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A Microwave-Enhanced, Lewis Acid-Catalyzed Synthesis of 1,3-Dioxolanes and Oxazolines from Epoxides

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Abstract: A fast and highly regio- and stereoselective transformation of non-conventional β-lactam-containing epoxides into the corresponding cyclic 1,3-dioxolanes and oxazolines is herein reported, using microwave irradiation as an efficient source of energy, in the presence of stoichiometric or catalytic amounts of Lewis acids, without an additional solvent. These cyclic compounds are the protected forms of diols and amino alcohols.

Keywords: dioxolanes; epoxides; lactams; Lewis acids; microwave heating

Introduction

1,3-Dioxolanes are widely used as protecting groups for carbonyl functions and 1,2-diols in the synthesis of naturally occurring compounds, and represent useful intermediates and end-products in pharmaceutical, fragrance and polymer industries.[1] Moreover, to date, a variety of chiral cyclic acetals have been designed and employed as chiral auxiliaries, ligands, and catalysts in a broad range of asymmetric reactions.[2]

Recently the transformation of epoxides with carbonyl compounds into 1,3-dioxolanes[3] using several Lewis acids and other catalysts, has received increasing interest.[4] However, this methodology, in most cases, has been applied to terminal epoxides that are known to be more reactive with respect to disubstituted ones. In these cases, the nucleophilic attack occurs preferentially on the less substituted methylene group, thus avoiding problems of regio- and stereoselectivity. For disubstituted examples, the stereochemistry of the reaction is accepted to proceed with inversion of the configuration at the reacting carbon position,[5] while the regioselectivity is strongly influenced by many factors.

As a part of an ongoing program in our laboratory directed to the synthesis of potential enzymatic inhibitors, we became interested in the introduction of hydroxylated functions at the C-1′ or C-2′ position of the alkenyl side chain of 3-bromo-3-alkenylazetidin-2-ones.[6] Aiming to achieve this result, we considered the helpful transformation of an epoxide into the corresponding acetal. Indeed, β-lactam-based structures containing hydroxy and keto functions in the C-3 side chain were recently found to be very potent cholesterol adsorption inhibitors (CAI).[7]

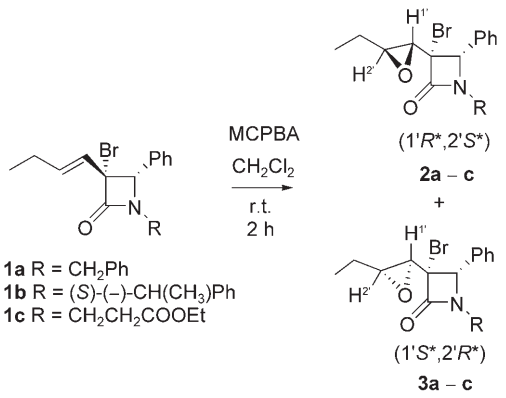
Continuing our work on the use of Lewis acids to carry out carbon-oxygen and carbon-nitrogen bond formation,[8] we report herein the completely regio- and stereoselective microwave-catalyzed transformation of enantiopure and racemic β-lactam-containing epoxides into the corresponding 1,3-dioxolanes and oxazolines in an extremely simple route. Microwave-assisted organic synthesis[9] is a rapidly expanding area of research, since it often offers the opportunity to reduce reaction times from hours to minutes and to increase product yield, performing solvent-free reactions in compliance with green-chemistry protocols.

Results and Discussion

The starting epoxides were prepared by treating 3-bromo-3-butenyl-β-lactams with an excess of *meta*-chloroperbenzoic acid (MCPBA) (Scheme 1).[10]

The epoxides were easily separated by flash chromatography and compound **2a** was characterized by single crystal X-ray analysis,[11] that allowed the (1′*R**,2′*S**) configuration to be attributed to the newly-introduced stereogenic centers (Figure 1).

Initial attempts involved the reaction of *rac*-**2a** and *rac*-**3a** with an excess of propanone used both as reagent and solvent in the presence of 1 equiv. of



Scheme 1. Synthesis of epoxides **2a–c** and **3a–c.**

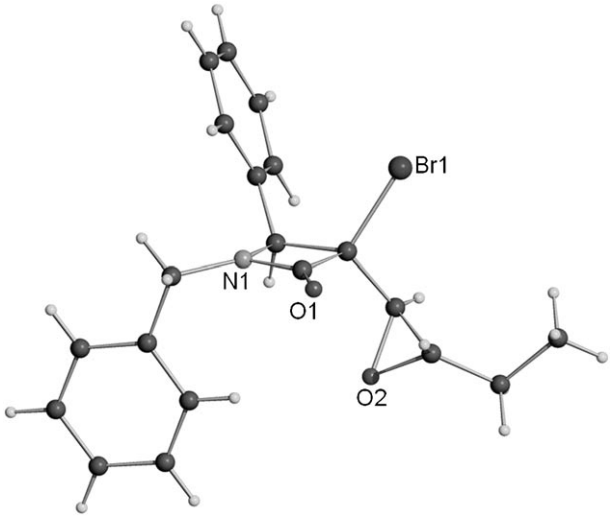
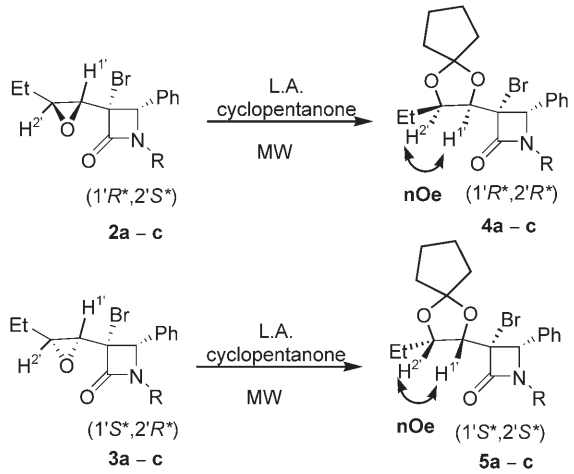


Figure 1. Crystal structure for **2a**.

$BF_3{\cdot}Et_2O$ at room temperaature for 48 h. The propanone, under $BF_3{\cdot}Et_2O$ catalysis, is the carbonyl compound most widely used to convert epoxides into the corresponding dioxolanes, while only few examples derived from other ketones have been reported.[4d,f] Unfortunately, the reaction with propanone furnished a mixture containing starting material, acetal and diol. With the aim to reduce the reaction times and the presence of undesired derivatives, a microwave-assisted methodology was applied to this reaction. Under these new conditions, the carbonyl compound of choice was the cyclopentanone,[12] more compatible with microwave irradiation but unreactive with our substrates both at room temperature or refluxing solvents.

Therefore, compounds **2a–c** or **3a–c** and $BF_3{\cdot}Et_2O$ in a 1:1 equiv. ratio and cyclopentanone (10 equivs.) were irradiated at 200 Watt for 5 min, giving 1,3-dioxolanes in good yield (Scheme 2). The reaction occurred under complete regio- and stereocontrol, as shown by the presence of a single diastereoisomer in



Scheme 2. MW-assisted ring opening of epoxides **2a–c** and **3a–c.**

the ^1H NMR spectrum of the crude mixture. Although no by-products and no traces of unreacted starting material could be detected in the spectrum, the pure dioxolanes were isolated by flash chromatography on alumina in yields ranging from 65% to 90%.[13] The results are collected in Table 1.

The regio- and stereochemistry of the ring opening were rigorously demonstrated. In fact, starting from the trans epoxides **2a** and **3a**, the acetals **4a** and **5a** were obtained, displaying a *cis* relationship between $H^{1'}$ and $H^{2'}$ attributed on the basis of NOE experiments. Furthermore, the X-ray analysis carried out on **5a**[14] confirmed that the ring opening occurred exclusively on the less hindered C-2′ position with inversion of the configuration (Figure 2).

Any attempt to reduce the loading of catalyst failed, due to the strong affinity of boron trifluoride for the oxygen. For this reason we substituted $BF_3{\cdot}Et_2O$ with $In(OTf)_3$, a catalyst with a lower affinity for oxygen.[15]

Indium complexes have received increasing attention in the last few years as catalysts for a variety of

Table 1. MW-assisted ring opening of epoxides in the presence of equimolar amount of boron trifluoride.

Entry	Epoxide	Product	Conversion[a] [%]	Yield[b] [%]
1	**2a**	**4a**	90	65
2	**2b**	**4b**	>95	60
3	**2c**	**4c**	>95	70
4	**3a**	**5a**	>95	70
5	**3b**	**5b**	>95	60
6	**3c**	**5c**	>95	90

[a] Conversion was calculated on the basis of ^1H NMR spectra signals.

[b] Yield of isolated product, after purification by chromatography on alumina.

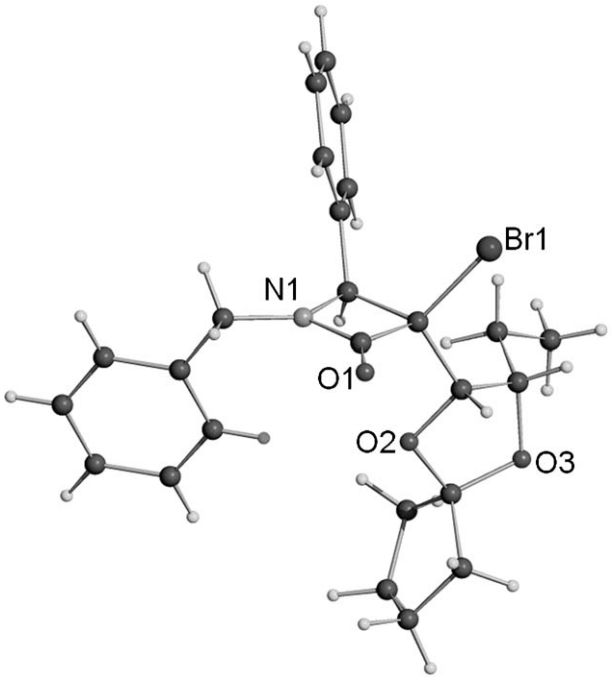
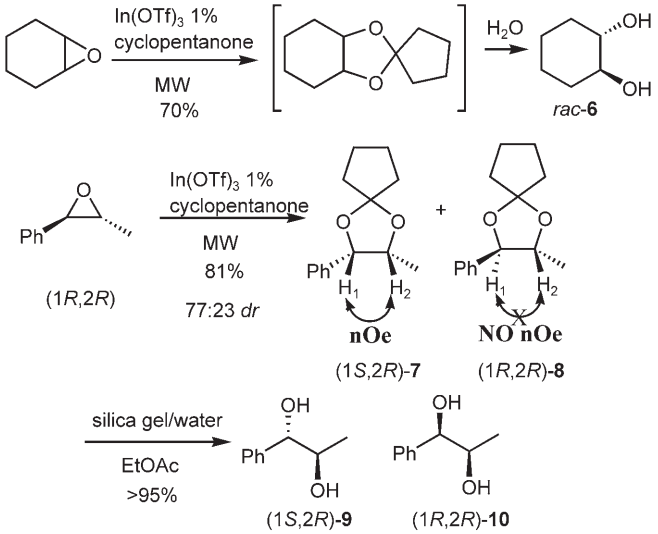


Figure 2. Crystal structure for **5a**.



Scheme 3. Microwave induced reaction of cyclopentanone with reactive epoxides.

organic reactions due to their fast coordination-dissociation equilibrium.[16] In particular, indium(III) bromide has been applied to the stereoselective epoxide ring opening,[17] while the indium(III) triflate has been recently applied to the thioacetalization of carbonyl derivatives[18] but it has never been used in the transformation of epoxides to dioxolanes.

Therefore, we first tested $In(OTf)_3$ on the very reactive cyclohexene oxide and (1*R*,2*R*)-phenylpropylene oxide under several sets of conditions, varying the loading of the L. A., the irradiation power and the time (Scheme 3).

Best results were obtained by performing the reaction of racemic cyclohexene oxide in the presence of 1 mol% of $In(OTf)_3$ with an irradiation power of 200 W for 1 min. When the crude reaction was diluted with an organic solvent and filtered on a celite pad, a mixture of diol, hemiacetal and cyclic acetal was obtained as determined by means of GC-MS analysis.[19] On the other hand when the reaction mixture was submitted to aqueous work-up, the *trans*-diol was exclusively obtained in 70% yield.

Under the same reaction conditions, (1*R*,2*R*)-phenylpropylene oxide afforded a mixture of *cis*-**7** and *trans*-**8** cyclic acetals in a 77:23 ratio and 81% total yield, after chromatography on silica gel. The formation of the minor *trans*-isomer can be ascribed to the partial racemization of the benzylic position.[20] Since a small difference in the H^1-H^2 vicinal coupling constants of the two diastereomers (7.0 Hz versus 8.4 Hz) was observed, the absolute stereochemistry of **7** and **8** was assigned on the basis of NOESY-1D experiments.

Table 2. MW-assisted ring opening of epoxides in the presence of catalytic amount of indium and copper Lewis acids.

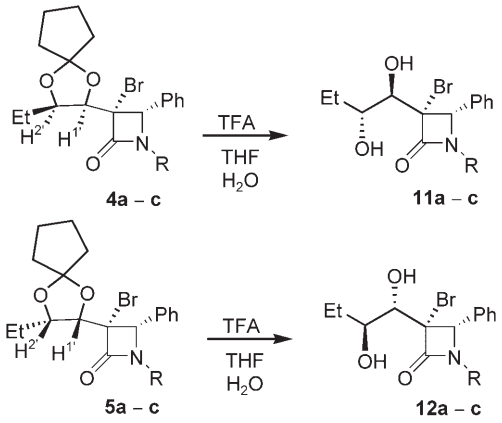
Entry	Epoxide	Product	Lewis acid (%)	Conversion[a] [%]	Yield[b] [%]
1	**2a**	**4a**	$In(OTf)_3$ (5)	>95	65
2	**2b**	**4b**	$In(OTf)_3$ (5)	>95	65
3	**2c**	**4c**	$In(OTf)_3$ (5)	>95	70
4	**3a**	**5a**	$In(OTf)_3$ (5)	>95	71
5	**3b**	**5b**	$In(OTf)_3$ (5)	>95	70
6	**3c**	**5c**	$In(OTf)_3$ (5)	>95	68
7	**2a**	**4a**	$Cu(BF_4)H_2O$ (10)	>95	50
8	**3a**	**5a**	$Cu(BF_4)H_2O$ (10)	>95	62

[a] Conversion was calculated on the basis of ^{1}H NMR spectra signals.

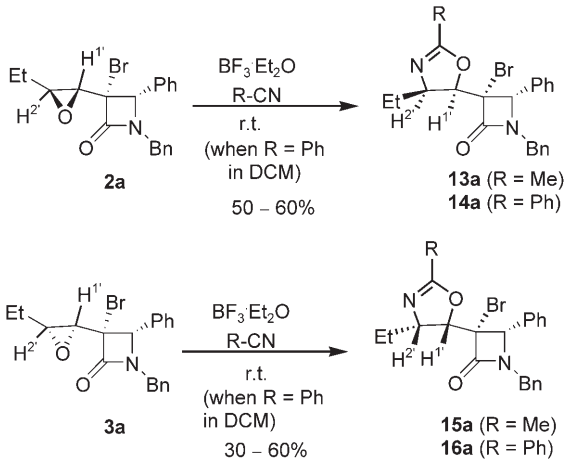
[b] Yield of isolated product, after purification by chromatography on alumina.

Treatment of compounds **7** and **8** with silica gel and water (10 equivs.) in ethyl acetate solution for 2 h, afforded the corresponding diols **9** and **10** in almost quantitative yield. Analytical data for *rac*-**6**, **9** and **10** were in complete agreement with literature data.[21]

In a similar way, the microwave induced transformation of **2a–c** and **3a–c** into the corresponding cyclopentanone acetals required 5% of catalyst and an irradiation power of 500 W for 10 min (Table 2). Under these conditions, satisfactory yields could be obtained and product purification resulted easier. Recently, copper salts have been used as catalysts for electrophilic activation in acylation and acetal formation.[22] When a 10% amount of $Cu(BF_4)_2 \cdot XH_2O$ was used as catalyst for ring opening of epoxides **2a** and **3a**, at



Scheme 4. Hydrolysis of dioxolanes **4a–c** and **5a–c**.



Scheme 5. Reactivity of epoxide **2a** and **3a** with nitrile derivatives.

300 W for 10 min, a lower yield of purified compound could be obtained after chromatography on alumina.

The hydrolysis of cyclopentanone acetals to the corresponding diols was carried out under the conditions reported in the literature for similar compounds.[23] Therefore, treatment of **4a–c** and **5a–c** in THF/H_2O with TFA afforded **11a–c** and **12a–c** in good yield, showing that the complete sequence of reactions allows the diol moiety to be obtained *via* the important acetal-protected form (Scheme 4).

On the basis of these results, we accomplished the epoxide ring opening with CH_3CN and PhCN as nucleophiles aiming to obtain the corresponding oxazolines, as the protected form of amino alcohols (Scheme 5).[24]

The reaction was first carried out on **2a** and **3a** under conventional conditions in the presence of an equimolar amount of boron trifluoride in CH_3CN (10 equivs.) that acts both as reagent and solvent, or with PhCN (10 equivs.) in CH_2Cl_2 at room temperature for 4.5 h, affording **13–16a** in moderate to good yield (Scheme 5).

Any attempt to perform the reaction in the presence of indium, aluminum or copper salts both at room temperature or in refluxing acetonitrile or benzonitrile failed, allowing the unreacted starting epoxides to be recovered. Finally, compounds **2a** and **3a** were treated under microwave irradiation in the presence equimolar amount of $BF_3{\cdot}Et_2O$ (Table 3).

Under these conditions epoxides **2a** and **3a** could be transformed into the corresponding oxazolines in short reaction times (5 min).

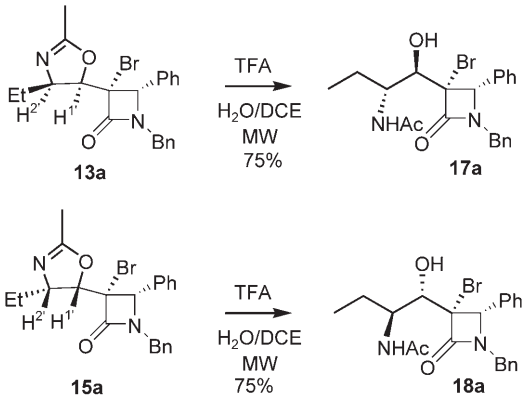
The microwave-assisted reaction of epoxides **2a** and **3a** with acetonitrile in the presence of 1 equivalent of $BF_3{\cdot}Et_2O$, was performed using a temperature program that avoided reaching of the boiling point (entries 1 and 2). Oxazolines **13a** and **15a** were isolated in good yield after flash chromatography on silica gel. The higher boiling temperature of benzonitrile allowed us to react **2a** and **3a** at 200 W. Complete conversion to **14a** and **16a** was observed after 5 min irradiation (entries 3 and 4). When the reaction was performed in the presence of a 10% amount of $In(OTf)_3$, maintaining the same irradiation parameter a very low conversion was observed. On the other hand, by using a higher microwave irradiation power and longer reaction times (10 min) complex mixtures of oxazoline and by-products were obtained.

In any case, the reaction afforded exclusively the oxazoline deriving from the regioselective attack of nitrile on the less hindered C-2′ position. The regiochemistry of the reaction was demonstrated by transformation of oxazolines **13a** and **15a** into the corre-

Table 3. MW assisted ring opening of epoxides in the presence of stoichiometric amount of boron trifluoride.

Entry	Epoxide	MW power	Reagent	Time [min]	Product	Conversion[a] [%]	Yield[b] [%]
1	**2a**	Program[c]	CH_3CN	5	**13a**	>95	71
2	**3a**	Program[c]	CH_3CN	5	**15a**	>95	70
3	**2a**	200 W	PhCN	5	**14a**	>95	72
4	**3a**	200 W	PhCN	5	**16a**	>95	65

[a] Calculated on the basis of ^1H NMR spectra signals.
[b] After purification by chromatography on alumina.
[c] Gradient of temperature from r.t. to 80 °C in 2.5 min, then $T = 80$ °C for 2.5 min.



Scheme 6. Hydrolysis of oxazolines **13a** and **15a**.

sponding *N*-acetylamido derivatives **17a** and **18a**, with TFA (10 equivs.) in water/dichloroethane (1:9), under microwave-assisted conditions (300 W for 5 min, Scheme 6). The signal relative to amide proton in the ^{1}H NMR spectra of **17a** and **18a**, being a doublet coupled with the H_2' multiplet, unambiguously clarified the product backbone, thus confirming the regiochemical outcome of the oxazoline formation.

Conclusions

In conclusion, for particular disubstituted complex epoxides, we reported simple conditions for the regio- and stereoselective transformation into the corresponding cyclic 1,3-dioxolanes, efficient protecting groups and precursors of diols. While the most widely used boron trifluoride was used in an equimolar amount, the reaction performed with indium triflate gave comparable results in the presence of a 5% amount of catalyst. Applying the same methodology to the reaction of epoxides with nitriles in the presence of boron trifluoride, the corresponding oxazolines were obtained with complete regio- and stereocontrol.

Finally, the use of microwave irradiation as efficient source of energy, without additional solvent, lowered the environmental impact of the transformation, allowing us to accomplish epoxide ring opening in a few minutes.

Experimental Section

General Remarks

All chemicals were purchased from commercial suppliers and used without further purification. Anhydrous solvents were purchased in sure seal bottles over molecular sieves and used without further drying. Flash chromatography was performed on alumina (150 mesh, neutral deactivated) or silica gel (230–400 mesh). NMR spectra were recorded with 200, 300 or 600 MHz spectrometers. Chemical shifts were reported as δ values (ppm) relative to the solvent peak of $CDCl_3$ set at $\delta = 7.27$ (^{1}H NMR) or $\delta = 77.0$ (^{13}C NMR). LC-MS analyses were performed on a liquid chromatograph coupled with an electrospray ionization mass spectrometer (LC-ESI-MS), using H_2O/CH_3CN as solvent at 25 °C (positive scan 100–500 *m*/*z*, fragmentor 70 V, gradient elution program from 80% water to 70% acetonitrile in 8 min). GC-MS analysis were performed on an HP5 (cross-linked 5% Ph Me silicone , 30 m × 0.32 mm × 0.25 μm thickness) using an injection program (initial temperature 50 °C for 2 min, then 10 °C min^{-1} up to 280 °C) in scan mode acquisition. Melting points were determined in open capillaries and are uncorrected. Microanalyses were performed with an EA 1108 CHNS-O Fisons Instrument. Microwave-assisted reactions were performed with a Milestone Mycrosynth multimode apparatus, keeping irradiation power fixed and monitoring internal reaction temperature with a built-in ATC-FO advanced fiber optic automatic temperature control. The reactions were performed in an open vessel, equipped with a refrigerator connected to a fume hood. Cyclohexene oxide and (1*R*,2*R*)-phenylpropylene oxide were purchased from commercial source. Compounds **6**, **9** and **10** were fully characterized and their analytical data were identical to those reported in the literature.[21]

General Procedure for the Epoxidation of 3-Alkylidene-3-bromoazetidin-2-ones 1a–c

To a stirred solution of **1** (1 mmol) in CH_2Cl_2 at room temperature, *m*-chloroperbenzoic acid (1.5 equivs, 0.258 g.) was added in one portion. The reaction mixture was stirred overnight and then diluted with a saturated solution of K_2CO_3 (5 mL) and CH_2Cl_2 (5 mL). The two phases were separated, the organic layer was dried over Na_2SO_4 and solvent was removed under reduced pressure. Compounds **2** and **3** were isolated by flash chromatography on silica gel (cyclohexane/ethyl acetate 9/1 as eluant).

2a: mp 145–147 °C; HPLC-MS: $R_t = 14.5$ min, (M + 1) = 386/388, (M + Na) = 408/410 *m*/*z*; IR (nujol): $\nu = 3073$, 2959, 2930, 1771, 1654, 1455, 1395, 1355, 1157, 1124, 1077 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 1.05$ (t, 3H, $J = 7.2$ Hz, CH_3), 1.53–1.77 (m, 2H, CH_2CH_3), 3.27 (1H, d, $J = 2.2$ Hz, BrCH*CH*O), 3.57 (1H, dt, $J = 2.2$, 5.6 Hz, CH_2*CH*O), 3.91 (d, 1H, $J = 15.0$ Hz, CH_2Ph), 4.78 (s, 1H, *CH*Ph), 4.99 (d, 1H, $J = 15.0$ Hz, CH_2Ph), 7.18–7.43 (m, 10H, CHAr); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 9.6$, 24.6, 44.9, 58.7, 59.5, 68.4, 127.7, 127.9, 128.2, 128.4, 128.7, 129.1, 133.7, 133.9, 163.5; anal. calcd. for $C_{20}H_{20}BrNO_2$: C 62.19, H 5.22, N 3.63; found: C 62.21, H 5.23, N 3.62.

3a: HPLC-MS: $R_t = 15.2$ min, (M + 1) = 386/388, (M + Na) = 408/410 *m*/*z*; IR (neat): $\nu = 2962$, 2928, 1775, 1494, 1454, 1392, 1351, 1147, 1072 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): $\delta = 1.02$ (t, 3H, $J = 7.6$ Hz, CH_3), 1.45–1.82 (m, 2H, CH_2CH_3), 2.89 (1H, dt, $J = 1.8$, 5.6 Hz, CH_2*CH*O), 3.45 (1H, d, $J = 1.8$ Hz, BrCH*CH*O), 3.93 (d, 1H, $J = 15.0$ Hz, CH_2Ph), 4.59 (s, 1H, *CH*Ph), 4.97 (d, 1H, $J = 15.0$ Hz, CH_2Ph), 7.16–7.44 (m, 10H, CHAr); ^{13}C NMR (150 MHz, $CDCl_3$): $\delta = 9.4$, 24.2, 44.9, 57.3, 58.9, 59.5, 68.8, 127.8, 127.9, 128.1, 128.4, 128.7, 128.9, 133.8, 134.0, 164.0; anal. calcd. for $C_{20}H_{20}BrNO_2$: C 62.19, H 5.22, N 3.63; found: C 62.17, H 5.24, N 3.66.

Boron Trifluoride-Catalyzed Synthesis of Acetals 4a–c and 5a–c under Microwave-Assisted Conditions.

Epoxide **2** or **3** (1 mmol) was diluted in cyclopentanone (10 equivs., 10 mmol, 0.88 mL) and $BF_3{\cdot}Et_2O$ (1 equiv., 1 mmol, 0.123 mL) was added in one portion. The mixture was submitted to microwave irradiation (power 200 W) for five minutes and then was diluted with ethyl acetate (20 mL) and washed twice with water (20 mL). The two phases were separated, the organic layer was dried over Na_2SO_4 and solvent was removed under reduced pressure. Compounds **4** and **5** were isolated by flash chromatography on alumina (cyclohexane/ethyl acetate, 98/2 as eluant).

Indium Triflate-Catalyzed Synthesis of Acetals 4a–c and 5a–c under Microwave-Assisted Conditions

Epoxide **2** or **3** (1 mmol) was diluted in cyclopentanone (10 equiv, 10 mmol, 0.88 mL) and $In(OTf)_3$ (0.05 equivs, 0.05 mmol, 28 mg) was added in one portion. The mixture was submitted to microwave irradiation (power 500 W) for ten minutes and then was diluted with ethyl acetate (20 mL) and washed twice with water (20 mL). The two phases were separated, the organic layer was dried over Na_2SO_4 and solvent was removed under reduced pressure. Compounds **4** and **5** were isolated by flash chromatography on alumina (cyclohexane/ethyl acetate, 98/2 as eluant).

4a: HPLC-MS: $R_t = 23.3$ min, $(M+1) = 470/472$, $(M+Na) = 492/494$ *m/z*; IR (neat): $\nu = 3087, 3064, 3031, 2964, 2931, 2874, 2356, 2323, 2252, 1772, 1655, 1616, 1496, 1455, 1395, 1115\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.07$ (t, 3H, $J = 7.5$ Hz, $CHCH_2CH_3$), 1.65–1.80 (m, 6H, CH_2ciclopentane), 1.87–2.04 (m, 3H, $CHCH_2$ + CH_2cyclopentane), 2.22–2.38 (m, 1H, CH_2CH_3), 3.95 (1H, d, $J = 15$ Hz, CH_2Ph), 4.06 (m, 1H, $OCHCH_2CH_3$), 4.14 (d, 1H, $J = 6.6$ Hz, BrC*CH*O), 4.95 (s, 1H, *CH*Ph), 6.00 (d, 1H, $J = 15$ Hz, CH_2Ph), 7.14–7.49 (m,10H, CHAr); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 11.3$, 23.4, 23.5, 23.6, 37.3 (2C), 44.5, 63.3, 63.6, 79.7, 80.8, 118.8, 127.8, 128.1, 128.4, 128.8, 128.9, 129.0, 134.3, 139.5, 168.4; anal. calcd. for $C_{25}H_{28}BrNO_3$: C 63.83, H 6.00, N 2.98; found: C 63.85, H 6.01, N 2.94.

5a: mp 118–120 °C; HPLC-MS: $r_t = 13.28$ min, $(M+1) = 470/472$ *m/z* ; IR (nujol): $\nu = 2930, 2874, 2855, 1777, 1655, 1637, 1457, 1425, 1215, 1151, 1109, 1068\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.98$ (t, 3H, $J = 7.4$ Hz, $CHCH_2CH_3$), 1.20–1.90 (m, 10H, $CHCH_2$ + CH_2 cyclopentane), 3.74 (1H, d, $J = 14.8$ Hz, CH_2Ph), 4.04 (m, 1H, $OCHCH_2CH_3$), 4.61 (d, 1H, $J = 6.4$ Hz, BrC*CH*O), 4.93 (d, 1H, $J = 14.8$ Hz, CH_2Ph), 4.94 (s, 1H, *CH*Ph), 7.15–7.60 (m,10H, CHAr); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 11.3$, 23.4, 23.5, 24.0, 36.1, 36.8, 44.4, 60.8, 69.1, 78.0, 79.7, 118.8, 128.3, 128.6, 128.9, 129.1, 129.3, 129.5, 133.6, 134.4, 165.3; anal. calcd. for $C_{25}H_{28}BrNO_3$: C 63.83, H 6.00, N 2.98; found: C 63.80, H 5.97, N 2.97.

Indium Triflate-Catalyzed Synthesis of 6, 7 and 8 under Microwave-Assisted Conditions; Hydrolysis of 7 and 8

Cyclohexene oxide (1 mmol) or (1*R*,2*R*)-phenylpropylene oxide (1 mmol) was diluted in cyclopentanone (10 equivs, 10 mmol, 0.88 mL) and $In(OTf)_3$ (0.01 equiv., 0.01 mmol, 6 mg) was added in one portion. The mixture was submitted to microwave irradiation (power 200 W) for one minute and then was diluted with ethyl acetate (20 mL) and washed twice with water (20 mL). The two phases were separated, the organic layer was dried over Na_2SO_4 and solvent was removed under reduced pressure. Compounds **6**, **7**, **8** were isolated by flash chromatography on silica gel (cyclohexane/ethyl acetate, 98/2 as eluant). Treatment of **7** and **8** with H_2O (10 equivs., 0.18 mL) and silica gel (0.1 g) in EtOAc (5 mL) allowed us to isolate, after filtration of the solid catalyst and solvent removal, diols **9** and **10** in almost quantitative yields. Analytical data for *rac*-**6**, (1*S*,2*R*)-**9** and (1*R*,2*R*)-**10** were in agreement with the data reported in the literature.[21]

(1*S*,2*R*)-7: $[\alpha]_D^{20}$: +14.1 (*c* 9, $CHCl_3$); GC-MS (EI): $R_t = 16.52$ min, $m/z = 218$ (10), 189 (65), 174 (100), 117 (80), 105 (82), 91 (95); IR (neat): $\nu = 3582, 3064, 3029, 2968, 1949, 1495, 1453, 1332, 1110\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.87$ (t, 3H, $J = 6.3$ Hz, $CHCH_3$), 1.78–2.29 (m, 8H, CH_2 cyclopentane), 4.49 (dq, 1H, $J = 6.6$, 6.3 Hz, $CHCH_3$), 5.10 (d, 1H, $J = 6.6$ Hz, *CH*Ph), 7.25–7.45 (m, 5H, CHAr); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 16.4$, 23.1, 24.0, 36.5, 36.7, 74.1, 80.1, 118.0, 126.7, 127.5, 127.9, 138.4; anal. calcd. for $C_{14}H_{18}O_2$: C 77.03, H 8.31; found: C 77.07, H 8.28.

(1*R*,2*R*)-8: $[\alpha]_D^{20}$: +74.6 (*c* 3.4, $CHCl_3$); GC-MS (EI): $R_t = 16.25$ min, $m/z = 218$ (20), 189 (80), 174 (65), 117 (100), 105 (90), 91 (95); IR (neat): $\nu = 3629, 3088, 2872, 1950, 1654, 1494, 1433, 1367, 1207\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.35$ (t, 3H, $J = 6.0$ Hz, $CHCH_3$), 1.78–2.20 (m, 8H, CH_2 cyclopentane), 3.87 (dq, 1H, $J = 8.4$, 6.0 Hz, $CHCH_3$), 4.43 (d, 1H, $J = 8.4$ Hz, *CH*Ph), 7.20–7.45 (m, 5H, CHAr); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 16.2$, 23.3, 23.5, 37.5(2C), 79.2, 84.7, 118.5, 126.4, 128.0, 128.4, 137.9; anal. calcd. for $C_{14}H_{18}O_2$: C 77.03, H 8.31; found: C 77.00, H 8.33.

General Procedure for the Hydrolysis of Acetals 4a–c and 5a–c

To a stirred solution of **4** or **5** (1 mmol) in THF/H_2O (1/1 solution, 5 mL) at room temperature, trifluoroacetic acid (10 equiv, 10 mmol, 0.74 mL) was added in one portion. The reaction was stirred overnight and then THF was removed under reduced pressure. The aqueous residue was diluted with water (5 mL) and extracted twice with CH_2Cl_2 (10 mL). The two phases were separated, the organic layer was dried over Na_2SO_4 and solvent was removed under reduced pressure. Compounds **11** and **12** were isolated by flash chromatography on silica gel (cyclohexane/ethyl acetate, 7/3 as eluant).

11a: HPLC-MS: $R_t = 9.36$ min, $(M-HBr+1) = 324$ *m/z*; IR (neat): $\nu = 3487, 2934, 2911, 2874, 2350, 2321, 2199, 1744, 1650, 1600, 1496, 1425, 1381, 1112\ cm^{-1}$; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.88$ (t, 3H, $J = 7.5$ Hz, $CHCH_2CH_3$), 1.56–1.80 (m, 2H, $CHCH_2CH_3$), 3.64 (m, 1H, $CHCH_2CH_3$), 3.85 (1H, d, $J = 15.5$ Hz, CH_2Ph), 4.49 (s, 1H, *CH*Ph), 4.61 (d, 1H, $J = 15.5$ Hz, CH_2Ph), 4.78 (d, 1H, $J = 6.5$ Hz, BrC*CH*O), 7.21–7.65 (m, 10H, CHAr); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 9.0$, 26.1, 30.3, 50.2, 66.6, 83.0, 100.0, 127.7, 129.7, 129.8, 129.9, 130.0 (2), 130.7, 131.6, 161.0; anal. calcd. for $C_{20}H_{22}BrNO_3$: C 59.42, H 5.48, N 3.46; found: C 59.41, H 5.44, N 3.49.

12a: HPLC-MS: $R_t = 9.57$ min, $(M+1) = 404/406$, $(M+Na) = 426/428$ *m/z*; IR (neat): $\nu = 3352, 2945, 2924, 2853, 2095, 1712, 1673, 1614, 1456, 1377, 1112\ cm^{-1}$; ^1H NMR

(300 MHz, $CDCl_3$): $\delta = 1.03$ (t, 3H, $J = 7.2$ Hz, $CHCH_2CH_3$), 1.45–1.80 (m, 2H, $CHCH_2CH_3$), 2.40–2.80 (bs, 2H, OH), 3.59 (d, 1H, $J = 7.5$ Hz, BrC*CH*O), 3.78 (m, 1H, $CHCH_2CH_3$), 3.95 (1H, d, $J = 15$ Hz, CH_2Ph), 4.76 (s, 1H, *CH*Ph), 4.96 (d, 1H, $J = 15$ Hz, CH_2Ph), 7.26–7.43 (m, 10H, CHAr); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 9.6$, 25.1, 30.3, 45.3, 64.9, 74.3, 90.7, 128.0, 128.3, 128.5, 128.6, 129.0, 129.1, 130.0, 133.8, 171.2; anal. calcd. for $C_{20}H_{22}BrNO_3$: C 59.42, H 5.48, N 3.46; found: C 59.40, H 5.47, N 3.45.

Boron Trifluoride-Catalyzed Synthesis of Oxazolines 13–16a under Conventional Conditions

Epoxide **2a** or **3a** (1 mmol) was diluted in CH_2Cl_2 (10 mL) and acetonitrile or benzonitrile (10 equiv) and $BF_3{\cdot}Et_2O$ (1 equiv., 1 mmol, 0.123 mL) were added in one portion. The mixture was stirred ar room temparature for four hours and then was washed twice with water (20 mL). The two phases were separated, the organic layer was dried over Na_2SO_4 and solvent was removed under reduced pressure. Compounds **13–16a** were isolated by flash chromatography on silica gel (cyclohexane/ethyl acetate, 95/5 as eluant).

Boron Trifluoride-Catalyzed Synthesis of Oxazolines 13–16a under Microwave-Assisted Conditions

Epoxide **2a** or **3a** (1 mmol) was diluted in acetonitrile or benzonitrile (10 equiv) and $BF_3{\cdot}Et_2O$ (1 equiv., 1 mmol, 0.123 mL) was added in one portion. The mixture was submitted to microwave irradiation (for acetonitrile: gradient of temperature from room temperature to 80 °C in 2.5 min, then $T = 80$ °C for 2.5 min; for benzonitrile: power 200 W for 5 min) and then was diluted with ethyl acetate (20 mL) and washed twice with water (20 mL). The two phases were separated, the organic layer was dried over Na_2SO_4 and solvent was removed under reduced pressure. Compounds **13–16a** were isolated by flash chromatography on silica gel (cyclohexane/ethyl acetate 95/5 as eluant).

13a: HPLC-MS: $R_t = 10.25$ min, $(M+1) = 427/429$ *m/z*; IR (neat): $\nu = 2973$, 2923, 1771, 1699, 1635, 1558, 1506, 1456 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.08$ (t, 3H, $J = 7.4$ Hz, $CHCH_2CH_3$), 1.65 (m, 2H, $CHCH_2CH_3$), 1.94 (s, 3H), 3.83 (d, 1H, $J = 15$ Hz, CH_2Ph), 4.02 (m, 1H, $NCHCH_2CH_3$), 4.74 (s, 1H, CHPh), 4.81 (d, 1H, $J = 9$ Hz, BrC*CH*O), 4.98 (d, 1H, $J = 15$ Hz, CH_2Ph), 7.20–7.46 (m,10H, CHAr); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 12.2$, 13.9, 24.5, 44.9, 63.4, 69.1, 70.9, 83.2, 128.1, 128.3, 128.5, 128.7, 128.8, 129.3, 132.8, 134.3, 165.1, 167.0; anal. calcd. for $C_{22}H_{23}BrN_2O_2$: C 61.83, H 5.42, N 6.56; found: C 61.85, H 5.41, N 6.52.

14a: HPLC-MS: $R_t = 12.56$ min, $(M+1) = 489/491$, $(M+Na) = 511/513$, $(2M+Na) = 999/1001$ *m/z*; IR (neat): $\nu = 2924$, 2853, 1771, 1654, 1462 1376, 1344, 1277, 1100, 1088 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.33$ (t, 3H, $J = 7.2$ Hz, $CHCH_2CH_3$), 2.25 (m, 2H, $CHCH_2CH_3$), 3.43 (d, 1H, $J = 15$ Hz, CH_2Ph), 4.10 (m, 1H, $NCHCH_2CH_3$), 4.66 (d, 1H, $J = 9$ Hz, BrC*CH*O), 4.80 (d, 1H, $J = 15$ Hz, CH_2Ph), 4.92 (s, 1H, *CH*Ph), 6.91–7.0 (m,13H, CHAr), 8.0 (m,2H, CHAr); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 12.0$, 13.0, 24.8, 44.8, 63.6, 70.7, 83.7, 128.0, 128.2, 128.3, 128.5, 128.6, 128.7, 128.9, 129.3, 131.8, 133.9, 134.1, 136.8, 162.1, 164.9; anal. calcd. for $C_{27}H_{25}BrN_2O_2$: C 66.26, H 5.15, N 5.72; found: C 66.25, H 5.12, N 5.74.

15a: HPLC-MS: $R_t = 10.29$ min, $(M+1) = 427/429$ *m/z*; IR (neat): $\nu = 2932$, 2875, 1776, 1679, 1547, 1495, 1455, 1387, 1399, 1219 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.06$ (t, 3H, $J = 7.2$ Hz, $CHCH_2CH_3$), 1.78 (m, 2H, $CHCH_2CH_3$), 1.81 (s, 3H), 3.68 (d, 1H, $J = 15$ Hz, CH_2Ph), 4.06 (m, 1H, $NCHCH_2CH_3$), 4.78 (s, 1H, *CH*Ph), 5.00 (d, 1H, $J = 15$ Hz, CH_2Ph), 5.11 (d, 1H, $J = 9.6$ Hz, BrC*CH*O), 7.18–7.48 (m,10H, CHAr); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 12.1$, 13.8, 25.6, 44.5, 61.2, 67.5, 70.1, 82.1, 128.1, 128.4, 128.5, 128.8, 129.2, 129.5, 132.9, 134.2, 163.2, 164.6; anal. calcd. for $C_{22}H_{23}BrN_2O_2$: C 61.83, H 5.42, N 6.56; found: C 61.80, H 5.43, N 6.55.

16a: HPLC-MS: $r_t = 12.35$ min, $(M+1) = 489/491$, $(M+Na) = 511/513$, $(2M+Na) = 999/1001$ *m/z*; IR (neat): $\nu = 2924$, 2853, 1777, 1655, 1495, 1466, 1399, 1363, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.14$ (t, 3H, $J = 7.2$ Hz, $CHCH_2CH_3$), 1.76 (m, 2H, $CHCH_2CH_3$), 3.77 (d, 1H, $J = 15$ Hz, CH_2Ph), 4.28 (m, 1H, $NCHCH_2CH_3$), 4.86 (s, 1H, *CH*Ph), 5.01 (d, 1H, $J = 15$ Hz, CH_2Ph), 5.30 (d, 1H, $J = 9$ Hz, BrC*CH*O), 7.11–7.57 (m,15H, CHAr); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 11.8$, 14.1, 22.7, 44.5, 61.6, 70.2, 82.3, 127.7, 127.9, 128.4, 128.5, 128.7, 128.9, 129.3, 129.5, 131.7, 132.0, 132.9, 133.9, 162.3, 164.6; anal. calcd. for $C_{27}H_{25}BrN_2O_2$: C 66.26, H 5.15, N 5.72; found: C 66.28, H 5.18, N 5.69.

General Procedure for the Hydrolysis of Oxazolines 13a and 15a

To a stirred solution of **13a** or **15a** (1 mmol) in dichloroethane/H_2O (9/1 solution, 5 mL) at room temperature, trifluoroacetic acid (10 equivs, 10 mmol, 0.74 mL) was added in one portion. The mixture was submitted to microwave irradiation (power 300 W) for five minutes The solution was diluted with water (5 mL) and extracted twice with CH_2Cl_2 (10 mL). The two phases were separated, the organic layer was dried over Na_2SO_4 and solvent was removed under reduced pressure. Compounds **17a** and **18a** were isolated by flash chromatography on silica gel (cyclohexane/ethyl acetate, 1/1 as eluant).

17a: HPLC-MS: $R_t = 8.62$ min, $(M+1) = 445/447$ *m/z*; IR (neat): $\nu = 3300$, 2924, 2853, 1752, 1701, 1654, 1640, 1457, 1376, 1266 cm^{-1}; ^1H NMR (300 MHz, C_6D_6): $\delta = 0.85$ (t, 3H, $J = 7.5$ Hz, $CHCH_2CH_3$), 1.62 (s, 3H), 1.80–2.0 (m, 2H, $CHCH_2CH_3$), 3.68 (d, 1H, $J = 15.3$ Hz, CH_2Ph), 4.03 (m, 1H, $NCHCH_2CH_3$), 4.11 (bs, 1H, BrC*CH*O), 4.69 (d, 1H, $J = 15.3$ Hz, CH_2Ph), 5.31 (s, 1H, *CH*Ph), 5.32 (d, 1H, $J = 8.7$ Hz, NH), 6.85–7.25 (m,10H, CHAr); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 11.4$, 23.3, 26.9, 45.3, 56.6, 60.4, 62.8, 73.0, 127.9, 128.2, 128.3, 128.5, 128.7, 128.8, 134.3, 134.5, 165.4, 172.8; anal. calcd. for $C_{22}H_{25}BrN_2O_3$: C 59.33, H 5.66, N 6.29; found: C 59.31, H 5.68, N 6.31.

18a: HPLC-MS: $R_t = 8.84$ min, $(M+1) = 445/447$ *m/z*; IR (neat): $\nu = 3345$, 2964, 1758, 1637, 1560, 1400, 1261, 1095, 1023 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 1.02$(t, 3H, $J = 7.5$ Hz, $CHCH_2CH_3$), 1.70–1.85 (m, 2H, $CHCH_2CH_3$), 2.14 (s, 3H), 3.60–3.80 (bs, 1H, OH); 4.02 (d, 1H, $J = 15.3$ Hz, CH_2Ph), 4.07–4.15 (m, 2H, $NCHCH_2CH_3$ + BrC*CH*O), 5.00 (s, 1H, *CH*Ph), 5.01 (d, 1H, $J = 15.3$ Hz, CH_2Ph), 6.56 (d, 1H, $J = 7.8$ Hz, NH), 7.20–7.60 (m,10H, CHAr); ^{13}C NMR

(75 MHz, $CDCl_3$): $\delta = 11.4$, 23.3, 26.9, 45.3, 56.6, 60.4, 62.8, 73.0, 127.9, 128.2, 128.3, 128.5, 128.7, 128.8, 134.3, 134.5, 165.4, 172.8; anal. calcd. for $C_{22}H_{25}BrN_2O_3$: C 59.33, H 5.66, N 6.29; found: C 59.36, H 5.65, N 6.26.

X-ray Crystallographic Study

Crystal data for **2a**: $C_{20}H_{20}Br_1NO_2$, M = 386.28, monoclinic $P21/c$, $a = 8.8729(11)$, $b = 19.734(2)$, $c = 21.236(3)$ Å, $\beta = 92.613(2)$, $V = 3714.5(8)$ Å3, $Z = 8$, $\rho x = 1.381$ Mgm^{-3}, $\mu = 2.224$ mm^{-1}, F(000) = 1584, $T = 296(2)$ K, $\theta_{max} = 25.40$, 34970 reflections collected, 4235 $I > 2\sigma(I)$. Final $R1 = 0.0474$, $wR2 = 0.1260$, GOF = 0.769. CCDC 286004. Crystallographic data (excluding structure factors) for the structure reported in this paper has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 286004. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: int. code + 44(1223)336–033; E-mail: deposit@ccdc.cam.ac.uk].

Crystal data for **5a**: $C_{25}H_{28}Br_1NO_3$, M = 470.39, triclinic $\bar{P}1$, $a = 10.3810(10)$, $b = 10.9710(10)$, $c = 12.426(2$ Å, $\alpha = 98.500(2)$, $\beta = 106.067(2)$, $\gamma = 117.1720(10)$, $V = 1145.9(2)$ Å3, $Z = 2$, $\rho x = 1.363$ Mgm^{-3}, $\mu = 1.819$ mm^{-1}, F(000) = 488, $T = 296(2)$ K, $\theta_{max} = 28.69$, 8540 reflections collected, 3629 $I > 2\sigma(I)$. Final $R1 = 0.0409$, $wR2 = 0.1088$, GOF = 1.028. CCDC 621038. Crystallographic data (excluding structure factors) for the structure reported in this paper has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 621038. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: int. code + 44(1223)336–033; E-mail: deposit@ccdc.cam.ac.uk].

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[12] Boiling point 130–131 °C.

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