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## Process intensification-assisted conversion of $\alpha$ , $\omega$ -alkanediols to dibromides

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### ABSTRACT

The increasingly widespread applications of  $\alpha$ , $\omega$ -dibromides motivated development of a scalable, inexpensive process to rapidly convert selected  $\alpha$ ,  $\omega$ -alkanediols to the corresponding dibromides. Diols were heated with only 48% aqueous HBr and an organic solvent, using a Dean-Stark apparatus modified to fractionate the azeotropic distillate, thereby maintaining a higher HBr concentration and reaction rate in the pot. Intensified distillation also increased the reaction rate. Various other substrate, solvent, and parameter effects have been discovered and rationalized.

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Thousands of publications pertaining to uses of  $\alpha$ ,  $\omega$ -dibromides have appeared in SciFinder.<sup>1</sup> Noting the (sometimes very) high prices of commercial dibromides, we decided to develop a convenient, efficient, scalable, and more economical laboratory method to make these compounds. The range of available methods includes reaction of diols or cyclic ethers with P or S reagents, aq HBr/H<sub>2</sub>SO<sub>4</sub>, gaseous HBr, metal-based or ionic liquid-based catalysts, and column chromatography for purification.<sup>2,3</sup> We opted for reaction of the (much) cheaper corresponding diols with 48% aqueous HBr, which, ideally, produces dibromide and H<sub>2</sub>O as the only products. The study included short-, long-, straight-, and branched-chain targets **1b-6b** (Scheme 1). Our methodology and its application to preparation of these targets are reported herein.

### Scheme 1. Selected dibromides

In 2000, Chong et al.<sup>4</sup> critically reviewed the history of diol-48% HBr-organic phase reactions. Their observations included: (1) Long heating times (9-72 h for C<sub>5</sub>-C<sub>12</sub> diols), using 1.2 equivalents of 48% HBr, were needed to obtain 79-94% yields of purified bromoalkanol. (2) Significant deviation of product distribution from the statistical 25:50:25 diol/bromoalkanol/diBr mixture was attributed, at least in part, to intrinsically lower reactivity of bromoalkanol versus diol. (3) Higher [HBr]<sub>aq</sub>, lower organic phase:substrate (v/w) ratio below a certain minimum, or azeotropic removal of water each can increase dibromide formation. Other relevant observations were reported by Segall and Shorr,<sup>5</sup> who desired high-yield, fast conversions of “lower alkanols” (up to C<sub>4</sub>) to bromides via reaction with HBr<sub>aq</sub>. Their study was limited to bromides that would distill out of the reaction mixture via an azeotrope containing very little HBr (no organic solvent phase was used). A fractionating column afforded a two-phase distillate in which the [HBr]<sub>aq</sub> was held to about 1% (w/w). This distillate was partly recycled to the column to suppress HBr distillation, thus maintaining the pot [HBr]<sub>aq</sub> (initially 48%) at about 43-46%. Dilution of the remaining acid seriously reduced the reaction rate. For an acceptable rate, they recommended a constant HBr:OH ratio greater than 3:1. Wrewsky et al.<sup>6</sup> showed that for distillation of up to nearly 40% HBr<sub>aq</sub>, the vapor contains only 1.25% HBr, but increases to 19.3% at 47.8% HBr<sub>aq</sub>. One can infer from these data that at ~40% HBr<sub>aq</sub>, distillation will deliver condensate with very little HBr. In the conversion of diols to bromoalkanols in the presence of an H<sub>2</sub>O-insoluble organic phase, both the chemoselectivity (at least partly) and the slow, selective diol reaction can be seen as consequences of the rapid decline of the [HBr]<sub>aq</sub>, its attendant loss of reactivity, and loss of ability to hold bromoalkanol in the aqueous phase and activate the remaining OH for displacement. Also, the H<sub>2</sub>O azeotropes of benzene and toluene boil at 69.25° and 84.1° (1 atm), respectively;<sup>7</sup> even at a very high boilup rate (intensified distillation; large  $\Delta T$  between bath and pot),<sup>8</sup> the cooling effect of the azeotrope removal hinders attainment of a sufficiently high pot temperature to achieve an acceptably high rate of bromoalkanol conversion to dibromide. Dibromide **1b** was included in the study as a potential substrate in desymmetrization reactions. Because of steric hindrance, it was expected to be much less reactive than diols **2a-6a**.<sup>9</sup> The only discovered large-scale (1 mole) preparation<sup>10</sup> of **1b** (2 h, 72%) cited a 1921 process (diol + NaBr + H<sub>2</sub>SO<sub>4</sub>) used to make dibromide **2b**.<sup>11</sup> In our first synthesis of **1b** (Table 1, entry 1), heptane was the organic phase (bp 98.4°, H<sub>2</sub>O azeotrope bp 79.2°).<sup>7</sup> The reaction flask was fitted with a vigreux column with a takeoff condenser and a cold-finger splitter. To favor dibromide formation, the initial 3.33:1 solvent:diol ratio (1.0 mole of diol) was lowered from the 20:1 ratio found optimal for preparation of bromoalkanols.<sup>4</sup> In a typical procedure, the condenser splitter was first set at total reflux, to allow buildup of the desired low-acid azeotrope. When the head temperature neared 80° (bath 105-106°), collection was begun, near a 1:1 reflux ratio. The initial aqueous condensate was nearly neutral. As it neared ~50% of the theoretical amount, the column head temperature rose fairly rapidly to 88°, and condensate titration showed [HBr]<sub>aq</sub> up to 24-25 wt%. Thus, for a sufficiently low [HBr]<sub>aq</sub>, essentially HBr-free octane-H<sub>2</sub>O (binary) azeotrope can be separated from ternary azeotrope(s) containing octane, H<sub>2</sub>O, and 48% HBr (constant bp 126°) behaving as a single entity. As slower-reacting bromoalkanol replaces diol in the pot, it appears that H<sub>2</sub>O formation does not keep up with the distillation rate of binary azeotrope, and ternary azeotrope(s) can reach the column head. After 23 h heating (replacing heptane twice), workup afforded 140 g

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**Table 1**

Dibromination of selected diols

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of **1b** (65%, crude) containing no detectable bromoalkanol **1c** ( $^1\text{H NMR}$ ).

Revised apparatus for the second synthesis of **1b** (entry 2) incorporated a vacuum-insulated, Raschig ring-packed, 19-cm fractionating column, cold finger splitter head, solvent return to the reaction flask, and a standard Dean-Stark graduated collector to remove condensed aqueous phase (Figure 1). Under conditions described in entry 2, Table 1, a 72% crude yield of **1b** was obtained (no **1c**). We will return to **1b** later.

#### Figure 1. Modified Dean-Stark apparatus

The widely used<sup>1</sup> straight-chain dibromides **2b**, **3b**, **5b**, and **6b** were chosen to explore the effects of chain length on the HBr-diol reaction. The 1921 preparation of **2b**<sup>11</sup> (5-6 h refluxing) yielded 88-95% of distilled product. A 2008 report,<sup>12</sup> using **2a**, anhydrous HBr, and toluene, claimed 100% yield of **2b**, but gave no experimental details. Our preparation of **2b** appears in entry 3, Table 1. The fair yield (66%) was attributed to a too-low pot temperature and loss of HBr in the high-boiling azeotrope.

Attention turned to **3b**. A viable preparation of this very useful dibromide<sup>1</sup> was first reported by von Braun (Eq. 1),<sup>13,14</sup> and has

been used as recently as 1986.<sup>15</sup> The first run with **3a** and 48% HBr (entry 4) used the same conditions as in entry 2 (**1a** to **1b**), with only slightly better results (77% crude **3b**). Looking for a higher-boiling organic phase (to raise the pot temperature and the reaction rate), we chose *p*-xylene (bp 138°). However,  $\alpha$ -bromo-*p*-xylene (lachrymator) was found in *p*-xylene-mediated preparations of **3b**, **4b**, **5b**, and **6b**. *Octane (easily recovered) was the only organic phase used after this discovery.* Although costs of piperidine (von Braun starting material) and **3a** are similar, the lower expense and greater convenience of reaction of **3a** with 48% HBr should greatly favor this method.<sup>16</sup> This work appears to be its first use in **3b** synthesis.<sup>17</sup>

In the preparations of **5b** and **6b** using *p*-xylene (entries 5 and 6, Table 1), before the benzylic bromide problem was recognized, bromoalknols (**5c** < **6c**) appeared in the organic phase. This behavior, not seen in reactions of shorter chain diols, was attributed to the increased lipophilicity of the longer chain compounds, to the extent that a high concentration of HBr<sub>aq</sub> no longer could hold them in the aqueous phase. Greater solubility of bromoalknols in the organic phase could account also for the decreased yields of **5b** and **6b**, through decreased exposure of **5c** and **6c** to HBr<sub>aq</sub>.

At this point, faced also with the undesirably long reaction times and low yields in entries 2 and 4, we took a closer look at a remarkable rate acceleration achieved by "intensified azeotropic distillation",<sup>8</sup> and at the more general concept of process intensification.<sup>18,19</sup> Consequently, the starting HBr:diol mole ratio was raised to 6.0:1, the starting octane/diol ratio (v:w) was lowered to ~7:1, to minimize accumulation of bromoalkanol in the organic phase, the bath temperature was held in the range 145-150 °C, and as soon as the head temperature rose 2-3° above the pure H<sub>2</sub>O-octane azeotrope value (89.6 °C),<sup>7</sup> the distillation fractionation head was set to total reflux. Only aqueous condensate (lower of two phases) was tapped off, forcing the condensed octane to return to the pot via the fractionating column.<sup>5</sup> The **3b**, **4b**, and **6b** preparations then were repeated using these conditions; the gratifying results are shown in Table 1 (entries 7-9). The cost of **5a** dissuaded us from repeating the **5b** preparation.

Dibromide **4b** was included in the study as another substrate of interest in desymmetrization reactions, and as a "medium" size member of the chosen range of compounds. The first reported preparation of **4b** used the von Braun method (65%),<sup>20</sup> which was used again in 1986 (61%).<sup>15</sup> Few other methods have appeared,<sup>1</sup> none from diol **4a**, despite its low cost availability. The optimized HBr-diol procedure (entry 8) again favors this method over the von Braun route.

The optimized procedure was applied also to preparation of **1b**, but gave no improvement in time or yield. No **1c** or diol was recovered, and  $^1\text{H NMR}$  analysis showed the presence of unsaturated material, indicating that extensive elimination had occurred. Thus,

the 1921 procedure<sup>11</sup>, involving H<sub>2</sub>SO<sub>4</sub>, remains to be improved upon.

In summary, introduction of a fractionating column, use of octane as the optimal non-aqueous phase, intensified distillation, and optimization of other parameters have enabled the reaction of a range of  $\alpha,\omega$ -diols with 48% aqueous HBr to become a simple, rapid, economical, and scalable route to very useful  $\alpha,\omega$ -dibromides. It appears likely that further scaleup, modification of the fractional distillation apparatus, and development of excess HBr recovery methodology could lead to a viable commercial process.

## Supplementary Data

General and selected experimental procedures;  $^1\text{H}$  and  $^{13}\text{C}$  NMR data for all dibromides.

## Acknowledgments

We thank the Syracuse University Department of Chemistry and the Hahn Gift Fund for financial support.

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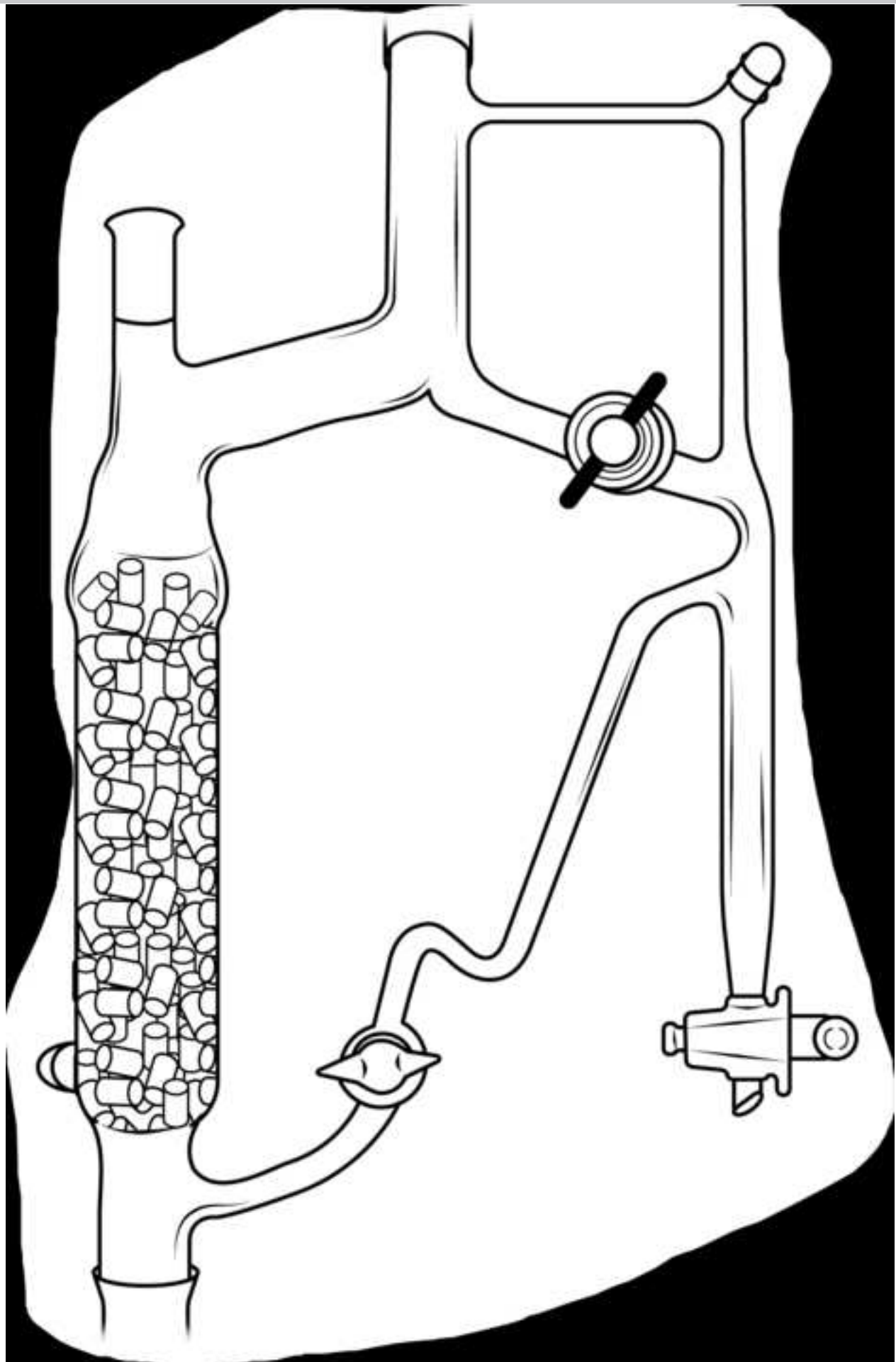
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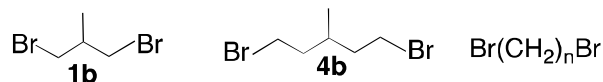
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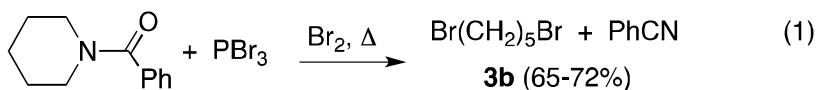
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**2b:** n = 3   **3b:** n = 5   **5b:** n = 8   **6b:** n = 10

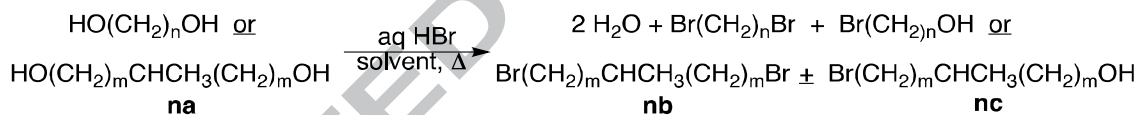
**Scheme 1.** Selected dibromides



Eq 1

**Table 1**

Dibromination of selected diols



Entry	Diol	n	m	t(hr)	Ratio <sup>a</sup> HBr:Diol	Solvent	Temp <sup>b</sup>	Ratio(v:w) Solvent/Diol	DiBr:BrOH <sup>a,c</sup> in Solvent	% Yield DiBr <sup>d</sup>
1	<b>1a</b>	---	1	23	5.0	heptane	106	3.3	<b>1b</b> only	65
2	"	---	1	14	3.7	octane	130-133	4.4	<b>1b</b> only	72
3	<b>2a</b>	3	---	12	6.0	heptane	115	19	<b>2b</b> only	66
4	<b>3a</b>	5	---	13	3.2	octane	130	3.9	<b>3b</b> only	77
5	<b>5a</b>	8	---	11	6.0	p-xylene	130	14	<b>5b</b> + <b>5c</b> 2.5:1	63
6	<b>6a</b>	10	---	6.5	6.0	p-xylene	130-135	20	<b>6b</b> + <b>6c</b> 5.8:1	61
7	<b>3a</b>	5	---	6	6.0	octane	148-150	7.7	<b>3b</b> only	88 <sup>e</sup>
8	<b>4a</b>	---	2	6	6.0	octane	147-148	6.8	<b>4b</b> only	83 <sup>e</sup>
9	<b>6a</b>	10	---	7	6 - 7.3	octane	145	7	<b>6b</b> + <b>6c</b> 19:1	91 <sup>e</sup>

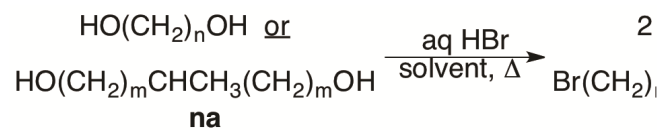
<sup>a</sup> Mole ratio

<sup>b</sup> Bath temp, °C

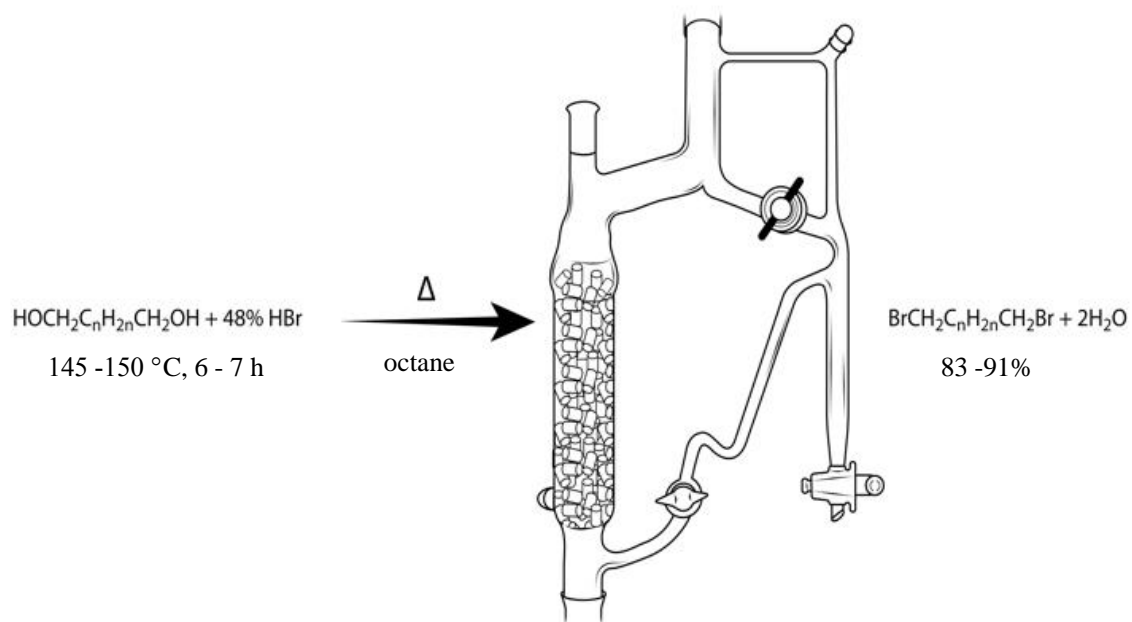
<sup>c</sup> <sup>1</sup>HNMR anal

<sup>d</sup> Crude yield

<sup>e</sup> Isolated yield

**Scheme 2.** Dibromination

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