Convenient Synthesis of Heterobicycles by Domino Heck−Diels−Alder Reactions

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Dedicated to Professor Frank-Gerrit Klärner on the occasion of his 60th birthday

Keywords: Heck reaction, intramolecular / Diels−Alder reaction / Tetrahydroisoindolines / Tetrahydroisoindolin-1-ones / Hexahydrobenzo[*c*]furans / Hexahydro-1*H*-[2]pyrindines

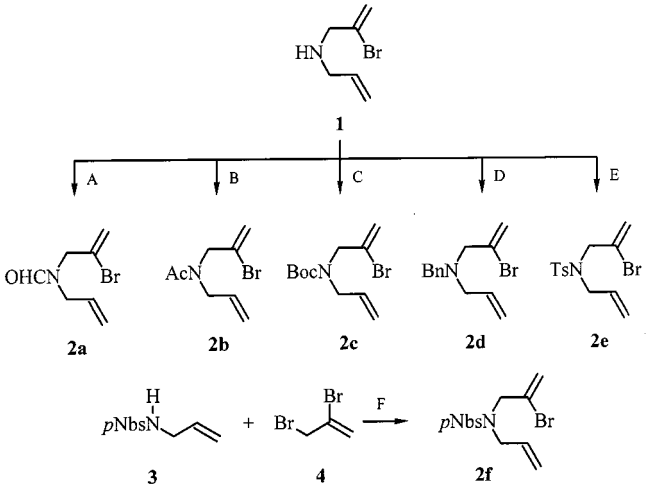
Palladium(0)-catalyzed intramolecular cross coupling of bromodialkenylamines, bromoalkenylalkenamides and bromodialkenyl ethers followed by in situ [4+2] cycloaddition with suitable dienophiles gave tetrahydroisoindolines (31–73% yield), tetrahydroisoindolin-1-ones (43–51%) and hexahydrobenzo[*c*]furans (35–55%), and hexahydro-1*H*-[2]pyrindines (66–75%), respectively, each in one-pot operations.

Introduction

Domino processes are particularly advantageous for the construction of bi-, tri-, and higher oligocyclic skeletons, as they allow the regio- and stereocontrolled formation of more than two new bonds in a single synthetic operation.[1] Important contributions to this area have been realized utilizing a combination of cationic, anionic, radical, carbenoid, and transition metal-catalyzed processes.[1a,2] Among these, the Heck reaction has in recent years[3] become one of the most important methods for carbon−carbon bond formation, since it allows the synthesis of a wide variety of compounds using only catalytic amounts of palladium. Furthermore, it is compatible with a large variety of functional groups. In earlier reports, we have described the facile construction of bicyclo[4.3.0]nonenes and bicyclo[4.4.0]decenes by a one-pot sequence consisting of an intramolecular Heck coupling and a subsequent Diels−Alder reaction.[4] Considering the important biological role of heterocyclic compounds, it was logical to extend our earlier work towards the synthesis of heterocycles having structural features related closely to those of biologically active natural products such as illudins,[5] ptaquilosin,[6] and cytochalasins.[7] We herein report on the palladium-catalyzed intramolecular cross coupling of various 2-bromo-4-aza- and 2-bromo-4-oxa-1,6-dienes leading to vicinal bis(methylene)pyrrolidines and -tetrahydrofurans, which upon in situ [4+2] cycloadditions with suitable dienophiles give substituted tetrahydroisoindolines, tetrahydroisoindolin-1-ones, and hexahydrobenzo[*c*]furans, respectively. We also report on the corresponding cyclization of an all-carbon 2-bromo-1,6-diene followed by Diels−Alder reaction with iminium ions to give hexahydro-1*H*-[2]pyrindines. Although intramolecular Heck couplings of bromodialkenylamines and bromodialkenyl ethers have been reported,[8,9] the subsequent Diels−Alder reactions of the resulting dienes have not been explored in sufficient detail, especially not in sequential one-pot operations.

Results and Discussion

Initial studies were carried out on the easily accessible 2-bromo-4-aza-1,6-heptadienes **2a**−**f** with a variety of standard protecting groups on the nitrogen atom in order to examine their influence on the outcome of the Heck−Diels−Alder reaction. The substrates **2a**−**e** were prepared from the known allyl(bromoallyl)amine **1**[8b] by



Boc = *t*BuOCO, Bn = $PhCH_2$, Ts = 4-$CH_3C_6H_4SO_2$, *p*Nbs = 4-$NO_2C_6H_4SO_2$

Scheme 1. Synthesis of **2a**−**f**: A: HCO_2Et, Et_3N, $TsOH·H_2O$, reflux, 24 h, 60%; B: Ac_2O, Et_3N, room temp., 2 d, 81%; C: (*t*BuO-CO)$_2$O, THF, reflux, 3 h, 54%; D: BnBr, Et_3N, Et_2O, 0 °C → room temp., 12 h, 80%; E: TsCl, Et_3N, THF, 0 °C → room temp., 5 h, 82%; F: K_2CO_3, DMF, room temp., 1 h, 98%

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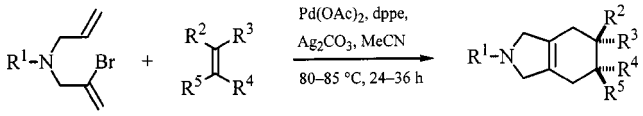
acylation, alkylation, or sulfonylation, whereas the 4-nitrobenzenesulfonamide **2f**[10a] was obtained by bromoallylation of *N*-allyl-4-nitrobenzenesulfonamide (**3**),[10b] which was in turn prepared by sulfonylation of allylamine in excellent yield (Scheme 1. The Pd^0-catalyzed intramolecular cross coupling of these terminally unsubstituted bromodienes **2a**−**f** led to the corresponding symmetrical 3,4-bis(methylene)-1-azacyclopentane derivatives. Upon in situ Diels−Alder reaction with symmetrically or unsymmetrically substituted dienophiles, these cyclopentane derivatives all gave single cycloadducts (Scheme 2, Table 1).



2a–f **5a–g** 31–73% **6**

2	R^1
a	CHO
b	Ac
c	Boc
d	Bn
e	Ts
f	4-$NO_2C_6H_4SO_2$

5	R^2	R^3	R^4	R^5
a	H	CO_2Me	H	H
b	H	CO_2tBu	H	H
c	H	CO_2tBu	CO_2tBu	H
d	H	CN	H	H
e	Cl	CN	H	H
f	H	CO_2Me	$-(CH_2CH_2)-$	
g	Cl	CO_2Me	$-(CH_2CH_2)-$	

Scheme 2. Heck−Diels−Alder reactions of **2a−f** with dienophiles **5a−g**; for details see Table 1

In a typical experiment, a solution of the *N*-formylazabromodiene **2a** (1.2 mmol), *tert*-butyl acrylate (**5b**) (2.4 mmol), silver carbonate (1.49 mmol), palladium acetate (5 mol-%), and 1,2-bis(diphenylphosphanyl)ethane[11] (dppe) (10 mol-%) in acetonitrile was heated at 80−85 °C for 24 h. The isolated product (54% yield) was characterized as *N*-formyltetrahydroisoindoline **6ab** (Scheme 2). The reactions of azabromodienes **2a−f** with dienophiles like methyl and *tert*-butyl acrylate (**5a** and **b**), di-*tert*-butyl maleate (**5c**), acrylonitriles **5d**,**e** also followed an analogous course to give the corresponding *N*-protected tetrahydroisoindolines **6ac−fe** in moderate to good yields (Entries 2−17, Table 1). Similarly, the treatment of **2a−c** and **2e** with cyclopropylideneacetates **5f**,**g**[12,13] under identical reaction conditions afforded the tricyclic adducts **6af−eg** in 41−69% overall yields (Entries 18−22, Table 1 and Scheme 2). Consistently, the cycloadducts containing *N*-Boc as well as *N*-benzyl groups were obtained in lower yields than those with *N*-acetyl and *N*-formyl groups. The yields of the cycloadducts were found to remain virtually constant when the reactions were run on a tenfold scale.

In order to study the scope of this domino process, as well as certain aspects of the regio- and stereochemistry, the simple *N*-protected bromodiene system **2** was modified in three features:

1) The nitrogen atom was replaced by oxygen; 2) a methyl group was introduced either at the bromoethenyl or at the ethenyl terminus; and 3) a carbonyl group was introduced next to the nitrogen atom, i.e. acrylamides were used instead of allylamines. In order to facilitate the analysis of the regiochemistry and relative configurations of the Heck−Diels−Alder products, methyl acrylate (**5a**) and methyl 2-cyclopropylideneacetate (**5f**) were used as dienophiles.

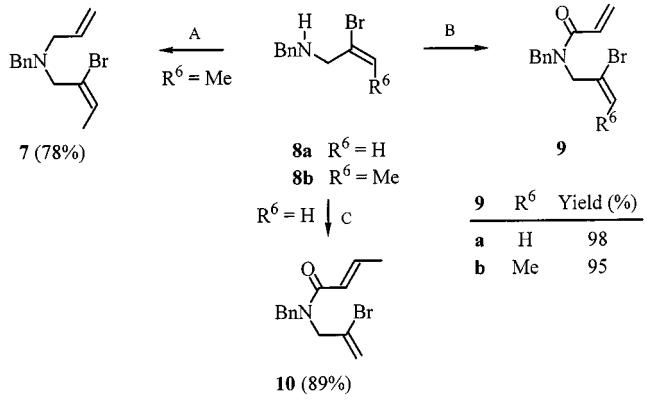
The methyl-substituted bromoallylamine **7** was prepared by allylation of *N*-benzyl-*N*-(2-bromo-2-butenyl)amine (**8b**) in 78% yield (Scheme 3). Acylation of the bromodialkylamines **8a**,**b** with acryloyl chloride and crotonyl chloride gave the corresponding amides **9a**,**b** and **10**, respectively, in nearly quantitative yields (Scheme 3). The oxygen-containing bromodienes **12** and **15** were prepared from the ap-

Table 1. Heck−Diels−Alder reactions of bromodialkenylamines **2a−f** with dienophiles **5a−g**

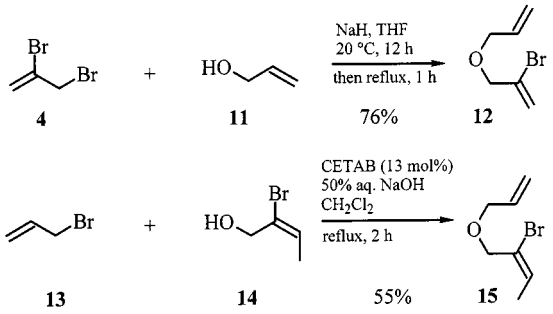
Entry[a]	Diene **2**	Dienophile **5**	Product **6**	R^1	R^2	R^3	R^4	R^5	Yield (%)
1	**a**	**b**	**ab**	CHO	H	CO_2tBu	H	H	54
2	**a**	**c**	**ac**	CHO	H	CO_2tBu	CO_2tBu	H	56
3	**a**	**d**	**ad**	CHO	H	CN	H	H	63
4	**a**	**e**	**ae**	CHO	Cl	CN	H	H	44
5	**b**	**a**	**ba**	MeCO	H	CO_2Me	H	H	54
6	**b**	**b**	**bb**	MeCO	H	CO_2tBu	H	H	62
7	**b**	**c**	**bc**	MeCO	H	CO_2tBu	CO_2tBu	H	55
8	**b**	**d**	**bd**	MeCO	H	CN	H	H	60
9	**b**	**e**	**be**	MeCO	Cl	CN	H	H	46
10	**c**	**a**	**ca**	Boc	H	CO_2Me	H	H	45
11	**d**	**a**	**da**	Bn	H	CO_2Me	H	H	46
12	**e**	**a**	**ea**	Ts	H	CO_2Me	H	H	45
13	**e**	**b**	**eb**	Ts	H	CO_2tBu	H	H	51
14	**e**	**d**	**ed**	Ts	H	CN	H	H	31
15	**e**	**e**	**ee**	Ts	Cl	CN	H	H	31
16	**f**	**a**	**fa**[b,c]	*p*Nbs[d]	H	CO_2Me	H	H	48
17	**f**	**b**	**fb**[b]	*p*Nbs	H	CO_2tBu	H	H	73
18	**a**	**f**	**af**	CHO	H	CO_2Me	$-(CH_2CH_2)-$		41
19	**a**	**g**	**ag**	CHO	Cl	CO_2Me	$-(CH_2CH_2)-$		45
20	**b**	**g**	**bg**	MeCO	Cl	CO_2Me	$-(CH_2CH_2)-$		69
21	**c**	**g**	**cg**	Boc	Cl	CO_2Me	$-(CH_2CH_2)-$		43
22	**e**	**g**	**eg**	Ts	Cl	CO_2Me	$-(CH_2CH_2)-$		44

[a] Reaction conditions: **2** (1.2 mmol), **5** (2.4 mmol), $Pd(OAc)_2$ (5 mol-%), dppe (10 mol-%), Ag_2CO_3 (1.49 mmol), MeCN, 80−85 °C, 24−36 h. − [b] Reaction time 2 h. − [c] PPh_3 (10 mol-%) instead of dppe. − [d] *p*Nbs = 4-$NO_2C_6H_4SO_2$.

propriate allyl alcohols **11** and **14**, and allyl bromides **4** and **13** by simple alkylation using NaH in anhydrous THF or basic phase transfer catalytic conditions for deprotonation of the alcohols, in 76 and 55% yields, respectively (Scheme 4).

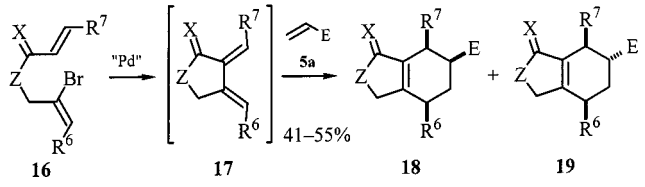


Scheme 3. Synthesis of **7**, **9**, and **10**: A: allyl bromide, Et_2O, 0 °C → room temp., 12 h, 78%; B: acryloyl chloride, Et_3N, Et_2O, 0 °C → room temp., 3 h; C: crotonyl chloride, Et_3N, Et_2O, 0 °C → room temp., 5 h, 89%

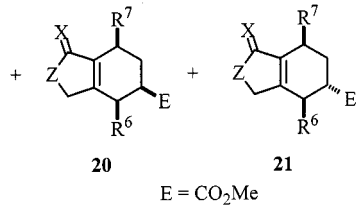


Scheme 4. Synthesis of **12** and **15**

by the terminal methyl group, preferring the *quasi-ortho* isomer (Scheme 5). Reaction of the amide **9a** with dienophile **5a** afforded two regioisomers in a 60:40 ratio in 43% yield. Thus, the amide group exerts a considerably weaker influence on the regioselectivity of the final Diels−Alder reaction than the terminal methyl group. Interestingly, the amide **10**, having an amide and a methyl group on the same side of the diene **17c**, under identical reaction conditions afforded only product **18c** in 46% yield. Evidently, both substituents "co-operate" to exert a decisive influence on the regio- and stereochemistry of the product **18c**. The amide **9b**, with the amide and the methyl group now on opposite sides of the diene intermediate, afforded an inseparable mixture of two regioisomers **18d/19d** and **20d/21d** in a 15:85 ratio (54% yield). The major regioisomer was a 4.4:1 mixture of diastereomers **20d** and **21d** (Scheme 5, Table 2).



16–21	Z	X	R6	R7
a	NBn	H2	Me	H
b	NBn	O	H	H
c	NBn	O	H	Me
d	NBn	O	Me	H
e	O	H2	H	H
f	O	H2	Me	H



Scheme 5. Heck−Diels−Alder reactions of **16** (corresponding to **7**, **9**, **10**, **12**, and **15**) with methyl acrylate (**5a**); "Pd": $Pd(OAc)_2$, dppe, Ag_2CO_3, MeCN, 80−85 °C; for further details see Table 2

The reaction of bromodialkenylamine **7** with methyl acrylate (**5a**) under Heck−Diels−Alder reaction conditions afforded an inseparable mixture of two pairs of regioisomeric diastereomers **18a/19a** and **20a/21a** in a 16:84 ratio and 41% yield. The major regioisomer was found to be a 5.8:1 mixture of diastereoisomers **20a** and **21a**, while the diastereomeric ratio of the minor regioisomer **18a/19a** could not be determined from the ^{1}H NMR spectrum of the mixture of these four diastereomers since the peaks were not well resolved. Apparently, the regioselectivity of the [4+2] cycloaddition of the intermediate diene from **7** is controlled

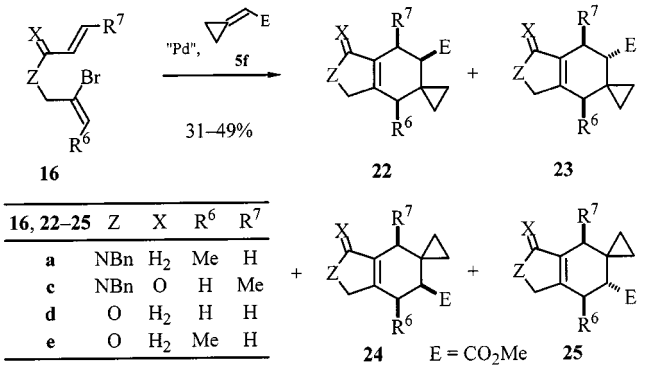
Treatment of the bromodialkenyl ether **12** with a palladium catalyst and methyl acrylate (**5a**) under Heck−Diels−Alder conditions gave the hexahydroisobenzofuran **18e** in 42% yield. The terminally monomethyl-substituted ether **15**, under identical reaction conditions, afforded the expected mixture of four diastereomers **18f**−**21f** in 55% yield. The major regioisomer was found to be a 4.2:1 mixture of diastereomers **20f** and **21f** (Scheme 5, Table 2). Further, the domino Heck−Diels−Alder reactions of bromodienes **7**, **10**, **12**, and **15** with methyl cyclopropylideneacetate **5f** also followed a similar course to give the corres-

Table 2. Domino Heck−Diels−Alder reactions of **16**, bromodiene **7**, **9**, **10**, **12**, or **15** and methyl acrylate (**5a**)

Entry[a]	Bromodiene	Main product	Yield (%)	Diast. ratio[b] of major regioisomer	Regioisomer ratio[b] (**18**+**19**)/(**20**+**21**)
1	**7**	**20a**	43	**20a/21a**, 5.8:1	16:84
2	**9a**	**18b**	43	–	60:40
3	**10**	**18c**	46	**18c**	–
4	**9b**	**20d**	54	**20d/21d**, 4.4:1	15:85
5	**12**	**18e**	42	–	–
6	**15**	**20f**	55	**20f/21f**, 4.2:1	14:86

[a] Reaction conditions: bromodiene (1.2 mmol), **5a** (2.4 mmol), $Pd(OAc)_2$ (5 mol-%), dppe (10 mol-%), Ag_2CO_3 (1.49 mmol), MeCN, 80−85 °C, 24−36 h. − [b] The ratios were determined by integration of the relevant peaks in the ^{1}H NMR spectra.

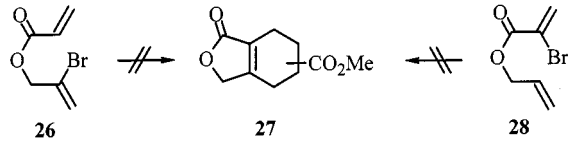
ponding spirocyclopropane-annelated adducts **22**−**25** in 31−49% overall yields (Scheme 6, Table 3). In those cases where regio- and diastereomers could be formed, **5f** consistently showed a higher selectivity than **5a** (compare e.g. Table 2, Entry 1 with Table 3, Entry 1).



16, 22–25	Z	X	R^6	R^7
a	NBn	H_2	Me	H
c	NBn	O	H	Me
d	O	H_2	H	H
e	O	H_2	Me	H

Scheme 6. Heck−Diels−Alder reactions of **16** (corresponding to **7**, **10**, **12**, and **15**) with methyl cyclopropylideneacetate (**5f**); "Pd": $Pd(OAc)_2$, dppe, Ag_2CO_3, MeCN, 80−85 °C; for further details see Table 3

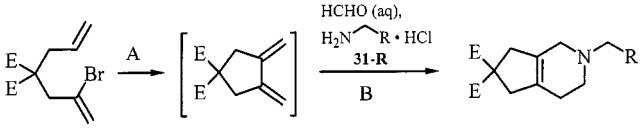
Although tetrahydroisoindolin-1-ones could be prepared by this route, an attempt to synthesize tetrahydrophthalides by the same strategy was not successful. The required allyl acrylates **26** and **28** were prepared by esterification[14] of acrylic acid and bromoacrylic acid with 2,3-dibromopropene and allyl bromide, respectively, in the presence of potassium fluoride in DMF in excellent yields. However, the esters **26** and **28** failed to give any clear-cut products under various reaction conditions (Scheme 7). From a mechanistic point of view it was also quite interesting to examine these systems under conditions of the Heck−Diels−Alder sequence since the alkenyl moiety of the bromodienes becomes increasingly electron deficient in the order of allylamines, allyl ethers, α,β-unsaturated amides, and α,β-unsaturated esters. This must be expected to have considerable



Scheme 7. Attempted cyclization of bromodienes **26** and **28**

influence on the Heck as well as the subsequent Diels−Alder reaction.

Our previously reported Heck−Diels−Alder sequence with the all-carbon bromodiene **29**[4] could be extended towards iminium ions as dienophiles to also give heterobicycles (Scheme 8).[15] This, however, requires a two-step procedure, yet still in one pot. Towards this end, after heating the bromodiene **29** with palladium acetate (6 mol-%), triphenylphosphane (13 mol-%), and silver carbonate (52 mol-%) in acetonitrile to 80−85 °C for 45 min to form the diene **30**, the reaction mixture was diluted with the same volume of water. Following this, aqueous formaldehyde solution (10 equiv.) and the amine hydrochloride **31** (2 equiv.) were added, and the reaction mixture was stirred for 4 d at ambient temperature. The hexahydro-1*H*-[2]pyrindines **32-R** were isolated in 66−75% yield. These compounds possess the ring system of tecomanine, which was reported to have hypoglycemic properties,[16] and related skytanthine[17] alkaloids. A benzannelated analog of **32** showed high affinity for the dopamine D_2 receptor.[18]



R	Yield (%)
CO_2Me	66
Ph	75

Scheme 8. Synthesis of 2,3,4,5,6,7-hexahydro-1*H*-[2]pyrindines **32**: A: $Pd(OAc)_2$ (6 mol-%), PPh_3 (13 mol-%), Ag_2CO_3 (0.52 equiv.), MeCN, 85 °C, 45 min; B: H_2O/MeCN 1:1, 20 °C, 4 d

Conclusion

A new one-pot synthesis of hitherto unknown hexahydro-1*H*-[2]pyrindines, tetrahydroisoindolines, tetrahydroisoindolin-1-ones, and hexahydrobenzo[*c*]furans has been accomplished. Although the yields of the latter three types of products are not very high, this approach is particularly attractive as the bromodialkenyl amines, ethers, and bromoalkenylalkenamides can be prepared efficiently on a large scale in good yields, and most of the cycloaddition reactions are reasonably regio- and stereoselective.

Table 3. Domino Heck−Diels−Alder reaction of **16**, bromodiene (**7**, **10**, **12**, or **15**), and methyl cyclopropylideneacetate (**5f**)

Entry[a]	Bromodiene	Main product	Yield (%)	Diastereomer ratio[b] of major regioisomer	Regioisomer ratio[b] (**22**+**23**)/(**24**+**25**)
1	**7**	**24a**	40	**24a/25a**, 11.1:1	9:91
2	**10**	**22c**	49	**22b**	–
3	**12**	**22d**	31	–	–
4	**15**	**24e**	41	**24d/25d**, 6.6:1	11:89

[a] Reaction conditions: bromodiene (1.2 mmol), **5f** (2.4 mmol), $Pd(OAc)_2$ (5 mol-%), dppe (10 mol-%), Ag_2CO_3 (1.49 mmol), MeCN, 80−85 °C, 24−36 h. − [b] The ratios were determined by integration of the relevant peaks in the ^1H NMR spectra.

Experimental Section

^{1}H NMR and ^{13}C NMR spectra were recorded with a Bruker AM 250 (250 MHz for ^{1}H, 62.9 MHz for ^{13}C) instrument at ambient temperature in $CDCl_3$ with TMS and the triplet of $CDCl_3$ (δ = 77.0), respectively, as internal standards. The line position or multiplets are given in ppm (δ) and the coupling constants (J) are given as absolute values in Hertz, while the signal multiplicities are abbreviated as follows: s (singlet), brs (broad singlet), d (doublet), t (triplet), q (quadruplet), m (multiplet), m_c (centered multiplet), AB (AB system). The proportions of the minor products in inseparable mixtures were assigned from the NMR spectra of the mixtures. Infrared spectra were recorded with a Bruker IFS 66 FT-IR instrument. − Mass spectra were recorded using electron impact ionization at 70 eV. High resolution mass spectra (HRMS) were recorded using preselected ion peak matching at $R \approx 10000$ to be within ±2 ppm. − All melting points were determined with a Reichert microscopic hot stage apparatus and are uncorrected. − Elemental analyses were carried out in the Mikroanalytisches Laboratorium der Universität Göttingen, Germany. − Solvents and reagents were dried and purified according to standard methods. All solvents for chromatography or recrystallizations were distilled prior to use, while dry diethyl ether and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl under nitrogen immediately before use. *N*-(2-Bromo-2-propenyl)-*N*-(2-propenyl)amine (**1**), *N*-(2-bromo-2-propen-1-yl)-*N*-(2-propenyl)acetamide (**2b**), 2-bromo-2-propen-1-yl 2-propenyl ether (**12**),[8b] *N*-benzyl-*N*-(2-bromo-2-propen-1-yl)-*N*-(2-propenyl)amine (**2d**),[19] and diethyl (2-bromo-2-propenyl)(2-propenyl)malonate (**29**)[4] were prepared according to previously reported methods.

***N*-(2-Bromo-2-propen-1-yl)-*N*-(2-propen-1-yl)formamide (2a):** A solution of *N*-(2-bromo-2-propenyl)-*N*-(2-propenyl)amine (**1**) (8.79 g, 50 mmol), triethylamine (5.05 g, 50 mmol), *p*-toluenesulfonic acid monohydrate (0.2 g), and ethyl formate (100 mL) was heated under reflux for 24 h (monitored by TLC). After cooling to room temperature, the reaction mixture was concentrated. The residue was dissolved in CH_2Cl_2 (100 mL), the solution washed with saturated aq. $NaHCO_3$ solution (2 × 25 mL) followed by water (2 × 50 mL). Drying with $MgSO_4$ and evaporation of the solvent yielded the crude product, which was distilled under reduced pressure (b.p. 43 °C/0.1 Torr) to yield 6.09 g (60%) of **2a** as a colorless oil. − IR (film): $\tilde{\nu}$ = 2917 cm^{-1}, 2867, 1679, 1642, 1397, 1283, 1217, 1145, 978, 926. − ^{1}H NMR (250 MHz, $CDCl_3$); 2 rotamers: δ = 3.87 (d, 1 H, ^3J = 5.9 Hz, CH_2CH=), 3.94 (d, 1 H, ^3J = 6.1 Hz, CH_2CH=), 4.00 (s, 1 H, CH_2CBr=), 4.20 (s, 1 H, CH_2CBr=), 5.18−5.39 (m, 2 H, CH=CH_2), 5.71−5.85 (m, 3 H, CH=CH_2 and CBr=CH_2), 8.14 and 8.20 (s, 1 H, CHO). − ^{13}C NMR (62.9 MHz, $CDCl_3$); 2 rotamers: δ = 43.5, 48.7 (*C*H_2CH=), 48.9, 54.3 (*C*H_2CBr=), 118.5, 119.0 (CH=*C*H_2), 119.2, 120.1 (CBr=*C*H_2), 127.0, 128.5 (*C*Br=CH_2), 131.4, 132.2 (*C*H=CH_2), 162.4, 162.5 (CHO). − MS (EI, 70 eV), *m*/*z* (%) = 205/203 (2/2) [M$^+$], 124 (100), 41 (18). − $C_7H_{10}BrNO$: 202.9945 (HRMS); calcd. C 41.20, H 4.94, N 6.86; found C 40.92, H 5.19, N 6.76.

***tert*-Butyl *N*-(2-Bromo-2-propen-1-yl)-*N*-(2-propen-1-yl)carbamate (2c):** To a stirred solution of **1** (3.52 g, 20 mmol) in THF (50 mL) was added di-*tert*-butyl dicarbonate (4.36 g, 20 mmol) at room temperature. The reaction mixture was heated under reflux for 3 h (monitored by TLC), then the solvent was evaporated. The crude product was purified by chromatography on silica gel, eluting with pentane/diethyl ether (9:1) to give 3.0 g (54%) of **2c** as a colorless oil. − IR (film): $\tilde{\nu}$ = 2978 cm^{-1}, 1710, 1640, 1455, 1404, 1366, 1248, 1161. − ^{1}H NMR (250 MHz, $CDCl_3$); 2 rotamers: δ = 1.46, 1.52 [s, 9 H, C(CH_3)$_3$], 3.75−3.96 (m, 2 H, CH_2CH=), 3.98−4.15 (m, 2 H, CH_2CBr=), 5.05−5.22 (m, 2 H, CH=CH_2), 5.08−5.83 (m, 3 H, CH=CH_2 and CBr=CH_2). − ^{13}C NMR (62.9 MHz, $CDCl_3$); 2 rotamers: δ = 27.3, 28.2 (CH_3), 48.5, 49.0 (*C*H_2CH=), 53.5 (*C*H_2CBr=), 80.2, 85.1 [*C*(CH_3)$_3$], 116.6 (CH=*C*H_2), 117.2 (CBr=*C*H_2), 129.6 (*C*Br=CH_2), 133.3 (*C*H=CH_2), 146.7, 157.6 [*C*O$_2$C(CH_3)$_3$]. − MS (EI, 70 eV), *m*/*z* (%) = 221/219 (12/12) [M$^+$ − C_4H_8], 140 (80), 57 (100), 41 (28). − $C_{11}H_{18}BrNO_2$: 275.0521 (HRMS).

***N*-(2-Bromo-2-propen-1-yl)-*N*-(2-propen-1-yl)-4-toluenesulfonamide (2e):** To a stirred solution of **1** (3.52 g, 20 mmol) in THF (50 mL) was added triethylamine (2.02 g, 20 mmol) at room temperature. The reaction mixture was cooled to 0 °C, and a solution of *p*-toluenesulfonyl chloride (3.81 g, 20 mmol) in THF (25 mL) was added dropwise. The resulting mixture was stirred at room temperature for 5 h. The reaction mixture was concentrated in a rotary evaporator. The residue was dissolved in CH_2Cl_2 (100 mL), and the solution washed with saturated aq. $NaHCO_3$ solution (2 × 15 mL) and water (2 × 25 mL), and dried with $MgSO_4$. After evaporation of the solvent, the crude product was purified by passing it through a short silica gel column eluting with hexane to give 5.41 g (82%) of **2e** as a colorless viscous liquid. − IR (film): $\tilde{\nu}$ = 2922 cm^{-1}, 1629, 1597, 1494, 1347, 1305, 1159, 1092, 902. − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 2.42, 2.48 (s, 3 H, CH_3), 3.83 (brd, 2 H, J = 6.6 Hz, CH_2CH=), 4.01 (s, 2 H, CH_2CBr=), 5.09−5.23 (m, 2 H, CH=CH_2), 5.55−5.62 (m, 1 H, CH=CH_2), 5.59 (brs, 1 H, CBr=CH_2), 5.84 (brs, 1 H, CBr=CH_2), 7.40 (d, 2 H, J = 8.4 Hz, Ar-H), 7.72 (d, 2 H, J = 8.4 Hz, Ar-H). − ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 21.5 (CH_3), 49.98 (*C*H_2CH=), 53.8 (*C*H_2CBr=), 119.3 (CH=*C*H_2), 119.9 (CBr=*C*H_2), 127.3, 129.7 (CH_{arom}), 131.9 (*C*H=CH_2), 137.1 (*C*Br=CH_2), 143.5, 158.1 (C_{arom}). − MS (EI, 70 eV), *m*/*z* (%) = 331/329 (1/1) [M$^+$], 250 (100), 155 (35), 91 (52). − $C_{13}H_{16}BrNO_2S$: 329.0085 (HRMS); calcd. C 47.28, H 4.88, N 4.24; found C 47.53, H 4.87, N 4.00.

***N*-(2-Bromo-2-propen-1-yl)-*N*-(2-propen-1-yl)-(4-nitrobenzene)-sulfonamide (2f):** To a stirred solution of sulfonamide **3** (2.30 g, 9.49 mmol) and 2,3-dibromo-1-propene (**4**) (2.08 g, 10.4 mmol) in DMF (20 mL) was added K_2CO_3 (2.62 g, 19.0 mmol) at room temperature, and stirring was continued for 1 h. The reaction mixture was worked up by adding water (30 mL), extracting with CH_2Cl_2 (4 × 20 mL), washing the combined organic phases with brine (30 mL), and drying with Na_2SO_4. The crude product obtained after removal of CH_2Cl_2 contained much DMF, and therefore did not crystallize. It was purified by chromatography on a silica gel column eluting with CH_2Cl_2 to give 3.35 g (98%) of **2f** as a colorless solid, m.p. 58−59 °C. − IR (non-solidified melt): $\tilde{\nu}$ = 3105 cm^{-1}, 2983, 2924, 2868, 1937, 1810, 1629, 1606, 1531, 1477, 1421, 1402, 1351, 1312, 1265, 1165, 1108, 1091, 1062, 1013, 992, 909. − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.92 (d, 2 H, ^3J = 6.4 Hz, CH_2CH=), 4.12 (s, 2 H, CH_2CBr=), 5.15−5.26 (m, 2 H, CH=CH_2), 5.62 (ddt, 1 H, ^3J = 16.7, ^3J = 10.4, ^3J = 6.4 Hz, CH=CH_2), 5.63 (d, 1 H, ^2J = 1.6 Hz, CBr=CH_2), 5.84 (dt, 1 H, ^2J = 1.6, ^4J = 1.3 Hz, CBr=CH_2), 8.01−8.07 and 8.33−8.39 (4 H, AA′BB′, Ar-H). − ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 49.8 (*C*H_2CH=), 53.9 (*C*H_2CBr=), 120.6 (CBr=*C*H_2), 120.7 (CH=*C*H_2), 124.2 (CH_{arom}), 127.1 (*C*Br=CH_2), 128.5 (CH_{arom}), 131.2 (*C*H=CH_2), 146.0, 149.9 (C_{arom}). − MS (70 eV), *m*/*z* (%) = 362/360 (1/1) [M$^+$], 335/333 (1/1), 281 (100), 255 (13), 241 (5), 186 (21) 176/174 (7/7), 148/146 (4/4), 122 (35), 121/119 (7/7), 94 (16), 76 (9). − $C_{12}H_{13}BrN_2O_4S$ (361.2): calcd. C 39.90, H 3.63, Br 22.12; found C 39.80, H 3.64, Br 21.92.

General Procedure for the Domino Heck−Diels−Alder Reactions: To a stirred solution of bromodiene (1.2 mmol) in acetonitrile (5 mL) in a screw-cap Pyrex bottle were added dienophile (2.4 mmol), $Pd(OAc)_2$ (14 mg, 5 mol-%), dppe (48 mg, 10 mol-%), and silver carbonate (410 mg, 1.49 mmol). The solution was purged with argon and then stirred in the sealed bottle at 80−85 °C for 24−36 h (monitored by TLC). The reaction mixture was filtered through a bed of charcoal and Celite, and the solvent was removed under reduced pressure. The residue was purified by chromatography on silica gel eluting with a 10−100% gradient of pentane/diethyl ether.

***tert*-Butyl 2-Formyl-4,5,6,7-tetrahydroisoindoline-5-carboxylate (6ab):** Colorless oil, 54%. − IR (film): $\tilde{\nu}$ = 2931 cm^{-1}, 1724, 1700, 1669, 1417, 1369. − ^1H NMR (250 MHz, $CDCl_3$); 2 rotamers: δ = 1.45 [s, 9 H, $C(CH_3)_3$], 1.68−1.82 (brm, 1 H, 6-H), 1.99−2.12 [brm, 3 H, 6(7)-H], 2.17−2.22 (brm, 2 H, 4-H), 2.49−2.59 (brm, 1 H, 5-H), 4.08, 4.20 [brs, 4 H, 1(6)-H], 8.29 (s, 1 H, CHO). − ^{13}C NMR (62.9 MHz, $CDCl_3$); 2 rotamers: δ = 22.1, 22.5 (C-6), 24.9, 25.0 (C-7), 25.3, 25.5 (C-4), 27.9 [C(CH_3)$_3$], 40.0 (C-5), 52.7, 52.8, 54.4, 54.5 [C-1(3)], 80.3 [$C(CH_3)_3$], 127.8, 128.6, 128.9, 129.7 [C-3a(7a)], 160.8 (CHO), 174.2 [$CO_2C(CH_3)_3$]. − MS (EI, 70 eV), *m*/*z* (%) = 251 (8) [M^+], 195 (100), 178 (20), 150 (53), 123 (44), 57 (38). − $C_{14}H_{21}NO_3$ (251.3): calcd. C 66.90, H 8.42, N 5.57; found C 66.69, H 8.39, N 5.58.

***N*-Benzyl-*N*-(2-bromo-2-buten-1-yl)-*N*-(2-propen-1-yl)amine (7):** To a stirred solution of **8b** (2.40 g, 10 mmol) in diethyl ether (25 mL) was added dropwise allyl bromide (0.60 g, 5 mmol) at 0 °C. The resulting mixture was stirred overnight at room temperature. The reaction mixture was filtered and the precipitate washed with diethyl ether (2 × 10 mL). The combined filtrates were washed with water (2 × 25 mL), dried with $MgSO_4$, and the solvent was evaporated. The crude product was purified by passing it through a short column of silica gel and eluting with pentane to give 1.09 g (78%) of **7** as a colorless oil. − IR (film): $\tilde{\nu}$ = 3026 cm^{-1}, 2920, 2804, 1642, 1494. − ^1H NMR (250 MHz, $CDCl_3$): δ = 1.70 (d, 3 H, ^3J = 7.3 Hz, CH_3), 3.13 (d, 2 H, ^3J = 6.3 Hz, CH_2CH=), 3.33 (s, 2 H, CH_2CBr=), 3.62 (s, 2 H, $CH_2C_6H_5$), 5.19−5.30 (m, 2 H, CH=CH_2), 5.88−6.07 (m, 1 H, CH=CH_2), 6.16 (q, 1 H, ^3J = 7.3 Hz, =C$H$$CH_3$), 7.30−7.45 (m, 5 H, Ar-H). − ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 15.4 (CH_3), 55.4 (CH_2CH=), 55.9 (CH_2CBr=), 57.2 ($CH_2C_6H_5$), 117.0 (CH=CH_2), 123.7 (CBr=$C$$HCH_3$), 126.9, 128.1, 128.9 ($CH_{arom}$), 130.5 ($C$H=$CH_2$), 135.5 ($C$Br=$CH_2$), 139.2 ($C_{arom}$). − MS (EI, 70 eV), *m*/*z* (%) = 281/279 (3/3) [M^+], 200 (7), 160 (30), 147 (20), 120 (10), 106 (15), 91 (100). − $C_{14}H_{18}BrN$: 279.0622 (HRMS).

***N*-Benzyl-*N*-(2-bromo-2-propen-1-yl)amine (8a):** To a stirred solution of benzylamine (2.14 g, 20 mmol) and triethylamine (2.02 g, 20 mmol) in diethyl ether (50 mL) was added dropwise a solution of 2,3-dibromopropene (3.99 g, 20 mmol) in diethyl ether (10 mL). The reaction mixture was stirred overnight at room temperature. This was then filtered, and the precipitate washed with diethyl ether (3 × 15 mL). The combined filtrates were washed with water (2 × 25 mL), dried with $MgSO_4$, and the solvent was evaporated. The crude product was chromatographed on silica gel eluting with hexane to give 3.21 g (71%) of **8a** as a colorless oil. − IR (film): $\tilde{\nu}$ = 3338 cm^{-1}, 3027, 2833, 1625. − ^1H NMR (250 MHz, $CDCl_3$): δ = 1.81 (brs, 1 H, NH), 3.47 (s, 2 H, CH_2CBr=), 3.74 (s, 2 H, $CH_2C_6H_5$), 5.61 (d, 1 H, ^2J = 1.7 Hz, CBr=CH_2), 5.80 (d, 1 H, ^2J = 1.7 Hz, CBr=CH_2), 7.28−7.39 (m, 5 H, Ar-H). − ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 51.4 (CH_2CBr=), 56.5 ($CH_2C_6H_5$), 117.9 (CBr=CH_2), 127.0, 128.2, 128.4 (CH_{arom}), 133.4 (CBr=CH_2), 139.5 (C_{arom}). − MS (EI, 70 eV), *m*/*z* (%) = 227/225 (11/11) [M^+], 146 (26), 120 (32), 91 (100). − $C_{10}H_{12}BrN$: 225.0153 (HRMS).

***N*-Benzyl-*N*-[(2*E*)-2-bromo-2-buten-1-yl]amine (8b):** This compound was prepared by alkylation of benzylamine (2.14 g, 20 mmol) with 1,2-dibromo-2-butene (4.28 g, 20 mmol) according to the procedure applied for the amine **8a**, and it was obtained as a colorless oil in 94% (4.5 g) yield. − IR (film): $\tilde{\nu}$ = 3328 cm^{-1}, 3026, 2917, 2837, 1644, 1603, 1494. − ^1H NMR (250 MHz, $CDCl_3$): δ = 1.60 (d, 3 H, ^3J = 7.3 Hz, CH_3), 1.82 (brs, 1 H, NH), 3.50 (s, 2 H, CH_2CBr=), 3.72 (s, 2 H, $CH_2C_6H_5$), 6.15 (q, 1 H, ^3J = 7.3 Hz, =C$H$$CH_3$), 7.28−7.35 (m, 5 H, Ar-H). − ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 15.0 (CH_3), 50.0 (CH_2CBr=), 51.2 ($CH_2C_6H_5$), 125.3 (CBr=$CHCH_3$), 127.0 (CBr=$C$$HCH_3$), 128.3, 128.4, 129.6 ($CH_{arom}$), 139.7 ($C_{arom}$). − MS (EI, 70 eV), *m*/*z* (%) = 241/239 (10/10) [M^+], 160 (23), 120 (17), 106 (30), 91 (100). − $C_{11}H_{14}BrN$: 239.0309 (HRMS).

***N*-Benzyl-*N*-(2-bromo-2-propen-1-yl)propenamide (9a):** To a stirred solution of **8a** (2.26 g, 10 mmol) and triethylamine (1.05 g, 10 mmol) in diethyl ether (25 mL) was added dropwise acryloyl chloride (0.90 g, 10 mmol) at 0 °C. The resulting mixture was stirred at room temperature for 3 h. The reaction mixture was filtered, and the precipitated triethylammonium hydrochloride was washed with diethyl ether (2 × 10 mL). The combined filtrates were washed successively with saturated aq. $NaHCO_3$ solution (10 mL) and water (2 × 25 mL). After drying with $MgSO_4$ and evaporating the solvent, the crude product was purified by passing it through a short column of silica gel eluting with pentane/diethyl ether (3:1) to yield 2.75 g (98%) of **9a** as a colorless oil. − IR (film): $\tilde{\nu}$ = 3030 cm^{-1}, 1654, 1618, 1495. − ^1H NMR (250 MHz, $CDCl_3$); 2 rotamers: δ = 4.07, 4.32 (s, 2 H, $CH_2C_6H_5$), 4.65 (s, 1 H, CH_2CBr=), 4.67 (s, 1 H, CH_2CBr=), 5.62−5.70 (m, 1 H, CH=CH_2), 5.71−5.83 (m, 2 H, CBr=CH_2), 6.45−6.59 (m, 2 H, CH=CH_2), 7.16−7.47 (m, 5 H, Ar-H). − ^{13}C NMR (62.9 MHz, $CDCl_3$); 2 rotamers: δ = 48.4, 50.2 (CH_2CBr=), 52.6, 54.1 ($CH_2C_6H_5$), 117.9, 118.7 (CH=CH_2), 126.4, 127.0, 127.6, 127.8, 128.3, 128.7, 128.9 (CH=CH_2 and CH_{arom}), 128.0 (CBr=CH_2), 129.5, 129.7 (CH=CH_2), 136.6 (C_{arom}), 166.9 (CO). − MS (EI, 70 eV), *m*/*z* (%) = 281/279 (10/10) [M^+], 200 (30), 160 (12), 155 (27), 140 (22), 120 (8), 106 (38), 91 (78), 86 (100), 55 (86). − $C_{13}H_{14}BrNO$: 279.0258 (HRMS).

***N*-Benzyl-*N*-[(2*E*)-2-bromo-2-buten-1-yl]propenamide (9b):** This compound was prepared by acylation of the amine **8b** (2.40 g, 10 mmol) with acryloyl chloride (0.90 g, 10 mmol) according to the procedure described for the amide **9a**, as a colorless oil in 95% (2.80 g) yield. − IR (film): $\tilde{\nu}$ = 2924 cm^{-1}, 1653, 1615. − ^1H NMR (250 MHz, $CDCl_3$); 2 rotamers: δ = 1.53, 1.57 (2 d, 3 H, ^3J = 7.5 Hz, =CHCH_3), 4.15, 4.39 (s, 2 H, $CH_2C_6H_5$), 4.66 (brs, 2 H, CH_2CBr=), 5.69−5.80 (m, 1 H, =C$H$$CH_3$), 6.12−6.19 (m, 1 H, C$H$=$CH_2$), 6.38−6.71 (m, 2 H, CH=CH_2), 7.18−7.46 (m, 5 H, Ar-H). − ^{13}C NMR (62.9 MHz, $CDCl_3$); 2 rotamers: δ = 14.9, 19.0 (CH_3), 46.3, 47.0 ($CH_2C_6H_5$), 47.4, 50.0 (CH_2CBr=), 119.8, 120.4 (CBr=$CHCH_3$), 125.6, 126.4, 127.6, 127.8, 128.0, 128.4, 128.7 (CBr=$C$$HCH_3$ and CH_{arom}), 129.0, 130.5 (CH=CH_2), 131.6, 131.8 (CH=CH_2), 136.2, 136.6 (C_{arom}), 166.9, 167.1 (CO). − MS (70 eV), *m*/*z* (%) = 295/293 (11/11) [M^+], 214 (65), 106 (46), 91 (100), 69 (91). − $C_{14}H_{16}BrNO$: 293.0415 (HRMS).

(2*E*)-*N*-Benzyl-*N*-(2-bromo-2-propen-1-yl)-2-butenamide (10): This amide was prepared by acylation of the amine **8a** (2.26 g, 10 mmol) with crotonyl chloride (1.05 g, 10 mmol) according to the procedure applied for the amide **9a**, as a light yellow viscous liquid in 89% (2.62 g) yield. − IR (film): $\tilde{\nu}$ = 3029 cm^{-1}, 2970, 2913, 1714,

1662, 1626, 1495. − ^{1}H NMR (250 MHz, $CDCl_3$); 2 rotamers: δ = 1.91 (dd, 3 H, ^3J = 6.9, ^4J = 1.6 Hz, CH_3), 4.06, 4.29 (s, 2 H, $CH_2C_6H_5$), 4.65 (brs, 2 H, CH_2CBr=), 5.63−5.79 (m, 2 H, CBr=CH_2), 6.12−6.32 (m, 1 H, CH=$CHCH_3$), 6.95−7.18 (m, 1 H, CH=$CHCH_3$), 7.19−7.41 (m, 5 H, Ar-H). − ^{13}C NMR (62.9 MHz, $CDCl_3$); 2 rotamers: δ = 18.3 (CH_3), 48.4, 50.0 (CH_2CBr=), 52.5, 54.1 ($CH_2C_6H_5$), 117.6, 118.3 (CBr=CH_2), 120.9, 121.1 (CH=$CHCH_3$), 127.5, 127.7, 128.2, 128.6, 128.9 (CH_{arom}), 127.9, 128.2 (CBr=CH_2), 136.9, 138.3 (C_{arom}), 143.6, 143.9 (CH=$CHCH_3$), 167.1 (CO). − MS (EI, 70 eV), *m/z* (%) = 295/293 (4/4) [M^+], 214 (75), 174 (11), 106 (25), 91 (100), 86 (10), 69 (85), 41 (36). − $C_{14}H_{16}BrNO$: 293.0415 (HRMS).

(2*E*)-2-Bromo-2-buten-1-yl 2-Propen-1-yl Ether (15): To a stirred solution of 2-bromo-2-butenol (**14**)[20] (3.02 g, 20 mmol) and allyl bromide (3.0 g, 25 mmol) in CH_2Cl_2 (50 mL) was added cetyltriethylammonium bromide (CETAB) (0.93 g, 2.5 mmol) followed by 50% aq. NaOH solution (25 mL). The resulting mixture was heated under reflux for 2 h. After cooling to room temperature the organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (2 × 25 mL). The combined filtrates were washed with brine (2 × 25 mL), dried with $MgSO_4$, and concentrated. The crude product was purified by passing it through a short silica gel column eluting with pentane to give 2.10 g (55%) of **15** as a colorless oil. − IR (film): $\tilde{\nu}$ = 2854 cm^{-1}, 1640. − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.74 (d, 3 H, ^3J = 6.9 Hz, CH_3), 4.00 (d, 2 H, ^3J = 7 Hz, CH_2CH=), 4.22 (s, 2 H, CH_2CBr=), 5.19−5.35 (m, 2 H, CH=CH_2), 5.87−6.05 (m, 1 H, CH=CH_2), 6.21 (q, 1 H, ^3J = 6.9 Hz, CBr=$CHCH_3$). − ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 15.3 (CH_3), 68.6 (CH_2CH=), 70.5 (CH_2CBr=), 117.7 (CH=CH_2), 121.2 (CBr=$CHCH_3$), 131.7 (CBr=$CHCH_3$), 134.4 (CH=CH_2). − MS (EI, 70 eV), *m/z* (%) = 192/190 (2/2) [M^+], 148 (7), 134 (20), 111 (14), 93 (8), 69 (20), 53 (83), 41 (100). − $C_7H_{11}BrO$: 189.9993 (HRMS).

2′-Bromo-2′-propen-1′-yl Propenoate (26): To a stirred suspension of 2,3-dibromopropene (1.99 g, 10 mmol), KF (0.87 g, 15 mmol) in DMF (25 mL), was added acrylic acid (0.72 g, 10 mmol). The resulting mixture was heated at 80 °C for 2 h. After cooling to room temperature, water (50 mL) was added, and the reaction mixture was extracted with ether (3 × 25 mL). The combined extracts were washed with water (2 × 20 mL), dried with $MgSO_4$, and the solvent was evaporated. The residue was passed through a short silica gel column eluting with pentane to give 1.70 g (89%) of pure **26** as a colorless oil. − IR (film): $\tilde{\nu}$ = 2941 cm^{-1}, 1745, 1634. − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 4.79 (t, 2 H, ^4J = 1.1 Hz, 1′-H), 5.60 (dt, 1 H, ^2J = 2.0, ^4J = 1.1 Hz, 3′-H), 5.89 [m, 2 H, 3′(3)-H], 6.16 (dd, 1 H, ^3J = 18.3, ^3J = 10.4 Hz, 2-H), 6.52 (dd, 1 H, ^3J = 18.3, ^2J = 1.4 Hz, 3-H). − ^{13}C NMR (62.9 Hz, $CDCl_3$): δ = 67.5 (C-1′), 119.0 (C-3′), 126.1 (C-2′), 127.7 (C-2), 131.9 (C-3), 165.1 (C=O). − MS (70 eV), *m/z* (%) = 192/190 (2/2) [M^+], 159 (3), 135 (2), 119 (43), 55 (100). − $C_6H_7BrO_2$: 189.9629 (HRMS).

2′-Propen-1′-yl 2-Bromopropenoate (28): A stirred solution of 2-bromopropenoic acid (0.75 g, 5.0 mmol), allyl bromide (0.52 mL, 0.72 g, 6.0 mmol), and KF (0.64 g, 11.0 mmol) in DMF (5 mL) was heated at 45 °C for 4 h. After cooling to room temperature, water (20 mL) was added, and the aqueous phase was extracted with ether (2 × 20 mL). The combined ether phases were washed successively with water (2 × 20 mL), brine (20 mL), dried with $MgSO_4$, and the solvent was evaporated. The residue was purified by column chromatography on silica gel eluting with petroleum ether/ether (20:1) to yield 0.71 g (74%) of **28** as a colorless oil. − IR (film): $\tilde{\nu}$ = 3088 cm^{-1}, 2955, 1733, 1650, 1610, 1456. − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 4.73 (dt, 2 H, ^3J = 5.7, ^4J = 1.4 Hz, 1′-H), 5.30 (dq, 1 H, ^3J = 10.4, ^4J = ^2J = 1.2 Hz, 3′-H), 5.39 (dq, 1 H, ^3J = 17.2, ^4J = ^2J = 1.5 Hz, 3′-H), 5.96 (ddt, 1 H, ^3J = 17.2, ^3J = 10.4, ^3J = 5.7 Hz, 2′-H), 6.30 (d, 1 H, ^2J = 1.7 Hz, 3-H_Z), 7.00 (d, 1 H, ^2J = 1.7 Hz, 3-H_E). − ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 67.1 (C-1′), 119.0 (C-3′), 121.1 (C-2), 130.9 (C-3), 131.2 (C-2′), 161.5 (C=O). − $C_6H_7BrO_2$ (191.0): calcd. C 37.73, H 3.69; found C 37.64, H 3.69.

Diethyl 2-Methoxycarbonylmethyl-2,3,4,5,6,7-hexahydro-1*H*-[2]pyrindine-6,6-dicarboxylate (32-CO_2Me): Diethyl (2-bromo-2-propen-1-yl)(2-propen-1-yl)malonate (**29**) (195 mg, 0.61 mmol) was treated with $Pd(OAc)_2$ (8 mg, 0.04 mmol), PPh_3 (21 mg, 0.08 mmol), and Ag_2CO_3 (88 mg, 0.32 mmol) in acetonitrile (5 mL) for 45 min at 85 °C in a thick-walled screw-cap Pyrex bottle. After cooling to ambient temp., aq. formaldehyde solution (0.6 mL, 6 mmol, approx. 10 M), methyl glycinate hydrochloride (**31-CO_2Me**) (153 mg, 1.22 mmol) and H_2O (5 mL) were added, and the mixture was stirred at ambient temp. for 4 d. The reaction mixture was filtered through Celite, which was then washed with H_2O (10 mL), and the filtrate was extracted with Et_2O (15 mL). The aqueous layer was basified (pH = 13) with 2 N NaOH and extracted with Et_2O (4 × 15 mL). The combined organic layers were washed with brine (20 mL) and dried with Na_2SO_4. Purification by column chromatography on silica gel, eluting with petroleum ether/ether (1:2) gave 137 mg (66%) of **32-CO_2Me** as a pale yellow oil, R_f (petroleum ether/ether 1:2) = 0.17. − IR (film): $\tilde{\nu}$ = 2982 cm^{-1}, 2906, 2839, 1733, 1444, 1389, 1366, 1257, 1177, 1103, 1068, 1017, 903, 860. − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.25 (t, 6 H, ^3J = 7.1 Hz, CH_2CH_3), 2.14 (very brs, 2 H, 4-H), 2.71 (t, 2 H, ^3J = 5.7 Hz, 3-H), 2.95 (brs, 4 H, 5-H, 7-H), 3.08 (brs, 2 H, 1-H), 3.36 (s, 2 H, $NCH_2CO_2CH_3$), 3.74 (s, 3 H, CO_2CH_3), 4.19 (q, 4 H, ^3J = 7.1 Hz, CH_2CH_3). Decoupling experiment: On irradiating the very broad singlet at δ = 2.14, the triplet at δ = 2.71 becomes a singlet. − ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT135): δ = 13.9 (+, CH_2CH_3), 25.6 (−, C-4), 41.8 and 43.3 (−, C-5, C-7), 49.6 (−, C-3), 51.6 (+, CO_2CH_3), 51.8 (−, C-1), 58.2 (C_{quat}, C-6), 58.5 (−, NCH_2CO_2), 61.4 (−, CH_2CH_3), 129.5 and 130.4 (C_{quat}, C-4a, C-7a), 170.9 (C_{quat}, CO_2CH_3), 172.1 (C_{quat}, $CO_2CH_2CH_3$). The assignments of the signals were confirmed by a C,H-COSY experiment. − MS (EI, 70 eV), *m/z* (%) = 339 (35) [M^+], 294 (5), 280 (100), 266 (48), 234 (4), 206 (23), 192 (19), 177 (9), 167 (15), 134 (6), 125 (41), 105 (11), 91 (17), 55 (10), 43 (15), 42 (32). − $C_{17}H_{25}NO_6$ (339.4): calcd. C 60.16, H 7.42; found C 59.89, H 7.70.

Diethyl 2-Benzyl-2,3,4,5,6,7-hexahydro-1*H*-[2]pyrindine-6,6-dicarboxylate (32-Ph): Using benzylamine hydrochloride (**31-Ph**) (175 mg, 1.22 mmol) under conditions otherwise identical to those for the preparation of **32-CO_2Me**, 163 mg (75%) of **32-Ph** was obtained as a pale yellow, unstable oil, R_f (petroleum ether/ether 1:1) = 0.23. − IR (film): $\tilde{\nu}$ = 3085 cm^{-1}, 3062, 3027, 2980, 2906, 2805, 1733, 1602, 1494, 1454, 1256, 1178, 1096, 1067, 1016, 966, 907, 860, 808, 743, 700, 613, 543. − ^{1}H NMR (250 MHz, $CDCl_3$): δ = 1.24 (t, 6 H, ^3J = 7.1 Hz, CH_2CH_3), 2.08 (very brs, 2 H, 4-H), 2.57 (t, 2 H, ^3J = 5.7 Hz, 3-H), 2.90−3.00 (brm, 6 H, 1-H, 5-H, 7-H), 3.61 (s, 2 H, NCH_2Ph), 4.18 (q, 4 H, ^3J = 7.1 Hz, CH_2CH_3), 7.25−7.35 (m, 5 H, Ar-H). Decoupling experiment: On irradiating the very broad singlet at δ = 2.08, the triplet at δ = 2.57 becomes a singlet. − ^{13}C NMR (62.9 MHz, $CDCl_3$, DEPT135): δ = 13.9 (+, CH_2CH_3), 25.8 (−, C-4), 41.9 and 43.3 (−, C-5, C-7), 49.6 (−, C-3), 52.5 (−, C-1), 58.1 (C_{quat}, C-6), 61.4 (−, CH_2CH_3), 62.5 (−, NCH_2Ph), 127.0, 128.2, 129.1 (+, CH_{arom}), 130.1 and 130.6 (C_{quat}, C-4a, C-7a), 138.2 (C_{quat}, C_{arom}), 172.2 (C_{quat}, $CO_2CH_2CH_3$). − MS (EI, 70 eV), *m/z* (%) = 357 (100) [M^+], 312 (7), 284 (34), 283 (17), 266 (5), 255 (2), 238 (2), 210 (9), 185 (82), 164 (6), 136 (4),

120 (4), 118 (3), 107 (4), 91 (35), 77 (6). – $C_{21}H_{27}NO_4$ (357.5): decomp., no elemental analysis possible.

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