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Synthesis of chiral 1,2,3-triols via organocatalyzed α-hydroxylation of protected β-hydroxyaldehydes

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ABSTRACT

Protected 1,2,3-triols were prepared by organocatalytic α-hydroxylation of β-hydroxyaldehydes followed by in situ reduction. All diastereoisomers were obtained with correct yields and good to excellent de. The absolute configurations of the new asymmetric centers were confirmed by derivatization into the corresponding epoxide.

1,2,3-Triols are important building blocks in organic synthesis, as proved by the occurrence of this pattern in numerous bioactive molecules. A relevant approach to such derivatives is the creation of one of the C–O bonds to obtain a configurationally controlled carbon atom, independently from the other chiral centers of the reactant. In this context, the organocatalyzed α-hydroxylation of carbonyls followed by an in situ reduction is a promising possibility, already well described as a good solution to the synthesis of 1,2-diols.[1]

Sometime after the description of the use of nitrosobenzene in the presence of silyl or metal enolates leading, respectively, to the formation of the C–O link (aminoxylation reaction) or the C–N link (oxyamination reaction) depending on the reaction's conditions,[2] Hayashi,[3] Mac Millan,[4] and Zhong[5] independently published the reaction of α-aminoxylation of aldehydes catalyzed by proline. The method is now well-used and can be noticed in many total syntheses.[6] Other oxygen donors are also efficient for the organocatalyzed asymmetric α-oxidation of aldehydes, namely *N*-sulfonyloxaziridine,[7] TEMPO,[8] benzoyl peroxide,[9] *o*-quinone,[10] and molecular oxygen.[11] Nevertheless, the use of nitrosobenzene remains the most studied case,[1a] where the effect of the structure of the catalyst or addition of an acid in the reaction medium has been shown to modify significantly the result of the reaction (aminoxylation or oxyamination).[12] The greater selectivity observed for the oxygen atom has been explained by the stronger basicity of the nitrogen atom. Indeed, N-protonation of the nitrosobenzene in the transition state by proline-type catalysts (meaning a catalyst bearing a Brønsted acid functionality) allows oxygen to become electrophilic, and lead to the α-oxygenated products. For other catalysts which give preferentially α-aminated products, additives are necessary to reverse the selectivity.[13] The catalytic cycle has been well studied, and would be in favor of an oxazolidinone species, precursor of an enamine-key intermediate which would react with nitrosobenzene.[1a] Using proline as the catalyst, McQuade[14] demonstrated in 2009 that the introduction of the additive 1-(2-(dimethylamino)ethyl)-3-phenylurea **1** in nonpolar solvents induced drastic increase of the kinetics without modification of the enantiomeric excesses (ee). This effect was explained by the existence of hydrogen bonds between the urea and the oxazolidinone intermediate, promoting the enamine formation with proline (rate limiting step).

Exploring the scope of organocatalytic α-heterofunctionalization of carbonyl compounds,[15] the formation of chiral 2-hydrazino-1,3-diols in good yields and diastereoisomeric excesses (de) was described recently by our team.[15c] We now extended the concept to the preparation of 1,2,3-triols via an organocatalyzed hydroxylation reaction of chiral β-hydroxyaldehydes. Indeed, the reaction of nitrosobenzene with such aldehydes in the presence of proline and **1** should lead to the corresponding 1,2,3-triols after in situ reduction using sodium borohydride in ethanol.

First, racemic 3-*tert*-butyldimethylsilyloxybutanal **2** was selected as model to optimize the reaction conditions (Scheme 1). The reaction was run at 0 °C, in the presence of DL-proline and 5% of urea **1** until coloration changes from blue to yellow. Then, the reaction mixture was transferred to a suspension of sodium borohydride (4 equiv) in ethanol and stirred 30 min at 0 °C. After treatment,

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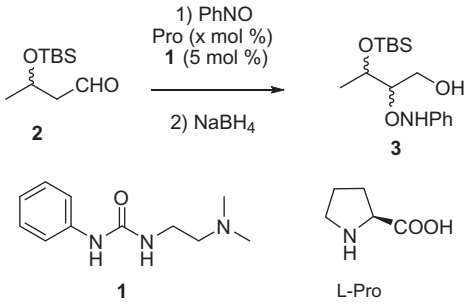


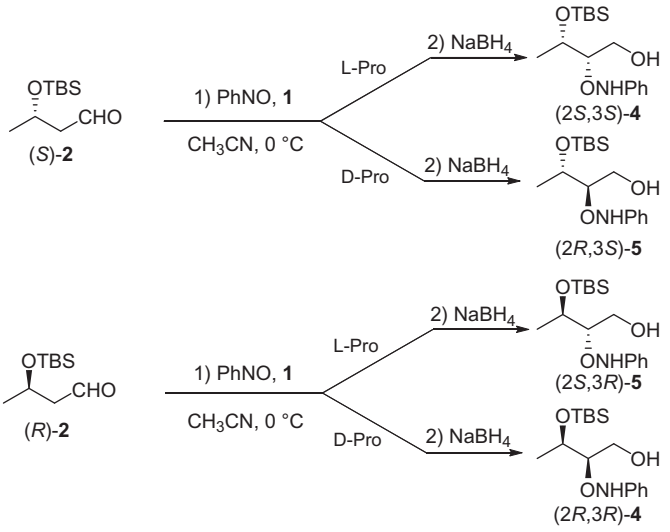
Scheme 1. Organocatalyzed aminoxylation of **2**.

purification by column chromatography on silica gel allowed to obtain **3** as a mixture of diastereoisomers.[16]

The results are summarized in Table 1. Applying McQuade's conditions,[14] that is, 5 mol % of **1** and proline in ethyl acetate at 0 °C with a 3/1 ratio of **2**/PhNO for 3 h gave the desired triol in a poor yield (10% related to nitrosobenzene, entry 1). Changing the solvent to acetonitrile (entry 2) increased the yield to 56% in the same time. For comparison, the same reaction in the absence of urea was not finished after 24 h, proving the importance of this catalyst. Then, increasing the amount of DL-proline to 10 and 20 mol% improved the yield, respectively, to 54% and 67% (entries 3 and 4). With this catalyst loading, acetonitrile remained the best solvent among all other tested (entries 5 and 6). Finally, lowering the quantity of **2** (entries 7–9) and/or increasing the amount of PhNO (entries 8 and 9) to modify the **2**/PhNO ratio gave 29% as best yield based on the aldehyde. From all theses results, it was decided to use the conditions described in entry 4 for the next experiments.

The two enantiomers of the hydroxyaldehyde, namely (*S*)-**2** and (*R*)-**2** were then aminoxylated separately under these conditions (ratio **2**/PhNO 3/1; 20 mol % Pro; 5 mol % **1**; MeCN; 3 h at rt then reduction) (Scheme 2, Table 2). Depending on the configuration of the proline used as the catalyst, we obtained the expected 3-*tert*-butyldimethylsilyloxy-2-(phenylaminoxy) butanols as *syn*- or *anti*-stereomers, respectively **4** and **5**.[16] The diastereoisomeric ratio was measured by UPLC (compared to the stoichiometric mixture of **4**/**5**). From (*S*)-**2**, the use of L-proline as the catalyst led to the aminoxylated *syn* product (2*S*,3*S*)-**4** with the excellent diastereoisomeric ratio of 97/3 and good yields (76%) (entry 1). The use of the D-catalyst gave access to the *anti* (2*R*,3*S*)-**5** with a similar ratio (4/96) and yield (entry 2). Correspondingly, (*R*)-**2** is the precursor of the two stereoisomers (2*S*,3*R*)-**5** or (2*R*,3*R*)-**4** with identical stereochemical results (dr 2/98 and 97/3; entries 3 and 4). Thus, the possibility to obtain each diastereoisomer and enantiomer by this method has been demonstrated.

The absolute configuration of the newly formed stereocenter was proved by derivatization of the triols (2*S*,3*S*)-**4** and (2*R*,3*S*)-**5**



Scheme 2. Asymmetric aminoxylation of (*S*)- and (*R*)-**2**.

Table 2
Hydroxylation of (*S*)- and (*R*)-**2**

Entry	Substrate	Catalyst	Product	Yield (%)	Syn/anti[a]
1	(*S*)-**2**	L-Pro	(2*S*,3*S*)-**4**	76	97/3
2	(*S*)-**2**	D-Pro	(2*R*,3*S*)-**5**	75	4/96
3	(*R*)-**2**	L-Pro	(2*S*,3*R*)-**5**	70	2/98
4	(*R*)-**2**	D-Pro	(2*R*,3*R*)-**4**	62	97/3

[a] Measured by UPLC.

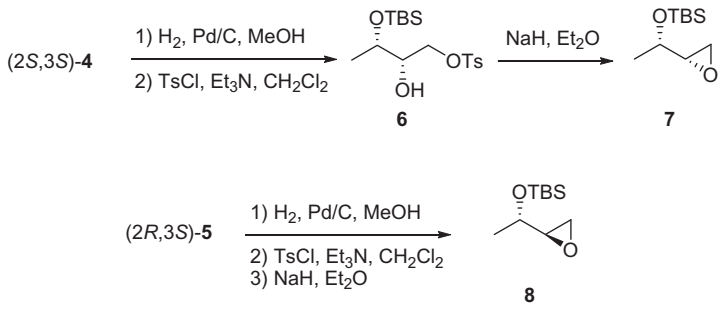
into the corresponding epoxides (Scheme 3). A three-step sequence starting with the hydrogenolysis of the N–O bond followed by a selective sulfonylation of the primary alcohol and a cyclization of **6** under basic treatment gave the epoxide **7** from **4**,[17] with concordant analytical data of the literature.[18] The unknown **8** was obtained with the same sequence from (2*R*,3*S*)-**5**.[19]

We extended the method using the long-chained **9** and the protected diol **10** as substrates (Table 3, Scheme 4). In all cases, the same conditions than previously described were used. We first applied racemic proline, and the obtained equimolar mixture of epimers at position 2 was used for NMR data and UPLC references. The hexadecanal **9**, prepared in five steps from palmitic acid, was reacted in the presence of either L- or D-proline. In both cases, protected triols **11** and **12**, respectively, were obtained in good yields and excellent diastereoisomeric ratios (entries 1 and 2). Then, the (*S*)-3,4-*O*-isopropylidenebutanal **10** in the presence of two antipods of the catalyst led, respectively, to the *anti* **13** (entry

Table 1
Optimization of the reaction of hydroxylation of **2**

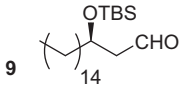
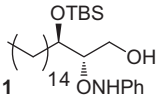
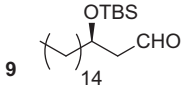
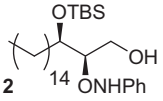
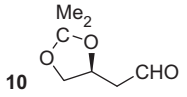
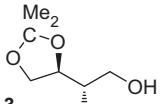
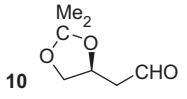
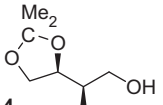
Entry	Solvent	Pro (mol %)	**2** (equiv)	PhNO (equiv)	Time (h)	Yield[a] (%)
1	EtOAc	5	3	1	3	10
2	MeCN	5	3	1	3	56
3	MeCN	10	3	1	4	54
4	MeCN	20	3	1	3	67
5	DMSO	20	3	1	1	41
6	DCM	20	3	1	70	8
7	MeCN	20	1.5	1	3	37
8	MeCN	20	1	1.2	3	17[b]
9	MeCN	20	1	1.5	15	29[b]

[a] Isolated yield based on PhNO.
[b] Isolated yield based on **2**.

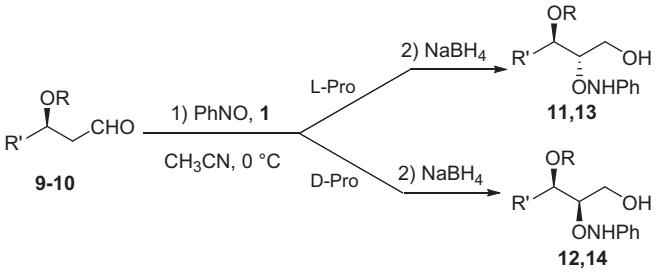


Scheme 3. Derivatization into epoxides **7** and **8**.

Table 3
Hydroxylation of compounds **9** and **10**

Entry	Substrate	Cat*	Product	Yield (%)	Syn/anti[a]
1	 **9**	L-Pro	 **11**	68	1/99
2	 **9**	D-Pro	 **12**	83	99/1
3	 **10**	L-Pro	 **13**	30	1/99
4	 **10**	D-Pro	 **14**	84	90/10

[a] Measured by UPLC.



Scheme 4. General asymmetric aminoxylation.

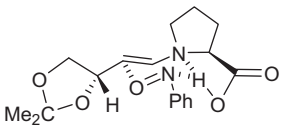


Figure 1. Proposed transition state with L-proline and **10**.

3) or *syn* **14** (entry 4). The low yield for **13** could be explained by the unstability of the product on silica gel during the column chromatography. In a similar way than observed during the α-hydrazination of this substrate,[15c] a significant difference of de between **13** (98%) and **14** (80%) was observed.

A model for the transition state for the α-aminoxylation reaction of β-hydroxyaldehyde could be proposed. The use of proline as the catalyst would favor the approach of the nitrosobenzene on the same face than the carboxylic acid function. In the case of L-proline and the substrate **10**, the transition state favored could explain excellent de and match effect (Fig. 1). Mismatch effect is observed with the D-proline. However the mismatch effect in the hydroxylation procedure is much lower compared to the amination reaction where D-proline gave no selectivity, because the steric hindrance is probably lower with nitrosobenzene than with azodicarboxylates.

In conclusion, we prepared the four protected butan-1,2,3-triols in good yields and de up to 96% by the use of organocatalysis in the presence of proline and urea. The process is applicable to more functionalized structures, and the excesses observed made of this method a very respectable proposal for the obtention of chiral triols.

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References and notes

1. Reviews: (a) Vilaivan, T.; Bhanthumnavin, W. *Molecules* **2010**, *15*, 917–958. and references therein; (b) de Figueiredo, R. M.; Christmann, M. *Eur J. Org. Chem.* **2007**, 2575–2600.
2. Momiyama, N.; Yamamoto, H. *J. Am. Chem. Soc.* **2003**, *125*, 6038–6039.
3. Hayashi, Y.; Yamaguchi, J.; Hibino, K.; Shoji, M. *Tetrahedron Lett.* **2003**, *44*, 8293–8296.

4. Brown, S. P.; Brochu, M. P.; Sinz, C. J.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 10808–10809.
5. Zhong, G. *Angew. Chem.* **2003**, *115*, 4379–4382.
6. For recent examples, see: (a) Yadav, J. S.; Subba Reddy, U. V.; Subba Reddy, B. V. *Tetrahedron Lett.* **2009**, *50*, 5984–5986; (b) Sawant, R. T.; Waghmode, S. B. *Tetrahedron* **2009**, *65*, 1599–1602; (c) Chandrasekhar, S.; Mahipal, B.; Kavitha, M. *J. Org. Chem.* **2009**, *74*, 9531–9534; (d) Jha, V.; Kondekar, N. B.; Kumar, P. *Org. Lett.* **2010**, *12*, 2762–2765; (e) Subba Reddy, B. V.; Phaneendra Reddy, B.; Pandurangam, T.; Yadav, J. S. *Tetrahedron Lett.* **2011**, *52*, 2306–2308.
7. Tong, S.-T.; Brimble, M. A.; Barker, D. *Tetrahedron* **2009**, *65*, 4801–4807.
8. Sibi, M. P.; Hasegawa, M. *J. Am. Chem. Soc.* **2007**, *129*, 4124–4125.
9. (a) Vaismaa, M. J. P.; Yau, S. C.; Tomkinson, N. C. O. *Tetrahedron Lett.* **2009**, *50*, 3625–3627; (b) Gotoh, H.; Hayashi, Y. *Chem. Commun.* **2009**, 3083–3085; (c) Kano, T.; Mii, H.; Maruoka, K. *J. Am. Chem. Soc.* **2009**, *131*, 3450–3451.
10. Hernandez-Juan, F. A.; Cockfield, D. M.; Dixon, D. J. *Tetrahedron Lett.* **2007**, *48*, 1605–1608.
11. (a) Córdova, A.; Sundén, H.; Engqvist, M.; Ibrahem, I.; Casas, J. *J. Am. Chem. Soc.* **2004**, *126*, 8914–8915; (b) Ibrahem, I.; Zhao, G.-L.; Sundén, H.; Córdova, A. *Tetrahedron Lett.* **2006**, *47*, 4659–4663.
12. Mielgo, A.; Velilla, I.; Gómez-Bengoa, E.; Palomo, C. *Chem. Eur. J.* **2010**, *16*, 7496–7502. and references therein.
13. Lu, M.; Zhu, D.; Lu, Y.; Zeng, X.; Tan, B.; Xu, Z.; Zhong, G. *J. Am. Chem. Soc.* **2009**, *131*, 4562–4563.
14. Poe, S. L.; Bogdan, A. R.; Mason, B. P.; Steinbacher, J. L.; Opalka, S. M.; McQuade, D. T. *J. Org. Chem.* **2009**, *74*, 1574–1580.
15. (a) Thomassigny, C.; Prim, D.; Greck, C. *Tetrahedron Lett.* **2006**, *47*, 1117–1119; (b) Ait-Youcef, R.; Kalch, D.; Moreau, X.; Thomassigny, C.; Greck, C. *Lett. Org. Chem.* **2009**, *6*, 377–380; (c) Ait-Youcef, R.; Sbargoud, K.; Moreau, X.; Greck, C. *Synlett* **2009**, 3007–3010; (d) Kalch, D.; Ait-Youcef, R.; Moreau, X.; Thomassigny, C.; Greck, C. *Tetrahedron: Asymmetry* **2010**, *21*, 2302–2306.
16. Typical procedure: To 25 mg of PhNO (0.2 mmol; 1 equiv) in MeCN (460 μL) was added L-proline (5 mg, 0.05 mmol, 0.2 equiv) and urea **1** (2 mg, 0.01 mmol, 0.05 equiv) at 0 °C. After stirring during 15 min, (*R*)-**2** (139 mg, 0.7 mmol, 3 equiv) was added and the overall was stirred for 2 h. Then the reaction mixture was poured on $NaBH_4$ (35 mg, 0.9 mmol, 4 equiv) in EtOH (1.5 mL) and stirred 30 min at 0 °C. The reaction mixture was neutralized with saturated aqueous $NaHCO_3$ (2 mL), and extracted with EtOAc (3 × 2 mL). The organic layers were dried, concentrated for give an yellow oil which was purified by silica gel chromatography (EtOAc/cyclohexane: 1:18 then 1:9) for give (2*S*,3*R*)-**5** (50 mg, 70%). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.29–7.23 (m, 2H), 7.02–6.94 (m, 3H), 4.19 (m, 1H), 3.95 (d, *J* = 6.0 Hz, 2H), 3.72 (m, *J* = 6.0 Hz, 1H), 1.28 (d, *J* = 6.5 Hz, 3H), 0.91 (s, 9H), 0.11 (d, *J* = 2.0 Hz, 3H), 0.10 (d, *J* = 2.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 148.6, 129.2, 122.4, 114.8, 86.7, 69.4, 61.8, 25.9, 20.8, 18.1, −4.4, −4.7; SM-HR-ES(+) *m*/*z* $C_{16}H_{30}O_3NSi$ M+H$^+$; calcd 312.1995, found 312.2003.
Compound **4**: ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.30–7.25 (m, 2H), 7.01–6.98 (m, 3H), 4.19 (m, 1H), 3.89 (d, 2H), 3.72 (m, 1H), 1.24 (d, *J* = 6.4 Hz, 3H), 0.89 (s, 9H), 0.10 (d, *J* = 2.6 Hz, 3H), 0.09 (d, *J* = 2.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 148.5, 129.2, 122.6, 115.0, 86.2, 68.5, 62.3, 26.0, 19.1, 18.2, −4.5, −4.7; SM-HR-ES(+) *m*/*z* $C_{16}H_{30}O_3NSi$ M+H$^+$; calcd 312.1995, found 312.1998.
ACQUITY UPLC BEH C_{18} 1.7 μm 2.1 * 50 mm; 0.45 mL/min; *T* = 40 °C; gradient MeCN + 0.1% solution of HCOOH: rt (**4**) = 4.30 min; rt (**5**) = 4.35 min.
17. Compound **7**: A mixture of (2*S*,3*S*)-3-(*tert*-butyldimethylsilyloxy)-2-(phenylaminooxy)butan-1-ol **4** (125 mg, 0.4 mmol) and 10% Pd/C (25 mg, 20% w/w) in MeOH (4 mL) was hydrogenated for 16 h at atmospheric pressure and the solvent was removed under reduced pressure. Ethyl acetate (10 mL) was added to the residue, the mixture was filtered on celite and the filtrate was evaporated under reduced pressure. Purification of the residue by column chromatography on silica gel using pentane/EtOAc: 5:1 to pentane/EtOAc: 2:1 provided (2*S*,3*S*)-3-(*tert*-butyldimethylsilyloxy)butan-1,2-diol as a colorless oil (81%, 72 mg) which was added to a solution of triethylamine (67 μL, 0.5 mmol) and tosyl chloride (67 mg, 0.4 mmol) in dichloromethane (3 mL). The reaction mixture was stirred for 16 h at room temperature and the solvent was removed under reduced pressure. Purification of the residue by column chromatography on silica gel using pentane/EtOAc: 10:1 to pentane/EtOAc: 5:1 provided compound **6** as a colorless oil (68 mg; 57%). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 7.79 (d, *J* = 8.1 Hz, 2H), 7.34 (d, *J* = 8.1 Hz, 2H), 3.98–3.86 (m, 3H), 3.58–3.53 (m, 1H), 2.44 (s, 3H), 2.35 (bs, 1H), 1.15 (d, *J* = 6.4 Hz, 3H), 0.83 (s, 9H), 0.06 (s, 3H), 0.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 144.9, 132.6, 129.8 (2C), 128.0 (2C), 72.6, 70.1, 67.3, 25.7 (3C), 21.1, 19.8, 17.8, −4.3, −5.1; HRMS (ESI) $C_{17}H_{30}O_5SSi$ M+Na$^+$; calcd 397.1481, found 397.1486.
Sodium hydride (60% in oil, 10.9 mg, 0.3 mmol) under argon was washed twice with pentane (2 mL). Then dry Et_2O (1 mL) and compound **6** (68 mg, 0.18 mmol) in dry Et_2O (1 mL) were added. The mixture was stirred for 16 h at room temperature and filtered on celite. The filtrate was evaporated under reduced pressure to afford compound **7** as a colorless oil (24.2 mg; 66%). $[\alpha]_D^{25}$ +4.3 (*c* 0.30, $CHCl_3$) (lit.[18] $[\alpha]_D^{25}$ +1.8 (*c* 1.1, $CHCl_3$)); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.56 (quin, *J* = 6.3 Hz, 1H), 2.96–2.92 (m, 1H), 2.77 (t, *J* = 4.6 Hz, 1H), 2.59–2.57 (m, 1H), 1.22 (d, *J* = 6.5 Hz, 3H), 0.91 (s, 9H), 0.11 (s, 3H), 0.08 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 70.1, 56.6, 44.5, 25.8 (3C), 20.2, 18.2, −4.7, −4.9.
18. Hatakeyama, S.; Sakurai, K.; Takano, S. *Heterocycles* **1986**, *24*, 633–636.
19. Compound **8**. The same sequence than for the obtention of **7** from **4** was applied to (2*R*,3*S*)-3-(*tert*-butyldimethylsilyloxy)-2-(phenylaminooxy)butan-1-ol **5**, and afforded the compound **8** as a colorless oil (16.6 mg; 29% over three steps). $[\alpha]_D^{25}$ +52.3 (*c* 0.33, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm): 3.76–3.68 (m, 1H), 2.87–2.82 (m, 1H), 2.72–2.63 (m, 2H), 1.23 (d, *J* = 6.2 Hz, 3H), 0.87 (s, 9H), 0.04 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm): 67.6, 55.6, 44.8, 25.7 (3C), 20.8, 18.1, −4.7, −4.9; SM-HR-ES(+) *m*/*z* $C_{10}H_{22}O_2Si$ M+H$^+$; calcd 203.1467, found 203.1467.