High-Pressure Promoted Cycloadditions of Enol Ethers and 3-Aryl-2-cyano-2-propenoates

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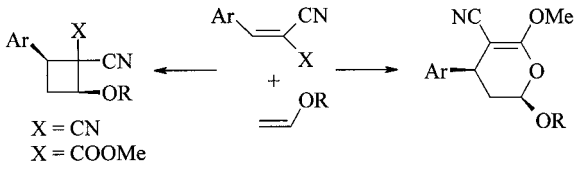
The high-pressure promoted cycloadditions of enol ethers (**1**) and alkyl 3-aryl-2-cyano-2-propenoates (**2**) lead stereoselectively in high yields to 2,6-dialkoxy-4-aryl-3,4-dihydro-2*H*-pyran-5-carbonitriles (**3**). These cycloadducts have a high potential for further synthesis due to the presence of various functionalities. This is illustrated with some representative conversions. As reactive cyclic ketene acetals the cycloadducts **3** were easily hydrolyzed to aldehydes (**6**) or ketones or alcoholized to acetals having additional ester and cyano groups (**5**). Removal of the ester group by decarboxylation gave γ-cyano acetals (**7**), which were further reduced to δ-amino acetals (**8**). Selective reduction of the cyano group gave access to acetals of β-amino acid esters (**9**). The potential of such amino acid esters is demonstrated in a straightforward synthesis of a paroxetin precursor **17** from **13**.

Introduction

Enol ethers, as masked aldehydes, can be of great interest in organic synthesis for the introduction of aldehyde functionalities. Their use in cycloadditions, however, is somewhat limited due to the fact that they are only moderately electron rich. Therefore in polar [2+2] cycloadditions, and in Diels Alder reactions in general, strongly electron-poor reaction partners are needed to get satisfactory conversions.[1] The use of Lewis acids, which can catalyze these cycloaddition reactions, may lead to polymerization of the enol ether.

The application of high pressure is an effective method to extend the scope of these cycloadditions.[1,2] In a preceding paper we showed that enol ethers react smoothly under high pressure conditions with a large variety of 1,1-dicyanoalkenes giving rise to a large variety of 1,1-dicyanocyclobutanes.[3] The reaction has a broad scope, allowing the introduction of substituents at every position of the cyclobutane skeleton.

In this paper we describe high-pressure promoted cycloaddition reactions of enol ethers with α-cyanocinnamates. A priori, [2+2] and [4+2] cycloadducts can be formed as given in Scheme 1.



Scheme 1

We reasoned that an easy and stereoselective access to this type of cycloadducts could open straightforward routes to cyclic and polycyclic compounds having an aryl-alkylamino unit, which is a basic motif of compounds that act on the central nervous system. In the cycloadducts the enol ether part is a masked aldehyde and the cyano functionality can be easily transformed into an aminomethyl group. Intramolecular interaction of the amino and aldehyde function would lead to cyclic arylalkylamino compounds. The synthetic potential of the novel 2,6-dialkoxy-4-aryl-3,4-dihydro-2*H*-pyran-5-carbonitriles (**3**) will be illustrated by their conversion into β-amino acid esters, δ-amino acetals, a δ-amino ketone and 4-arylpiperidines.

Results and Discussion

Cycloaddition Reactions of 2-Cyano-3-aryl-2-propenoates with Enol Ethers

At pressures of 15 Kbar a variety of enol ethers reacted with 3-aryl-2-cyano-2-propenoates (**2**) at room temperature to give the 2,6-dialkoxy-4-phenyl-3,4-dihydro-5*H*-pyran-5-

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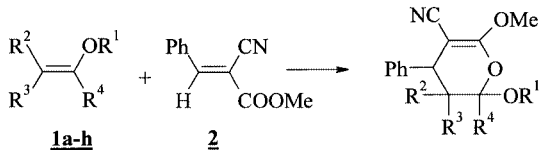
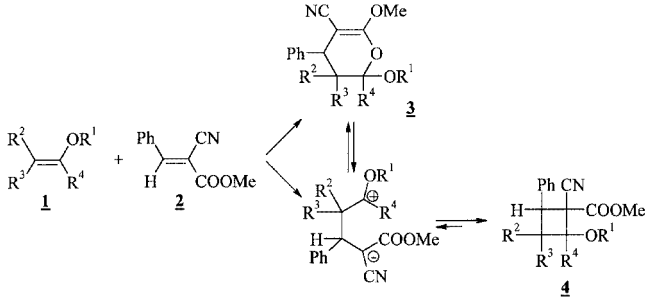


Enol ether	R^1	R^2	R^3	R^4	Dihydro-pyran	δ H-C-OR^1 (J, Hz)	δ H-CPh (J, Hz)
1a	Et	H	H	H	3a	5.27 (2.0; 8.6)	
1b	*t*Bu	H	H	H	3b	5.50 (2.2; 8.8)	3.76 (10.4;6.3)
1c	Ph(Me)CH	H	H	H	3c	5.09 (1.9; 8.4)	3.62 (10.0; 6.4)
1d	*p*-MeOPh(Me)CH	H	H	H	3d	5.06 (1.9; 8.5)	3.62 (10.0; 6.4)
1e	*i*Pr	Me	H	H	3e	5.30 (2.1)	3.84 (6.7)
1f	*i*Pr	H	Me	H	3f	4.94 (8.4)	3.20 (10.0)
1g	- $(CH_2)_2$ -		H	H	3g	5.72 (3.3)	4.21 (6.4)
1h	Me	H	H	Me	3h		

Scheme 2

carbonitriles **3a−h** (Scheme 2). Quantitative conversions were usually found after reacting overnight.

Only small amounts of cyclobutanes were found when the reaction was performed at 50 °C. For *tert*-butoxyethene, however, the reaction mixture contained about 30% of the cyclobutane derivative **4b** at room temperature whereas 70% of this cyclobutane was found at 50 °C. When pure dihydropyrans were kept under high pressure at 50 °C partial isomerization to cyclobutanes was observed. The fact that in most cases at room temperature the dihydropyrans **3** are the only products supports a mechanism whereby the dihydropyrans are the kinetic products. At higher temperatures **3** can ring-open to form dipolar intermediates, which can subsequently ring-close again to form dihydropyrans or cyclobutanes (see Scheme 3). It is known that the formation of dipolar intermediates from neutral cycloadducts is stimulated by high pressure.[2] Dipolar ring-opening becomes increasingly facile with increasing stabilization of the positive charge by the alkoxy group, which explains the presence of the cyclobutane at room temperature in the case of *tert*-butoxyethene.



Scheme 3

The cyclobutanes are more stable against dipolar ring-opening than the dihydropyrans, and as a consequence of this are also more stable against acid-catalyzed solvolysis. The cyclobutanes can therefore be purified by chromatography. Dihydropyrans decompose more easily during chromatography but in some cases they can be purified by crystallization.

The cycloaddition reactions are completely regioselective and also highly *endo*-selective. This *endo* selectivity is the result of an expected strong donor-acceptor interaction between the oxygen lone pair of the enol ether and the carbonyl of the ester function (Figure 1).

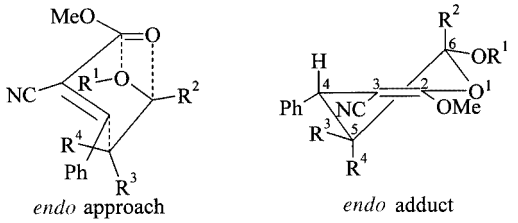


Figure 1. *endo* selectivity

The *endo* selectivity can be concluded from the ^{1}H NMR spectra (see Scheme 2). Compounds **3a−e** and **3g** show coupling constants greater than 8 Hz for protons H4 and about 10 Hz for H6, in agreement with the proposed structure of the *endo* product in which these protons are in a pseudo-axial position and couple with the axial H5 proton. The $H4_{ax}$-$H5_{eq}$ coupling is between 6.3 and 6.7 Hz. Also, for compounds **3e** and **3g**, derived from *cis* enol ethers, ^{1}H NMR spectroscopy supports an *endo* structure with the phenyl and alkoxy groups in a pseudo-equatorial position and with small coupling constants for H4 and H6 due to coupling with neighboring equatorial protons. For compounds **3b** and **3g** formation of the *endo* product was further supported by NOE contacts between H4 and H6.

A priori, introduction of chirality via removable auxiliaries could be achieved with a chiral ester function in **2** or a chiral alkoxy group in **1**. Initial experiments showed that the best results could be expected from chiral enol ethers (**1**). We studied chiral induction using α-arylethoxy groups, which had previously shown good results in Diels Alder reactions of 1-alkoxydienes and quinones.[4] In the reaction of **1c** with **2** the ratio of diastereomers reached 4:1. No better results were obtained with **3d**. The main diastereomer of **3c** was obtained pure by chromatography followed by crystallization from diisopropyl ether. X-ray analysis of the

crystals showed[5] that an *S*-configuration of the phenylethoxy group generated an *S*-configuration at C4 (see Figure 2).

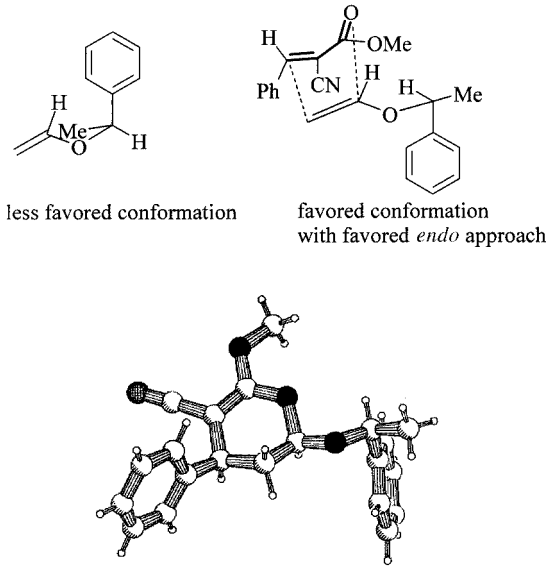
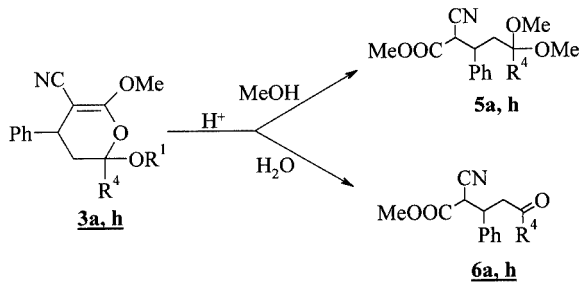


Figure 2. *endo* adduct from (*S*)-1-phenylethyl vinyl ether

The observed diastereoselectivity can be explained by the less-hindered *endo* approach of the propenoate **2** to the enol ether **1** after adopting the more stable conformation pictured in Figure 2. Analogous explanations have been used in Diels Alder reactions for related alkoxy dienes having phenylethoxy or *O*-methyl mandelate as chiral auxiliaries.[6,7] In the transition state the enol ether is supposed to adopt the sterically favored conformation in which the phenyl group is orientated opposite to the approaching propenoate.

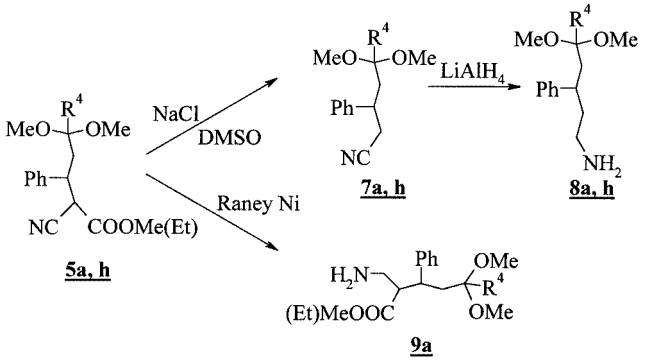
Synthetic Applications

The dihydropyrans **3** are promising starting compounds for further synthesis. Like cyclic ketene acetals they are easily hydrolyzed or alcoholyzed under acidic conditions. Some representative reactions that illustrate the synthetic potential of these compounds are presented in Scheme 4. Methanolysis or hydrolysis resulted quantitatively in open acetals **5** or carbonyl compounds **6**, respectively.



Scheme 4

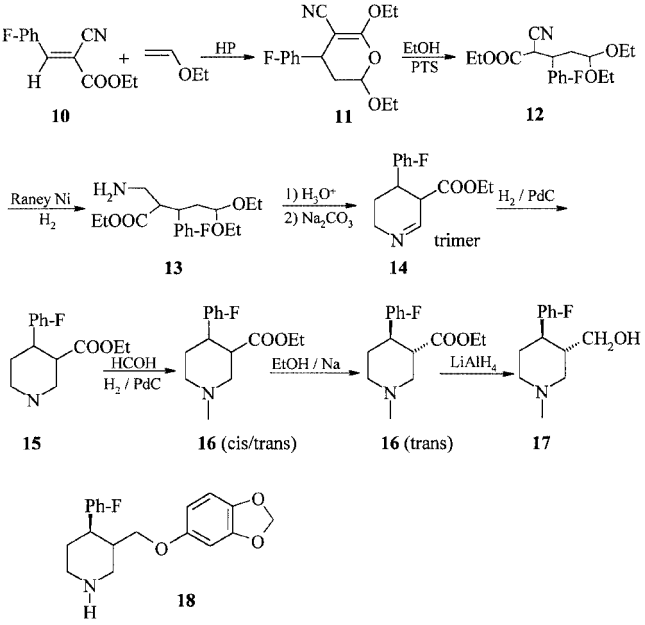
As expected, these reactions are not stereoselective so that mixtures of diastereomers are formed. The acetals **5** were easily decarboxylated by heating in DMSO in the presence of sodium chloride to give the γ-cyano acetals **7**. Reduction of the cyano group with lithium aluminum hydride led to δ-amino acetals **8** in high yield. On the other hand, the cyano group in **5** was selectively reduced with Raney Nickel, which gave access to acetals of β-amino acids **9** (Scheme 5).



Scheme 5

Compounds **8** and **9** have an interesting potential for further synthesis as is illustrated below and in the following paper.[8]

Compounds **8** and **9** contain an arylpropylamino moiety, which is a common motif in compounds that act on the central nervous system. A well-known example of this type of compounds is paroxetin[9,10] (**18**), an antidepressant. One of the major uses of compounds **3** is for syntheses in this field and is well illustrated by the conversion of cyanopropenoate **10** into the *N*-methylparoxetin precursor **17**[10] as given in Scheme 6.



Scheme 6

The conversion of **10** into **13** proceeds analogously to that of **2** into **5**. The ring opening of **11** was not stereoselective and so **12** was obtained as a mixture of diastereomers, which for reasons of efficacy were not separated. Also, for the conversion of the following compounds **13**−**16** the diastereomeric mixture was used as such. After acid hydrolysis of the acetal group in **13** and neutralization with sodium carbonate an amorphous solid precipitated. ^{1}H NMR spectroscopy showed a complex mixture in which no iminium proton was detected. It is well-known that 2,3,4,5-tetrahydropyridines with no substituents in the 2-position, easily trimerize to a mixture of two trimeric compounds.[11] The NMR spectrum is in agreement with a mixture of such trimers and it may even contain some polymeric compounds. As these trimers are supposed to be in equilibrium in solution with the monomers we decided to do no further purification but to hydrogenate a solution of the trimeric mixture of **14**. Indeed **15** was isolated from that mixture in a yield of 81%. Reductive methylation of **15** gave **16** in 90% yield. Now we had to address the problem that **16** was a mixture of cis and trans compounds. This mixture was easily isomerized to the trans derivative **16** by treatment with sodium ethoxide. After reduction of *trans*-**16** with $LiAlH_4$, **17** was obtained in an overall yield of 38%. Due to high yields and clean conversions in most steps, it was possible to carry out the eight reaction steps without chromatographic purification of the intermediate compounds.

Application of the chiral enol ether **1c** in this sequence could lead to the synthesis of chiral **17**.

Conclusions

High-pressure promoted cycloadditions of enol ethers and 3-aryl-2-cyano-2-propenoates lead stereoselectively in high yields to 2,6-dialkoxy-4-aryl-dihydro-2*H*-pyran-5-carbonitriles (**3**). In this paper, conversions of **3** into β-amino acid esters, δ-cyano acetals, δ-amino acetals, δ-amino aldehydes (ketones) and 4-arylpiperidinnes have been presented. Furthermore, a straightforward synthesis of the paroxetin precursor **17** is given. Other applications of **3** in the generation and use of *N*-acyliminium ions will be given in the following paper.[8]

Compounds **3** have a high potential to be used as scaffolds in combinatorial synthesis as they contain three different functionalities, which can be selectively modified, and because they can be transformed into a large variety of cyclic and noncyclic compounds having an aryl propylamine moiety. This moiety is an important motif in several compounds acting on the central nervous system. Further applications in this field are under investigation.

Experimental Section

General: The FTIR spectra were recorded on a Genesis Series Mattson instrument. The ^{1}H NMR were recorded using a Bruker AM 300 (300 MHz) or a Bruker AM 400 (400 MHz) spectrometer in $CDCl_3$ solutions. The ^{13}C NMR spectra were measured in $CDCl_3$ (75 MHz). The 2D NOESY spectra were recorded on a Bruker 400 (400 MHz) spectrometer. Chemical shift values are reported as δ values in parts per million (ppm) relative to tetramethylsilane as an internal standard. Mass spectra were determined using a double focusing VG 7070E spectrometer. Melting points were measured on a Reichert Thermopan microscope and are uncorrected. The high-pressure apparatus used in this study has been described before.

General Procedure for the Preparation of 6-Alkoxy-2-methoxy-4-phenyl-3,4-dihydro-2*H*-pyran-5-carbonitriles (3a−h) from 2-Cyano-3-phenyl-2-propenoate (2) and Enol Ethers 1a−h: Compound **2** (2.0 g, 10.7 mmol) was added to enol ethers **1a**−**h** (22 mmol) in a 15 mL Teflon vessel and mixed well. The resulting solution was diluted with dichloromethane until the vessel was full and then closed tightly with a cap. The vessel was pressurized at 15 Kbar and room temp. for 16 h. After release of pressure, the mixture was concentrated in vacuo at room temp. The obtained crude products were analyzed by NMR spectroscopy. The compounds are very sensitive to moisture and traces of acids. In some cases, further purification was possible by crystallization or MPLC (Jobin Yvon) using Baker silica gel 60H pretreated with sodium bicarbonate.

Compound 3a: Oil. IR ($CHCl_3$): $\tilde{\nu}$ = 1630 cm^{-1}. Further purification of the crude reaction mixture was not possible. ^{1}H NMR: δ = 1.24 (t, *J* = 7.2 Hz, 3 H), 1.85−1.96 (m, 1 H), 2.25−2.32 (m, 1 H), 3.64−3.77 (m, 2 H), 3.84 (s, 3 H), 3.85−3.96 (m, 1 H), 5.27 (dd, *J* = 2.0, 8.6 Hz, 1 H), 7.21−7.34 (m, 5 H) ppm.

Compound 3b: The high pressure mixture was concentrated at room temp./10 Torr. ^{1}H NMR spectroscopy showed that **3b** and **4b** were present in a 7:3 ratio. *i*Pr_2O ether was added to the residue whereupon the main isomer **3b** crystallized in 35% yield. The filtrate contained **4b** (see compound **4b**). M.p. 106−107 °C. IR ($CHCl_3$): $\tilde{\nu}$ = 1630 cm^{-1}. $C_{17}H_{21}NO_3$ (287.36): calcd. C 71.06, H 7.37, N 4.87; found C 70.89, H 7.26, N 4.97. ^{1}H NMR: δ = 1.30 (s, 9 H), 1−89−1.98 (m, 1 H), 2.14−2.20 (m, 1 H), 3.76 (dd, *J* = 10.7, 6.3 Hz, 1 H), 3.82 (s, 3 H), 5.50 (dd, *J* = 2.0, 8.8 Hz, 1 H), 7.21−7.33 (m, 5 H) ppm. ^{13}C NMR: δ = 165.3, 141.4, 128.5, 127.3, 127.1, 118.5, 98.3, 63.1, 54.8, 38.3, 37.7, 28.3 ppm.

Compound 3c and 3c^1: The high pressure mixture was concentrated at 60 °C/0.5 Torr. ^{1}H NMR spectroscopy showed the presence of *endo*-**3c** and diastereomer **3c^1** in a 4:1 ratio. *i*Pr_2O ether was added to the residue whereupon a mixture of **3c** and **3c^1** crystallized; yield 65% (ratio 4:1). The filtrate was concentrated at 30 °C/10 Torr and further purified by MPLC, silica gel 60H (pretreated with $NaHCO_3$), eluent: *i*Pr_2O/pentane (4:1). Yield 6% **3c** and 4% **3c^1**.

3c: M.p. 104−105 °C. IR ($CHCl_3$): $\tilde{\nu}$ = 1625 cm^{-1}. $C_{21}H_{21}NO_3$ (335.41): calcd. C 75.20, H 6.31, N 4.18; found C 75.40, H 5.74, N 4.23. ^{1}H NMR: δ = 1.49 (d, *J* = 6.8 Hz), 1.91−2.00 (m, 1 H), 2.17−2.23 (m, 1 H), 3.62 (dd, *J* = 6.4, 10.0 Hz, 1 H), 3.90 (s, 3 H), 4.95 (q, *J* = 6.7 Hz, 1 H), 5.08 (dd, *J* = 1.9, 8.4 Hz, 1 H), 7.21−7.39 (m, 5 H) ppm.

3c^1: M.p. 116−118 °C. IR ($CHCl_3$): $\tilde{\nu}$ = 1625 cm^{-1}. $C_{21}H_{21}NO_3$ (335.41): calcd. C 75.20, H 6.31, N 4.18; found C 75.15, H 5.93, N 4.22. ^{1}H NMR: δ = 1.44 (d, *J* = 6.8 Hz, 3 H), 1.96−2.05 (m, 1 H), 2.30−2.36 (m, 1 H), 3.24 (s, 3 H), 3.74 (dd, *J* = 6.4, 10.0 Hz, 1 H), 4.76 (q, *J* = 6.5 Hz, 1 H), 5.42 (dd, *J* = 2.0, 8.4 Hz, 1 H), 7.26−7.39 (m, 5 H).

Compound 3d: The high pressure mixture was concentrated at 70 °C/0.8 Torr. ^{1}H NMR spectroscopy showed *endo*-**3d** and its diastereomer in a 4:1 ratio. *i*Pr_2O was added to the residue whereupon **3d**

crystallized; yield 45%. M.p. 99−103 °C. IR ($CHCl_3$): $\tilde{\nu}$ = 1630 cm^{-1}. $C_{22}H_{23}NO_4$ (365.43): calcd. C 72.31, H 6.34, N 3.83; found C 72.10, H 6.03, N 3.90. ^1H NMR: δ = 1.48 (d, *J* = 6.5 Hz, 3 H), 1.89−1.98 (m, 1 H), 2.14−2.20 (m, 1 H), 3.62 (dd, *J* = 6.4, 10.0 Hz, 1 H), 3.81 (s, 3 H), 3.90 (s, 3 H), 4.91 (q, *J* = 6.5 Hz, 1 H), 5.06 (dd, *J* = 1.9, 8.5 Hz, 1 H), 6.89 (s, 1 H), 6.91 (s, 1 H), 7.17−7.33 (m, 7 H) ppm. ^{13}C NMR: δ = 164.9, 159.6, 141.3, 133.0, 128.5, 127.7, 127.4, 127.1, 118.3, 114.1, 100.2, 76.2, 63.7, 55.2, 54.9, 37.4, 36.9, 23.7 ppm.

Compound 3e: The high pressure mixture was concentrated at room temp./10 Torr. *i*Pr_2O was added to the residue whereupon **3e** crystallized; yield 45%. M.p. 76−77 °C. IR ($CHCl_3$): $\tilde{\nu}$ = 1630 cm^{-1}. $C_{17}H_{21}NO_3$ (287.36): calcd. C 71.06, H 7.37, N 4.87; found C 71.23, H 7.33, N 4.92. ^1H NMR: δ = 0.71 (d, *J* = 8.0 Hz, 3 H), 1.13 (d, *J* = 6.2 Hz, 3 H), 1.26 (d, *J* = 6.2 Hz, 3 H), 2.20−2.27 (m, 1 H), 3.84 (d, partly hidden under singlet, *J* = 6.7 Hz, 1 H), 3.86 (s, 3 H), 3.96−4.02 (m, 1 H), 5.30 (d, *J* = 2.1 Hz, 1 H), 7.20−7.44 (m, 5 H) ppm. ^{13}C NMR: δ = 165.1, 138.0, 129.5, 127.6, 126.8, 119.0, 104.0, 72.6, 62.2, 54.8, 42.0, 35.9, 23.1, 21.5, 9.8 ppm.

Compound 3f: The high pressure mixture was concentrated at room temp./10 Torr. Cyclohexane was added to the residue whereupon **3f** crystallized; yield 40%. M.p. 97−100 °C. IR ($CHCl_3$): $\tilde{\nu}$ = 1630 cm^{-1}. $C_{17}H_{21}NO_3$ (287.36): calcd. C 71.06, H 7.37, N 4.87; found C 71.06, H 7.38, N 4.85. ^1H NMR: δ = 0.89 (d, *J* = 6.7 Hz, 3 H), 1.23 (d, *J* = 6.4 Hz, 3 H), 1.31 (d, *J* = 6.3 Hz, 3 H), 1.85−1.94 (m, 1 H), 3.20 (d, *J* = 10.0 Hz, 1 H), 3.85 (s, 3 H), 4.00−4.10 (m, 1 H), 4.94 (d, *J* = 8.4 Hz, 1 H), 7.20−7.32 (m, 5 H) ppm.

Compound 3g: The high pressure mixture was concentrated at room temp./10 Torr. *i*Pr_2O was added to the residue whereupon **3g** crystallized; yield 70%. M.p. 111−112 °C. IR ($CHCl_3$): $\tilde{\nu}$ = 1630 cm^{-1}. $C_{15}H_{15}NO_3$ (257.29): calcd. C 70.02, H 5.88, N 5.44; found C 69.80, H 5.86, N 5.39. ^1H NMR: δ = 1.33−1.41 (m, 1 H), 1.74−1.85 (m, 1 H), 2.60−2.67 (m, 1 H), 3.85 (s, 3 H), 3.90 (dd, *J* = 7.6, 10.0 Hz, 1 H), 4.13−4.18 (m, 1 H), 4.21 (d, *J* = 6.4 Hz, 1 H), 5.72 (d, *J* = 3.4 Hz, 1 H), 7.24−7.35 (m, 5 H) ppm. ^{13}C NMR: δ = 164.6, 139.0, 128.6, 127.8, 127.4, 118.5, 104.5, 69.0, 59.3, 55.0, 44.4, 38.0, 23.8 ppm.

Compound 3h: ^1H NMR spectroscopy of the high pressure reaction mixture showed 100% conversion to give **3h** as an oil. Further purification of the crude reaction mixture was not possible. Diast. 1: ^1H NMR: δ = 1.49 (s, 3 H), 2.35 (dd, *J* = 8.5, 11.3 Hz, 1 H), 2.73 (t, *J* = 11.2 Hz, 1 H), 3.44 (s, 3 H), 3.89 (s, 3 H), 3.97 (dd, *J* = 8.5, 12.1 Hz, 1 H), 7.23−7.38 (m, 5 H, diast.1+2) ppm. Diast. 2: ^1H NMR: δ = 1.58 (s, 3 H), 2.07 (d, *J* = 7.7 Hz, 2 H), 3.38 (s, 3 H), 3.70 (t, *J* = 7.7 Hz, 1 H), 3.87 (s, 3 H), 7.23−7.38 (m, 5 H, diast.1+2) ppm. HRMS calcd. for $C_{15}H_{17}NO_3$: 259.1208; found 259.1205.

Compound 4b: The residue obtained after evaporation of *i*Pr_2O (see **3b**) was purified by MPLC, silica gel 60H (pretreated with $NaHCO_3$); eluent: pentane/*i*Pr_2O. The best yield of **4b** was obtained from the high pressure mixture treated at 50 °C at 15 Kbar, in which the ratio **3b**:**4b** was 30:70. Yield **4b**: 68% (and 18% **3b**). M.p. 80−81 °C. IR ($CHCl_3$): $\tilde{\nu}$ = 1730 cm^{-1}. ^1H NMR: δ = 1.22 (s, 9 H), 2.62−2.70 (m, 2 H), 3.71 (dd, *J* = 9.3, 9.5 Hz, 1 H), 3.84 (s, 3 H), 4.54 (t, 8.2 Hz, 1 H), 7.21−7.35 (m, 5 H) ppm. $C_{17}H_{21}NO_3$ (287.36): calcd. C 71.06, H 7.87, N 4.87; found C 70.96, H 7.33, N 4.85.

Compound 5a (Mixture of Diastereomers): Compound **3a**, prepared from **2** (2.0 g, 10.7 mmol), was dissolved in 75 mL of methanol and a pinpoint of *p*-toluenesulfonic acid was added. The mixture was refluxed for 8 h. After addition of 0.25 g of Na_2CO_3 the reaction mixture was concentrated in vacuo. Dichloromethane was added, the mixture washed with water and the organic layer dried with Na_2CO_3. B.p. 155 °C/0.8 Torr (bulb-to-bulb distillation). Yield 2.5 g (84%). Diast. 1: ^1H NMR: δ = 2.10−2.29 (m, 2 H, diast. 1+2), 3.23 (d, *J* = 4.7 Hz, 6 H), 3.49−3.58 (m, 1 H, diast. 1+2), 3.70 (s, 3 H), 3.71 (d, *J* = 5.9 Hz, 1 H), 4.10 (dd, *J* = 3.3, *J* = 8.3 Hz, 1 H), 7.26−7.37 (m, 5 H, diast. 1+2) ppm. Diast. 2: ^1H NMR: δ = 2.10−2.29 (m, 2 H, diast. 1+2), 3.29 (d, *J* = 6.8 Hz, 6 H), 3.49−3.58 (m, 1 H, diast. 1+2), 3.62 (s, 3 H), 4.02 (d, *J* = 5.9 Hz, 1 H), 4.20 (dd, *J* = 3.7, *J* = 7.1, 1 H), 7.26−7.37 (m, 5 H, diast. 1+2) ppm. HRMS calcd. for $C_{15}H_{19}NO_4$: 277.1314; found 277.1310.

Compound 5 h (Mixture of Diastereomers): The crude mixture obtained after reaction of **2** (1.0 g, 5.35 mmol) and **1h** (0.8 g, 11 mmol) in dichloromethane at room temp. and 15 Kbar was concentrated at room temp./10 Torr. The,n 40 mL of methanol and a pinpoint of *p*-toluenesulfonic acid were added and the mixture was refluxed for 1 h. After addition of Na_2CO_3 (0.25 g) the mixture was concentrated in vacuo. Dichloromethane was added, the mixture washed with water and dried with Na_2CO_3. B.p. 155 °C/10 mm. Yield 1.05 g (94%). Diast. 1: ^1H NMR: δ = 1.06 (s, 3 H), 2.14 (dd, *J* = 8.3, 14.5 Hz, 1 H), 2.44 (dd, *J* = 4.7, 14.5 Hz, 1 H), 3.07 (s, 3 H), 3.16 (s, 3 H), 3.53−3.58 (m, 2 H, diast. 1+2), 3.70 (d, *J* = 4.3 Hz, 1 H), 3.70 (s, 3 H), 7.25−7.34 (m, 5 H, diast. 1+2) ppm. Diast. 2: ^1H NMR: δ = 1.26 (s, 3 H), 1.98 (dd, *J* = 4.9, 14.6 Hz, 1 H), 2.50 (dd, *J* = 8.9, 14.8 Hz, 1 H), 3.19 (s, 3 H), 3.22 (s, 3 H), 3.53−3.58 (m, 1 H, diast. 1+2), 3.60 (s, 3 H), 4.31 (d, *J* = 5.1 Hz, 1 H), 7.25−7.34 (m, 5 H, diast. 1+2) ppm. HRMS: 276 [M − CH_3]

Compound 6a (Mixture of Diastereomers): Compound **3a**, prepared from **2** (2.0 g,10.7 mmol) and **1a**, was dissolved in 5 mL of THF and 5 mL of 1 N aqueous HCl was added. After 1 h the mixture was neutralized with a saturated aqueous solution of Na_2CO_3 and the organic layer was dried with Na_2SO_4. B.p. 160 °C/0.8 Torr (bulb-to-bulb distillation). Yield: 2.2 g (67%). Diast. 1: ^1H NMR: δ = 3.03−3.21 (m, 2 H, diast. 1+2), 3.63 (s, 3 H), 3.95−4.00 (m, 1 H, diast. 1+2), 4.13 (d, *J* = 5.8 Hz, 1 H), 7.28−7.37 (m, 5 H), 9.73 (s, 1 H) ppm. Diast. 2: ^1H NMR: δ = 3.03−3.21 (m, 2 H, diast. 1+2), 3.73 (s, 3 H), 3.82 (d, *J* = 5.2 Hz, 1 H), 3.95−4.00 (m, 1 H, diast. 1+2), 7.28−7.37 (m, 5 H), 9.67 (s, 1 H) ppm. HRMS calcd. for $C_{14}H_{15}NO_3$: 231.0895; found 231.0893.

Compound 6h (Mixture of Diastereomers): Crude compound **3h**, prepared from **2** (1 g, 5.35 mmol) and **1h** (0.8 g, 11 mmol), was dissolved in 3 mL THF and 3 mL 1 N HCl was added. After 1 h the reaction mixture was diluted with dichloromethane, washed with $NaHCO_3$ and the organic layer was dried with Na_2SO_4. Bp. 150 °C/0.8 Torr (bulb-to-bulb distillation). Yield: 1 g (75%). Diast. 1: ^1H NMR: δ = 2.13 (s, 3 H), 3.07 (dd, *J* = 7.4, *J* = 17.9 Hz, 1 H), 3.18 (dd, *J* = 6.6, *J* = 17.8 Hz, 1 H), 3.73 (s, 3 H), 3.81 (d, *J* = 4.9 Hz, 1 H), 3.89−3.97 (m, 1 H, diast. 1+2), 7.27−7.36 (m, 5 H, diast. 1+2) ppm. Diast. 2: ^1H NMR: δ = 2.17 (s, 3 H), 2.99 (dd, *J* = 5.1, *J* = 18.5 Hz, 1 H), 3.17 (dd, *J* = 9.3, *J* = 18.5 Hz, 1 H), 3.62 (s, 3 H), 3.89−3.97 (m, 1 H, diast. 1+2), 4.22 (d, *J* = 5.7 Hz, 1 H), 7.27−7.36 (m, 5 H, diast. 1+2) ppm. HRMS calcd. for $C_{14}H_{15}NO_3$: 245.1051; found 245.1048.

Compound 7a

Method A: Compound **5a** (2.5 g, 9 mmol) was added to a mixture of 25 mL of DMSO, 3 mL of water and 5 g of NaCl. The mixture was heated for 2 h at 150 °C (oil bath). It was then poured onto ice and extracted with dichloromethane. The organic layer was dried with Na_2SO_4.

Method B: Compound **5a** (2.5 g, 9 mmol) was added to a mixture of 25 mL of DMSO, 3 mL of water and 5 g of NaCl. The reaction mixture was exposed to microwave irradiation conditions for 15 min at 850 W. The reaction mixture was poured onto ice and extracted with dichloromethane. The organic layer was dried with Na_2SO_4. B.p. 145 °C/0.8 Torr (bulb-to-bulb distillation). Yield: 1.6 g (81%). ^{1}H NMR: δ = 1.95−2.02 (m, 1 H), 2.11−2.18 (m, 1 H), 2.64 (d, *J* = 7.4 Hz, 2 H), 3.09−3.17 (m, 1 H), 3.26 (s, 3 H), 3.30 (s, 3 H), 4.15 (dd, *J* = 3.9, *J* = 7.5 Hz, 1 H), 7.23−7.29 (m, 3 H), 7.33−7.37 (m, 2 H) ppm. ^{13}C NMR: δ = 141.1, 128.8, 127.3, 126.9, 118.2, 102.1, 53.0, 52.6, 37.9, 37.4, 24.7 ppm. HRMS calcd. for $C_{13}H_{17}NO_2$: 219.1259; found 219.1260.

Compound 7h: Compound **5h** (0.5 g, 1.7 mmol) was dissolved in a mixture of DMSO (8 mL) and a saturated aqueous solution of Na_2CO_3 (1 mL). The reaction mixture was exposed to microwave irradiation conditions for 12 min at 600 W. After cooling to room temp. a 50% aqueous solution of Na_2CO_3 (20 mL) was added. The water layer was extracted with dichloromethane and the organic layer was dried with Na_2CO_3. B.p. 150 °C/0.8 Torr (bulb-to-bulb distillation). Yield: 0.3 g (75%). ^{1}H NMR: δ = 1.15 (s, 3 H), 1.96, 197, 1.99, 2.01 (part A of ABX pattern, 1 H), 2.21, 2.22, 2.24, 2.26 (part B of ABX pattern, 1 H), 2.61, 2.63, 2.65, 2.68 (part A of ABX pattern, 1 H), 2.71, 2.72, 2.75, 2.76 (part B of ABX pattern, 1 H), 3.09−3.15 (m, 1 H), 3.10 (s, 3 H), 3.20 (s, 3 H), 7.24−7.26 (m, 3 H), 7.31−7.35 (m, 2 H) ppm. ^{13}C NMR: δ = 142.8, 128.7, 127.2, 127.1, 118.6, 100.9, 48.2, 47.9, 41.3, 38.0, 25.6, 21.4 ppm. HRMS calcd. for $C_{14}H_{19}NO_2$: 233.1416; found 233.1416.

Compound 8a: A solution of **7a** (1.6 g, 7.4 mmol) in diethyl ether was added dropwise to $LiAlH_4$ (0.55 g, 14.5 mmol) also in diethyl ether at room temperature. After 15 min the excess of $LiAlH_4$ was carefully destroyed by adding a 0.5 N aqueous solution of $NaHCO_3$. The water layer was extracted with diethyl ether and the combined layers were dried with Na_2SO_4. B.p. 150 °C/0.8 Torr (bulb to bulb distillation). Yield: 1.4 g (86%). ^{1}H NMR: δ = 1.23 (br. s, 2 H), 1.70−1.86 (m, 2 H), 1.93−1.99 (m, 1 H), 2.49−2.57 (m, 2 H), 2.74−2.81 (m, 1 H), 3.16−3.27 (m, 1 H), 3.21 (s, 3 H), 3.29 (s, 3 H), 4.06 (dd, *J* = 3.9, 7.9 Hz, 1 H), 7.12−7.21 (m, 3 H), 7.25−7.31 (m, 2 H) ppm. HRMS calcd. for $C_{13}H_{21}NO_2$: 223.1573; found 223.1572.

Compound 8h: A solution of **7h** (0.5 g, 2.1 mmol) in diethyl ether was added dropwise to $LiAlH_4$ (0.3 g, 8 mmol) in diethyl ether at room temp. After 10 min the excess of $LiAlH_4$ was carefully destroyed by adding a 0.5 N solution of $NaHCO_3$. The water layer was extracted with diethyl ether and the combined layers were dried with Na_2CO_3. B.p. 150 °C/0.8 Torr (bulb-to-bulb distillation). Yield: 0.36 g (71%). ^{1}H NMR: δ = 1.05 (s, 3 H), 1.19 (br. s, 2 H), 1.70−1.76 (m, 1 H), 1.81−1.86 (m, 1 H), 1.93−2.02 (m, 2 H), 2.45−2.50 (m, 1 H), 3.00 (s, 3 H), 3.17 (s, 3 H), 7.15−7.19 (m, 3 H), 7.25−7.29 (m, 2 H) ppm. ^{13}C NMR: δ = 145.7, 128.3, 127.6, 126.0, 101.5, 48.0, 47.7, 43.3, 40.8, 39.5, 39.1, 21.6 ppm. HRMS calcd. for $C_{14}H_{23}NO_2$: 237.1729; found 237.1726.

Compound 9a (Mixture of Diastereomers): Compound **5a** (2.0 g, 7.2 mmol) was dissolved in 20 mL of ethyl acetate. Raney Ni (0.5 g, dry in methanol) and Na_2CO_3 (0.25 g) were added and the reaction mixture was placed in an autoclave. The reaction mixture was stirred under 25 bar hydrogen atmosphere for 48 h at 75 °C (oil bath). After cooling to room temp. and release of the pressure the mixture was filtered and concentrated in vacuo. B.p. 160 °C/0.8 Torr (bulb-to-bulb distillation). Yield: 1.8 g (90%). Diast. 1: ^{1}H NMR: δ = 1.74−1.92 (m, 2 H), 2.60−2.70 (m, 2 × 1 H), 2.90−3.05 (2 H, diast. 1+2 and 1 H diast. 2), 3.15 (s, 3 H), 3.20 (s, 3 H), 3.38 (s, 3 H), 3.94 (dd, *J* = 3.3, 8.5 Hz, 1 H), 7.10−7.23 (m, 5 H, diast.1+2) ppm. Diast. 2: ^{1}H NMR: δ = 2.04 (dd, *J* = 4.1, *J* = 8.8 Hz, 1 H), 2.07 (dd, *J* = 3.8, 8.5 Hz, 1 H), 2.43−2.52 (m, 1 H), 2.90−3.05 (2 H, diast. 1+2 and 1 H), 3.10 (s, 3 H), 3.17 (s, 3 H), 3.71 (s, 3 H), 3.84 (dd, *J* = 3.3, *J* = 8.2 Hz, 1 H), 7.10−7.23 (m, 5 H, diast.1+2) ppm. HRMS calcd. for $C_{15}H_{23}NO_4$: 281.1627; found 281.1626.

Compound 11: Prepared from **10**[12] and **1a** as described for **3a**. After concentration in vacuo the crude reaction mixture was used in the next step without further purification.^{1}H NMR spectroscopy showed 100% conversion. HRMS calcd. for $C_{16}H_{18}NO_3F$: 291.1267; found 291.1270.

Compound 12: A mixture of compound **11** (2.0 g, 2.0 mmol) in 50 mL of ethanol and a pinpoint of *p*-toluenesulfonic acid was refluxed for 1.5 h. and worked up as described for **5a**. B.p. 170 °C/0.8 Torr (bulb-to-bulb distillation). Yield: 93%. HRMS calcd. for $C_{18}H_{24}NO_4F$: 337.1682; found 337.1689.

Compound 13: Compound **12** (2.0 g, 5.9 mmol) was dissolved in ethanol (20 mL), Raney Ni (0.5 g, dry in methanol) and Na_2CO_3 (0.25 g) were added, and the reaction mixture was placed in an autoclave. It was stirred under 25 bar hydrogen atmosphere for 16 h at 80 °C (oil bath). After cooling to room temp. and release of the pressure the mixture was filtered and concentrated in vacuo. B.p. 170 °C/0.8 Torr (bulb-to-bulb distillation). Yield: 1.9 g (95%). HRMS calcd. for $C_{18}H_{28}NO_4F$: 341.2002; found 341.2002.

Compound 14: To compound **13** (1.9 g, 5.6 mmol) was added 8 mL of a 10% aqueous HCl solution. After about 15 min (the water layer must be clear) the water layer was extracted with diethyl ether. Then the water layer was made basic with solid Na_2CO_3 and extracted with dichloromethane. The combined organic layers were dried with Na_2SO_4. Yield 1.28 g (92%). Mixture of trimers. ^{1}H NMR: δ = 0.88−1.25 (m, 3 H), 1.61−1.95 (m, 1 H), 2.05−2.36 (m, 1 H), 2.70−4.05 (m, 6 H), 6.95−7.28 (m, 4 H) ppm.

Compound 15: Compound **14** (1.28 g, 5.1 mmol) was dissolved in ethanol, a catalytic amount of 10% palladium on activated coal was added and the mixture was placed in an autoclave. The reaction mixture was stirred under a 25 bar hydrogen atmosphere for 16 h at 70 °C (oil bath). After cooling to room temp. and release of the pressure the mixture was filtered and concentrated in vacuo. B.p. 150 °C/0.8 Torr (bulb-to-bulb distillation). Yield: 1.05 g (81%). HRMS calcd. for $C_{14}H_{18}NO_2F$: 251.1322; found 251.1322.

Compound 16 (*trans*): A mixture of **15** (1.28 g, 4.2 mmol), HCHO (8 mL of a 36% solution), ethanol (10 mL) and palladium on activated charoal (60 mg, 10%) was placed in an autoclave. The reaction mixture was stirred under a 10 bar hydrogen atmosphere for 16 h at room temp. After release of the pressure the mixture was concentrated in vacuo, extracted with dichloromethane and dried with Na_2SO_4. B.p. 160 °C/0.8 Torr (bulb-to-bulb distillation.). Yield: 1.0 g (90%) of a mixture of *cis*- and *trans*-**16** (ratio 3:7). Some typical signals for both isomers: ^{1}H NMR: δ = 0.96 (t, 3 H, cis), 1.05 (t, 3 H, trans), 2.28 (s, 3 H, cis), 2.34 (s, 3 H, trans), 3.15−3.20 (m, 1 H, cis), 3.06−3.11 (m, 1 H, trans). The *cis*/*trans* mixture of **16** (1.0 g, 3.77 mmol) was dissolved in a mixture of ethanol (20 mL) and Na (25 mg). The mixture was heated for 16 h at 70 °C and concentrated in vacuo. B.p. 160 °C/0.8 Torr (bulb-to-bulb distillation). Yield: 0.87 g (87%). HRMS calcd. for $C_{15}H_{20}NO_2F$: 265.1478; found 265.1478. ^{1}H NMR: δ = 0.94 (t, *J* = 7.1 Hz, 3 H), 1.76−1.83 (m, 2 H), 2.04−2.17 (m, 2 H), 2.36 (s, 3 H), 2.67−2.87 (m, 2 H), 2.91−2.95 (m, 1 H), 3.04−3.09 (m, 1 H), 3.82−3.92 (m, 2 H), 6.91−6.96 (m, 2 H), 7.13−7.16 (m, 2 H) ppm.

Compound 17: A solution of **16** (0.87 g, 3.28 mmol) in diethyl ether was added dropwise to $LiAlH_4$ (0.2 g, 5.25 mmol) in diethyl ether at room temp. After 10 min the excess of $LiAlH_4$ was carefully destroyed by adding a saturated aqueous solution of NH_4Cl. The water layer was extracted with diethyl ether and the combined layers were dried with Na_2SO_4. After evaporation of the solvent in vacuo the residue was recrystallized from ethyl acetate/cyclohexane. M.p. 118−120 °C. Yield: 0.66 g (90%). $C_{13}H_{18}FNO$ (257.29): calcd. C 69.93, H 8.13, N 6.27; found C 70.08, H 8.19, N 6.22. HRMS calcd. for $C_{13}H_{18}FNO$: 223.1372; found 223.1372. ^1H NMR: δ = 1.70 (br. s, OH), 1.74−2.02 (m, 5 H), 2.25−2.33 (m, 1 H), 2.33 (s, 3 H), 2.90−2.97 (m, 1 H), 3.15−3.19 (m, 1 H), 3.20 (d, J = 6.8 Hz) and 3.24 (d, J = 6.8 Hz, 1 H, A part of ABX pattern), 3.38 (d, J = 3.2 Hz) and 3.43 (d, J = 3.2 Hz, 1 H, B part of ABX pattern), 6.95−7.01 (m, 2 H), 7.14−7.26 (m, 2 H) ppm. ^{13}C NMR: δ = 163.0, 159.8, 139.9, 128.7, 115.4, 115.1, 63.4, 59.6, 56.1, 46.4, 44.4, 43.7, 34.4, 26.8 ppm.

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