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Stereoselective Meisenheimer rearrangement using BTAa's as chiral auxiliaries

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Abstract

The Meisenheimer rearrangement involves the [2,3]-sigmatropic rearrangement of allylic tertiary amine-*N*-oxides to *O*-allyl hydroxylamines. Various BTAa's (bicycles derived from tartaric acid and α-amino acids) were employed as chiral auxiliaries in the Meisenheimer rearrangement of the *N*-oxides of *N*-allylamines obtained by the coupling of BTAa's with cinnamyl bromide and (*E*)-2-methyl-2-pentenyl acetate. While the formation of the *N*-oxides was highly diastereoselective, the asymmetric induction in the rearrangement was generally low. However, the interaction between the 4-*endo* group on the BTAa and a 2′-substituent on the allylic moiety allowed a more efficient chirality transfer in the [2,3]-sigmatropic process, affording d.e. values as high as 65% in the best case. The cleavage of the N–O bond in the rearrangement products was possible by using $Mo(CO)_6$ with a good recovery of both alcohol and chiral auxiliary.

1. Introduction

The Meisenheimer rearrangement involves the [2,3]-sigmatropic rearrangement of allylic tertiary amine-*N*-oxides **1** to *O*-allyl hydroxylamines **3** (Scheme 1). The cleavage of the N–O bond in **3** affords secondary or tertiary allylic alcohols **4**.[1]

So far, only very few authors have illustrated the potential of this process for the enantioselective synthesis of allylic alcohols from enantiopure tertiary amine-*N*-oxides.[2–7] Enders[5] and Coldham,[2,4] in particular, have reported on the use of enantiopure proline- and camphidine-based secondary amines (Fig. 1) as chiral auxiliaries for the preparation of allylic tertiary amine-*N*-oxides. However, in the subsequent rearrangement processes, the diastereoselectivity in the formation of the *O*-allyl hydroxylamines was not higher than 60–70%, due to either the

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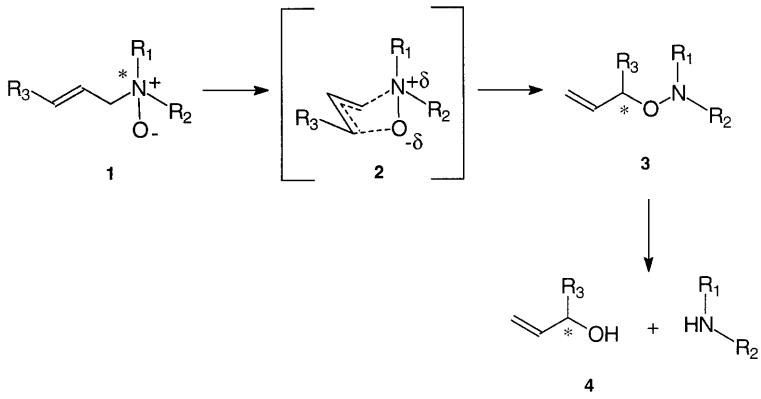


Scheme 1.

Figure 1.

oxidation step of the *N*-allyl tertiary amines, which led to diastereomeric mixtures of *N*-oxides, or the lack of stereocontrol in the rearrangement itself.

Aimed at evaluating the BTAa's[8] (bicycles from tartaric acid and amino acid), recently described by us (Fig. 2), as chiral auxiliaries in organic synthesis, we envisioned that BTAa's could be very useful scaffolds to prepare enantiopure *N*-allyl tertiary amines and their *N*-oxides to study the Meisenheimer rearrangement. Since BTAa are quite rigid structures,[8] the oxidation step could give rise to only one diastereomerically pure *N*-oxide. Moreover, a series of BTAa derivatives may be prepared by simply changing the α-amino acid precursor, allowing a possible control of the steric effects exerted by the substituent on the chiral scaffold.

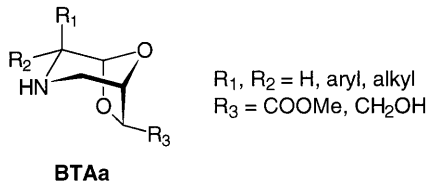
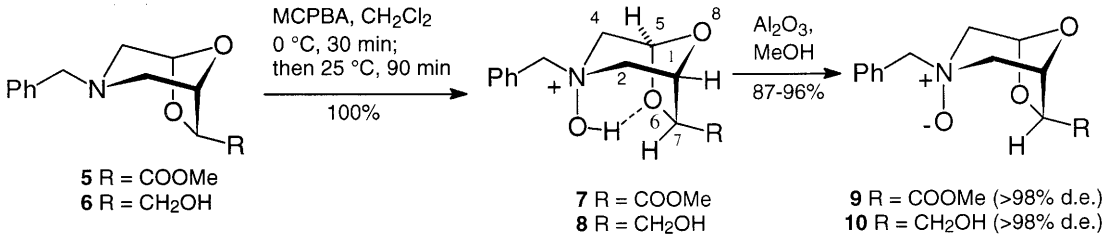


Figure 2.

2. Results and discussion

To assess the diastereoselectivity in the formation of *N*-oxides from BTAa's, we first studied the oxidation by *m*-chloroperbenzoic acid (MCPBA) of *N*-benzylamino ester **5** and *N*-benzyl-

amino alcohol **6** (Scheme 2) taken as model compounds. A 2 hour treatment of **5** with the organic peracid[9] in CH_2Cl_2 at 0–25°C led to the quantitative formation of *N*-hydroxylammonium benzoate **7** as a single diastereoisomer (>98% d.e. by ^1H and ^{13}C NMR analysis of the crude products). The corresponding *N*-oxide **9** was obtained in 96% yield after elution of the salt with MeOH through a column filled with alkaline Al_2O_3.



Scheme 2.

We were unable to obtain a single crystal suitable for X-ray diffraction of this highly hygroscopic compound; however, the stereochemistry of **7** (and the corresponding *N*-oxide **9**) can be easily assigned by analysis of their ^1H NMR spectra recorded in $CDCl_3$. In analogy to BTAa tertiary amines, a chair-like conformation of the six-membered ring of **7** can be assigned by the coupling constant values of H-1 and H-5 with both protons on C-2 and C-4, respectively, which are close to 0 Hz and make protons H-1 and H-5 appear as singlets in the spectra of both **7** and the isolated *N*-oxide **9**.[8] The chemical shift values of protons H-1, H-5, and H-7 in **7** are then consistent with the *endo* orientation of the N–OH group in the *N*-hydroxylammonium salt: of the three protons, only the *endo* H-7 (5.79 ppm) suffers from the magnetic anisotropy of the N–OH bond, undergoing a strong downfield shift ($\Delta\delta$ +1.19 ppm) with respect to the same proton in the corresponding tertiary amine **5** (4.60 ppm). Instead, the chemical shifts of both H-1 (4.90 ppm) and H-5 (5.83 ppm) are almost unaffected by the formation of the salt. A NOESY spectrum of *N*-oxide **9** showed correlation between the benzylic protons and both the axial (*exo*) protons on C-2 and C-4 and this can be accounted for only by assuming the *exo* orientation for the *N*-benzyl group, thus confirming the formation of an *endo*-*N*-oxide. In the formation of proline-based *N*-oxides (Fig. 1),[2,10] the high diastereoselectivity has been associated with the presence of a hydrogen bond donor (e.g. an OH group) group on the proline carboxylate side chain. In our case the possible H bond between the approaching peracid and the oxygen at position 6 could explain the high *endo* preference in the formation of *N*-oxides from BTAa (Fig. 3). Moreover, with this approach, the benzyl group maintains its equatorial position on the six-membered ring, and this could further favour the *endo* attack by the peracid.

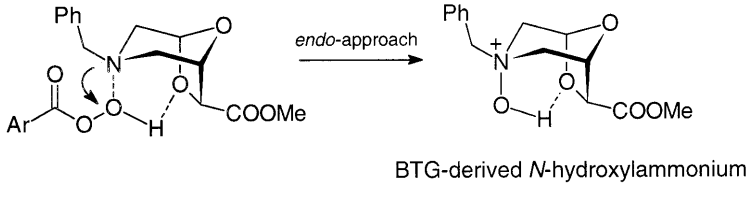
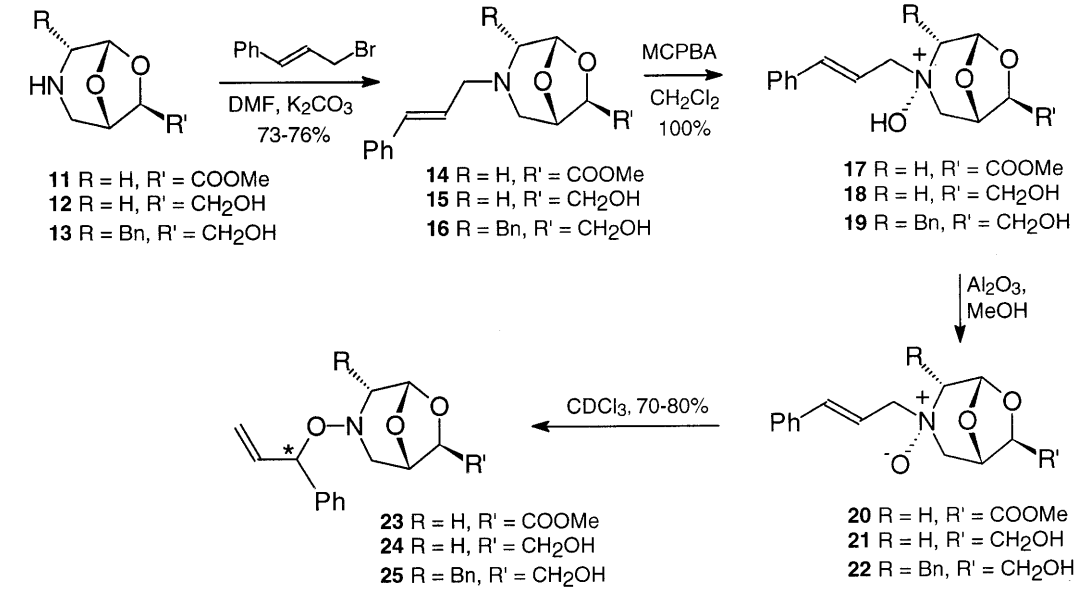


Figure 3.

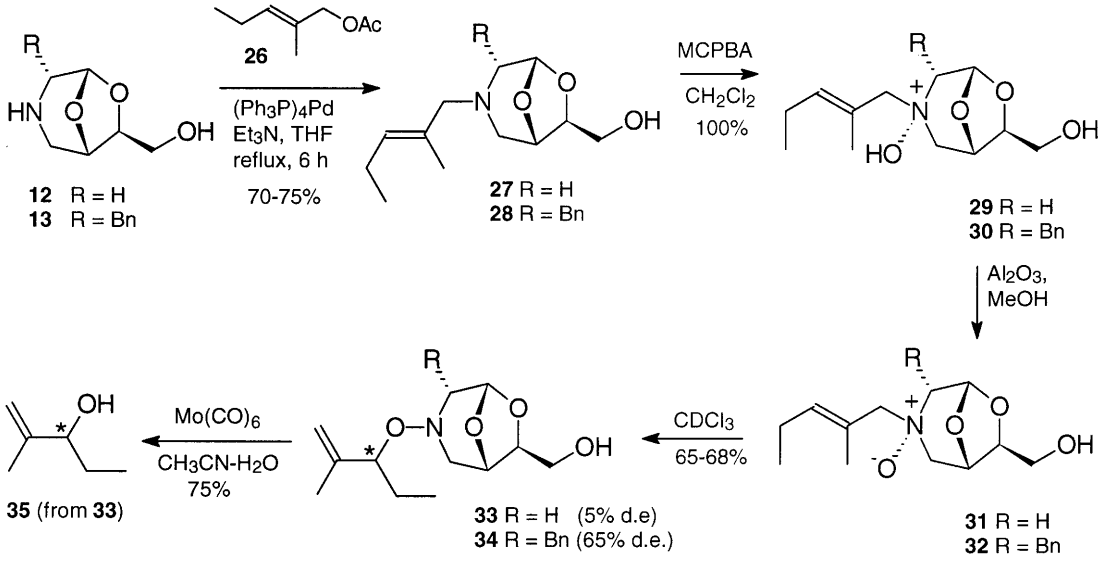
Based on the same analysis we found that the presence at position 7 of a CH_2OH group (compound **6**, Scheme 2) in place of the carbomethoxy group did not affect the *endo*

diastereoselectivity (>98%) of the oxidation process and, similarly, it was possible to assign the *endo* stereochemistry for the N–OH group to all *N*-hydroxylammonium salts described later and employed for the rearrangement experiments.

We chose unsubstituted BTG (G stands for glycine) derivatives **11** and **12**, and 4-*endo*-substituted BTf (f stands for unnatural phenylalanine) derivative **13** as chiral auxiliaries, and the cinnamyl (Scheme 3) and (*E*)-2-methyl-2-pentenyl (Scheme 4) groups as the allylic moieties for studying the rearrangement. Compounds **11**–**13** were treated with cinnamyl bromide in DMF to give the corresponding allylic tertiary amines **14**–**16** in 73–76% yield. The *N*-hydroxylammonium



Scheme 3.



Scheme 4.

m-chlorobenzoates **17**–**19** were obtained as single diastereoisomers (>98% d.e. by ^{1}H NMR) by oxidation with MCPBA in CH_2Cl_2 as described above. These salts were stable as solutions in both protic (MeOH) and aprotic (CH_2Cl_2) solvents. To generate the *N*-oxides, salts **17**–**19** were eluted with MeOH through a column filled with basic Al_2O_3 (ten times the weight of the salt).

The rearrangement process was very slow in MeOH, the conversion of *N*-oxides **20** and **21** from **17** and **18**, respectively, to the corresponding *O*-alkyl hydroxylamines **23** and **24** occurring with a 65% conversion after 30 days (compounds **20** and **21** and the following *N*-oxides were not isolated or characterized). This allowed us to evaporate the MeOH solutions of the *N*-oxides and dissolve the residues in $CDCl_3$ to follow directly the rearrangement process by ^{1}H NMR. The rearrangement was much faster in $CDCl_3$, being complete at room temperature after 24 h for *N*-oxide **20**, while it took 3 days for *N*-oxide **21** to rearrange completely. The rearrangement of the *N*-oxide **22** to give **25** was faster than in the case of BTG *N*-oxide derivatives, being complete in 45 min. The relative stability of the *N*-oxides in MeOH can be explained by the strong coordination of the N–O group by the solvent which stabilises the *N*-oxide, therefore slowing the rearrangement process. For the same reason, the rearrangement of *N*-oxide **21** in $CDCl_3$ was slower compared to that of **20** due to possible intermolecular interactions between the 7-*exo*-CH_2OH and the N–O groups. The d.e. values of **23** (10%), **24** (11%) and **25** (16%) were very low as determined by NMR analysis of the final mixtures. In accordance with a previous observation by Enders on the rearrangement of pyrrolidine-based allylic *N*-oxides,[5] the diastereoselectivity of the process was only slightly sensitive to the temperature: keeping the $CDCl_3$ solution of the *N*-oxide **20** at −16°C, the rearrangement was complete after 14 days, affording **23** with a 17% d.e value. In the rearrangement of **22** carried out at 0°C, the reaction was complete in 7.5 h and again we observed only a small improvement in the d.e. value (26%). Since no particular effect on the diastereoselectivity was apparently due to the substituent at position 7, we employed 7-hydroxymethyl-substituted amines **12** and **13** to prepare *N*-(2′-methyl-2′-pentenyl)amines **27** and **28** (Scheme 4) by Pd-catalysed reaction of the secondary amines with (*E*)-1-acetyloxy-2-methyl-2-pentene **26**, which gave the two compounds in 75 and 70% yield, respectively. Oxidation of **27** and **28** gave *N*-hydroxylammonium *m*-chlorobenzoates **29** and **30**, which were then treated with Al_2O_3 as usual. We worked in particular on about 1.5 g of **27** to assess the applicability of a BTAa as chiral auxiliary to a larger scale.

Once again, the *N*-oxide from the BTf-derived auxiliary **13** rearranged in $CDCl_3$ much faster than that from BTG derivative **12**, the rearrangement being in the latter case complete after 24 h and in the former in 45 min. The d.e. of **34** (65%) was determined by recording the ^{13}C NMR spectrum of the mixture and confirmed by HPLC analysis. In the case of **33** the d.e. was very low (5%) and determined by the ^{1}H NMR spectrum of the mixture. The rearrangement of the *N*-oxide **32** was also carried out at 0°C, without any significant increase of the d.e. The results reported above are in accordance with the model depicted in Fig. 4: for the rearrangement of *N*-oxide **32** the steric hindrance in the case **B** between the 4-*endo* benzyl group (R_2) on the chiral auxiliary and the 2′-methyl group could lead to a greater stereopreference for the other face of the allyl moiety in the cyclic transition state and gives rise to a rearrangement product **34** with the highest d.e. value. While the asymmetric induction in the Meisenheimer rearrangement has been reported to be low for non-C_2-chiral amines, the value obtained in the rearrangement of *N*-oxide **32** is instead very close to the best d.e. values (62–73%) reported by Enders in the rearrangement of C_2-symmetric pyrrolidine-based *N*-allyl-*N*-oxides.[5]

The cleavage of the N–O bond in the rearrangement products to obtain the allylic alcohol and recover the chiral auxiliary was quite troublesome due to an unpredictable high resistance of this

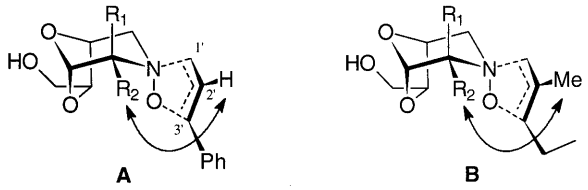


Figure 4.

bond to several reagents normally employed for performing such a reaction. Reductive cleavage by Zn in acetic acid, carried out under various conditions,[11] failed to give the desired products, affording in most cases the unreacted starting material. In some cases we observed either reductive deoxygenation at position 7 or the retro-Meisenheimer process with subsequent deoxygenation to the starting *N*-allylamines. Also, the use of $TiCl_3$ in water,[12] SmI_2 in THF,[13] and $LiAlH_4$ in refluxing THF[14] failed to give the allylic alcohols. In our hands only $Mo(CO)_6$ in water–acetonitrile[15] effected the reductive cleavage of the N–O bond in compound **33** to furnish allylic alcohol **35** in 75% yield and the recovery of the chiral auxiliary **12** in 63% yield. The specific rotation of alcohol **35** $\{[\alpha]_D^{25}$ −0.43 (*c* 0.7, $CHCl_3)\}$ is consistent with the d.e. determined for **33** {the reported specific rotation of enantiopure (*S*)-alcohol **35** is $[\alpha]_D^{25}$ −4.9 in $CHCl_3\}$.[16]

3. Conclusions

In conclusion, we have shown that BTAa's are suitable chiral auxiliaries to perform the Meisenheimer rearrangement. The formation of the chiral *N*-oxides occurs in highly diastereoselective manner and the cleavage of the N–O bond in the rearrangement products is possible by using $Mo(CO)_6$ with a good recovery of both alcohol and chiral auxiliary. The asymmetric induction is generally low, but a possible steric interaction between the 4-*endo* group on the BTAa and a 2′-substituent on the allylic moiety determines higher d.e. (65% in the best case) in the [2,3]-sigmatropic process. Better d.e. could be obtained if more sterically demanding substituents are present at position 4 of the BTAa auxiliary and studies in this direction are now in progress.

4. Experimental

All the reactions requiring dry conditions were performed under nitrogen and anhydrous solvents. Chromatographic separations were performed under pressure on silica gel using flash column techniques; R_f values refer to TLC carried out on 25 mm silica gel plates (Merck F254), with the same eluant indicated for the column chromatography. Melting points (mp) are uncorrected. IR spectra were recorded on a Perkin–Elmer 881 spectrophotometer in $CDCl_3$ solution. ^1H NMR (200 MHz) and ^{13}C NMR (50 MHz) spectra were recorded on a Varian XL 200 instrument in $CDCl_3$ solution. The NOESY spectrum of **9** was recorded at 500 MHz on a Bruker DRX instrument. Mass spectra were carried out in EI at 70 eV on 5790A–5970A Hewlett–Packard and QMD 1000 Carlo Erba instruments. Microanalyses were carried out with a Perkin–Elmer 2400/2 elemental analyzer. Optical rotations were determined on a JASCO DIP-370 instrument. Compounds **5**, **6**, and **11**–**13** were prepared as reported.[8]

4.1. Methyl (1S,3S,5S,7R)-3-benzyl-6,8-dioxa-3-azabicyclo[3.2.1]octane-7-exo-carboxylate N-oxide (9)

A solution of pure *m*-chloroperbenzoic acid (MCPBA) (66 mg, 0.38 mmol) in CH_2Cl_2 (4 mL) was added dropwise to solution of **5** (70 mg, 0.27 mmol) in CH_2Cl_2 (1 mL) cooled at 0°C. The resulting solution was stirred for 30 min at 0°C and then at room temperature for 90 min. After evaporation of the solvent, crude **7** (162 mg, 98%) (as *m*-chlorobenzoate salt) was obtained: ^{1}H NMR ($CDCl_3$) δ 8.05 (s, 1H), 7.94 (d, $J=7.3$ Hz, 1H), 7.55–7.25 (m, 7H), 5.83 (s, 1H), 5.79 (s, 1H), 4.90 (s, 1H), 4.78 (s, 2H), 4.22 (d, $J=12.5$ Hz, 1H), 3.91 (d, $J=12.8$ Hz, 1H), 3.77 (dd, $J=12.5$, 2.9 Hz, 1H), 3.74 (s, 3H), 3.41 (d, $J=12.9$ Hz, 1H). Crude **7** was dissolved in CH_2Cl_2 (2 mL) and eluted through a short column filled with alkaline Al_2O_3 (1.6 g, ten times the weight of the *N*-hydroxide) first with CH_2Cl_2 (4 mL) to remove all impurities and then with MeOH (15 mL) to obtain, after evaporation of the solvent, *N*-oxide **9** (73 mg, 96%) as a yellowish gummy solid: $[\alpha]_D^{25}$ −52.0 (*c* 0.6, MeOH); ^{1}H NMR ($CDCl_3$) δ 7.48–7.43 (m, 2H), 7.39–7.33 (m, 3H), 6.05 (s, 1H), 5.73 (s, 1H), 4.82 (s, 1H), 4.28 (AB system, $J=12.1$ Hz, 2H), 3.80 (dd, $J=12.4$, 2.9 Hz, 1H), 3.70 (s, 3H), 3.53 (d, $J=12.4$ Hz, 1H), 3.38 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 170.8 (s), 132.7 (d, 2C), 129.9 (d), 128.6 (s), 128.5 (d, 2C), 99.1 (d), 78.7 (d), 74.7 (d), 74.0 (t), 66.4 (t), 66.1 (t), 52.5 (q); MS *m*/*z* (%) 279 (M^+, 2), 91 (100); IR ($CHCl_3$) 3668, 1758 cm^{-1}. Anal. calcd for $C_{14}H_{17}NO_5$: C, 60.19; H, 6.13; N, 5.01. Found: C, 60.37; H, 6.01; N, 4.96.

4.2. (1S,3S,5S,7S)-3-Benzyl-6,8-dioxa-7-exo-hydroxymethyl-3-azabicyclo[3.2.1]octane N-oxide 10

Prepared as reported for **9**. Starting from **6** (50 mg, 0.21 mmol), after isolation and elution of *N*-hydroxide **8** through Al_2O_3, *N*-oxide **10** (45 mg, 85%) was obtained as a hygroscopic white solid.

8: ^{1}H NMR ($CDCl_3$) δ 8.05 (s, 1H), 7.95 (d, $J=7.4$ Hz, 1H), 7.60–7.25 (m, 7H), 5.64 (s, 1H), 5.41 (t, $J=5.9$ Hz, 1H), 4.81 (AB system, $J=12.5$ Hz, 2H), 4.58 (s, 1H), 4.28 (d, $J=12.8$ Hz, 1H), 3.81 (m, 2H), 3.70–3.35 (m, 3H).

10: mp 84–85°C; $[\alpha]_D^{25}$ −51.4 (*c* 0.07, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.51–7.37 (m, 5H), 5.56 (s, 1H), 5.44 (dd, $J=7.8$, 5.2 Hz, 1H), 4.52 (s, 1H), 4.36 (AB system, $J=12.5$ Hz, 2H), 3.83–3.57 (m, 3H), 3.36 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 132.9 (d, 2C), 130.0 (s), 129.1 (d), 128.6 (d, 2C), 97.8 (d), 78.2 (d), 77.1 (d), 72.3 (t), 66.5 (t), 65.9 (t), 63.1 (t); MS *m*/*z* (%) 251 (M^+, 1), 91 (100); IR ($CHCl_3$) 3660, 3200 (br) cm^{-1}. Anal. calcd for $C_{13}H_{17}NO_4$: C, 62.13; H, 6.82; N, 5.57. Found: C, 61.87; H, 7.01; N, 5.31.

4.3. Methyl (1S,5S,7R)-3-cinnamyl-6,8-dioxa-3-azabicyclo[3.2.1]octane-7-exo-carboxylate 14

To a solution of **11** (338 mg, 1.95 mmol) in anhydrous DMF (7 mL) cooled at 0°C were added, under a N_2 atmosphere, solid Na_2CO_3 (207 mg, 1.95 mmol) and then cinnamyl bromide (384 mg, 1.95 mmol). After stirring for 30 min at 0°C and then 5 h at room temperature, water (10 mL) was added, and the resulting mixture was extracted with CH_2Cl_2 (3×15 mL), the combined organic layers washed with water (2×50 mL) and dried over Na_2SO_4. After filtration and evaporation of the solvent the crude oil was chromatographed (CH_2Cl_2–MeOH, 100:3; R_f 0.38) furnishing **14** (412 mg, 73%) as yellowish oil: $[\alpha]_D^{25}$ −36.5 (*c* 0.1, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.36–7.20 (m, 5H), 6.50 (d, $J=15.8$ Hz, 1H), 6.17 (dt, $J=15.8$, 6.5 Hz, 1H), 5.63 (s, 1H), 4.77

(s, 1H), 4.64 (s, 1H), 3.75 (s, 3H), 3.17 (t, $J=6.5$ Hz, 2H), 2.89 (m, 2H), 2.52 (d, $J=11.7$ Hz, 1H), 2.29 (d, $J=11.3$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 167.0 (s), 136.6 (s), 133.4 (d), 128.6 (d, 2C), 127.7 (d), 126.3 (d, 2C), 125.7 (d), 101.4 (d), 76.8 (d), 75.9 (d), 59.5 (t), 56.1 (t), 54.9 (t), 52.4 (q); MS m/z (%) 289 (M^+, 4), 117 (100); IR ($CHCl_3$) 1754 cm^{-1}. Anal. calcd for $C_{16}H_{19}NO_4$: C, 66.45; H, 6.62; N, 4.84. Found: C, 66.16; H, 6.42; N, 4.81.

4.4. (1S,5S,7S)-3-Cinnamyl-6,8-dioxa-7-exo-hydroxymethyl-3-azabicyclo[3.2.1]octane **15**

Prepared as reported for compound **14**. Starting from **12** (147 mg, 1.01 mmol), pure **15** (201 mg, 76%) was obtained as yellowish oil after chromatography (CH_2Cl_2–MeOH 100:3, R_f 0.2): $[\alpha]_D^{25}$ −49.5 (c 1.8, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.36–7.16 (m, 5H), 6.49 (d, $J=16.2$ Hz, 1H), 6.18 (dt, $J=16.2$, 6.6 Hz, 1H), 5.46 (s, 1H), 4.39 (t, $J=5.5$ Hz, 1H), 4.27 (s, 1H), 3.56 (d, $J=5.5$ Hz, 2H), 3.15 (m, 2H), 2.89–2.79 (m, 2H), 2.47 (dd, $J=11.3$, 1.4 Hz, 1H), 2.28 (d, $J=11.3$ Hz, 1H), 2.06 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 136.7 (s), 133.2 (d), 128.6 (d, 2C), 127.6 (d), 126.3 (d, 2C), 126.0 (d), 100.2 (d), 78.3 (d), 74.4 (d), 64.3 (t), 59.8 (t), 56.7 (t), 55.1 (t); MS m/z (%) 261 (M^+, 5), 117 (100); IR ($CHCl_3$) 3597 (br) cm^{-1}. Anal. calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.32; N, 5.36. Found: C, 68.75; H, 7.17; N, 5.03.

4.5. (1S,4R,5S,7S)-3-Cinnamyl-4-endo-benzyl-6,8-dioxa-7-exo-hydroxymethyl-3-azabicyclo-[3.2.1]octane **16**

Prepared as reported for compound **14**. Starting from **13** (75 mg, 0.32 mmol) pure **16** (84 mg, 75%) was obtained after chromatography (EtOAc–petroleum ether 1:1, R_f 0.2), as a yellowish oil: $[\alpha]_D^{25}$ −106.4 (c 0.14, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.40–7.14 (m, 10H), 6.55 (d, $J=16.4$ Hz, 1H), 6.24 (ddd, $J=16.4$, 8.5, 4.8 Hz, 1H), 5.03 (s, 1H), 4.34 (t, $J=5.2$ Hz, 1H), 4.26 (s, 1H), 3.69 (ddd, $J=14.7$, 5.1, 1.5 Hz, 1H), 3.57 (m, 2H), 3.23 (m, 2H), 2.86 (dd, $J=11.7$, 1.8 Hz, 1H), 2.71–2.61 (m, 3H), 2.00 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 138.0 (s), 136.8 (s), 133.2 (d), 129.4 (d), 128.5 (d), 128.4 (d), 127.5 (d), 126.3 (d), 126.2 (d), 125.6 (d), 100.7 (d), 77.7 (d), 74.5 (d), 64.3 (t), 63.9 (d), 55.5 (t), 54.6 (t), 35.5 (t); MS m/z 351 (M^+, 1), 117 (100); IR ($CHCl_3$) 3591 cm^{-1}. Anal. calcd for $C_{22}H_{25}NO_3$: C, 75.19; H, 7.17; N, 3.99. Found: C, 75.40; H, 7.41; N, 3.97.

4.6. Methyl (1S,5S,7R)-3-[(R,S)-2-phenyl-3-propenyl-1-oxy]-6,8-dioxa-3-azabicyclo-[3.2.1]octane-7-exo-carboxylate **23**

A solution of pure MCPBA (156 mg, 0.90 mmol) in CH_2Cl_2 (9 mL) was added dropwise to a solution of **14** (250 mg, 0.86 mmol) in CH_2Cl_2 (3 mL) cooled at 0°C. The resulting solution was stirred for 30 min at 0°C and then at room temperature for 90 min. After evaporation of the solvent crude **17** (263 mg, 100%) (as m-chlorobenzoate salt) was obtained as a single diastereoisomer: ^{1}H NMR ($CDCl_3$) δ 8.03 (s, 1H), 7.92 (d, $J=9.0$ Hz, 1H), 7.50–7.23 (m, 7H), 6.78 (d, $J=16.1$ Hz, 1H), 6.50 (dt, $J=16.1$, 7.0 Hz, 1H), 5.84 (s, 2H), 4.96 (s, 1H), 4.40 (m, 3H), 4.09 (d, $J=13.5$ Hz, 1H), 3.76 (s, 3H), 3.75 (m, 1H), 3.41 (d, $J=13.5$ Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 170.3 (s), 169.5 (s), 142.1 (s), 134.8 (s), 134.1 (s), 132.1 (d), 129.8 (d), 129.4 (d), 129.3 (d), 128.8 (d), 127.8 (d), 127.1 (d), 115.5 (t), 98.7 (d), 75.2 (d), 74.9 (d), 73.7 (t), 64.8 (t, 2C), 52.6 (q).

Salt **17** was then dissolved in CH_2Cl_2 (3 mL) and the solution was eluted through a column filled with Al_2O_3 (2.6 g), first CH_2Cl_2 (6 mL) and then with MeOH (25 mL). The MeOH was

evaporated without heating, the residue dissolved in $CDCl_3$ and the rearrangement was monitored by ^1H NMR. When the rearrangement was complete, the solvent was evaporated and the residue chromatographed (petroleum ether–EtOAc, 3:2, R_f 0.61) affording the diastereomeric mixture **23** (200 mg, 77%) as a thick oil: ^1H NMR ($CDCl_3$) δ 7.39–7.27 (m, 5H+5H), 6.06–5.80 (m, 1H+1H), 5.60 (s, 1H), 5.55 (s, 1H), 5.29–5.14 (m, 2H+2H), 5.07 (s, 1H), 5.04 (s, 1H), 4.65 (s, 1H), 4.62 (s, 1H), 4.53 (s, 1H), 4.38 (s, 1H), 3.82 (s, 3H), 3.73 (s, 3H), 3.37 (m, 2H), 3.13 (d, J=8.9 Hz, 1H), 2.92 (d, J=10.2, 1H), 2.89 (dd, J=9.5, 2.2 Hz, 2H), 2.20 (t, J=9.5 Hz, 2H); MS m/z (%) 305 (M^+, 1), 117 (100) (for both diastereoisomers).

*4.7. (1*S,*5*S,*7*S*)-3-[(*R,S*)-2-Phenyl-3-propenyl-1-oxy]-6,8-dioxa-7-*exo*-hydroxymethyl-3-aza-bicyclo[3.2.1]octane* **24**

Obtained as reported for **23**. Starting from **15** (60 mg, 0.23 mmol), compound **24** (42 mg, 80%) was obtained as yellowish oil after elution of intermediate salt **18** through Al_2O_3 as reported above.

18. Single diastereoisomer. ^1H NMR ($CDCl_3$) δ 8.00 (s, 1H), 7.88 (d, J=7.3 Hz, 1H), 7.45–7.20 (m, 7H), 6.75 (d, J=16.1 Hz, 1H), 6.40 (dt, J=16.1, 7.4 Hz, 1H), 5.65 (s, 1H), 5.27 (t, J=6.4 Hz, 1H), 4.62 (s, 1H), 4.39 (m, 2H), 4.25 (d, J=13.5 Hz, 1H), 4.02 (d, J=13.6 Hz, 1H), 3.75 (dd, J=13.6, 2.6 Hz, 1H), 3.65–3.38 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 169.8 (s), 142.1 (s), 134.8 (s), 134.1 (s), 132.0 (d), 129.8 (d), 129.4 (d), 129.3 (d), 128.8 (d), 127.8 (d), 127.1 (d), 115.4 (t), 97.5 (d), 77.1 (d), 75.2 (d), 71.9 (t), 65.4 (t), 65.3 (t), 63.2 (t).

24. Mixture of diastereoisomers. ^1H NMR ($CDCl_3$) δ 7.30–7.23 (m, 5H+5H), 6.09–5.90 (m, 1H+1H), 5.48 (s, 1H), 5.42 (s, 1H), 5.32–5.14 (m, 2H+2H), 5.11 (s, 1H), 5.07 (s, 1H), 4.26 (s, 1H), 4.26 (t, J=5.5 Hz, 1H), 4.14 (s, 1H), 4.04 (t, J=5.5, 1H), 3.53 (d, J=5.4 Hz, 2H), 3.46 (d, J=5.5 Hz, 2H), 3.41 (dd, J=10.5, 1.9 Hz, 1H), 3.31 d, J=11.0 Hz, 1H), 3.18 (d, J=11.0 Hz, 1H), 2.98 (d, 10.6 Hz, 1H), 2.86 (m, 2H), 2.73 (t, J=10.2 Hz, 2H); MS m/z (%) 277 (1), 117 (100) (for both diasteroisomers).

*4.8. (1*S,*3*S,*4*R,*5*S,*7*S*)-3-[(*R,S*)-2-phenyl-3-propenyl-1-oxy]-4-*endo*-benzyl-6,8-dioxa-7-*endo*-hydroxymethyl-3-azabicyclo[3.2.1]octane* **25**

Prepared as reported for **23**. Starting from **16** (145 mg, 0.41 mmol), compound **25** (100 mg, 70%) was obtained as yellowish thick oil after elution of intermediate salt **19** through Al_2O_3 as reported above.

19. Single diastereoisomer. ^1H NMR ($CDCl_3$) δ 8.05 (s, 1H), 7.95 (d, J=7.4 Hz, 1H), 7.55–7.20 (m, 12H), 6.80 (d, J=15.7 Hz, 1H), 6.28 (m, 1H), 5.44 (t, J=5.9 Hz, 1H), 5.28 (s, 1H), 4.74 (dd, J=15.0, 6.6 Hz, 1H), 4.60 (m, 2H), 4.30 (m, 1H), 4.00–3.20 (m, 6H).

25. Mixture of diastereoisomers. ^1H NMR ($CDCl_3$) δ 7.40–7.13 (m, 10H+10H), 6.15–5.95 (m, 1H+1H), 5.32–5.05 (m, 2H+2H), 5.03 (s, 1H+1H), 4.28 (s, 1H), 4.28 (t, J=4.6 Hz, 1H), 4.06 (s, 1H), 4.00 (t, J=4.8 Hz, 1H), 3.56 (m, 2H), 3.44 (m, 2H), 3.34 (dd, J=12.8, 3.3 Hz, 1H), 3.12 (dd, J=12.8, 3.3 Hz, 1H), 3.02 (dd, J=10.7, 1.9 Hz, 1H), 2.96–2.74 (m, 3H), 2.63 (AB system, J=11.3 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 140.1 (s), 139.6 (s), 138.0 (d), 137.6 (s), 137.5 (s), 137.1 (d), 129.6 (d), 128.6 (d), 128.5 (d), 128.4 (d), 128.3 (d), 128.1 (d), 127.1 (d), 126.6 (d), 126.4 (d), 118.0 (t), 117.0 (t), 100.6 (d), 87.5 (d), 86.7 (d), 77.8 (d), 74.6 (d), 74.4 (d), 70.1 (t), 70.0 (t), 64.1 (d), 59.2 (t), 58.7 (t), 35.3 (t), 35.0 (t).

*4.9. (1*S,*5*S,*7*S*)-3-[(*E*)-2-Methyl-2-pentenyl]-7-*exo*-hydroxymethyl-6,8-dioxa-3-azabicyclo-[3.2.1]octane (**27**)*

To a solution of $(Ph_3P)_4Pd$ (115 mg, 0.1 mmol) in anhydrous THF (8 mL) was added, under a nitrogen atmosphere, a solution of **12** (397 mg, 2.74 mmol) in THF (20 mL) and Et_3N (0.46 mL, 3.28 mmol), followed by a solution of **26** (429 mg, 3.01 mmol) in THF (4 mL). The resulting solution was refluxed for 8 h, then the solvent was evaporated and water (20 mL) was added. The mixture was extracted with CH_2Cl_2 (3×20 mL), dried over Na_2SO_4, filtered and evaporated, yielding a crude oil which was chromatographed (petroleum ether–EtOAc, 3:1, R_f 0.16) to give pure **27** (467 mg, 75%) as a light yellow oil: $[\alpha]_D^{25}$ −44.0 (*c* 0.2, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 5.40 (s, 1H), 5.23 (t, J=6.8 Hz, 1H), 4.33 (t, J=5.2 Hz, 1H), 4.21 (s, 1H), 3.52 (m, 2H), 2.86–2.59 (m, 4H), 2.33 (d, J=10.8 Hz, 1H), 2.16 (d, J=10.8 Hz, 1H), 2.07–1.92 (m, 2H), 1.60 (s, 3H), 0.89 (t, J=7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 130.9 (s), 130.1 (d), 100.1 (d), 78.1 (d), 74.2 (d), 66.0 (t), 64.1 (t), 56.3 (t), 54.4 (t), 20.4 (t), 14.2 (q), 14.0 (q); MS *m*/*z* 227 (M^+, 5), 55 (100); IR 3500 (br) cm^{-1}. Anal. calcd for $C_{12}H_{21}NO_3$: C, 63.40; H, 9.31; N, 6.16. Found: C, 63.37; H, 9.41; N, 5.84.

*4.10. (1*S,*4*R,*5*S,*7*S*)-3-[(*E*)-2-Methyl-2-pentenyl]-4-*exo*-benzyl-7-*endo*-hydroxymethyl-6,8-dioxa-3-azabicyclo[3.2.1]octane **28***

Prepared as reported for **27**. Starting from **13** (548 mg, 2.33 mmol) pure **28** (518 mg, 70%) was obtained after chromatography (petroleum ether–EtOAc, 4:1, R_f 0.31) as a white solid: mp 57°C; $[\alpha]_D^{25}$ −127.4 (*c* 0.13, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 7.31–7.16 (m, 5H), 5.33 (t, J=7.4 Hz, 1H), 5.00 (s, 1H), 4.30–4.23 (m, 2H), 3.59 (m, 3H), 3.07 (dd, J=13.6, 3.6 Hz, 1H), 2.74–2.35 (m, 4H), 2.02 (t, J=7.0 Hz, 2H), 1.63 (s, 3H), 0.96 (t, J=7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 138.2 (s), 131.3 (s), 130.0 (d), 129.4 (d, 2 C), 128.4 (d, 2 C), 126.2 (d), 100.7 (d), 77.6 (d), 74.6 (d), 64.9 (t), 64.5 (d), 62.2 (t), 54.1 (t), 36.0 (t), 21.1 (t), 14.6 (q), 14.2 (q); MS *m*/*z* 317 (M^+, 1), 55 (100); IR 3505 (br) cm^{-1}. Anal. calcd for $C_{19}H_{27}NO_3$: C, 71.89; H, 8.57; N, 4.41. Found: C, 71.26; H, 8.63; N, 4.06.

*4.11. (1*S,*5*S,*7*S*)-3-[(1*S,R)-1-Ethyl-2-methyl-2-propenyl-1-oxy)]-7-*exo*-hydroxymethyl-6,8-dioxa-3-azabicyclo[3.2.1]octane **33***

Prepared as reported for **23**. Starting from **27** (1.44 g, 6.32 mmol), compound **33** (1.045 g, 68%) was obtained as a yellowish thick oil after elution of intermediate salt **29** through Al_2O_3 as reported above.

29. Single diastereoisomer. ^{1}H NMR ($CDCl_3$) δ 8.00 (s, 1H), 7.90 (d, J=7.7 Hz, 1H), 7.45–7.20 (m, 2H), 5.67 (s, 1H), 5.65 (t, J=5.5 Hz, 1H), 5.39 (t, J=5.8 Hz, 1H), 4.59 (s, 1H), 4.41 (d, J=15.6 Hz, 1H), 4.31 (d, J=12.8 Hz, 1H), 4.08 (d, J=12.8 Hz, 1H), 3.91 (d, J=12.2 Hz, 1H), 3.71–3.48 (m, 3H), 3.30 (d, J=12.2 Hz, 1H), 2.15–2.02 (m, 2H), 1.94 (s, 3H), 0.98 (t, J=7.2 Hz, 3H).

33. Mixture of diastereoisomers. ^{1}H NMR ($CDCl_3$) δ 5.46 (s, 1H), 5.42 (s, 1H), 4.90–4.84 (m, 2H+2H), 4.30–4.23 (m, 2H+2H), 3.87 (td, J=7.0, 3.0 Hz, 1H+1H), 3.50 (dd, J=5.2, 2.6 Hz, 2H+2H), 3.31–3.13 (m, 2H+2H), 2.85 (dd, J=10.8, 2.0 Hz, 1H+1H), 2.64 (d, J=10.2 Hz, 1H+1H), 1.63 (s, 3H+3H), 1.59–1.28 (m, 2H+2H), 0.81 (t, J=7.4 Hz, 3H+3H); ^{13}C NMR ($CDCl_3$) δ 144.8 (s), 144.6 (s), 113.6 (t), 113.2 (t), 100.2 (d), 87.8 (d), 87.2 (d), 77.9 (d), 74.4 (d), 64.1 (t), 60.2 (t), 59.4 (t), 58.9 (t), 58.2 (t), 24.9 (q), 24.8 (q), 17.3 (t), 17.0 (t), 10.2 (q), 10.1 (q); MS *m*/*z* (%) 243 (M^+, 2), 81 (100) (for both diastereoisomers).

4.12. (1S,5S,7S)-3-[(1S,R)-1-Ethyl-2-methyl-2-propenyl-1-oxy)]-4-endo-benzyl-7-exo-hydroxymethyl-6,8-dioxa-3-azabicyclo[3.2.1]octane **34**

Prepared as reported for **23**. Starting from **28** (300 mg, 0.95 mmol), compound **34** (205 mg, 65%) was obtained as a yellowish thick oil after elution of intermediate salt **30** through Al_2O_3 as reported above and purification by chromatography (CH_2Cl_2–MeOH 40:1, R_f 0.25).

30. Single diastereoisomer. ^{1}H NMR ($CDCl_3$) δ 8.05 (s, 1H), 7.96 (d, $J=7.4$ Hz, 1H), 7.60–7.15 (m, 7H), 5.87 (t, $J=3.0$ Hz, 1H), 5.34 (t, $J=5.4$ Hz, 1H), 5.21 (s, 1H), 4.65–4.21 (m, 4H), 3.71–3.20 (m, 6H), 2.19–2.12 (m, 2H), 1.95 (s, 3H), 1.03 (t, $J=7.8$ Hz, 3H).

34. *Major diastereoisomer*: ^{1}H NMR ($CDCl_3$) δ 7.36–7.17 (m, 5H), 5.06 (s, 1H), 4.95 (s, 2H), 4.34–4.26 (m, 2H), 4.00 (t, $J=6.4$ Hz, 1H), 3.57 (d, $J=5.2$ Hz, 2H), 3.35 (dd, $J=10.6$, 2.2 Hz, 1H), 3.20 (dd, $J=12.4$, 2.8 Hz, 1H), 3.00–2.58 (m, 3H), 1.73 (s, 3H), 1.66–1.27 (m, 2H), 0.87 (t, $J=7.2$ Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 143.1 (s), 137.8 (s), 129.5 (d, 2C), 128.4 (d, 2C), 126.2 (d), 114.3 (t), 100.6 (d), 88.3 (d), 77.7 (d), 74.6 (d), 69.9 (t), 64.1 (d), 58.8 (t), 35.4 (t), 24.5 (q), 17.6 (t), 9.7 (q). *Minor diastereoisomer*: ^{13}C NMR ($CDCl_3$) δ 144.2 (s), 137.7 (s), 129.5 (d, 2C), 128.4 (d, 2C), 126.2 (d), 115.1 (t), 100.6 (d), 90.0 (d), 77.7 (d), 74.6 (d), 70.2 (t), 64.1 (d), 58.8 (t), 35.1 (t), 24.4 (q), 16.4 (t), 10.2 (q).

4.13. Cleavage of the N–O bond in compound **33**

To a solution of **33** (662 mg, 2.72 mmol) in CH_3CN–H_2O 7:1 (72 mL) was added $Mo(CO)_6$ (2.155 g, 8.16 mmol) and the resulting suspension was vigorously stirred for 10 min at room temperature before refluxing for 24 h. After cooling to room temperature, 1 M HCl was added up to pH 1 and the mixture was extracted with Et_2O (3×50 mL), dried over Na_2SO_4, filtered and evaporated. The crude mixture was chromatographed (CH_2Cl_2) affording alcohol **35** (202 mg, 75%, R_f 0.45) as a colorless oil and some unreacted starting material **33** (127 mg, 19%, R_f 0.05).

In order to recover the chiral auxiliary, the aqueous layer was instead treated with a 30% NH_4OH aqueous solution up to pH 11 and extracted with CH_2Cl_2. The solvent was evaporated and the residue chromatographed (petroleum ether–EtOAc, 1:1, R_f 0.25) yielding amine **6** (251 mg, 63%).

35. $[\alpha]_D^{25}$ −0.43 (*c* 0.7, $CHCl_3$); ^{1}H NMR ($CDCl_3$) δ 4.91 (s, 1H), 4.82 (s, 1H), 3.97 (t, $J=6.4$ Hz, 1H), 1.69 (s, 1H), 1.63–1.48 (m, 2H), 1.61 (br s, 1H), 0.87 (t, $J=7.4$ Hz, 1H).

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