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An Optimized Process to 10-Bromo-1-decanol

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Abstract:

A multivariate design and optimization study for the synthesis of the bromoalkanol 10-bromo-1-decanol using decane-1,10-diol as substrate is reported. The bromination process was supported by the phase transfer catalyst tetrabutylammonium bromide with aqueous HBr (48%) as the brominating reagent. The optimized batch protocol provided a yield of 64% of 10-bromo-1-decanol 2 TM with a conversion of 80%, and 10% of the dibrominated alkane 1,10-dibromodecane 3, a characteristic byproduct, was formed.

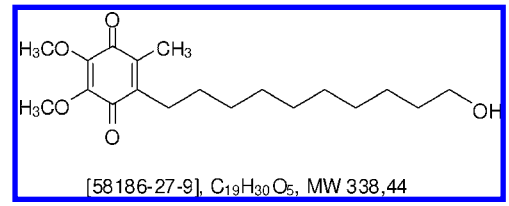
Introduction

For a project dedicated to a novel total synthesis of idebenol (Chart 1) and derivates thereof we needed access to 10-bromo-1-decanol **2** on a multigram scale with a prospective future requirement of multikilogram scale.

Alcohols can be converted to the corresponding alkyl halides via a multitude of reagents, and this transformation has thus in the past been a subject for extensive studies that have resulted in a series of sophisticated protocols. Unfortunately, harsh reaction conditions are often mandatory in several of these procedures. Reagents that have been reported for the alcohol to halide transformation embrace a wide range of methods.[1−10] The advantage of several of these reagents is the relatively low cost, but the drawbacks include toxicity, handling problems (especially on large scale), and low selectivity in some of them.

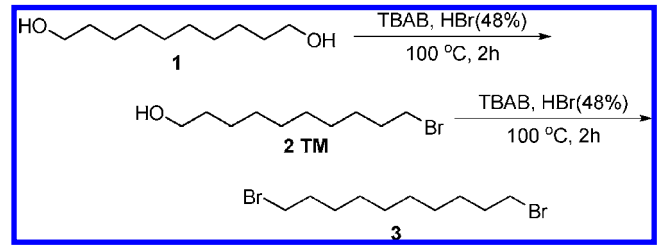
After evaluating the various synthetic routes to alkyl bromides from alcohols,[11] a pathway that appeared attractive to us involved decane-1,10-diol **1** as substrate that is readily available at low cost. Moreover, such a synthetic protocol involves only a simple bromination step at one of the two available hydroxyl centers.[11a] However, drawbacks exist in such a process, namely the requirements of a highly chemoselective process since the desired product 10-bromo-1-decanol **2** can readily undergo a second bromination to produce 1,10-dibromodecane **3**, Scheme 1, an unwanted byproduct that reduces effective yield of the desired product **2**.

Chart 1. **Idebenol [2-(10-hydroxydecyl)-5,6-dimethoxy-3-methylcyclohexa-2,5-diene-1,4-dione]**



[58186-27-9], $C_{19}H_{30}O_5$, MW 338,44

Scheme 1. **Process to 10-bromo-1-decanol 2**



Methods and Results

Design and Analysis of the Experimental Investigation. We commenced this study by a combined synthetic route discovery and pre-experimental design study, that brought us to a synthetic protocol disclosed in this journal.[10] With the basis in that protocol we elaborated an Ishikawa cause−effect (ICE) diagram,[12] Figure 1, that also encompasses prospective process variables that must be taken into account for an eventually future scale-up project.

However, for the present experimental optimization study we decided to perform an investigation of the variables related to the synthetic protocol, which are the branches enumerated 1, 2, 5, 6, 7, and 8 in the ICE diagram (Figure 1). We believed that the reaction temperature, the reaction time, the quantities of the brominating reagent, the phase transfer catalyst, and the solvent volume were the variables that influenced the performance in terms of the yield and selectivity. The solvent, other than in the bromination reagent (HBr in water), was not used, that is the diol **1** was added neat to the reaction flask.

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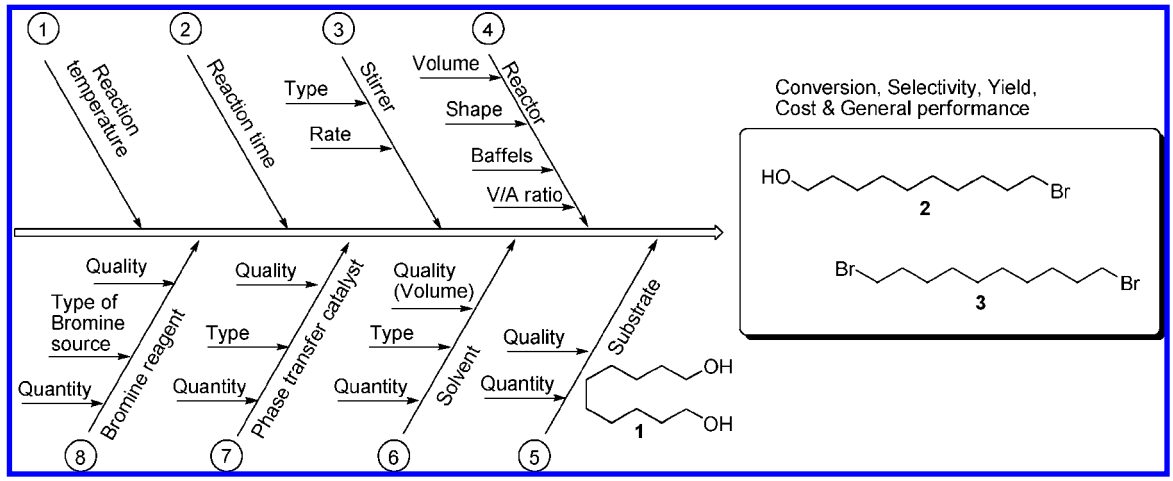

Figure 1. **Ishikawa diagram for a potential bromination of decane-1,10-diol 1 to achieve 10-bromo-1-decanol 2 and minimize the production of the byproduct 1,10-dibromodecane 3.**

Table 1. **Statistical experimental design for the investigation of the bromination of decane-1,10-diol 1**

	experimental variables[a]			response variables[b]		
#	x_1	x_2	x_3	c_{120}	s_{120}	y_{120}
1	−1	−1	−1	36	89	32
2	+1	−1	−1	35	89	31
3	−1	+1	−1	54	81	44
4	+1	+1	−1	53	72	38
5	−1	−1	+1	38	89	34
6a	+1	−1	+1	38	87	33
6b	+1	−1	+1	44	82	36
7	−1	+1	+1	53	77	41
8a	+1	+1	+1	69	72	50
8b	+1	+1	+1	49	84	41
9	0	0	0	46	80	37
10	0	0	0	64	78	50
11	−2	0	0	23	94	22
12	+2	0	0	55	77	42
13	0	−2	0	63	75	47
14	0	+2	0	25	92	23
15	0	0	−2	44	84	37
16	0	0	+2	79	78	62

[a] Procedure: decane-1,10-diol **1** (2.87 mmol, 0.500 g) was used as substrate in all of the experiments. Experimental variables: x_k (definition) [levels: −2, −1, 0, +1, +2]: x_1 (reaction temperature) [85 °C, 90 °C, 95 °C, 100 °C, 105 °C,]; x_2 (quantity of hydrobromic acid) [0.15, 0.30, 0.45, 0.60, 0.75 equiv]; x_3 (quantity of tetrabutylammonium bromide) [0.01, 0.10, 0.20, 0.30, 0.40 equiv]. [b] Responses measured by GC: c_t = conversion at time t = 120 min, s_t = selectivity at time t = 120 min, and y_t = yield at time t = 120 min.

The experimental study was planned to be implemented by means of statistical experimental design[13] and multivariate modeling[14] to simultaneously optimize the two responses, yield and selectivity, respectively. Such an approach will furthermore furnish a picture of the process robustness and at the same time provide an indication on the cheapest performance.

The original experimental design **D**, entries # 1−10, Table 1, was a full factorial design (2^k) of $k = 3$ independent experimental variables (x_1, x_2, x_3) at two experimental levels (denoted as −1 and +1) with $c = 2$ experiments in the center of the experimental domain, that provides in total $2^k + c = 2^3 + 2 = 10$ experiments. The selectivity (s_t t = 120 min) and the yield (y_t t = 120 min) of each experiment were measured by means of gas chromatography and utilized as the responses. The numerical values of the responses are provided in the right-hand columns adjacent to the statistical experimental design of Table 1. The experimental variables and levels that were investigated are described in the footnotes of Table 1. Each of the experimental variables (x_i, $i = 1, ..., 3$) was scaled according to eq 1[15] in order to facilitate the calculation of the regression coefficients (the numerical values of the β coefficients) of the predictive empirical mathematical model provided in eq 2.

$$x_i = \frac{z_i - \left\{z_{i,\mathrm{L}} + \frac{1}{2} \times (z_{i,\mathrm{H}} - z_{i,\mathrm{L}})\right\}}{z_{i,\mathrm{H}} - \left\{z_{i,\mathrm{L}} + \frac{1}{2} \times (z_{i,\mathrm{H}} - z_{i,\mathrm{L}})\right\}}, i = 1, ..., 3 \quad (1)$$

$$y = f(x_1, x_2, x_3) = \beta_0 + \sum_{i=1}^{3} \beta_1 x_1 + \sum_{i=1}^{2} \sum_{j=2}^{3} \beta_{ij} x_1 x_j + \sum_{i=1}^{3} \beta_{ii} x_i^2 \quad (2)$$

x_i of eqs 1 and 2 is the experimental variable i given in scaled units, z_i is the experimental variable i given in real units, $z_{i,\mathrm{L}}$ and $z_{i,\mathrm{H}}$ are the selected low and high experimental values in real units, of the experimental variable i.[15]

Prior to carrying out in the laboratory the initial experimental design, that is objects #1−10 of Table 1, the extreme points, namely, objects #1, #8, and #9 were conducted in order to assess whether the selected experimental levels represented a sufficient span to provide significant variations in the responses. Moreover, these experiments could also provide information whether quadratic terms intervened in the prospective models. Figure 2 shows the reaction profile for the three extreme point experiments, object #1, 8, and 9.

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(15) When scaling is performed according to eq 1, the scaled low value is set at −1, and the scaled high value becomes set at +1.

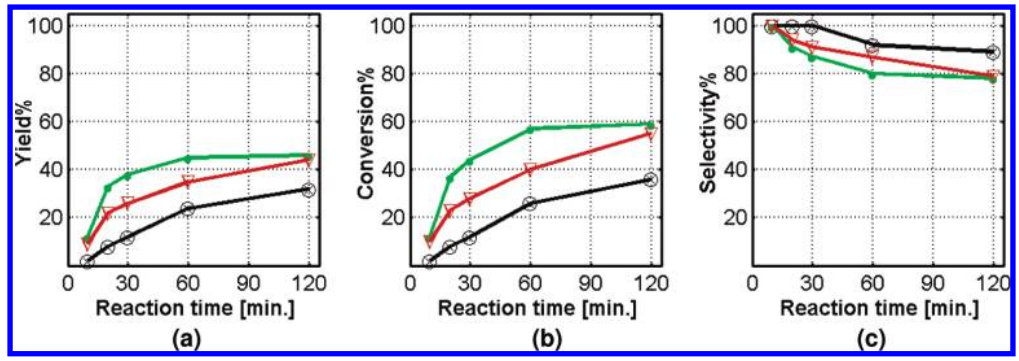


Figure 2. **Reaction profiles for (a) yield, (b) conversion, and (c) selectivity for the three experiments: #1 (⊗) where (x_1 x_2 x_3) = [−1 −1 −1], #8 (•) mean of two runs where (x_1 x_2 x_3) = [+1 +1 +1], and #9 (∇) mean of two runs where (x_1 x_2 x_3) = [0 0 0].**

The experimental span appeared to be sufficient with a $y_{max} - y_{min} = 18$, at the reaction time $t = 120$ min. Furthermore, it appeared that the reaction system is influenced by some nonlinear terms; experiment #1 and #9 provide almost quite similar results ($\Delta y \approx 5$) at the maximum value at reaction time $t = 120$ min, while experiment #3 provides substantially higher yield throughout the whole reaction profile, an experiment that moreover provides the maximum yield at $t = 60$ min. On this basis we decided to eventually also take into account quadratic terms by expanding the original design (objects #1−10) to including a centered star design (through the center point) which in total constitute a central composite design, see object #1−16 of Table 1. The experiments were conducted in the laboratory, and the responses were carefully measured on GC.

A model matrix $\mathbf{X}_{16\ \text{lines}\times 10\ \text{columns}} = [\mathbf{1}\ \boldsymbol{x}_1\ \boldsymbol{x}_2\ \boldsymbol{x}_3\ \boldsymbol{x}_1 \times \boldsymbol{x}_2\ \boldsymbol{x}_1 \times \boldsymbol{x}_3\ \boldsymbol{x}_2 \times \boldsymbol{x}_3\ \boldsymbol{x}_1^2\ \boldsymbol{x}_2^2\ \boldsymbol{x}_3^2]$ was created on the basis of the design matrix **D**. The model matrix **X** with the adjacent yield and selectivity values of target molecule **2** was submitted for multivariate regression using the partial least-squares regression method (PLSR).[16] Rough evaluations of the predictive models were performed using cumulative normal probability plots and the adjacent bar plots, shown in a and b of Figure 3. The final variable pruned empirical mathematical models, that describe the variation of the yield $y_{120\ \text{min}} = f(x_1,x_2,x_3)$ and the selectivity $s_{120\ \text{min}} = g(x_1,x_2,x_3)$ when the reaction time is $t = 120$ min, are given in eqs 3 and 4.

The model for the yield: $y_{120\ \text{min}} = f(x_1,x_2,x_3)$ was described by $a = 5$ PLS components, a model that accounts for ≈96.8% [$= 87.307_{(a=1)} + 2.164_{(a=2)} + 5.017_{(a=3)} + 2.190_{(a=4)} + 0.102_{(a=5)}$] of the variance in the data. The model for the selectivity: $s_{120\ \text{min}} = g(x_1,x_2,x_3)$ was described by $a = 3$ PLS-components, a model that account for ≈99.5% [$= 84.117_{(a=1)} + 13.936_{(a=2)} + 1.442_{(a=3)}$] of the data.

Despite the high number of the explained variance in the two models, the product statistics[17,18] of the models apparently indicate a somewhat weak fitting of the data: the model for the yield shows (with $a = 5$ PLS components) $R_y^2 = 0.424$ and $\text{RMSEP}_y = 7.19$; the model for the selectivity shows (with $a = 3$ PLS components): $R_s^2 = 0.451$ and $\text{RMSEP}_s = 5.86$. The models should prove to have highly predictive power.

$$y_{120} = f(x_1, x_2, x_3) = 41.799 + 2.034 \times x_1 + 3.231 \times x_3 + 0.897 \times x_1 \times x_2 + 0.897 \times x_2 \times x_3 - 2.874 \times x_1^2 - 2.124 \times x_2^2 + 1.501 \times x_3^2 \quad (3)$$

$$s_{120} = g(x_1, x_2, x_3) = 79.889 - 3.429 \times x_1 - 0.636 \times x_3 - 1.542 \times x_1 \times x_2 + 3.024 \times x_1 \times x_3 + 0.942 \times x_1^2 + 1.429 \times x_2^2 \quad (4)$$

Optimization Experiments. The two models shown in eqs 3 and 4 were used for the production of the isocontour maps in Figure 4. The isocontour maps describe the selectivity and the yield as a function of the three experimental variables (x_1, x_2, x_3). The isocontour projections of the response surfaces were used for the purpose of prediction of a few of the optimized protocols (Table 2) for the bromination of decane-1,10-diol **1**.

Prediction of Optimized Conditions. The conditions for the first optimization experiment (O1, ⊗) were selected as the following: $T = 100$ °C, 0.45 equiv of HBr, and 0.50 equiv of TBAB, that represent an extrapolation of experimental variable x_3 (TBAB = +3 in coded unit, eq 1). The obtained result of this experiment proved to be very promising, see Figure 5, and according to predicted values ($y_{\text{pred}} = 65\%$, $s_{\text{pred}} = 85$). Spurred by those results, we performed another two optimization experiments (O2 (•) and O3 (∇) of Table 2). Both of those experiments represented "extremes" to medium long-range extrapolations involving the two experimental variables quantity of HBr (x_2) and quantity of TBAB (x_3). Experiment O2 of Table 2 provided a reasonable result with a yield of 66% of **TM** with a selectivity of 79% and conversion of 84%. The only observed side product was the dibrominated alkane **3**. In the third optimization experiment (O3) we attempted an extreme extrapolation in the experiment variable x_3 (the quantity of tetrabutylammonium bromide). In this experiment a quantitative

(16) Malinowski, E. R. *Factor Analysis in Chemistry*, 3rd ed.; Wiley: New York, 2002.

(17) Product statistics are calculated according to the following equation: $R^2 = 1 - \text{SS}_{\text{residual}}/(\text{SS}_{\text{model}} + \text{SS}_{\text{residual}})$]. Root means squares error of prediction (RMSEP) is an estimate of the prediction error expressed in real units, in this case, % yield and % selectivity:

$$\text{RMSEP} = \sqrt{\frac{\sum_{i=1}^{I} (y_i^{\text{Pred}} - y_i)^2}{I}}$$

(18) Malinowski, E. R. *Factor Analysis in Chemistry*, 3rd ed.; Wiley: New York, 2002.

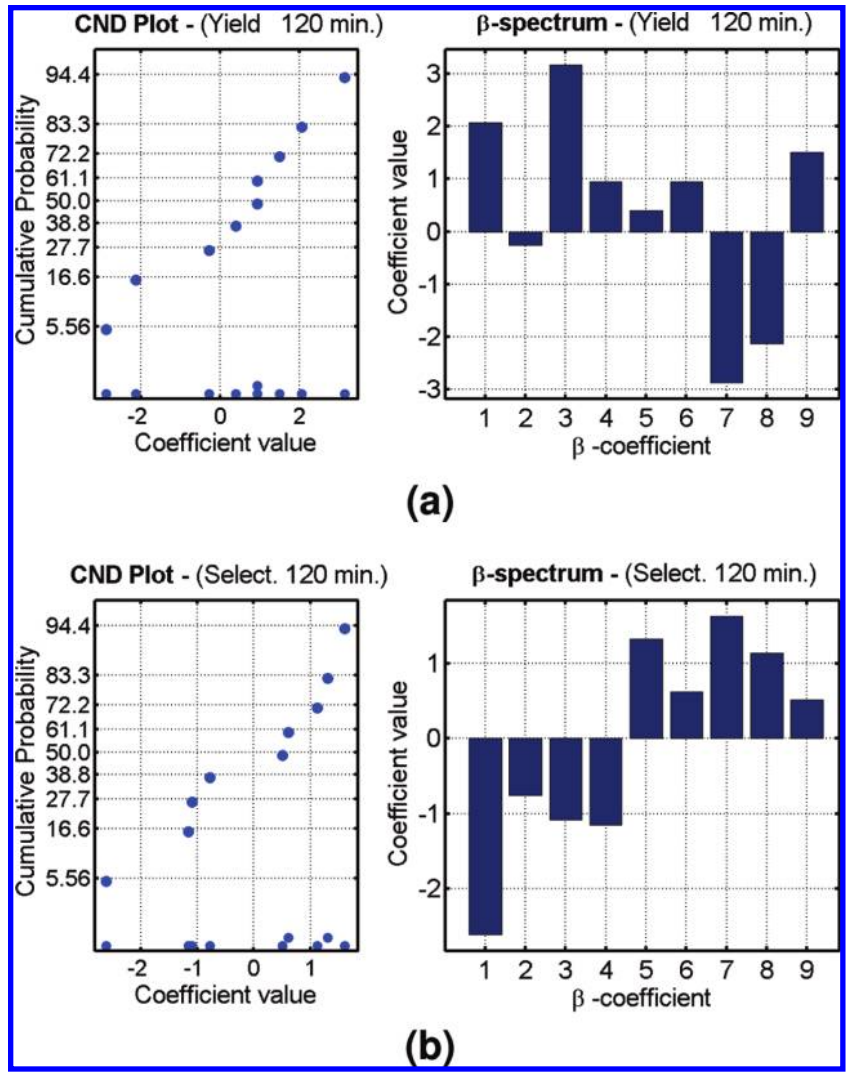


Figure 3. **(a) First model including all of the model parameters with yield of product at time 120 min as response variable. (b) First model including all of the model parameters with selectivity of product at time 120 min as response variable.**

conversion of the substrate was observed, but the yield of **TM** was slightly reduced compared to the yields of the optimization experiments O1 and O2. In the O3 experiment, a subsequent reaction had taken place under the formation of 10-bromodec-1-ene **4** in a quantity of ≈20% (measured by means of GC/MS). The remaining part of the converted substrate **1** was transformed to the byproduct 1,10-dibromodecane **3**. A prolonged reaction time (t > 120 min) resulted in a significantly augmentation of the quantity of the side product **3** and a minor increase in the quantity of the byproduct **4**.

The Robustness of the Process. Even though the product statistic[17] parameter RMSEP shows values in the range 6−7, the long-distance (outside the experimental domain) model predictions, the models shows surprisingly small deviation between the predicted and achieved value of the optimization experiment. The RMSEP values can be explained by the steep ascent from the saddle point and towards the expected optimum area. The steep ascent of the area in close proximity to the expected optimal operational range for the brominating process can be a drawback, since the process is much affected by even small changes in the control variables (x_1, x_2, x_3). As such, the process is not robust in the sense that it will not provide high yield and selectivity without precise control of the reaction temperature and exactly measured amounts of the substrate, the reagent, and the phase transfer catalyst.

Scaled-Up Optimized Experiment. The optimized procedure was attempted scaled-up using 50 g of the substrate **1**. The reaction was conducted in a cylindrical flat-bottomed glass reactor with no baffles (D 78 mm, H 140 mm, $V \approx 500$ mL). The reactor was equipped with a radial turbine stirrer (flat blades, 50 mm, and stirrer rate = 200 turns × min^{-1}). The experiment was run for 2 h 30 min to provide a yield of ≈60% of desired product **2**, that is slightly lower than in the original scale (64%) used during the optimization study.

Conclusion

With the presence of two identical reactive sites in substrate molecule such as decane-1,10-diol **1**, it is well-known that a high selectivity can be achieved by means of a strictly restricted conversion of the substrate but often low yield of desired product. However, in this work we have concurrently optimized the selectivity and the yield of the brominating process by means of multivariate experimental design and modeling using response surface methodology. Multivariate empirical model were derived on the basis of experimental data that subsequently was used to predict optimized protocols for the production of target

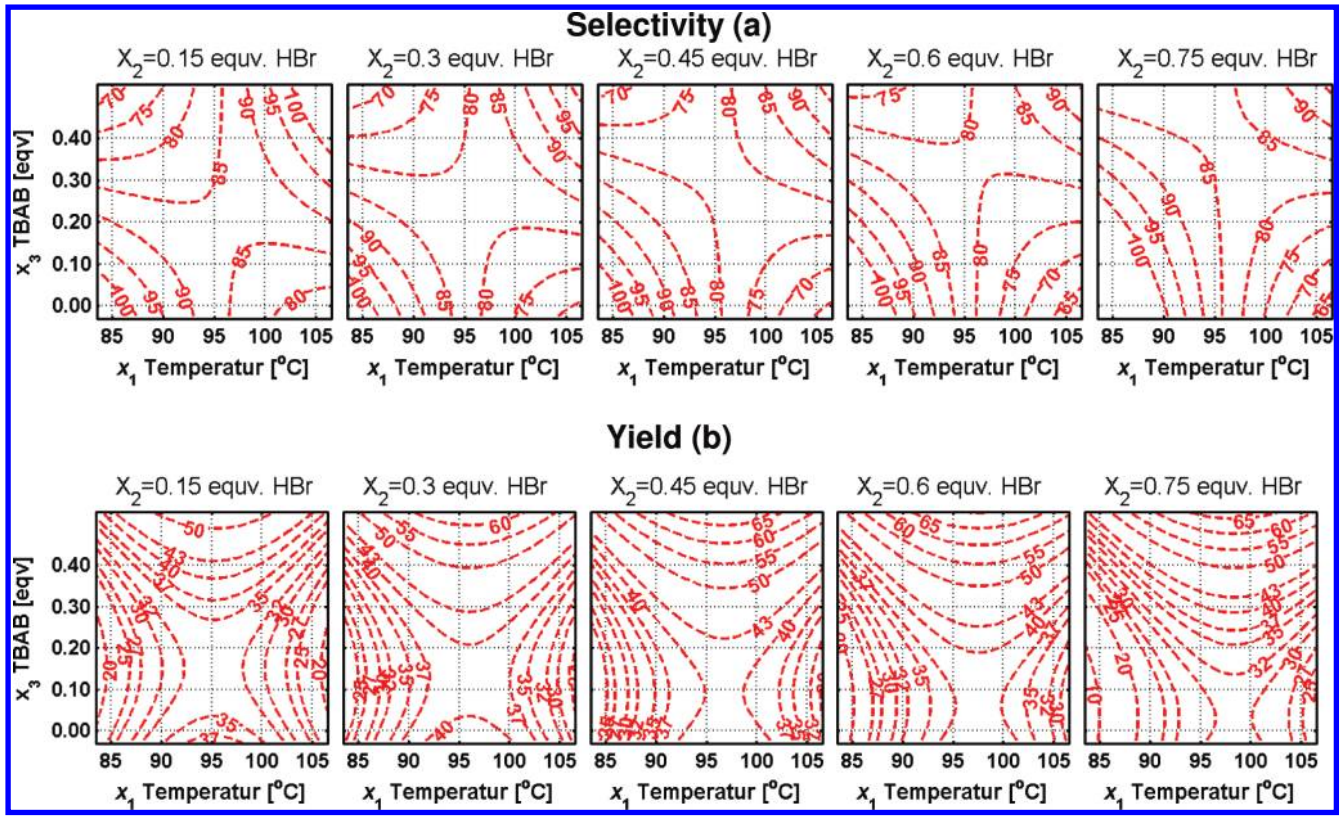


Figure 4. **(a) Isocontour projection of the response surface of the response *selectivity*. (b) Isocontour projection of the response surface of the response *yield*.**

Table 2. **Optimization experiments: bromination of decane-1,10-diol 2**

	experimental variables[a]					
expt.	x_1		x_2		x_3	
O1	+1	100	0	0.45	+3	0.50
O2	+1	100	0	0.45	+8	1.00
O3	+1	100	+1	0.60	+5	0.70

[a] Procedure: decane-1,10-diol **1** (2.87 mmol, 0.500 g) was used as substrate in all of the experiments. Experimental variables: x_k (definition) [levels: −2, −1, 0, +1, +2]: x_1 (reaction temperature) [85 °C, 90 °C, 95 °C, 100 °C, 105 °C,]; x_2 (quantity of hydrobromic acid) [0.15, 0.30, 0.45, 0.60, 0.75 equiv]; x_3 (quantity of tetrabutylammonium bromide) [0.01, 0.10, 0.20, 0.30, 0.40 equiv]. [b] Responses measured by GC: c_t = conversion at time t, s_t = selectivity at time t, and y_t = yield at time t, where $t \in$ [10, 20, 30, 60, 120 min].

molecule 10-bromodecan-1-ol **2** with concomitantly reasonable yield and good selectivity (y = 64%, s = 85%) despite some initial concerns about the validity of the predictive ability of the derived models. Moreover, the developed protocol is solvent free, except for the water found in the aqueous HBr used as brominating reagent.

Experimental Section

General Methods. GLC analyses were performed on a capillary gas chromatograph equipped with a fused silica column (L 25 m, 0.20 mm i.d., 0.33 μm film thickness) at a helium pressure of 200 kPa, split less/split injector and flame ionization detector.

Mass spectra were acquired on a GC/MS instrument, using a gas chromatograph equipped with fused silica column (L 30 m, 0.25 mm i.d., 0.25 μm film thickness) and He as carrier gas.

Structure controls were conducted by means of ^{1}H NMR spectra recorded on a NMR spectrometer operating at 400 MHz. Chemical shifts were referenced to internal TMS.

Typical Reaction Protocol (Corresponds to Experiment #8 of Table 1). Starting materials and reagents were purchased commercially and used without further purification. 1,10-Decandiol **1** (2.87 mmol, 0.500 g), the phase transfer catalyst tetrabutylammonium bromide (TBAB, 0.86 mmol, 0.277 g), and aqueous HBr (48%, 1.72 mmol, 0.2 mL) were transferred to a round-bottom flask (100 mL). The reaction mixture was stirred at medium-high speed using a magnetic stirrer bar and heated at a temperature of 105 °C for a period of 2 h. Samples were withdrawn from the reaction mixture during the course of the reaction (at times t = 10, 20, 30, 60, and 120 min). The collected samples were analyzed on GC/MS to measure the conversion of the substrate **1** and the selectivity in the formation of the monobrominated product **2**.

Work-Up. Water (10 mL) was added to the reaction mixture from which the unconverted substrate **1** precipitated. The solid was filtered off, and the liquid mixture was then extracted with dichloromethane (3 × 10 mL), the organic phases were combined, washed with saturated aqueous sodium hydrogen carbonate (2 × 10 mL), a saturated aqueous solution of sodium chloride (2 × 10 mL), and water (1 × 20 mL). The organic phase was dried over anhydrous sodium sulfate and filtered, and the solvent was removed under reduced pressure using a rotary evaporator to receive the raw product as a colorless oil. This raw product was purified on flash chromatography using hexane/ethylacetate = 8:2 as mobile phase. Silica 60A, 40−

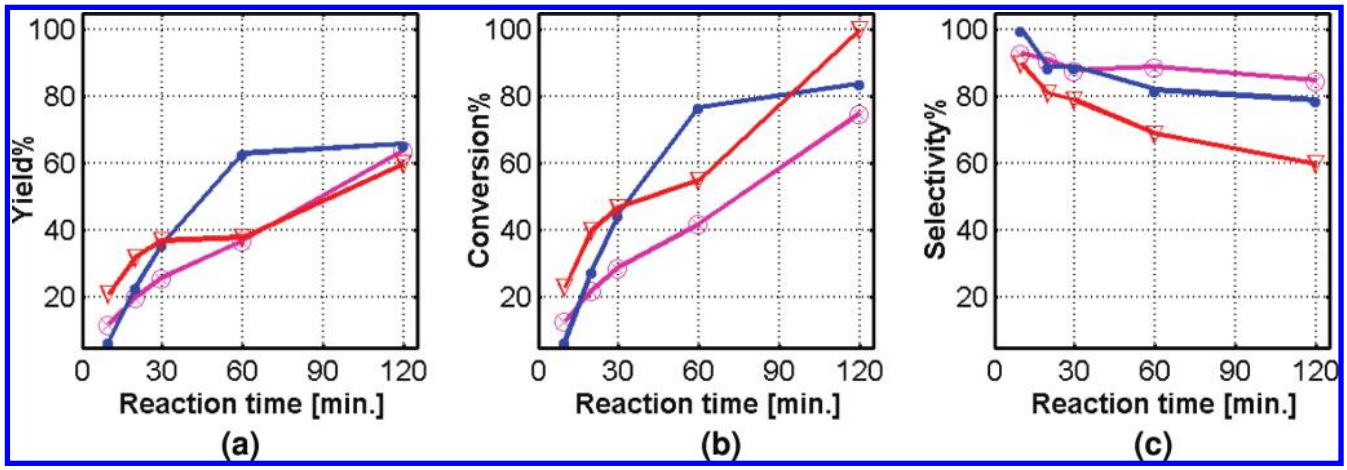
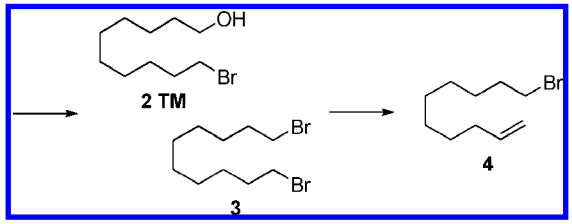


Figure 5. **Reaction profiles for (a) yield, (b) conversion, and (c) selectivity for the three optimization experiments (O1−O3). O1 (⊗): T = 100 °C, 0.45 equiv of HBr, and 0.50 equiv of TBAB. O2 (•): T = 100 °C, 0.45 equiv of HBr, and 1 equiv of TBAB. O3 (∇): T = 100 °C, 0.60 equiv of HBr, and 0.70 equiv of TBAB.**

Scheme 2. **Consecutive reaction of the process to 10-bromo-1-decanol 2 that provided 10-bromodec-1-ene 4 as a by-product**



60 μm, pH 7, 550 $m^2\ g^{-1}$ was used as stationary phase. TLC: $R_{f\ (2)}$ = 0.4 and $R_{f\ (3)}$ = 0.86.

Up-Scaled Reaction Protocol. 1,10-Decandiol **1** (287 mmol, 50 g), the phase transfer catalyst tetrabutylammonium bromide (TBAB, 142 mmol, 46 g), and aqueous HBr (48%, 115 mmol, 15 mL) were transferred to cylindrical flat-bottomed glass reactor (D 78 mm, H 140 mm, $V \approx$ 500 mL). The reaction mixture was stirred at a rate of 200 turns × min^{-1} using a radial turbine (flat blades, 50 mm) and heated at a temperature of 105 °C for a period of 2 h 30 min.

Work-Up Procedure. The reaction mixture was cooled at room temperature and transferred to a separatory funnel (500 mL). Then, ethyl acetate (30 mL) was added followed by saturated solution of sodium bicarbonate (20 mL). The mixture was agitated vigorously, and the layers were separated. The pH of the organic phase was adjusted to basic by adding small portions of sodium bicarbonate. The mixture was washed with saturated sodium chloride solution (2 × 20 mL), dried over anhydrous sodium sulfate, and filtered, and finally the solvent was removed under reduced pressure using a rotary evaporator. The reaction crude was leaved for 2 days at room temperature allowing the unconverted substrate to crystallize. The substrate was isolated by filtration as pure product (12.85 g, 26% of the starting amount). The target raw product (76 g) contained small amounts of both TBAB and the substrate **1**. The purity of the raw product was estimated to be ≈80% by means of ^{1}H NMR, which corresponded to a yield of ≈61% of target product **2**.

10-Bromodecan-1-ol 2 [53463-68-6]. ^{1}H NMR (400 MHz, $CDCl_3$, ppm): δ = 1.29 [br s, 10H], 1.42 [qn, 2H], 1.56 [qn, 2H], 1.85 [qn, 2H], 2.17 [s, 1H], 3.40 [t, 2H], 3.64 [t, 2H]. ^{13}C NMR (200 MHz): δ = 26.13, 28.56, 29.14, 29.76, 29.83, 33.20, 33.23, 34.44, 63.48. MS *m*/*z* (%): 192 (6), 190 (7), 164 (14), 162 (16), 150 (46), 148 (48), 137 (22), 135 (23), 97 (80), 83 (86), 69 (100), 55 (94). IR (FT): ν = 3327, 2923, 2852, 1463, 1371, 1256, 1054, 721, 644, 561. TLC system: hexane/ethyl acetate = 8:2, R_f = 0.40.

Computing and Software. In-house developed function library for MATLAB (by HRB) were used for the multivariate calculations and for the productions of line graphics and iso-contour projections of the response surfaces. This library was used under the MATLAB program version 6.5.0.180913a Release 13 of June 18, 2002[19] that was run with Microsoft Windows XP Professional version 5.1.2600 with service pack 3.0 as operating system.

Previously, the in-house developed function library have been benchmarked against various commercial software such as SAS, Modde, and Statgraphics.[20]

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Supporting Information Available

^{1}H NMR, ^{13}C NMR, and IR spectra of title compound 10-bromodecan-1-ol **2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) Various software versions (2004−2007) of: (a) *SAS for Windows*; SAS Institute Inc.: Cary, NC, U.S.A. (b) *MODDE - Design of Experiments*; Umetrics: Umeå, Sweden. (c) *Statgraphics Software*; Statpoint Technologies, Inc.: Warrenton, VA, U.S.A.