1H), 4.96 (dd, J = 12.7, 7.0 Hz, 1H), 3.88, 3.87 and 3.86 (3s, 9H), 3.73 (td, J = 4.0, 12.4 Hz, 1H), 3.26 (td, J = 12.3, 3.1 Hz, 1H), 2.90−2.84 (m, 1H), 2.74−2.63 (m, 3H); ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ = 192.6, 165.3, 160.9, 148.2, 147.9, 129.6 (2C, CH), 128.1, 127.3, 126.2, 114.0 (2C, CH), 111.1 (CH), 108.7 (CH), 102.7 (CH), 57.9 (CH), 56.0 (CH_3), 55.9 (CH_3), 55.4 (CH_3), 46.2 (CH_2), 44.9 (CH_2), 30.2 (CH_2); MS (150 °C) *m/e* 366 (22), 365 (100), 350 (8), 338 (7), 337 (30), 336 (21), 322 (26), 258 (7), 230 (9), 200 (5), 175 (9), 134 (11); HRMS (150 °C) *m/e* calcd for $C_{22}H_{23}NO_4$ (365.43) 365.1627, found 365.1614.

9,10-Dimethoxy-2-oxo-3,4,6,7-tetrahydrobenzo[*a*]quinolizine (26d). Procedure A: 15 h; yield 13%. Procedure B: 6 h; 17%; brownish amorphous solid; silica gel TLC R_f 0.10 (1:4 hexane−acetone); not fully separable from PPh_3O; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.16 (s, 1H), 6.67 (s, 1H), 5.69 (s, 1H), 3.92 (s, 3H), 3.88 (s, 3H), 3.63 (t, J = 8.0 Hz, 2H), 3.39 (t, J = 7.1 Hz, 2H), 2.95 (t, J = 7.1 Hz, 2H), 2.59 (t, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 192.1, 157.8, 151.6, 148.1, 128.8, 120.8, 110.3 (CH), 108.3 (CH), 95.0 (CH), 56.0 (2C, CH_3), 51.5 (CH_2), 48.9 (CH_2), 35.6 (CH_2), 28.5 (CH_2); MS (125 °C) *m/e* 278 (21), 277 (36), 259 (100), 258 (54), 231 (23), 230 (53), 228 (11), 216 (12), 201 (6), 189 (10), 177 (8), 129 (5); HRMS (125 °C) *m/e* calcd for $C_{15}H_{17}NO_3$ (259.31) 259.1208, found 259.1196.

9,10-Dimethoxy-2-oxo-1,6,7,11b-tetrahydrobenzo[*a*]-quinolizine (27d). Procedure B: 11 h; yield 35%; yellowish solid; mp 169−170 °C; silica gel TLC R_f 0.31 (1:4 hexane−acetone); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.19 (d, J = 7.2 Hz,

1H), 6.67 (s, 1H), 6.61 (s, 1H), 5.06 (d, J = 7.2 Hz, 1H), 4.68 (dd, J = 4.3, 14.5 Hz, 1H), 3.88 (s, 3H), 3.84 (s, 3H), 3.63 (m, 1H), 3.44 (td, J = 12.5, 3.5 Hz, 1H), 3.10 (ddd, J = 5.0, 12.5, 16.5 Hz, 1H), 2.82 (m, 1H), 2.75 (dd, J = 4.3, 14 Hz, 1H), 2.51 (dd, J = 11.5, 14 Hz, 1H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 192.9, 151.2 (CH), 148.3, 148.0, 126.7, 125.4, 110.5 (CH), 108.1 (CH), 98.4 (CH), 56.4 (CH), 56.1 (CH_3), 56.0 (CH_3), 49.8 (CH_2), 44.9 (CH_2), 29.8 (CH_2); MS (120 °C) *m/e* 260 (15), 259 (100), 258 (5), 244 (6), 231 (20), 230 (61), 216 (15), 200 (7), 175 (12), 115 (6), 43 (3); HRMS (120 °C) *m/e* calcd for $C_{15}H_{17}NO_3$ (259.31) 259.1208, found 259.1218.

9,10-Dimethoxy-2-oxo-4-propyl-3,4,6,7-tetrahydrobenzo[*a*]quinolizine (26e). Procedure B: 5 h; yield 26%; brown viscous oil; silica gel TLC R_f 0.17 (1:4 hexane−acetone); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.16 (s, 1H), 6.67 (s, 1H), 5.56 (s, 1H), 3.92 (s, 3H), 3.88 (s, 3H), 3.77−3.55 (m, 1H, 4-H), 3.47 (t, J = 6.4 Hz, 2H), 2.94−2.86 (m, 3H), 2.41 (br d, J = 16.6 Hz, 1H), 1.25−1.94 (m, 4H), 0.94 (t, J = 6.5 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125.7 MHz) δ 191.0, 155.5, 151.9, 148.5, 129.4, 121.9, 110.6 (CH), 109.2 (CH), 93.7 (CH), 61.5 (CH), 56.4 (2C, CH_3), 47.6 (CH_2), 39.4 (CH_2), 31.6 (CH_2), 29.3 (CH_2), 19.6 (CH_2), 14.4 (CH_3); MS (120 °C) *m/e* 302 (17), 301 (100), 300 (30), 259 (98), 258 (58), 242 (11), 232 (15), 231 (74), 230 (38), 216 (17), 214 (11), 207 (17), 205 (12), 150 (8), 129 (11), 43 (8); HRMS (120 °C) *m/e* calcd for $C_{18}H_{23}NO_3$ (301.39) 301.1677, found 301.1667.

9,10-Dimethoxy-2-oxo-4-propyl-1,6,7,11b-tetrahydrobenzo[*a*]quinolizine (27e). Procedure B: 8 h; yield 42%; brown glassy solid; silica gel TLC R_f 0.25 (1:2 hexane−acetone); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.65 (s, 1H), 6.62 (s, 1H), 5.11 (s, 1H), 4.69 (dd, J = 16.0, 3.8 Hz, 1H), 3.98 (ddd, J = 12.3, 4.0, 2.6 Hz, 1H), 3.88 (s, 3H), 3.84 (s, 3H), 3.15 (td, J = 12.1, 2.7 Hz, 1H), 3.00 (ddd, J = 15.5, 11.7, 4.0 Hz, 1H), 2.76 (dd, J = 15.5, 2.4, 1H), 2.69 (dd, J = 4.0, 16.3 Hz, 1H), 2.45 (dd, J = 16.0, 16.2 Hz, 1H), 2.37 (m, 2H), 1.62 (sext, J = 7.5 Hz, 2H), 1.03 (t, J = 7.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100.5 MHz) δ 192.2, 166.2, 148.2, 147.9, 127.3, 125.7, 111.0 (CH), 108.4 (CH), 100.7 (CH), 58.0 (CH), 55.9 (2C, CH_3), 45.0 (CH_2), 43.6 (CH_2), 35.9 (CH_2), 29.9 (CH_2), 21.2 (CH_2), 13.9 (CH_3); MS (110 °C) *m/e* 302 (16), 301 (89), 300 (26), 286 (8), 273 (28), 272 (100), 258 (24), 245 (13), 244 (63), 207 (14), 190 (14), 150 (9), 124 (8), 82 (10); HRMS (110 °C) *m/e* calcd for $C_{18}H_{23}NO_3$ (301.39) 301.1677, found 301.1671.

General Procedure for the Heck-Type Cyclization of 3-Ethyl-Substituted Enaminones under Heterogeneous Conditions. A mixture of 1 mmol of the respective enaminone **16**, 5 mol % of $Pd_2(dba)_3$·$CHCl_3$, 20 mol % of the used phosphine, 8−10 mmol of K_2CO_3, and 1.1−1.2 mmol NEt_4Cl was dried under reduced pressure by carefully heating. After addition of toluene (40 mL), the resulting solution was stirred at 40 °C until the color turned to yellow and then was refluxed for several hours (see Table 5). The solvent was evaporated in vacuo, and the residue was purified by flash chromatography using hexane−acetone mixtures as eluents.

According to the procedure described above, the following 1-ethenyl-substituted benzo[*a*]quinolizinones were prepared.

9,10-Dimethoxy-1-ethylenyl-2-oxo-4-phenyl-1,3,4,6,7,-11b-hexahydrobenzo[*a*]quinolizine (36a/37a): brownish amorphous solid; mp 79−81 °C; silica gel TLC R_f 0.35 (4:3 hexane−acetone). **(1*E*)-Isomer 36a:** ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.42−7.29 (m, 5H), 7.02 (q, J = 7.3 Hz, 1H), 6.64 (s, 1H), 6.44 (s, 1H), 5.39 (br. s, 1H), 4.09 (dd, J = 4.1, 10.7 Hz, 1H), 3.85 (s, 3H), 3.76 (s, 3H), 3.18 (dd, J = 5.6, 12.6 Hz, 1H), 3.10 (dd, J = 6.4, 14.1 Hz, 1H), 2.86−2.77 (m, 1H), 2.61 (dd, J = 10.7, 16.9 Hz, 1H), 2.53 (dd, J = 4.1, 16.9 Hz, 1H), 2.36 (dd, J = 5.4, 17.2 Hz, 1H), 1.94 (d, J = 7.3, 3H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 198.3, 148.1, 147.6, 141.8, 136.9, 135.5 (CH), 128.8 (2C, CH), 127.8 (CH), 127.6 (2C, CH), 126.6, 124.9, 112.3 (CH), 110.4 (CH), 59.4 (CH), 56.6 (CH), 55.9 (2C, CH_3), 48.8 (CH_2), 46.9 (CH_2), 22.6 (CH_2), 14.2 (CH_3); MS (110 °C) *m/e* 363 (100), 362 (51), 348 (14), 294 (41), 231 (8), 218 (39), 192 (22), 191 (12), 190 (20), 176 (5), 91 (5). **(1*Z*)-Isomer 37a:** ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.6−7.1 (m, 5H), 6.63 (s, 1H), 6.51 (s, 1H), 5.81 (q, J = 7.1 Hz, 1H), 4.98 (s, 1H), 4.00 (dd, J = 4.2, 10.3 Hz, 1H), 3.87 (s, 3H), 3.81 (s, 3H), 3.02 (t, J = 6.2 Hz, 2H), 2.86 (dd, J = 10.4, 15.6 Hz, 1H), 2.80−2.66 (m, 2H), 2.60 (dd, J = 4.2, 15.6 Hz, 1H), 2.06 (d, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 201.3, 148.0, 147.2, 142.1, 137.0, 136.6 (CH), 128.6 (2C, CH), 127.6 (CH), 127.4 (2C, CH), 126.8, 125.5, 111.6 (CH), 111.2 (CH), 63.5 (CH), 60.1 (CH), 56.0 (CH_3), 55.9 (CH_3), 48.7 (CH_2), 46.2 (CH_2), 25.5 (CH_2), 15.1 (CH_3); MS (105 °C) *m/e* 363 (100), 362 (49), 348 (13), 320 (4), 294 (50), 231 (10), 218 (47), 192 (36), 191 (22), 190 (37), 176 (12), 131 (8), 104 (9), 103 (11), 91 (10), 77 (7); HRMS (110 °C) *m/e* calcd for $C_{23}H_{25}NO_3$ (363.46) 363.1834, found 363.1825.

9,10-Dimethoxy-1(*E*)-ethylenyl-2-oxo-1,3,4,6,7,11b-hexahydrobenzo[*a*]quinolizine (36d): 6 h; yield 24%; brownish amorphous solid; mp 146−150 °C; silica gel TLC R_f 0.12 (1:1 hexane−acetone); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.99 (q, J = 7.4, 1H), 6.63 (s, 1H), 6.38 (s, 1H), 5.19 (s, 1H), 3.86 (s, 3H), 3.76 (s, 3H), 3.50 (ddd, J = 6.1, 12.5, 13.7 Hz, 1H), 3.35 (dd, J = 6.8, 13.8 Hz, 1H), 3.17−3.03 (m, 2H), 2.92−2.87 (m, 1H), 2.69−2.59 (m, 2H), 2.43 (ddd, J = 2.1, 3.6, 17 Hz, 1H), 1.90 (d, J = 7.3, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 198.4, 148.0, 147.5, 136.8, 136.1 (CH), 125.8, 124.9, 112.2 (CH), 110.4 (CH), 58.5 (CH), 55.9 (2C, CH_3), 51.2 (CH_2), 43.2 (CH), 39.82 (CH_2), 22.84 (CH_2), 14.2 (CH_3); IR (drift) 1691, 1606, 1513 cm^{-1}; UV (λ_{max} (ϵ), MeOH) 202 (26 700), 225 (12 600), 257 (sch, 6250), 278 (sch, 5100), 308 (3900), 350 (2200) nm; MS (115 °C) *m/e* 287 (42), 286 (25), 272 (100), 256, 228 (3), 207 (8), 178 (4), 150 (4), 123 (3), 84 (5); $C_{17}H_{21}NO_3$ (287.36); HRMS (115 °C) *m/e* calcd for $C_{17}H_{21}NO_3$ (M^+, 287.36) 287.1512, found 287.1533.

9,10-Dimethoxy-1-ethylenyl-4-heptyl-2-oxo-1,3,4,6,7,-11b-hexahydrobenzo[*a*]quinolizine (36e/37e): 48 h. **(1*E*)-Isomer 36e:** yield 20%; dark yellow glassy solid; silica gel TLC R_f 0.23 (3:1 hexane−acetone); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 6.99 (q, J = 7.4 Hz, 1H), 6.64 (s, 1H), 6.37 (s, 1H), 5.26 (s, 1H), 3.86 (s, 3H) 3.75 (s, 3H), 3.59 (dd, J = 6.3, 14.2 Hz, 1H), 3.35 (ddd, J = 5.5, 12.6, 14.2 Hz, 1H), 3.09−2.99 (m, 2H), 2.57 (dd, J = 5.3, 17.0 Hz, 1H), 2.47 (dd, J = 4.3, 16.5 Hz, 1H), 2.29 (dd, J = 9.2, 16.5 Hz, 1H), 1.88 (d, J = 7.4 Hz, 3H), 1.40−1.27 (br. m, 12 H), 0.88 (t, J = 6.9 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 198.9, 147.9, 147.5, 136.9, 135.3 (CH), 126.7, 126.1, 112.2 (CH), 109.9 (CH), 59.2 (CH), 55.9 (2C, CH_3), 50.8 (CH), 47.1 (CH_2), 44.3 (CH_2), 34.5 (CH_2), 31.8 (CH_2), 29.9 (CH_2), 29.2 (CH_2), 24.7 (CH_2), 22.8 (CH_2), 22.6 (CH_2), 14.1 (CH_3), 14.0 (CH_3); IR (film) 1693, 1622, 1518 cm^{-1}; UV (λ_{max} (ϵ), MeOH) 202 (42 850), 225 (sch, 16 200), 286 (7400), 31 (sch, 4950) nm; MS (80 °C) *m/e* 386 (7), 286 (50), 254 (15), 253 (13), 252 (12), 236 (47), 234 (30), 218 (21), 189 (41), 165 (18), 152 (16), 131 (100), 103 (47), 91 (25), 77 (35); HRMS (80 °C) *m/e* calcd for $C_{24}H_{35}NO_3$ (385.55) 385.2617, found 385.2607. **(1*Z*)-Isomer 37e:** yield 20%; dark yellow glassy solid; silica gel TLC R_f 0.33 (3:1 hexane−acetone); ^{1}H NMR ($CDCl_3$, 400 MHz) δ 6.63 (s, 1H), 6.45 (s, 1H), 5.39 (q, J = 7.2 Hz, 1H), 4.81 (s, 1H), 3.86 (s, 3H), 3.80 (s, 3H), 3.15−3.09 (m, 1H), 2.99−2.88 (m, 2H), 2.84 (ddd, J = 3.1, 6.2, 11.2 Hz, 1H), 2.71 (td, J = 3.5, 15.7 Hz, 1H), 2.69 (dd, J = 5.5, 15.5 Hz, 1H), 2.47 (dd, J = 6.3, 15.2 Hz, 1H), 1.90 (d, J = 7.2 Hz, 3H), 1.71−1.61 (m, 1H), 1.55−1.44 (m, 1H), 1.36−1.26 (br m, 10H), 0.87 (t, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 203.1, 148.1, 146.9, 138.9, 135.3 (CH), 127.3, 125.5, 111.7 (CH), 111.7 (CH), 60.2 (CH), 59.4 (CH), 56.0 (CH_3), 55.9 (CH_3), 46.2 (CH_2), 44.5 (CH_2), 35.2 (CH_2), 31.9 (CH_2), 29.7 (CH_2), 29.3 (CH_2), 28.4 (CH_2), 26.2 (CH_2), 22.7 (CH_2), 15.0 (CH_3), 14.2 (CH_3); IR (Film) 1693, 1624, 1607 cm^{-1}; UV (λ_{max} (ϵ), MeOH) 202 (43 550), 227 (17 000), 285 (7500), 328 (sch, 2750) nm; MS (85 °C) *m/e* 385 (11), 286 (100), 234 (12), 218 (37), 210 (15), 191 (13), 189 (23), 165 (36), 131 (21), 113 (13), 103 (13), 77 (15), 60 (15); HRMS (85 °C) *m/e* calcd for $C_{24}H_{25}NO_3$ (385.55) 385.2617, found 385.2605.

(6*S*,11b*RS*)-6-(Carboxymethyl)-9,10-dimethoxy-1(*E*)-ethyliden-2-oxo-1,3,4,6,7,11b-hexahydrobenzo[*a*]quinolizine (40): 3 h; yield 32%; dr 2:1; reddish glassy solid; major stereoisomer at C-11b; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.10 (q, J = 7.3 Hz, 1H), 6.74 (s, 1H), 6.42 (s, 1H), 5.12 (br s, 1H), 3.88 (s, 3H), 3.80 (s, 3H), 3.55 (t, J = 7.1 Hz, 1H), 3.14−3.03 (m, 2H), 2.97−2.93 (m, 1H), 2.85−2.61 (m, 2H), 2.44−2.37 (m, 1H), 1.78 (d, 3H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 197.8, 173.4, 148.3, 147.7, 137.7 (CH), 134.9, 126.5, 125.5, 111.7 (CH), 109.9 (CH), 62.5 (CH), 56.1 (CH_3), 56.0 (CH_3), 54.5 (CH), 52.4 (CH_3), 47.5 (CH_2), 40.0 (CH_2), 26.8 (CH_2), 14.1 (CH_3); minor stereo-

isomer at C-11b; ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.02 (q, 7.3 Hz, 1H), 6.68 (s, 1H), 6.39 (s, 1H), 5.30 (br s, 1H), 4.22 (dd, J = 5.7, 12.6 Hz, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.21 (dd, J = 12.6, 14.5 Hz, 1H), 2.97−2.93 (m, 1H), 2.85−2.61 (m, 3H), 2.44−2.37 (m, 1H), 1.90 (d, J = 7.3 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125.8 MHz) δ 197.8, 171.8, 148.3, 147.9, 136.7 (CH), 136.5, 125.0, 124.1, 112.2 (CH), 110.5 (CH), 61.8 (CH), 60.4 (CH), 56.0 (CH_3), 55.9 (CH_3), 52.5 (CH_3), 39.5 (CH_2), 39.2 (CH_2), 24.8 (CH_2), 14.3 (CH_3); MS (120 °C) *m*/*e* 345 (11), 344 (5), 330 (12), 305 (22), 286 (100), 284 (16), 259 (7), 258 (7), 257 (5), 190 (6), 165 (5), 88 (7), 86 (94), 84 (76), 49 (8), 74 (25), 45 (6), 43 (55); HRMS (120 °C) *m*/*e* calcd for $C_{19}H_{22}NO_5$ (345.39) 345.1576, found 345.1594.

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Supporting Information Available: Experimental details and NMR spectra of selected new compounds (60 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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