ORGANIC PROCESS RESEARCH & DEVELOPMENT
OPR&D
Article
Cite This: Org. Process Res. Dev. XXXX, XXX, XXX−XXX
pubs.acs.org/OPRD

Stereoselective Acetalization for the Synthesis of Liquid-Crystal Compounds Possessing a *trans*-2,5-Disubstituted 1,3-Dioxane Ring with Saturated Aqueous Solutions of Inorganic Salts

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Supporting Information

ABSTRACT: Stereoselective process for the synthesis of *trans*-2,5-disubstituted 1,3-dioxane derivatives, which are important liquid-crystal compounds, was developed. The acetalization reaction between aldehydes and 2-substituted 1,3-propanediols in the presence of acids gave the corresponding 2,5-disubstituted 1,3-dioxane derivatives with high *trans* selectivity (*trans*/*cis* = >96:<4), when the reaction was performed with saturated aqueous solutions of inorganic salts having high water solubility, such as $CaCl_2$, LiCl, and $ZnCl_2$.

KEYWORDS: *liquid-crystal compound, acetalization, 1,3-dioxane ring, saturated aqueous solution of inorganic salts, stereoselective synthesis*

INTRODUCTION

Since the 1990s, liquid-crystal displays (LCDs) have been playing a central role in flat panel for televisions (TVs), personal computer (PC) monitors, smartphones, and tablet computers, because active-matrix (AM) technology,[1] in which each pixel is separately controlled by thin-film transistor, progressed rapidly. With this advancement, a wide variety of liquid-crystal (LC) compounds with appropriate physical properties, including wide nematic range, large dielectric anisotropy ($\Delta\varepsilon$), high birefringence, small absorption loss, and low viscosity, have been developed for AM-LCDs to meet demands such as high contrast, wide-angle views, rapid switching times, and low power consumption.[2] Both twisted nematic (TN) display[3] and in-plane switching (IPS) display[4] require LC compounds showing positive dielectric anisotropy ($\Delta\varepsilon$) values; therefore, considerable attention has been devoted to the development of positive $\Delta\varepsilon$-type LC compounds. Several efforts were made to increase the value of positive $\Delta\varepsilon$ by augmenting the molecular dipole moment parallel to the long molecular axis direction. For that, the following structural modifications of LC compounds were applied: (i) introduction of a polar functional group such as fluorine atom, trifluoromethyl group, trifluoromethoxy group, and pentafluorosulfanyl group into the *para* and/or *meta* positions of the terminal phenyl or cyclohexane rings,[2] (ii) introduction of a difluorooxymethylene bridge within the mesogenic core,[5] and (iii) replacement of a cyclohexane ring by a 1,3-dioxane ring.[6,7]

After intensive investigations in the pursuit of large positive $\Delta\varepsilon$-type LC compounds, the Chisso (now JNC) group found a new LC compound **1**, *trans*-5-propyl-2-(*trans*-4-(3,4,5-trifluorophenyl)cyclohexyl)-1,3-dioxane (Figure 1), in 1996,[8] which showed a high $\Delta\varepsilon$ value (23.7). Considering that its structurally related compound **2** possessed a $\Delta\varepsilon$ value of 8.3,[9]

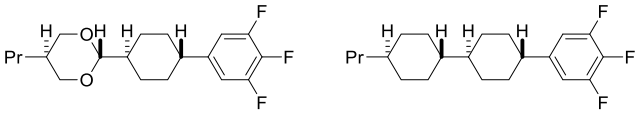


Figure 1. Structures of LC compounds **1** and **2**.

the 1,3-dioxane ring in **1** is regarded to be an essential mesogenic subunit to enhance $\Delta\varepsilon$.

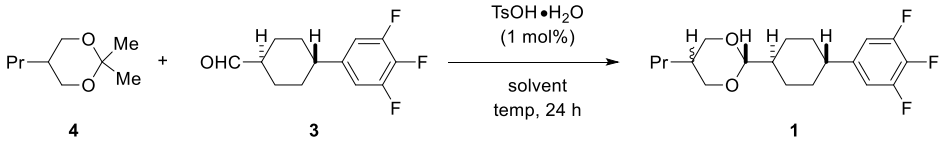
The 1,3-dioxane ring is an important functional group found in biological active compounds,[10] supramolecules,[11] and fragrances[12] as well as LC compounds, and this moiety also serves as a temporary protecting group for 1,3-diols, aldehydes, and ketones in chemical synthesis.[13] In general, the 1,3-dioxane is formed by acetalization of the corresponding carbonyl compounds and 1,3-propanediols in the presence of an acid catalyst such as *p*-toluenesulfonic acid (TsOH).[14] As the acetalization reaction is an equilibrium reaction, the reaction is executed in organic solvents with removing the resultant water from the reaction media by azeotropic distillation (using benzene, toluene, etc.) or using molecular sieves to prevent reverse hydrolysis. LC compounds incorporating the 2,5-disubstituted 1,3-dioxane ring were also prepared by the TsOH-catalyzed acetalization of aldehydes with 2-substituted-1,3-propanediols in refluxing toluene,[6−8] where two possible diastereomers with respect to the formed disubstituted 1,3-dioxane ring were usually obtained with unsatisfactory selectivity (*trans*/*cis* = ca. 60−80:40−20). As the *trans* isomer

Special Issue: Japanese Society for Process Chemistry

Received: November 30, 2018

DOI: 10.1021/acs.oprd.8b00408
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

Table 1. Synthesis of LC Compound 1 in Various Solvents



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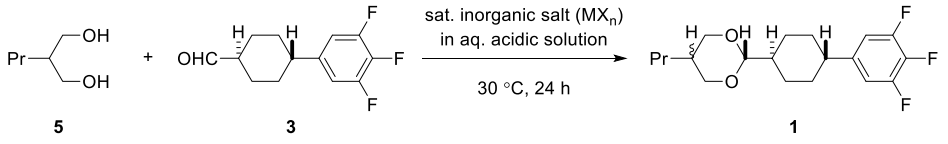
entry	solvent	temperature	*trans*-**1**/*cis*-**1**
1	toluene	−18 °C	56:44
2	toluene	rt	83:17
3	toluene	reflux	76:24
4	hexane	rt	82.1:17.9
5	cyclohexane	rt	80.3:19.7
6	chloroform	rt	81.1:18.9
7	THF	rt	78.6:21.4
8	DME	rt	77.9:22.1
9	CPME	rt	79.9:20.1
10	acetone	rt	77.5:22.5
11	DMSO	rt	60.2:39.8
12	DMF	rt	62.0:38.0
13	DMI	rt	58.9:41.1
14	DMPU	rt	58.1:41.9
15	NMP	rt	58.1:41.9
16	H_2O	rt	60.2:39.8
17	[Bmim]BF_4	rt	98.5:1.5
18	[Bmim]PF_6	rt	98.2:1.8

Table 2. Acetalization with Saturated Aqueous Solution of Several Inorganic Salts



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entry	satd MX_n in aq. acidic solution	solubility of MX_n (g/100 g of H_2O)[a]	*trans*-**1**/*cis*-**1**
1	1 M HCl		58.5:41.5
2	satd LiCl in 0.1 M HCl	83.5	97.3:2.7
3	satd NaCl in 1 M HCl	35.9	68.6:31.4
4	satd KCl in 1 M HCl	34.2	59.5:40.5
5	satd $MgCl_2$ in 1 M HCl	54.6	90.0:10.0
6	satd $CaCl_2$ in 1 M HCl	74.5	97.8:2.2
7	satd $BaCl_2$ in 1 M HCl	35.8	59.9:40.1
8	satd $ZnCl_2$ in H_2O	395	98.8:1.2
9	satd $AlCl_3$ in H_2O	45.8	53.5:46.5
10	1 M H_2SO_4		58.5:41.5
11	satd Na_2SO_4 in 0.5 M H_2SO_4	19.5	58.0:42.0
12	satd $MgSO_4$ in 0.5 M H_2SO_4	33.7	59.0:41.0

[a]Solubility at 20 °C (ref 22).

is responsible for exhibiting liquid crystal properties, 1,3-dioxane **1**, obtained as a *trans-cis* mixture from aldehyde **3** and 1,3-propanediol **5**, was required to be subject to repeated recrystallization to obtain pure *trans*-**1**.[8]

Since the current process toward *trans*-**1** lacks stereoselectivity and involves the substrate-waste repeated recrystallization steps, thereby resulting in decreasing the yield of *trans*-**1**, it was desired to develop an improved method to synthesize **1** with *trans* selective manner. Furthermore, in terms of green chemistry it is highly recommended to use environmentally friendly solvents (e.g., ionic liquids[15] and H_2O[16]) for the synthetic process from chemical industry. Herein, we report a stereoselective synthesis of *trans*-2,5-disubstituted 1,3-dioxane derivatives, such as LC compound **1**, through an acid-catalyzed acetalization reaction of 2-substituted 1,3-propanediols and aldehydes in the presence of saturated aqueous solutions of inorganic salts.

RESULTS AND DISCUSSION

Acetalization in Various Solvents. In the beginning, to evaluate solvent effect for the synthesis of **1** we examined the transacetalization reaction[17] in various solvents as shown in Table 1. All reactions were performed by treatment of aldehyde **3**[8] with acetonide **4** in the presence of a catalytic amount (1 mol%) of TsOH for 24 h, producing an almost quantitative yield of the desired 1,3-dioxane **1** in the indicated *trans-cis* ratio. We regarded that the acetalization progressed kinetically at low temperature (entry 1) and the equilibrium

DOI: 10.1021/acs.oprd.8b00408
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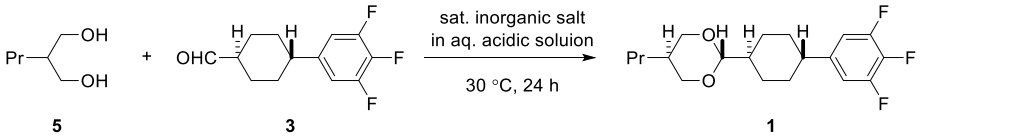
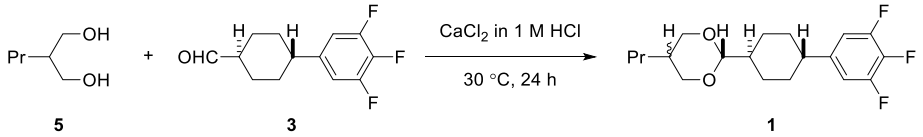
Scheme 1. Synthesis of 1 with Saturated Aqueous $CaCl_2$ and $ZnCl_2$ Solution



96% (*trans*-**1** : *cis*-**1** = 96.1 : 3.9) with sat. $CaCl_2$ in 1 M HCl
85% (*trans*-**1** : *cis*-**1** = 98.2 : 1.3) with sat. $ZnCl_2$ in H_2O

Table 3. Acetalization with Several Concentrations of Aqueous $CaCl_2$Solution



entry	concentration of $CaCl_2$[a] (wt%) in 1 M HCl (0.2 mL)	*trans*-**1**/*cis*-**1**
1	0	58.5:41.5
2	22.6 (36.8)	60.5:39.5
3	32.7 (61.3)	64.3:35.7
4	36.9 (73.6)	71.2:28.9
5	38.8 (79.8)	78.6:21.3
6	40.5 (85.9)	84.5:15.5
7	44.2 (100)	97.8:2.2

[a]Parentheses indicate degree of saturation of $CaCl_2$ solution in 1 M HCl.

occurred over room temperature to produce an ~8:2 mixture of **1** (entries 2−3). Less polar solvents (toluene, hexane, cyclohexane, chloroform, tetrahydrofuran (THF), dimethoxyethane (DME), cyclopentyl methyl ether (CPME), and acetone) are effective to show moderate *trans* selectivity (entries 2−10), while polar solvents (dimethyl sulfoxide (DMSO), *N*,*N*-dimethylformamide (DMF), 1,3-dimethyl-2-imidazolidinone (DMI), *N*,*N*'-dimethylpropyleneurea (DMPU), and *N*-methylpyrrolidone (NMP)) decreased the selectivity (entries 11−15). Interestingly, the acetalization with water[18] also took place to give **1** with a high conversion but incomplete selectivity (entry 16). Fortunately, when the reaction was performed in the presence of ionic liquids[19] such as 1-butyl-3-methylimidazolium tetrafluoroborate ([Bmim]BF_4) and 1-butyl-3-methylimidazolium hexafluorophosphate ([Bmim]PF_6) (entries 17−18), we found that dioxane **1** was afforded with an almost complete *trans* selectivity (*trans*/*cis* = >98:<2).

Acetalization with Saturated Aqueous Solution of Several Inorganic Salts. Ionic liquids are environmentally benign solvents due to low volatility, nonflammable nature, and ease of recycling;[15] however, their cost is still high for industrial-scale process compared with that of organic solvents.[20] After considering the alternative solvent system in place of ionic liquids, we came up with the idea to use saturated aqueous solutions of inorganic salts[21] for the acetalization (Table 2). Initially, we attempted the reaction of aldehyde **3** and 2-propyl-1,3-propanediol (**5**) by using 1 M HCl, giving **1** as a kinetic product (entry 1, *trans*/*cis* = 58.5/41.5) with an almost quantitative conversion. In this reaction, the desired product **1** was precipitated out with progressing reaction, and this precipitation from the reaction media probably assisted in preventing reverse hydrolysis. Next, several saturated aqueous solutions of inorganic salts (LiCl, NaCl, KCl, $MgCl_2$, $CaCl_2$, $BaCl_2$, $ZnCl_2$, $AlCl_3$, Na_2SO_4, and $MgSO_4$) with acids (HCl or H_2SO_4) were investigated. In the presence of saturated (satd) LiCl solution in 0.1 M HCl, the selectivity dramatically changed, giving rise to a 97.3/2.7 mixture of **1** (entry 2). Although some inorganic salts (NaCl, KCl, $BaCl_2$, $AlCl_3$, Na_2SO_4, and $MgSO_4$) were fruitless under the same condition, we fortunately found that aqueous saturated solutions of $MgCl_2$, $CaCl_2$, and $ZnCl_2$ are also effective to obtain **1** with high *trans*-selectivity (*trans*/*cis* = >90/<10). The common property of these effective inorganic salts is high solubility in water (>50 g in 100 g of H_2O at 20 °C)[22] as shown in Table 2.

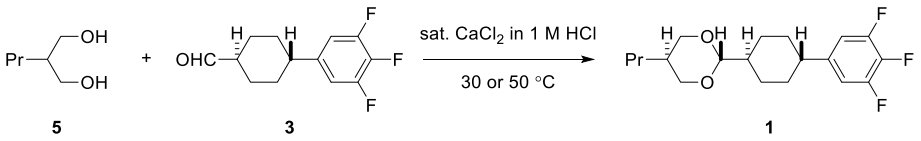
Synthesis of 1 with Saturated Aqueous $CaCl_2$ and $ZnCl_2$ Solution. Two representative solvent systems showing high *trans* selectivity were then used for the synthesis and isolation of **1** as shown in Scheme 1. Aldehyde **3** was subjected to reaction with 1.1 equiv of 1,3-propanediol **5** with satd $CaCl_2$ solution in 1 M HCl or satd $ZnCl_2$ solution in H_2O at 30 °C for 24 h. The resulting products were purified by passing through a silica gel column, giving rise to the targeted compound **1** in 96% isolated yield (*trans*/*cis* = 96.1/3.9) and in 85% isolated yield (*trans*/*cis* = 98.1/1.3), respectively.

Acetalization with Several Concentrations of Aqueous $CaCl_2$ Solution. Having obtained a good solvent system for the stereoselective acetalization to **1**, we next investigated the effect of concentration of $CaCl_2$ solution in 1 M HCl. The acetalization reaction of **3** (0.2 mmol) and **5** was performed in the presence of several concentrations of $CaCl_2$ solution in 1 M HCl (0.2 mL, 0%~100% satd $CaCl_2$ solution) as shown in Table 3. All reactions proceeded to give 1,3-dioxane **1** with the indicated *trans*-*cis* ratio. These results pointed out that the reaction with higher saturated solution of $CaCl_2$ gave **1** with higher *trans* selectivity and using satd $CaCl_2$ solution was mandatory to obtain *trans*-**1** with satisfactory stereoselectivity.

Time-Dependent Change of the trans-cis Ratio in Acetalization. To confirm the reaction pathway, we also observed the time-dependent change of the ratio of *trans*-*cis* isomers of **1**. As shown in Table 4, we ran three to five

DOI: 10.1021/acs.oprd.8b00408
Org. Process Res. Dev. XXXX, XXX, XXX−XXX

Table 4. Time-Dependent Change of the *trans-cis* Ratio in Acetalization



5 3 1

reaction time (h)	reaction at 30 °C *trans*-**1**/*cis*-**1**	reaction at 50 °C *trans*-**1**/*cis*-**1**
1	58.3:41.7	67.7:32.3
3	65.2:34.9	92.2:7.8
9	91.1:8.9	98.7:1.3
24	97.9:2.1	
72	98.4:1.6	

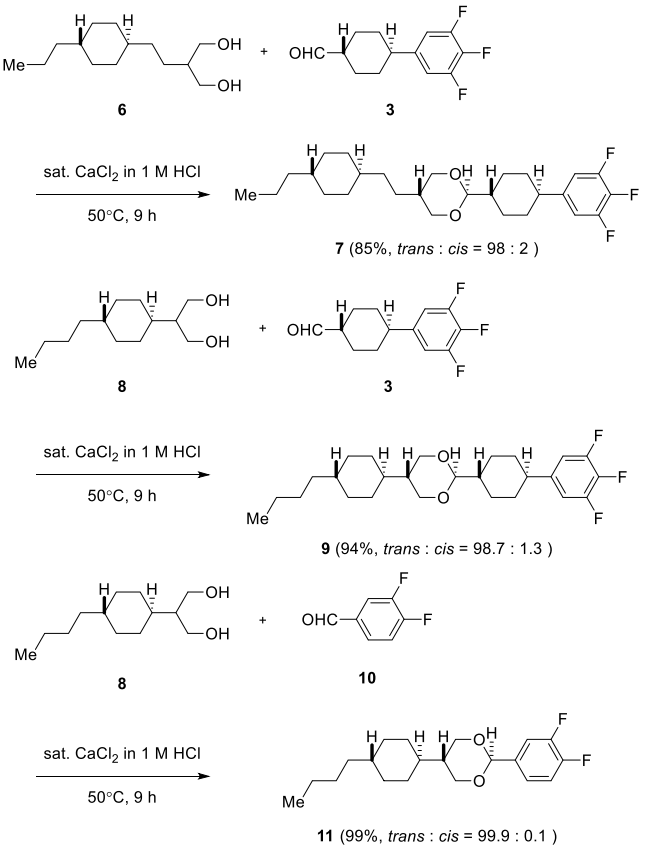
experiments with satd $CaCl_2$ solution in 1 M HCl at 30 and 50 °C and checked the *trans-cis* ratio of **1** after the indicated reaction time. The acetalization at 30 °C was completed within 1 h to give **1** as a kinetically favored product (*trans*/*cis* = 58.3:41.7), which was gradually isomerized to the desired *trans* isomer **1**(*trans*/*cis* = >97:<3) after 24 h. At 50 °C the equilibrium reaction was fast, giving rise to *trans*-**1** for 9 h.

Consideration of the High Stereoselectivity. We concluded that the optimized condition for the synthesis of **1** with high *trans* selectivity (*trans*/*cis* >96:4) was heating of aldehyde **3** and 1,3-propanediol **5** at 50 °C with satd $CaCl_2$ solution in 1 M HCl. The possible reason for this high stereoselectivity is considered to be as follows. At the beginning of the reaction, a mixture of substrates and satd $CaCl_2$ solution formed two liquid phases (organic phase (**3** and **5**) and aqueous phase), and as the reaction proceeded the organic liquid phase disappeared. On the one hand, the *trans-cis* mixture of acetal **1** precipitated out of water. On the other hand, when the reaction was performed at 70 °C the initial two-liquid-phase system was maintained, and the precipitation was not observed due to the melting of the product, affording **1** in a moderate ratio (*trans*/*cis* = 83:17). Furthermore, hexane was used as a cosolvent, and the reaction was conducted at 30 °C with keeping two-liquid-phase system (hexane and satd $CaCl_2$ solution in 1 M HCl) to produce **1** with a moderate selectivity (*trans*/*cis* = 76:24). Therefore, the key to obtain *trans*-**1** with high selectivity is the precipitation of **1** during the reaction and using saturated aqueous solution of inorganic salts having high water solubility. On the basis of the fact that a 59:41 mixture of *trans*-**1** and *cis*-**1** is liquid and a 99:1 mixture is solid (see experimental), *cis*-**1** may be liquid or solidify slowly during the reaction. Then, satd $CaCl_2$ solution in 1 M HCl would assist the isomerization of liquid *cis*-**1** to solid *trans*-**1**, resulting in the formation of *trans*-**1** with stereoselective manner.[23] The role of saturated aqueous solution is currently under investigation.

100 g Scale Synthesis of 1. We then applied the developed method to a 100 g scale synthesis of LC compound **1**. At 50 °C under Ar, 77.7 g of aldehyde **3** was allowed to react with 39.8 g of 1,3-propanediol **5** with satd $CaCl_2$ solution in 1 M HCl (320 mL), and the reaction was completed for 30 h, generating 105 g of the targeted compound **1** (95% isolated yield) with a high *trans*/*cis* ratio (*trans*/*cis* = 99.0:1.0) without any difficulties.

Application of the Developed Method to Synthesis of Other LC Compounds. Finally, other three LC compounds (**7**, **9**, and **11**[24]) incorporating a 2-substituted 1,3-dioxane ring were synthesized by applying the developed method as shown in Scheme 2. Under the optimized condition,

Scheme 2. Synthesis of Other LC Compounds



the acetalizations of diols (**6**[25] and **8**[26]) with aldehydes (**3** and **10**) smoothly progressed to give each compound in good yields with high *trans* selectivity.

CONCLUSION

In conclusion, we developed a stereoselective method to synthesize *trans*-2,5-disubstituted 1,3-dioxane derivatives, which are important liquid crystal compounds. The acetalization reaction of aldehydes and 2-substituted 1,3-propanediols in the presence of acids with saturated aqueous solutions of inorganic salts having high water solubility, such as $CaCl_2$, LiCl, and $ZnCl_2$, proceeded to give the corresponding 2,5-disubstituted 1,3-dioxane derivatives with high *trans* selectivity (*trans*/*cis* > 96/4).

EXPERIMENTAL

General. All reactions involving air- and moisture-sensitive reagents were performed using oven-dried glassware and

DOI: 10.1021/acs.oprd.8b00408
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standard syringe-septum cap techniques. Routine monitoring of reaction was performed using glass-supported Merck silica gel 60 F_{254} thin-layer chromatography (TLC) plates. Flash column chromatography was performed on Kanto chemical Silica Gel 60 N (spherical, neutral 40−50 μm). All solvents and reagents were obtained from commercial supplier and were used without further purification. Infrared (IR) spectral measurements were performed with a HORIBA FT-720 spectrometer. ^{1}H, ^{13}C, and ^{19}F NMR spectra were measured with a Bruker Ascend 400 spectrometer. Chemical shifts are expressed in parts per million (ppm) using tetramethylsilane (δ = 0, ^{1}H NMR and ^{13}C NMR) and trichlorofluoromethane (δ = 0, ^{19}F NMR) as standard substances. Multiplicities are indicated by s (singlet), d (doublet), t (triplet), dd (doublet of doublet), dt (doublet of triplet), ddd (doublet of doublet of doublet), td (triplet of doublet), tt (triplet of triplet), and m (multiplet). Melting points were taken on Mettler Toledo MP70 melting point system and uncorrected. Gas chromatography−mass spectrometry (GC-MS) analysis was performed on a Shimadzu GCMS-QP2010 equipped with a fused silica capillary DB-5MS column (30 m × 0.25 mm, and 0.25 μm film thickness, Agilent Technologies). The analytes were ionized using EI (electron ionization) method. The inlet temperature was maintained at 280 °C. The oven temperature was initially held at 80 °C for 3 min and was then programmed to 300 °C at 20 °C/min, where it was held constant for 8 min. Helium was used as carrier gas.

Synthesis of a Mixture of *trans*/*cis*-5-Propyl-2-(trans-4-(3,4,5-trifluorophenyl)cyclohexyl)-1,3-dioxane (1) with TsOH. 2-Propyl-1,3-propanediol (**5**) (1.00 g, 8.5 mmol) and *trans*-4-(3,4,5-trifluorophenyl)cyclohexanecarbaldehyde (**3**) (1.86 g, 7.7 mmol) were placed in a 20 mL glass centrifuge tube equipped with a Teflon-coated stir bar. To this mixture, DMF (8.0 mL) and *p*-toluenesulfonic acid monohydrate (15.0 mg, 0.079 mmol) were added, and the resulting mixture was stirred at room temperature for 24 h under Ar. The reaction mixture was diluted with water and extracted with hexane. The organic phase was dried over anhydrous K_2CO_3 and concentrated in vacuo to obtain a *trans*/*cis* mixture of **1** as a colorless liquid (2.19 g, 83%, *trans*/*cis* = 58.7:41.3, GC purity 94.3%): ^{1}H NMR for *cis* isomer (400 MHz, $CDCl_3$) δ: 6.83−6.74 (2H, m, overlap with *trans* isomer), 4.31 (1H, d, J = 5.0 Hz), 3.95−3.85 (4H, m), 2.40 (1H, m, overlap with *trans* isomer), 2.04−1.86 (5H, m, overlap with *trans* isomer), 1.57 (1H, m, overlap with H_2O and *trans* isomer), 1.73−1.66 (2H, m), 1.44−1.17 (6H, m, overlap with *trans* isomer), 0.94 (3H, t, J = 7.3 Hz). The GC retention time is 13.2 min.

Synthesis of trans-5-Propyl-2-(*trans*-4-(3,4,5-trifluorophenyl)cyclohexyl)-1,3-dioxane (1) with Saturated $CaCl_2$ Solution in 1 M HCl. 2-Propyl-1,3-propanediol (**5**) (650 mg, 5.5 mmol) and *trans*-4-(3,4,5-trifluorophenyl)-cyclohexanecarbaldehyde (**3**) (1.21 g, 5.0 mmol) were placed in a 25 mL glass test tube equipped with a Teflon-coated stir bar. To this mixture, saturated $CaCl_2$ solution in 1 M HCl (5.0 mL) was added, and the resulting mixture was stirred at 30 °C for 24 h under Ar. The reaction mixture was cooled to room temperature, diluted with water, and extracted with toluene. The organic phase was dried over anhydrous K_2CO_3 and concentrated in vacuo. The residue was filtered through silica gel pad (eluent: hexane) to obtain **1** as a white powder (1.65 g, 96%, *trans*/*cis* = 96.1:3.9, GC purity >99.5%); mp 92.2−93.2 °C; IR ν_{max} (neat) 2958, 2920, 2852, 2359, 2333, 1612, 1531, 1442, 1348, 1226, 1153, 1034, 945, 849, 783, 700 cm^{-1}; ^{1}H NMR for *trans* isomer (400 MHz, $CDCl_3$) δ: 6.81−6.76 (2H, m, Ar-H), 4.21 (1H, d, J = 5.1 Hz, C_2-H), 4.08 (2H, dd, J = 4.6 Hz, 11.7 Hz, C_4-H_{eq}, C_6-H_{eq}), 3.29 (2H, t, J = 11.4 Hz, C_4-H_{ax}, C_6-H_{ax}), 2.40 (1H, tt, J = 3.2 Hz, 11.8 Hz, C_{benzyl}-H), 2.01−1.88 (5H, m, C_5-H), 1.57 (1H, m, overlap with H_2O), 1.38−1.18 (6H, m), 1.04−0.98 (2H, m), 0.90 (3H, t, J = 7.3 Hz, Me); ^{13}C NMR for *trans* isomer (101 MHz, $CDCl_3$) δ: 151.1 (2C, ddd, J = 4.1 Hz, 9.7 Hz, 244.4 Hz), 143.8 (1C, dt, J = 4.5 Hz, 6.5 Hz), 137.6 (1C, td, J = 15.4 Hz, 248.6 Hz), 110.6 (2C, dd, J = 5.3 Hz, 15.4 Hz), 104.8, 72.3 (2C), 43.6, 41.8, 34.3, 33.4 (2C), 30.4, 27.3 (2C), 19.6, 14.2; ^{19}F{1H} NMR for *trans* isomer (377 MHz, $CDCl_3$) δ: −135.9 (2F, d, J = 20.4 Hz), −165.2 (1F, t, J = 20.4 Hz); Anal. Calcd for $C_{19}H_{25}F_3O_2$: C, 66.65; H, 7.36; F, 16.65; O, 9.35. Found: C, 66.53; H, 7.32%. The GC retention times are 13.2 min for *cis*-**1** and 13.4 min for *trans*-**1**. GCMS-EI: m/z 342 $[M]^+$ (0.9), 341 $[M\text{-}H]^+$ (1.2), 129 $[M\text{-}C_{12}H_{12}F_3]^+$ (100).

Synthesis of trans-5-Propyl-2-(*trans*-4-(3,4,5-trifluorophenyl)cyclohexyl)-1,3-dioxane (1) with Saturated Aqueous $ZnCl_2$ Solution. 2-Propyl-1,3-propanediol (**5**) (260 mg, 2.2 mmol) and *trans*-4-(3,4,5-trifluorophenyl)-cyclohexanecarbaldehyde (**3**) (485 mg, 2.0 mmol) were placed in a 20 mL glass centrifuge tube equipped with a Teflon-coated stir bar. To this mixture, saturated aqueous $ZnCl_2$ solution (2.0 mL) was added, and the resulting mixture was stirred at 30 °C for 24 h under Ar. The reaction mixture was cooled to room temperature and extracted with toluene. The organic phase was dried over anhydrous K_2CO_3 and concentrated in vacuo. The residue was filtered through silica gel pad (eluent: hexane) to obtain **1** as a white powder (583 mg, 85%, *trans*/*cis* = 98.7:1.3, GC purity >99.5%).

Large-Scale Synthesis of *trans*-5-Propyl-2-(*trans*-4-(3,4,5-trifluorophenyl)cyclohexyl)-1,3-dioxane (1). *trans*-4-(3,4,5-Trifluorophenyl)cyclohexanecarbaldehyde (**5**) (77.7 g, 0.32 mol) and 2-propyl-1,3-propanediol (**3**) (39.8 g, 0.34 mol) were placed in a 500 mL glass recovery flask equipped with a Teflon-coated stir bar and an air-cooled condenser. To this mixture, saturated $CaCl_2$ solution in 1 M HCl (320 mL) was added, and the resulting mixture was stirred at 50 °C for 18 h under Ar. To the reaction mixture, concentrated HCl (1.00 mL) and $CaCl_2$ (50.0 g) were added, and the resulting suspension was stirred, until the ratio of *cis*-**1** decreased to less than 2.5% (monitored by GC-MS) (12 h). The reaction mixture was cooled to room temperature, and the resulting suspension was filtered. The solid was thoroughly washed with water and dried to obtain **1** as a white crystal (105 g, 95%, *trans*/*cis* = 99.0:1.0, GC purity >99.5%).

Synthesis of *trans*-5-(2-(*trans*-4-Propylcyclohexyl)-ethyl)-2-(*trans*-4-(3,4,5-trifluorophenyl)cyclohexyl)-1,3-dioxane (7). 2-(2-(*trans*-4-Propylcyclohexyl)ethyl)-1,3-propanediol (**6**) (91.4 mg, 0.40 mmol) and *trans*-4-(3,4,5-trifluorophenyl)cyclohexanecarbaldehyde (**3**) (96.9 mg, 0.40 mmol) were placed in a 10 mL glass test tube equipped with a Teflon-coated stir bar. To this mixture, saturated $CaCl_2$ solution in 1 M HCl (800 μL) was added, and the resulting mixture was stirred at 50 °C for 9 h under Ar. The reaction mixture was cooled to room temperature, diluted with water, and extracted with toluene. The organic phase was dried over anhydrous K_2CO_3 and concentrated in vacuo to obtain **7** as a white powder (154.2 mg, 85%, *trans*/*cis* = 98.0:2.0, GC purity 98.8%); mp 100.0−106.4 °C; IR ν_{max} (neat) 2910, 2850, 2359, 2339, 1533, 1442, 1344, 1227, 1153, 1136, 1041, 947, 852, 700

DOI: 10.1021/acs.oprd.8b00408
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cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.82−6.75 (2H, m, Ar-H), 4.20 (1H, d, J = 5.1 Hz, C_2-H), 4.08 (2H, dd, J = 4.6 Hz, 11.6 Hz, C_4-H_{eq}, C_6-H_{eq}), 3.28 (2H, t, J = 11.4 Hz, C_4-H_{ax}, C_6-H_{ax}), 2.40 (1H, tt, J = 3.2 Hz, 11.8 Hz, C_{benzyl}-H), 1.97−1.87 (5H, m), 1.72−1.68 (4H, m), 1.57 (1H, m, overlap with H_2O), 1.37−1.08 (12H, m), 1.06−1.00 (2H, m), 0.88−0.82 (7H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 151.1 (2C, ddd, J = 4.0 Hz, 9.7 Hz, 245 Hz), 143.7 (1C, dt, J = 4.5 Hz, 6.5 Hz), 137.9 (1C, td, J = 15.4 Hz, 248.6 Hz), 110.6 (2C, dd, J = 5.3 Hz, 15.4 Hz), 104.8, 72.3 (2C), 43.6, 41.8, 39.8, 37.9, 37.5, 34.7, 33.9, 33.4 (2C), 33.2 (2C), 33.2 (2C), 27.3 (2C), 25.6, 20.0, 14.4; ^{19}F{^{1}H} NMR (377 MHz, $CDCl_3$) δ: −135.9 (2F, d, J = 20.6 Hz), −165.2 (1F, t, J = 20.5 Hz); Anal. Calcd for $C_{27}H_{39}F_3O_2$: C, 71.65; H, 8.69; F, 12.59; O, 7.07. Found: C, 71.45; H, 8.72%. The GC retention times are 19.1 min for *cis*-**7** and 20.3 min for *trans*-**7**. GCMS-EI: m/z 452 $[M]^+$ (0.8), 451 $[M\text{-}H]^+$ (0.5), 239 $[M\text{-}C_{12}H_{12}F_3]^+$ (26.6), 55 $[C_4H_7]^+$ (100).

Synthesis of *trans*-5-(*trans*-4-Butylcyclohexyl)-2-(*trans*-4-(3,4,5-trifluorophenyl)cyclohexyl)-1,3-dioxane (9). 2-(*trans*-4-Butylcyclohexyl)-1,3-propanediol (**8**) (85.8 mg, 0.40 mmol) and *trans*-4-(3,4,5-trifluorophenyl)cyclohexanecarbaldehyde (**3**) (96.9 mg, 0.40 mmol) were placed in a 10 mL glass test tube equipped with a Teflon-coated stir bar. To this mixture, saturated $CaCl_2$ solution in 1 M HCl (800 μL) was added, and the resulting mixture was stirred at 50 °C for 9 h under Ar. The reaction mixture was cooled to room temperature, diluted with water, and extracted with toluene. The organic phase was dried over anhydrous K_2CO_3 and concentrated in vacuo to obtain **9** as a white powder (165.5 mg, 94%, *trans*/*cis* = 98.7:1.3, GC purity 98.9%); mp 115.2−122.0 °C; IR ν_{max} (neat) 2918, 2843, 2362, 2330, 1531, 1444, 1348, 1228, 1155, 1138, 1032, 847, 704 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 6.82−6.75 (2H, m, Ar-H), 4.18 (1H, d, J = 5.0 Hz, C_2-H), 4.16 (2H, dd, J = 4.6 Hz, 11.8 Hz, C_4-H_{eq}, C_6-H_{eq}), 3.40 (2H, t, J = 11.4 Hz, C_4-H_{ax}, C_6-H_{ax}), 2.40 (1H, tt, J = 3.0 Hz, 11.8 Hz, C_{benzyl}-H), 1.97−1.88 (4H, m), 1.76−1.73 (3H, m), 1.67−1.63 (2H, m), 1.56 (1H, m, overlap with H_2O), 1.38−1.12 (11H, m), 1.00−0.93 (3H, m), 0.89−0.78 (5H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 151.1 (2C, ddd, J = 4.0 Hz, 9.7 Hz, 244.5 Hz), 143.7 (1C, dt, J = 4.5 Hz, 6.5 Hz), 137.9 (1C, td, J = 15.4 Hz, 248.6 Hz), 110.6 (2C, dd, J = 5.2 Hz, 15.4 Hz), 104.6, 70.8 (2C), 43.6, 41.8, 39.6, 37.5, 37.4, 37.1, 33.4 (2C), 33.0 (2C), 29.9 (2C), 29.1, 27.3 (2C), 23.0, 14.1; ^{19}F NMR (377 MHz, $CDCl_3$) δ: −135.9 (2F, d, J = 20.5 Hz), −165.2 (1F, t, J = 20.6 Hz); Anal. Calcd for $C_{26}H_{37}F_3O_2$: C, 71.20; H, 8.50; F, 13.00; O, 7.30. Found: C, 71.05; H, 8.51%. The GC retention times are 18.5 min for *cis*-**9** and 19.2 min for *trans*-**9**. GCMS-EI: m/z 438 $[M]^+$ (0.6), 437 $[M\text{-}H]^+$ (1.3), 225 $[M\text{-}C_{12}H_{12}F_3]^+$ (70.4), 55 $[C_4H_7]^+$ (100).

Synthesis of *trans*-5-(*trans*-4-Butylcyclohexyl)-2-(3,4-difluorophenyl)-1,3-dioxane (11). 2-(*trans*-4-Butylcyclohexyl)-1,3-propanediol (**8**) (85.8 mg, 0.40 mmol) and 3,4-difluorobenzaldehyde (**10**) (56.8 mg, 0.40 mmol) were placed in a 10 mL glass test tube equipped with a Teflon-coated stir bar. To this mixture, saturated $CaCl_2$ solution in 1 M HCl (800 μL) was added, and the resulting mixture was stirred at 50 °C for 9 h under Ar. The reaction mixture was cooled to room temperature, diluted with water, and extracted with toluene. The organic phase was dried over anhydrous K_2CO_3 and concentrated in vacuo to obtain **11** as a white powder (133.7 mg, 99%, *trans*/*cis* = >99.5:<0.5, GC purity >99.5%); mp 86.9−87.6 °C; IR ν_{max} (neat) 2922, 2843, 2359, 2333, 1518, 1429, 1389, 1281, 1153, 1130, 1115, 1032, 891, 806, 771, 683 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.32 (1H, ddd, J = 2.1 Hz, 8.0 Hz, 10.6 Hz, Ar_6-H), 7.20 (1H, m, Ar_2-H), 7.13 (1H, m, Ar_5-H), 5.32 (1H, s, C_2-H), 4.30 (2H, dd, J = 4.6 Hz, 11.7 Hz, C_4-H_{eq}, C_{6eq}-H_{eq}), 3.62 (2H, t, J = 11.5 Hz, C_4-H_{ax}, C_6-H_{ax}), 1.89 (1H, m, C_5-H), 1.78−1.68 (4H, m), 1.30−1.21 (4H, m), 1.20−1.12 (3H, m), 1.09−0.95 (3H, m), 0.92−0.78 (5H, m); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 150.6 (1C, dd, J = 14.8 Hz, 250.9 Hz), 149.1 (1C, dd, J = 14.5 Hz, 249.5 Hz), 135.7 (1C, m), 122.3 (1C, dd, J = 3.8 Hz, 6.4 Hz), 116.9 (1C, dd, J = 1.1 Hz, 16.2 Hz), 115.5 (1C, dd, J = 2.7 Hz, 16.7 Hz), 99.8, 71.2 (2C), 39.2, 37.5, 37.3, 37.0, 33.0 (2C), 29.9 (2C), 29.1, 23.0, 14.1; ^{19}F{^{1}H} NMR (377 MHz, $CDCl_3$) δ: −138.4 (1F, d, J = 20.6 Hz), −138.5 (1F, d, J = 20.6 Hz); Anal. Calcd for $C_{20}H_{28}F_2O_2$: C, 70.98; H, 8.34; F, 11.23; O, 9.45. Found: C, 70.95; H, 8.19%. The GC retention times are 13.8 min for *cis*-**11** and 14.3 min for *trans*-**11**. GCMS-EI: m/z 338 $[M]^+$ (12.2), 337 $[M\text{-}H]^+$ (24.6), 319 $[M\text{-}F]^+$ (0.8), 225 $[M\text{-}C_6H_3F_3]^+$ (1.5), 113 $[C_6H_3F_3]^+$ (55.4), 67 $[C_5H_7]^+$ (100).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.oprd.8b00408.

Optimization experiments and ^{1}H, ^{13}C, and ^{19}F NMR spectra of all synthetic compounds (**1**, **7**, **9**, and **11**) (PDF)

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Notes

The authors declare no competing financial interest.

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