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Practical Hydroxymethylation of Aldehydes and Ketones via Pinacol Cross-Coupling Reactions with Paraformaldehyde

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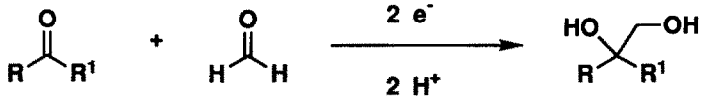
Abstract: *A general and practical method for the direct hydroxymethylation of aldehydes and ketones via pinacol cross-coupling with paraformaldehyde is described. The reaction is promoted by vanadium(II) ions which are conveniently generated from the reduction of $VCl_3(THF)_3$ with zinc dust. Excellent yields of terminal diols are obtained and stereoselective coupling is observed with some chiral aldehydes and ketones.*

Hydroxymethylation of aldehydes or ketones, leading to terminal 1,2-diols, represents a potentially useful strategy for the one carbon extension of carbonyls. Existing methodology in this area has focused on the use of nucleophilic, hydroxymethyl synthons.[1] In the majority of cases, such reagents lead to either 1°-protected diols or to masked diol functions that require a subsequent oxidative step to form the diol group. A simple, and direct (one step) approach to hydroxymethylation of carbonyls would involve the pinacol cross-coupling of aldehydes or ketones with formaldehyde (eq 1). Clerici and Porta have demonstrated the viability of such a



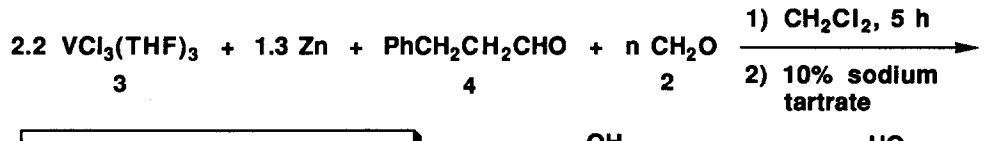
(1)

reaction in the course of their extensive studies on the reductive coupling chemistry of aqueous titanium(III) reagents.[2] However, this particular method, which employs formalin as the source of formaldehyde, suffers from a lack of generality with regard to the carbonyl substrate. We have demonstrated that the vanadium(II) reagent, $[V_2Cl_3(THF)_6]_2[Zn_2Cl_6]$ (**1**), is able to promote a variety of pinacol cross-coupling reactions between aldehydes.[3] Herein we describe a general and practical method for direct hydroxymethylation of ketones and aldehydes via pinacol cross-coupling with paraformaldehyde (**2**).

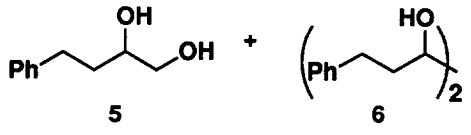
RESULTS

We began this work by examining the cross-coupling reaction between **2** (10 equiv) and 3-phenylpropanal (**4**). In all of these studies, reagent **1** was generated in situ from $VCl_3(THF)_3$ (**3**) and zinc dust in dichloromethane (the concentration of vanadium(II) was ca. 0.2 M). After a reaction time of 5 h, the mixture was worked up with 10% sodium tartrate and the desired product, 4-phenyl-1,2-butanediol (**5**) was isolated in 84% yield. Approximately 5% of 1,6-diphenyl-3,4-hexanediol (**6**), the product of homocoupling of **4**, was also isolated. In an effort to optimize the conditions for this reaction, we varied the concentration of vanadium(II), keeping the amounts of **2** and **4** constant. Upon increasing the concentration of vanadium(II) to ca. 1.0 M, the yield of **5** decreased (73%) while the amount of **6** increased (22%). At this point we returned to the original vanadium(II) concentration of 0.2 M and varied the amount of **2**. These results are presented in Table 1 and clearly indicate that using less than 10 equiv of **2** has a deleterious effect on the yield of **5**.

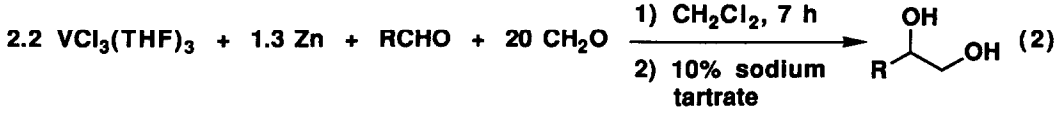
Table 1. Optimization of the Cross-Coupling of **4** with **2**.



Equiv of 2 n	Isolated Yield 5	6
1	42	28
5	45	17
10	84	5
15	92	5
20	95	<1



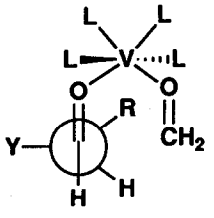
Therefore, we chose the conditions outlined in equation 2 as being "optimal" for cross-coupling reactions between **2** and aldehydes.



At this point it is worth discussing a few other observations made during these first set of experiments. We have found that in most cases, the order of addition of substrates to the solution of vanadium(II) is not crucial. In fact, in one case, a mixture of **1** and 20 equiv of **2** was allowed to stir for 3 h prior to addition of **4**. After another 5 h, **5** was isolated in 93% yield. We also examined other potential sources of formaldehyde. For example, trioxane (30 equiv) gave no detectable amount of **5** under standard cross-coupling conditions. When

nitrogen purged solutions of formalin were used, some product was obtained, but there was always a significant amount of green oil that formed upon addition of the formalin to the dichloromethane solution of vanadium(II). We believe this is most likely attributed to the formation of vanadium(II) aquo complexes that would have limited solubility in dichloromethane.[4]

Having found suitable conditions for cross-coupling reactions between aldehydes and **2** we turned our attention to chiral aldehydes in order to examine any potential stereoselectivity associated with this reaction. From our previous work in this area, it is important to consider two classes of chiral aldehydes. The first involves those which cannot form chelates with the metal center (non-chelating aldehydes). The second class consists of aldehydes which possess the potential for forming chelates with vanadium. In the former category, we examined cross-coupling reactions with 2-phenyl propanal (**7**) and 2-((*tert*-butyldimethylsilyl)oxy)-2-cyclohexyl ethanal (**9**). In both cases, excellent yields of the desired products were obtained and diastereofacial selectivity ranged from modest to good (Table 2). The major isomer from each of these reactions is shown in Table 2 and is that predicted from a typical Felkin-Ahn model (Figure 1.).[5] No selectivity was observed in the cross-coupling reaction between (±)-*N*-tosyl valinal[6] and **2**.



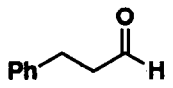
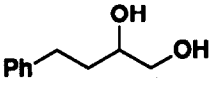
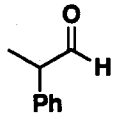
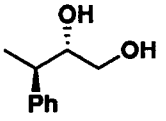
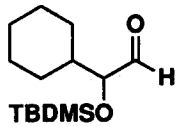
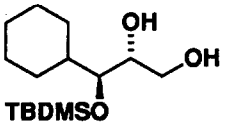
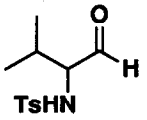
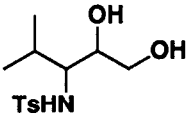
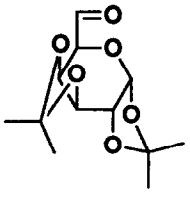
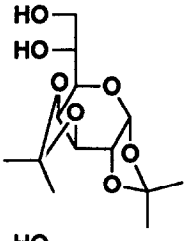
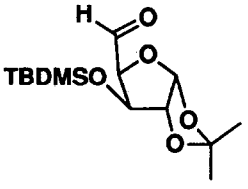
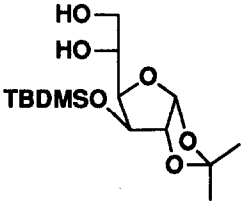
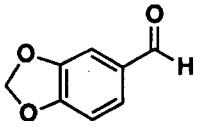
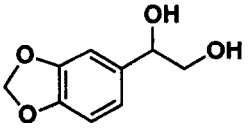
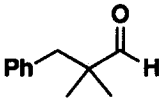
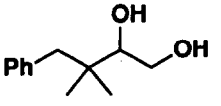
7: Y=Ph, R=Me
9: Y=OTBDMS, R=Cy

Figure 1. Felkin-Ahn model for the reaction of aldehydes 7 and 9 with 2.

Turning to aldehydes that have the potential for forming chelates with a vanadium(II) center, the two dialdoses, **13** and **15** were examined. Although the yields of cross-coupled products were high in both cases, selectivity was only modest. In both examples, the major isomer is that predicted from a non-chelation control model (at least via the ring oxygens).[7]

The successful cross-coupling of the last two aldehydes shown in Table 2 required some deviation from the procedure outlined in equation 2. Aryl aldehydes such as piperonal (**17**) are known to undergo efficient homocoupling in the presence of **1**.[3a,b] Therefore, we were not surprised to find that a substantial amount of homocoupling product (ca. 50%) was obtained when the standard coupling procedure was employed. This problem was alleviated by slow addition (5 h) of **17** to the reaction mixture, which reduced the amount of homocoupling product to 7% and provided an 88% of the desired product **18**. In the case of the hindered, non-chelating aldehyde **19**, we found that employing the standard conditions for aldehydes resulted in unacceptable yields of **20** due to the sluggish rate of reaction of this substrate (15% of unreacted **19** was recovered). Therefore, we resorted to the optimized conditions for hindered ketones (see equation 3) which led to complete consumption of **19** and an 89% yield of **20**.

Table 2. Cross-Coupling of Aldehydes with 2 (eq 2).

Substrate	(No.)	Product[a]	(No.)	Yield[b] (ds)
	4		5	96
	7		8	93 (3:1)
	9 [19]		10	89 (8:1)
	11 [20]		12	70 (1:1)
	13 [21]		14	84 (2:1)
	15 [22]		16	99 (3:1)
	17		18	88[c]
	19 [23]		20	89[d]

a. Only the major diastereomer is shown. b. Isolated Yield. c. 5 h slow addition of 17. d. The conditions in eq. 3 were used.

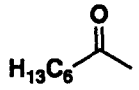
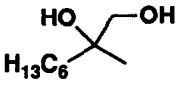
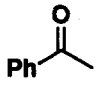
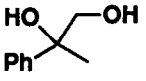
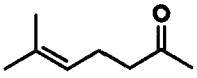
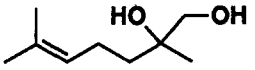
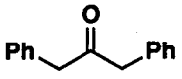
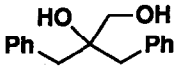
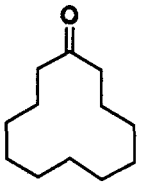
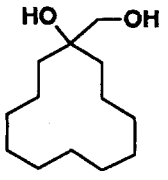
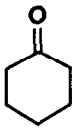
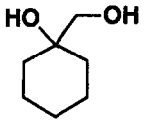
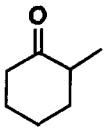
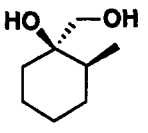
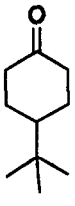
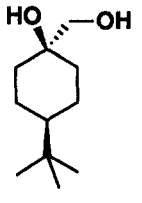
In general, ketones have been poor substrates in the pinacol cross-coupling chemistry we have developed using reagent **1**. Therefore, when we cross-coupled 2-octanone (**21**) and **2** (20 equiv) using the conditions described for aldehydes (eq 2), we were pleased to obtain an excellent yield of the desired product, 2-methyl-1,2-octanediol (**22**) (91%). Similar results were achieved with acetophenone (83%). However, when we turned to the more hindered ketone, 1,3-diphenyl-2-propanone (**27**), the reaction slowed down as evidenced by the presence of a significant amount of starting material after a reaction time of 7 h (61% of **28**, 32% of **27** recovered). Letting the same reaction proceed for 14 h led to insignificant improvement in the yield of **28** (66%), while continuing the reaction for 2 days led to substantial decomposition of product and/or starting material. Seeking to optimize the yields of cross-coupled products in these reactions, we found, after several permutations, that doubling the amount of vanadium used in equation 1 led to improved yields of **28** (82%, 18% of **27** recovered). However, from a practical standpoint, the use of extra vanadium is not very attractive. One potential method of keeping the effective concentration of vanadium(II) high in a given reaction, without using excess vanadium, is to regenerate vanadium(II) ions from the vanadium(III) products formed in these coupling reactions. Some recent work in our laboratories[8] has demonstrated that all three chloride ligands on a molecule of $VCl_3(THF)_3$ can be reduced off in a stepwise manner and in a single reaction flask (i.e. three V(III) to V(II) reductions). This allows one to employ only 1 equiv of $VCl_3(THF)_3$ in conjunction with 1.5 equiv of zinc dust to couple 3 equiv of certain aldehydes. It is important to note that this process does not represent a catalytic cycle since the organic product from the reaction is not being released from the metal center. Therefore, we examined the effect of using an excess of zinc (5 equiv) in a reaction similar to that shown in equation 2, and found that an excellent yield of **28** (96%) was obtained after 12 h (eq 3).[9] To substantiate the hypothesis that vanadium(II) is

$$2.2\ VCl_3(THF)_3 + 5\ Zn + RC(O)R^1 + 20\ CH_2O \xrightarrow[2)\ 10\%\ \text{sodium tartrate}]{1)\ CH_2Cl_2,\ 12\ h} \underset{R}{\overset{HO}{\diagdown}}\!\!\overset{\diagup}{\diagdown}\!\!\underset{R^1}{\overset{OH}{\diagup}} \quad (3)$$

being regenerated in these particular cross-coupling reactions, we used only 1 equiv of $VCl_3(THF)_3$ (instead of the normal 2 equiv) in equation 3. If regeneration was not occurring in the presence of extra zinc, the maximum yield of product would be 50%. However, after a reaction time of 12 h, a 77% yield of product was obtained (23% of starting material was recovered), thus confirming that regeneration is possible. The presence of vanadium in these reactions is necessary as evidenced by the fact that when no $VCl_3(THF)_3$ is used in equation 3, no **28** was detected after a reaction time of 13 h.

Having developed this set of conditions for hindered ketones, we first went back and examined the methyl ketones **21**, **23** and **25**. In the first two cases, improvement was negligible. However, when we originally cross-coupled alkenyl ketone **25** under the conditions outlined in equation 2, we obtained a 64% yield of **26**. This relatively poor yield was due to secondary reactions of the product.[10] Such side reactions were completely avoided using the conditions prescribed in equation 3. Several other ketones were also examined using the cross-coupling conditions outlined in equation 3, and in all cases excellent yields of the desired products were obtained (Table 3). Stereoselective addition to two different substituted cyclohexanones (**33** and **35**) was observed. In both of these cases, the major diastereomer is that expected from reaction on the least hindered face of the ketone.

Table 3. Cross-Coupling of Ketones with 2 (eq 3).

Substrate	(No.)	Product[a]	(No.)	Yield[b] (ds)
	21		22	91[c]
	23		24	86
	25		26	84[d]
	27		28	96
	29		30	93
	31		32	81
	33		34	83 (8:1)
	35		36	89 (5:1)

a. Only the major diastereomer is shown. b. Isolated Yield. c. 8 h reaction time. d. 4 h reaction time.

DISCUSSION

One aspect of this chemistry that is worthy of comment is the apparent absence of formaldehyde homocoupling (i.e. producing ethylene glycol). Although we did not actually attempt to isolate ethylene glycol from any of these reactions, the fact that a 93% yield of cross-coupled product **5** was isolated from a reaction where 20 equiv of **2** was allowed to stir in the presence of **1** for 3 h prior to the addition of **4**, indicates no significant amount of vanadium(II) had been consumed in the first part of this reaction. For comparison, if 20 equiv of **4**, a more hindered aldehyde, is stirred in the presence of **1** for 3 h, a 53% yield of homocoupled product **6** is obtained. Therefore, it would appear that the concentration of free (or metal bound) formaldehyde is not sufficiently high at any point during the course of these reactions. The low solubility of **2** in the reaction medium certainly plays a part in this chemistry. That is, a significant amount (by visual inspection) of **2** remains undissolved throughout the course of the reaction. The rather poor Lewis acidic character of the vanadium(II) and (III) species present in these reactions probably also contributes to the low concentrations of **2**. This latter point is substantiated by the fact that trioxane, which is completely soluble under the standard reaction conditions, does not function as a source of formaldehyde in these reactions. Other Lewis acids are known to effectively decyclize trioxane even at low temperatures.[11]

Prior to the beginning of this project, we had deemed ketones to be rather poor substrates in pinacol cross-coupling reactions promoted by reagent **1**. Therefore, we were very pleased to find the conditions outlined in equation 3 that have allowed us to perform cross-coupling reactions between **2** and a variety of ketones. At this point in time, we do not completely understand all of the subtleties associated with this particular reaction. For example, we believe that the role of the extra zinc is to regenerate vanadium(II) species from the vanadium(III) pinacolate products formed in these reactions.[12] This might involve the direct reduction of such species, thus leading to vanadium(II) pinacolate complexes. Alternatively, one can envision the disproportionation of vanadium(III) pinacolate complexes to generate $VCl_3(THF)_3$ which in turn would be reduced to regenerate **1**. Obviously more work remains to be done in this area.

In summary, we have described a practical method for the direct hydroxymethylation of aldehydes and ketones. Noteworthy features of this method are the high yields of products, the convenient reaction conditions, and the ready availability of starting materials. We believe that this reaction represents the most general method for direct hydroxymethylation of aldehydes and ketones and will find utility in organic synthesis.

EXPERIMENTAL

General. General experimental details have been described elsewhere.[3e] Multiplicities of $^{13}C\{^1H\}$NMR resonances were determined by distortionless enhancement by polarity transfer (DEPT) spectroscopy. Fast atom bombardment (FAB) mass spectral data was obtained in the positive ion mode employing a glycerol/thioglycerol mixture (1:1, v:v) as the matrix solvent unless indicated otherwise. Vanadium(III) chloride and paraformaldehyde were purchased from Aldrich and used as received. All reactions were carried out under an atmosphere of nitrogen.

General procedure for the hydroxymethylation of aldehydes with paraformaldehyde. $VCl_3(THF)_3$[13] (1.64 g, 4.4 mmol), zinc dust (0.17 g, 2.6 mmol) and dichloromethane (10 mL) were combined and the mixture was stirred until the reaction solution turned from red to green (10-30 min). The paraformaldehyde (1.20 g, 40 mmol) was added directly into the reaction flask followed by a dichloromethane solution (10 mL) of the aldehyde (2.0 mmol). At this point the solution color was dark red. The reaction mixture was stirred for 7 h and then opened to the air and transferred into a mixture of aqueous sodium tartrate (30 mL, 10% w:w) and dichloromethane (30 mL). This mixture was stirred vigorously for 30 min, filtered through a fritted funnel packed with Celite, and the solids were washed with 10 mL of dichloromethane producing a colorless organic phase and a green aqueous layer. The aqueous phase was separated and extracted with dichloromethane (2 x 50 mL). The combined organics were dried with $MgSO_4$, filtered, and concentrated to yield the crude product.

4-Phenyl-1,2-butanediol (5).[1g] 0.32 g (96%), oil (purified by flash chromatography on a silica gel column (2.5 x 12 cm) using a gradient of 30-50% (v/v) EtOAc in hexane): **IR** (film, cm^{-1}) ν 3380; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.28-7.25 (m, 2H), 7.19-7.16 (m, 3H), 3.68 (m, 1H), 3.61 (dd, J = 2.7, 11.2, 1H), 3.43 (dd, J = 7.7, 11.2, 1H), 2.91 (br s, 2H O*H*), 2.82-2.76 (m, 1H), 2.69-2.63 (m, 1H), 1.75-1.70 (m, 2H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 141.7 (C), 128.41 (CH), 128.36 (CH), 125.9 (CH), 71.5 (CH), 66.7 (CH_2), 34.6 (CH_2), 31.8 (CH_2); **TLC** (EtOAc/hexane, 50%) R_f 0.22.

(2*SR*, 3*RS*)-3-Phenyl-1,2-butanediol (8).[14] 0.15 g (93%), oil (purified by flash chromatography on a silica gel column (2.5 x 12 cm) using a gradient of 5-50% (v/v) methanol in dichloromethane): **IR** (film, cm^{-1}) ν 3382, 1603; **^{1}H NMR** (400 MHz, $CDCl_3$, 1 drop of D_2O added) δ 7.35-7.15 (m, 5H), 3.76-3.68 (m, 1.31H), 3.49 (dd, J = 7.7, 11.9, 0.31H), 3.39 (dd, J = 2.9, 11.3, 0.69H), 3.28 (dd, J = 7.7, 11.3, 0.69H), 2.83 (m, 0.31H), 2.74 (m, 0.69H), 1.33 (d, J = 7.0, 2.07H), 1.24 (d, J = 7.1, 0.93H); **^{13}C NMR** (100 MHz, $CDCl_3$) Major: δ 143.7 (C), 128.6 (CH), 128.5 (CH), 127.5 (CH), 76.6 (CH), 65.0 (CH_2), 42.8 (CH), 17.7 (CH_3); Minor: δ 143.1 (C), 127.9 (CH), 126.7 (CH), 126.5 (CH), 76.2 (CH), 64.5 (CH_2), 42.7 (CH), 17.4 (CH_3); **TLC** (methanol/dichloromethane, 5%) R_f 0.33.

(2*SR*, 3*SR*)-3-((*tert*-Butyldimethylsilyl)oxy)-3-cyclohexyl-1,2-propanediol (10).[15] 0.26 g (89%), oil (purified by flash chromatography on a silica gel column (2.5 x 12 cm) using a gradient of 10-20% (v/v) EtOAc in hexane): **IR** (film, cm^{-1}) ν 3381; **^{1}H NMR** (400 MHz, $CDCl_3$, 1 drop of D_2O added) δ 3.77-3.62 (m, 2.9H), 3.54 (dd, J = 4.1, 5.7, 0.88H) 3.45 (m, 0.11H), 3.40 (dd, J = 3.1, 3.9, 0.11H) 1.84-1.54 (m, 5H), 1.47-1.38 (m, 1H), 1.24-0.95 (m, 5H), 0.89 (s, 1H), 0.88 (s, 8H), 0.09 (s, 2.67H), 0.08 (s, 0.33H), 0.062 (s, 2.67H), 0.057 (s, 0.33H); **^{13}C NMR** (100 MHz, $CDCl_3$) Major: δ 79.2 (CH), 72.3 (CH), 63.7 (CH_2), 41.3 (CH), 29.8 (CH_2), 28.7 (CH_2), 26.4 (CH_2), 26.0 (CH_3), 18.3 (C), -4.1 (CH_3), -4.4 (CH_3); Minor: δ 75.3 (CH), 71.1 (CH), 65.2 (CH_2), 43.0 (CH), 28.4 (CH_2), 29.8 (CH_2), 26.3 (CH_2), 25.9 (CH_2), 18.3 (C), -4.0 (CH_3), -4.5 (CH_3); **MS** (FAB, 4-nitrobenzyl alcohol, m/z), 289 (MH^+); **Anal. Calcd.** for $C_{15}H_{32}O_3Si$: C, 62.45; H, 11.18; Found: C, 62.79; H, 10.98; **TLC** (EtOAc/hexane, 30%) R_f 0.36.

4-Methyl-3-[*N*-(*p*-toluenesulfonyl)amino]-1,2-pentanediol (12). 0.20 g (70%), oil (purified by flash chromatography on a silica gel column (2.5 x 12 cm) using a gradient of 20-60% (v/v) EtOAc in hexane): **IR** ($CDCl_3$, cm^{-1}) ν 3488, 3388, 3298, 1599; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.75 (d, J = 8.2, 4H), 7.30 (d, J = 8.0, 2H), 7.29 (d, J = 8.0, 2H), 5.21 (d, J = 9.0, 1H), 4.95 (d, J = 8.4, 1H), 3.96 (dd, J = 3.7, 12.1, 1H), 3.83 (m, 1H), 3.74 (dd, J = 2.7, 12.1, 1H), 3.62 (dd, J = 5.4, 11.5, 1H), 3.55 (m, 2H), 3.18 (m,

1H), 3.11 (m, 1H), 2.88 (br. s, 4H, O*H*), 2.42 (s, 6H), 1.97 (m, 1H), 1.76 (m, 1H), 0.77 (d, J = 6.8, 3H), 0.72 (d, J = 6.8, 3H), 0.66 (d, J = 6.8, 3H), 0.54 (d, J = 6.9, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 143.3 (C), 143.1 (C), 138.4 (C), 137.8 (C), 129.5 (CH), 129.4 (CH), 127.0 (CH), 126.8 (CH), 71.9 (CH), 70.9 (CH), 64.2 (CH_2), 63.4 (CH_2), 60.6 (CH), 60.1 (CH), 30.3 (CH), 28.2 (CH), 21.4 (CH_3), 20.1 (CH_3), 19.6 (CH_3), 18.9 (CH_3), 16.9 (CH_3); **MS** (FAB, m/z) 288 (MH^+); **Anal. Calcd.** for $C_{13}H_{21}NO_4S$: C, 54.33; H, 7.37; Found: C, 54.69; H, 7.08; **TLC** (EtOAc/hexane, 50%) R_f 0.10.

1,2:3,4-Di-*O*-isopropylidene-α-D-*glycero*-D-*galacto*-heptopyranose (14).[16] 0.49 g (84%), oil (purified by flash chromatography on a silica gel column (2.5 x 12 cm) using a gradient of 20-50% (v/v) EtOAc in hexane): **IR** (film, cm^{-1}) ν 3450; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.52 (d, J = 5.0, 0.35H), 5.44 (d, J = 5.0, 0.65H), 4.57 (dd, J = 2.4, 8.0, 0.65H), 4.55 (dd, J = 2.4, 9.4, 0.35H), 4.40 (dd, J = 1.8, 8.0, 0.65H), 4.28-4.24 (m, 1.35H), 3.89-3.62 (m, 4H), 3.12 (br. s, 2H, O*H*), 1.46 (s, 3H), 1.39 (s, 3H), 1.30 (s, 1.95H), 1.27 (s, 1.05H), 1.263 (s, 1.05H), 1.255 (s, 1.95H); **^{13}C NMR** (100 MHz, $CDCl_3$) Major: δ 109.2, 108.7, 96.2, 70.6, 70.51, 70.48, 69.8, 67.2, 63.7, 25.82, 24.9, 24.3; Minor δ 109.4, 108.8, 96.3, 71.4, 71.3, 70.7, 70.4, 67.7, 62.3, 25.82, 25.75, 24.9, 24.1; **TLC** (EtOAc/hexane, 50%) R_f 0.23.

3-*O*-(*tert*-Butyldimethylsilyl)-1,2-*O*-isopropylidene-α-D-glucofuranose (16).[17] 0.33 g (99%), oil (purified by flash chromatography on a silica gel column (2.5 x 12 cm) using a gradient of 10-30% (v/v) EtOAc in hexane): **Major**: **IR** (film, cm^{-1}) ν 3462; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.86 (d, J = 3.6, 1H), 4.34 (d, J = 3.6, 1H), 4.29 (d, J = 2.7, 1H), 4.04 (dd, J = 2.7, 8.0, 1H), 3.90 (m, 1H), 3.81 (dd, J = 3.5, 11.4, 1H), 3.73 (dd, J = 5.4, 11.4, 1H), 2.41 (br. s, 1H, O*H*), 2.04 (br. s, 1H, O*H*), 1.46 (s, 3H), 1.29 (s, 3H), 0.88 (s, 9H), 0.14 (s, 3H), 0.12 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 111.8, 105.0, 85.3, 80.9, 75.8, 68.8, 64.6, 26.8, 26.3, 25.7, 18.0, -4.8, -5.1; **Minor**: **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.95 (d, J = 3.7, 1H), 4.35 (d, J = 3.7, 1H), 4.25 (d, J = 3.2, 1H), 4.15 (dd, J = 3.2, 4.6, 1H), 4.00 (dd, J = 4.8, 10.0, 1H), 3.69 (m, 2H), 1.46 (s, 3H), 1.29 (s, 3H), 0.88 (s, 9H), 0.15 (s, 3H), 0.13 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 111.9, 104.6, 85.7, 79.9, 77.2, 70.5, 63.5, 26.8, 25.7, 25.6, 17.8, -4.5, -5.2; **MS** (FAB, m/z) 335 (MH^+); **Anal. Calcd.** for $C_{15}H_{30}O_6Si$: C, 53.86; H, 9.04; Found: C, 53.68; H, 9.28; **TLC** (EtOAc/hexane, 50%) R_f 0.41.

2-(3,4-Methylenedioxyphenyl)-1,2-ethanediol (18). $VCl_3(THF)_3$[13] (1.64 g, 4.4 mmol), zinc dust (0.17 g, 2.6 mmol) and dichloromethane (15 mL) were combined and the mixture was stirred until the reaction solution turned from red to green (10-30 min). The paraformaldehyde (1.20 g, 40 mmol) was added directly into the reaction flask and the mixture was stirred for 30 min. A dichloromethane solution (5 mL) of piperonal was added over 5 h via syringe pump. After stirring another 2 h, the reaction mixture was worked up as described for the standard coupling reaction. The product was purified by flash chromatography on a silica gel column (2.5 x 12 cm) using a gradient of 10-30% (v/v) EtOAc in hexane to give 0.32 g (88%) of a colorless oil: **IR** (film, cm^{-1}) ν 3405; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.86 (s, 1H), 6.82-6.77 (m, 2H), 5.95 (s, 2H), 4.72 (dd, J = 3.5, 8.2, 1H), 3.69 (dd, J = 3.5, 11.2, 1H), 3.61 (dd, J = 8.2, 11.2, 1H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 147.6 (C), 147.0 (C), 134.4 (C), 119.4 (CH), 108.1 (CH), 106.6 (CH), 100.9 (CH_2), 74.4 (CH), 67.8 (CH_2); **TLC** (EtOAc/hexane, 50%) R_f 0.22.

3,3-Dimethyl-4-phenyl-1,2-butanediol (20). This product was prepared via the procedure described for hydroxymethylation of ketones (see below); 0.17 g (89%), oil (purified by flash chromatography on a silica gel column (2.5 x 12 cm) using a gradient of 10-30% (v/v) EtOAc in hexane): **IR** ($CDCl_3$, cm^{-1}) ν

3414, 1603; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.28-7.24 (m, 2H), 7.22-7.16 (m, 3H), 3.76 (dd, J = 2.6, 10.9, 1H), 3.57 (dd, J = 9.5, 10.9, 1H), 3.43 (dd, J = 2.6, 9.5, 1H), 3.05 (br. s, 2H, O*H*), 2.75 (d, J = 13.0, 1H), 2.49 (d, J = 13.0, 1H), 0.90 (s, 3H), 0.83 (s, 3H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 138.3 (C), 130.7 (CH), 127.8 (CH), 126.0 (CH), 77.7 (CH), 63.0 (CH_2), 45/0 (CH_2), 37.3 (C), 23.2 (CH_3), 22.5 (CH_3); **MS** (FAB, m/z) 195 (MH^+); **Anal. Calcd.** for $C_{12}H_{18}O_2$: C, 74.19; H, 9.34; Found: C, 74.18; H, 9.37; **TLC** (EtOAc/hexane, 30%) R_f 0.19.

General procedure for the hydroxymethylation of ketones with paraformaldehyde. $VCl_3(THF)_3$[13] (1.64 g, 4.4 mmol), zinc dust (0.65 g, 10 mmol) and dichloromethane (5 mL) were combined and the mixture was stirred until the reaction solution turned from red to green (ca. 10 min). The paraformaldehyde (1.20 g, 40 mmol) was added directly into the reaction flask followed by a dichloromethane solution (5 mL) of the ketone (2.0 mmol). The reaction mixture was stirred for 12 h and then opened to the air and transferred into a mixture of aqueous sodium tartrate (30 mL, 10% w:w) and dichloromethane (30 mL). This mixture was stirred vigorously for 30 min, filtered through a fritted funnel packed with Celite, and the solids were washed with 10 mL of dichloromethane producing a colorless organic phase and a green aqueous layer. The aqueous phase was separated and extracted with dichloromethane (2 x 50 mL). The combined organics were dried with $MgSO_4$, filtered, and concentrated to yield the crude product.

2-Methyl-1,2-octanediol (22).[1g] 0.29 g (91%), oil (purified by flash chromatography on a silica gel column (2.5 x 12 cm) using a gradient of 10-30% (v/v) EtOAc in hexane): **IR** (film, cm^{-1}) ν 3382; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.43 (d, J = 10.9, 1H), 3.36 (d, J = 10.9, 1H), 2.48 (br. s, 1H, O*H*), 2.20 (br. s, 1H, O*H*), 1.44 (m, 2H), 1.29-1.26 (m, 8H), 1.12 (s, 3H), 0.85 (t, J = 6.7, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 73.0, 69.6, 38.6, 31.7, 29.8, 23.7, 23.6, 22.5, 14.0; **TLC** (EtOAc/hexane, 50%) R_f 0.33.

2-Phenyl-1,2-propanediol (24).[1h] 0.26 g (86%), oil (purified by flash chromatography on a silica gel column (2.5 x 12 cm) using a gradient of 20-40% (v/v) EtOAc in hexane): **IR** (film, cm^{-1}) ν 3397; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43-7.41 (m, 2H), 7.37-7.33 (m, 2H), 7.29-7.25 (m, 1H), 3.68 (d, J = 11.3, 1H), 3.55 (d, J = 11.3, 1H), 3.50 (br. s, 2H, O*H*), 1.48 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 144.9 (C), 128.2 (CH), 126.9 (CH), 125.0 (CH), 74.8 (C), 70.6 (CH_2), 25.8 (CH_3); **TLC** (EtOAc/hexane, 50%) R_f 0.32.

2,6-Dimethyl-5-heptene-1,2-diol (26). 0.27 g (84%), oil (purified by flash chromatography on a silica gel column (2.5 x 12 cm) using a gradient of 30-50% (v/v) EtOAc in hexane): **IR** (film, cm^{-1}) ν 3383; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.11 (m, 1H), 3.46 (d, J = 10.7, 1H), 3.40 (d, J = 10.7, 1H), 2.24 (br. s, 1H, O*H*), 2.10 (br. s, 1H, O*H*), 2.05 (m, 2H), 1.68 (s, 3H), 1.62 (s, 3H), 1.55-1.49 (m, 2H), 1.17 (s, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 132.0 (C), 124.2 (CH), 73.0 (C), 69.8 (CH_2), 38.4 (CH_2), 25.7 (CH_3), 23.2 (CH_3), 22.4 (CH_2), 17.6 (CH_3); **MS** (FAB, 4-nitrobenzyl alcohol with LiCl[18]), m/z) 165 (MLi^+); **High Res. FAB MS.** Calcd. for $C_9H_{18}LiO_2$ (MLi^+): 165.1467. Found 165.1465; **TLC** (EtOAc/hexane, 50%) R_f 0.25

2-Benzyl-3-phenyl-1,2-propanediol (28).[1g] 0.23 g (96%), oil (purified by flash chromatography on a silica gel column (2.5 x 12 cm) using a gradient of 10-25% (v/v) EtOAc in hexane): **IR** (film, cm^{-1}) ν 3423, 1602; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.33-7.30 (m, 4H), 7.26-7.25 (m, 6H), 3.37 (s, 2H), 2.86 (m, 4H), 1.97 (s, 1H, O*H*), 1.82 (br. s, 1H, O*H*); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 136.7 (C), 130.5 (CH), 128.3 (CH), 126.6 (CH), 74.3 (C), 66.2 (CH_2), 43.2 (CH_2); **TLC** (EtOAc/hexane, 30%) R_f 0.33.

1-(Hydroxymethyl)-1-clododecanol (30).[1h] 0.20 g (93%), white solid (recrystallized from dichloromethane and hexane): **mp** 95-96 °C; **IR** ($CDCl_3$, cm^{-1}) ν 3417; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.42 (s, 2H), 1.84 (br. s, 2H, O*H*), 1.58-1.51 (m, 2H), 1.47-1.36 (m, 20H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 75.9 (C), 68.6 (CH_2), 30.7 (CH_2), 26.3 (CH_2), 26.0 (CH_2), 22.4 (CH_2), 21.9 (CH_2), 19.1 (CH_2).

1-(Hydroxymethyl)-1-cyclohexanol (32).[1d] 0.21 g (81%), white solid (recrystallized from dichloromethane and hexane): **mp** 73-74 °C; **IR** ($CDCl_3$, cm^{-1}) ν 3580, 3415; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 3.62 (br. s, 1H, O*H*), 3.39 (s, 2H), 3.07 (br. s, 1H, O*H*), 1.60-1.25 (m, 10H); **^{13}C NMR** (125 MHz, $CDCl_3$) δ 71.9 (C), 69.8 (CH_2), 33.9 (CH_2), 25.8 (CH_2), 21.8 (CH_2).

***cis*-1-(Hydroxymethyl)-2-methyl-1-cyclohexanol (34).**[1c] 0.24 g (83%), oil (purified by flash chromatography on a silica gel column (2.5 x 12 cm) using a gradient of 30-40% (v/v) EtOAc in hexane): **IR** (film, cm^{-1}) ν 3407; **^{1}H NMR** (400 MHz, $CDCl_3$) δ 3.57 (d, J = 11.0, 0.89H), 3.47 (m, 0.22H), 3.31 (d, J = 11.0, 0.89H), 2.89 (br. s, 2H, O*H*), 1.77-1.12 (m, 9H), 0.87 (d, J = 7.0, 0.33H), 0.84 (d, J = 6.7, 2.67H); **^{13}C NMR** (100 MHz, $CDCl_3$) Major: δ 73.2 (C), 68.8 (CH_2), 36.2 (CH), 33.7 (CH_2), 30.4 (CH_2), 25.0 (CH_2), 21.4 (CH_2), 15.0 (CH_3), Minor: δ 74.4 (C), 64.9 (CH_2), 38.1 (CH), 32.4 (CH_2), 30.4 (CH_2), 23.3 (CH_2), 22.5 (CH_2), 15.1 (CH_3); **TLC** (EtOAc/hexane, 50%) R_f 0.25.

***cis*-4-*tert*-Butyl-1-(hydroxymethyl)-1-cyclohexanol (36).**[1c] 0.17 g (89%), oil (purified by flash chromatography on a silica gel column (2.5 x 12 cm) using a gradient of 30-40% (v/v) EtOAc in hexane): **IR** ($CDCl_3$, cm^{-1}) ν 3582, 3414; **^{1}H NMR** (500 MHz, $CDCl_3$, 1 drop of D_2O added) δ 3.56 (s, 0.34H), 3.38 (s, 1.66H), 1.93 (m, 0.34H), 1.76-1.71 (m, 2H), 1.63 (m, 1.66H), 1.36-1.20 (m, 4H), 1.03-0.89 (m, 1H), 0.86 (s, 7.5H), 0.84 (s, 1.5H); **^{13}C NMR** (125 MHz, $CDCl_3$) Major: δ 71.7 (CH_2), 71.2 (C), 48.1 (CH), 34.0 (CH_2), 32.4 (C), 27.5 (CH_3), 21.9 (CH_2); Minor: δ 72.6 (C), 65.6 (CH_2), 47.4 (CH), 35.3 (CH_2), 32.2 (C), 27.5 (CH_3), 24.3 (CH_2); **TLC** (EtOAc/hexane, 50%) R_f 0.27.

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