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Tetrahedron
Tetrahedron 63 (2007) 2235–2243

A convenient synthesis of 2-*C*-methyl-D-erythritol 4-phosphate and isotopomers of its precursor

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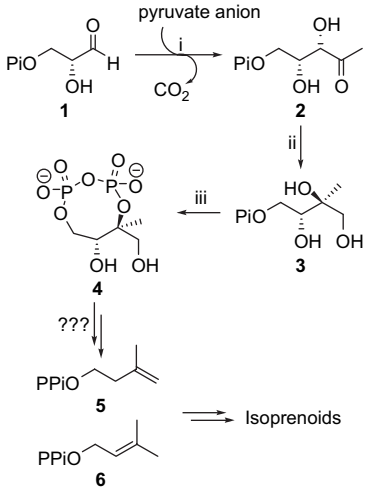
Received 27 November 2006; revised 21 December 2006; accepted 21 December 2006
Available online 28 December 2006

Abstract—A new synthetic approach toward 2-*C*-methyl-D-erythritol 4-phosphate (MEP), a key intermediate in the mevalonate-independent biosynthetic pathway for isoprenoids, and deuterated analogues of its precursor, 2-*C*-methyl-D-erythritol acetonide, is described. This procedure uses 2-*C*-methyl-D-erythrose acetonide as starting material and delivers, through a mono-protection strategy, the target compounds in a short way and in high yield.

1. Introduction

Isopentenyl diphosphate (IPP, **5**, Scheme 1) and dimethylallyl diphosphate (DMAPP, **6**) are the two-isoprenoid universal precursors.[1] It was considered, until lately, that these compounds are biosynthetically prepared in the cells of all organisms via the mevalonate (MVA) pathway. However, recent labeling experiments in the laboratories of Rohmer et al.[2] and Arigoni et al.[3] independently revealed an alternative biosynthetic route to both of them. It is of unique interest that this newly discovered route, MIP,[4] is only present in bacteria,[5] plant chloroplast,[6] and algae metabolism.[7] Additionally, MEP (**3**), a key intermediate of MIP, was identified as a critical metabolite in the development of *Plasmodium falciparum*, the parasite responsible for malaria.[8] Consequently, a thorough investigation and exploitation of MIP could enable the development of new classes of herbicides and specific drugs against pathogenic microorganisms. Indeed, during the last decade,[9] an extensive research activity has been realized regarding this field. Nevertheless, the complete elucidation of MIP has not yet been achieved. Whereas, the initial steps of it are well documented,[10] the last ones are still left to be explored (Scheme 1). The genes responsible for these last transformations (*gcpE* and *lytB*) are already known,[11] but their enzymatic expressions lack identification. For this reason, each facile preparative method for the known intermediates of MIP could be highly useful.[12]

A number of synthetic schemes using either asymmetric dihydroxylation[14] or chiral pool approaches,[15] along with a biosynthetic method,[16] for the preparation of MEP have been published. There is always, however, a great need for simple and high yielding sequences, which could lead to enantiopure **3** and labeled analogues.[17]



Scheme 1. The MIP pathway to isoprenoids. Conditions: (i) DXP synthase (Pi=–PO_3^{2-}); (ii) MEP synthase; (iii) (1) CDP-ME synthase; (2) CDP-ME kinase; (3) MECDP synthase.[13]

MEP and a plethora of natural products and compounds with pharmaceutical and biological interest contain a chiral tertiary alcohol moiety. Stereoselective construction of this quaternary carbon center usually represents a major challenge in the planned synthetic route.[18] A part of our recent research work focuses on the synthesis of such compounds starting from inexpensive commercially available asymmetric materials, like carbohydrates.[19]

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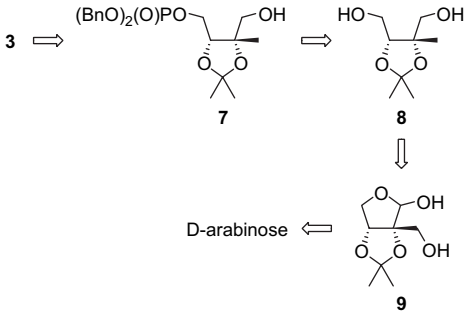
0040–4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2006.12.078

2. Results and discussion

In continuation of our previous work, we envisaged the retrosynthesis of **3**, as depicted in Scheme 2. According to this plan, the desired target could be reached by deprotection of intermediate **7**, which is the 4-*O*-phosphorylated derivative of 2-*C*-methyl-D-erythritol acetonide (**8**). Obviously, the latter could be used as the precursor of phosphate **7**. 1,4-Diol **8** leads back to the hydroxymethyl lactol **9**, which in turn could be simply prepared from D-arabinose.



Scheme 2. Retrosynthetic analysis.

Indeed, lactol **9**, which is easily prepared on a multigram scale from D-arabinose acetonide, and unambiguously has the correct stereochemistry at the quaternary carbon center,[20] served as the starting material of our choice (Scheme 3). In order to obtain the D-erythritol acetonide key intermediate **8**, the *C*-hydroxymethyl derivative **9** was used to obtain tosylate **10** initially. Practically, this transformation was found to be quite intriguing since preliminary experiments employing different bases and/or higher temperatures yielded to some extent the bis-tosylated by-products and in some cases the 2′-chloro-derivatives **11**. It seems that higher temperatures favor the nucleophilic displacement of tosyloxy group by chloride. However, pyridine at ambient temperature proved to be more reliable, although the reaction rate was rather lower. Subsequently, tosylate **10** was left to react under reflux with a reasonable excess amount of $LiAlH_4$. This caused the concomitant reduction of the lactol moiety and the replacement of tosyl group by hydride,[21] and **8** was obtained almost quantitatively.[22]

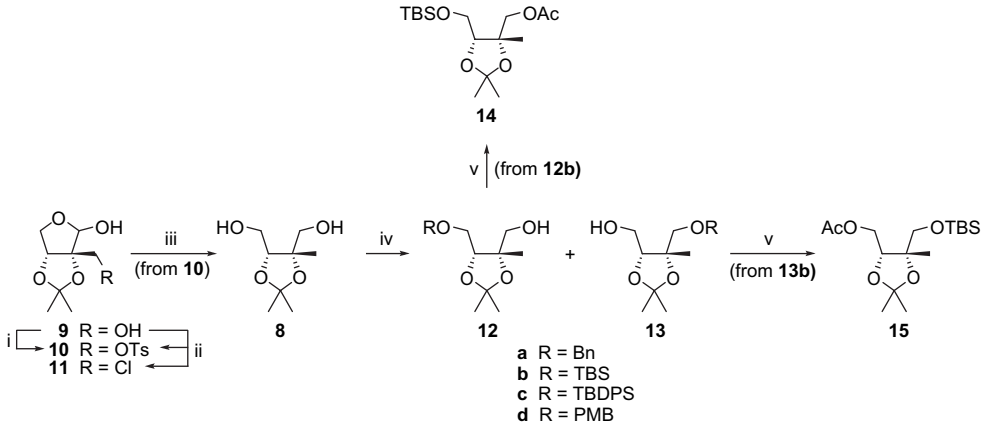
Having a few grams of diol **8** in our hands,[23] we then sought to investigate a suitable way to obtain phosphate **7**. Thus, selective introduction of a protecting group to one of the free hydroxyls in **8** was our next goal. However, the fact that both of these hydroxyl groups are primary raises the serious question of bisubstitution. Moreover, it was assumed that the 4-*O*-protected regioisomer would be the major product in the case of mono-protection, taking into account that the 2-*C*-methyl group slightly imposes a steric hindrance to the neighboring hydroxyl of C-1. After solving the problem of monosubstitution, the expected 4-*O*-mono-protected derivative could be used, employing the appropriate manipulations, to complete the synthesis.

To address the issue of monosubstitution, the well-established tin-mediated mono-derivatization of vicinal 1,2- or 1,3-diols[24] was initially investigated. Although our system is a 1,4-diol, the formation of a tin-participating seven-membered ring cannot be excluded. Mono-benzylation of **8** was achieved according to this method affording **12a** and **13a** (Scheme 3) in an excellent combined yield, but without any significant selectivity (Table 1, entry 1).[25] Such a behavior can be attributed to a number of reasons. First, it is not clear whether the tin-intermediate resulted through an intramolecular or an intermolecular fashion. Additionally, the steric hindrance induced by the methyl group is probably not significantly powerful to differentiate the two hydroxyls under these reaction conditions.

Table 1. Mono-derivatization of diol **8**

Entry	EX	Procedure[a]	Products (ratio)[b]	Yield %[c]
1	BnCl	A	**12a/13a** (1.1:1)	97
2	TBSCl	B	**12b/13b** (1:1)	97
3	TBDPSCl	B	**12c/13c** (2.6:1)	86[d]
4	BnBr	B	**12a/13a** (2.8:1)	96
5	PMBCl	B	**12d/13d** (2.6:1)	89
6	TBSCl	C	**12b/13b** (5:1)	88
7	TBDPSCl	C	**12c/13c** (>20:1)	89

[a] Conditions were as follows: (A) (1) Bu_2SnO, toluene, 110 °C; (2) EX, TBAI, toluene, 110 °C; (B) (1) NaH, THF, 25 °C; (2) EX, THF, 25 °C; (C) EX, imidazole, Et_3N, CH_2Cl_2, 25 °C.
[b] Calculated on isolated pure regioisomers unless otherwise mentioned.
[c] Combined yields for both regioisomers.
[d] It was impossible to obtain pure **13c**.



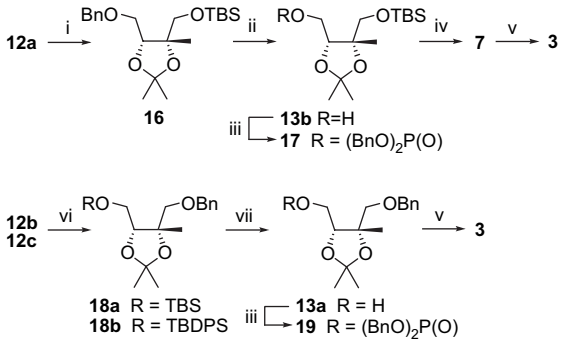
Scheme 3. Synthesis and mono-protection of diol **8**. Reagents and conditions: (i) TsCl, pyridine, 25 °C, 90%; (ii) TsCl, pyridine, 60 °C, 29% of **10** and 54% of **11**; (iii) $LiAlH_4$, THF, 60 °C, 98%; (iv) see Table 1; (v) Ac_2O, Et_3N, CH_2Cl_2, 0–25 °C, 98% for **14**, 97% for **15**.

Benzyl ethers **12a** and **13a** could both be employed in our synthetic plan, but we were keen to investigate other approaches deeper as well. The results regarding the tin-mediated mono-benzylation support the hypothesis that diol **8** behaves as a rather symmetric system. A method for mono-silylation of symmetrical diols was known to us from a previous work.[26] When this protocol was applied to **8**, using TBSCl as electrophile, the mono-substituted derivative **12b** was obtained along with its regioisomer **13b** in a very good combined yield[27] and in a ratio of ca. 1.1:1 (entry 2). The structures of **12b** and **13b** were assigned by double resonance ^{1}H NMR experiments and assured[28] through their conversion to the corresponding acetates **14** and **15**. In order to check the influence of the protective group bulkiness, TBDPSCl was also employed, applying the same protocol (entry 3). We were not surprised to find that both mono-silylated regioisomers, **12c** and **13c** were again produced but with a significant preference for the less hindered one, **12c** (ratio of ca. 2.6:1). It was not, however, possible to separate the minor one (**13c**) from its regioisomer using routine column chromatography. The same procedure was also investigated using BnBr as electrophile (entry 4). In this case the easily separable mono-benzyl regioisomers **12a** and **13a** were formed again in an excellent combined yield, and with a better preference for the less hindered one, **13a** (ratio of ca. 2.8:1). The difference between silyl and benzyl mono-protections is probably due to the fact that the latter is much slower and therefore more selective. PMBCl was also examined (entry 5) and the expected regioisomers **12d** and **13d** were obtained in an almost similar ratio (ca. 2.6:1) but this reaction required prolonged time to reach completion and a tedious column chromatography separation to obtain both regioisomers free from traces of *p*-methoxybenzyl alcohol.

As a final attempt the mono-silylation of **8** with TBSCl and TBDPSCl was checked in the presence of imidazole and a catalytic amount of triethylamine (entries 6 and 7, respectively).[29] To our delight, this approach gave even better results with both electrophiles. Especially in the case of the TBDPS protection the more hindered regioisomer (**13c**) was not practically detectable in the reaction mixture.

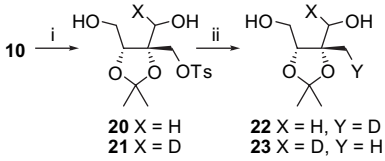
The above given results prompted us to check the feasibility of a direct mono-phosphorylation of **8**. However, employing $(BnO)_2P(O)Cl$[30] as electrophile in the tin-mediated protocol repeatedly led to very complicated reaction mixtures from which it was impossible to obtain pure samples of phosphate **7** and its regioisomer, though we were able to confirm their formation by ^{1}H NMR spectroscopy.[31] Similarly, the phosphorylations of **8** using either NaH or imidazole as base were proved unreliable having a polymeric mass formed in the first minutes of reaction. A direct phosphorylation of **8** using $(BnO)_3P$ in the presence of iodine[32] was also not successful since none of the expected phosphates were obtained even under forced conditions.

Next, the mono-protected silyl and benzyl derivatives were selected for the completion of the synthesis. Applying a high yielding two-step sequence the benzylated alcohol **12a** was used to obtain **13b** through **16** (Scheme 4). Analogously, 4-*O*-silyl protected alcohols **12b** and **12c** gave **13a** through the corresponding fully protected tetrols **18a** and **18b**. In this way both regioisomers for each case were used. Having successfully addressed the issue of mono-protection and after performing the required manipulations, the phosphorylation took place for both advanced intermediates **13a** and **13b** using standard conditions[32] and without incident. The obtained phosphates **17** and **19** were then subjected to deprotection protocols to obtain **3**. Thus, **17** was smoothly desilylated to give **7**. Finally, a previously described two-step sequence[15a] was applied to **7** and **19** furnishing enantiopure MEP (**3**) in good overall yields.[33]



Scheme 4. Final steps to MEP (**3**). Reagents and conditions: (i) TBSCl, imidazole, CH_2Cl_2, 25 °C, 98%; (ii) H_2, Pd/C, MeOH, 25 °C, 98%; (iii) $(BnO)_3P$, I_2, CH_2Cl_2, pyridine, −10–25 °C, 92% for **17**, 97% for **19**; (iv) TBAF, AcOH, THF, −10–25 °C, 96%; (v) (1) H_2, Pd/C, MeOH, H_2O, 25 °C; (2) MeOH, H_2O, 60 °C, 58% from **7**, 55% from **19**; (vi) NaH, BnBr, THF, 25 °C, 94% for **18a**, 91% for **18b**; (vii) TBAF, THF, 25 °C, 100% from **18a**, 98% from **18b**.

Since new synthetic approaches toward labeled analogues of **3** are always important, we decided to take advantage of a possible stepwise reduction of tosylate **10** in order to obtain isotopomers of **8**,[34] the direct precursor of **3**. The solution to this specific task was to initially reduce the lactol moiety with application of a standard mild protocol ($NaBH_4$ or $NaBD_4$) and subsequently remove the tosyloxy group under more forced conditions ($LiAlH_4$ or $LiAlD_4$). Using the above mentioned reducing agents in the appropriate order led to very good yields through the partially reduced diols **20** and **21**, to 2′- and 1-deuterated analogues of **8** (**22** and **23**), respectively (Scheme 5).[35] Obviously, the prepared analogues could be incorporated into the general synthetic scheme in order to obtain the corresponding isotopomers of **3**.



Scheme 5. Synthesis of labeled analogues of **8**. Reagents and conditions: (i) $NaBH_4$ (or $NaBD_4$), MeOH, 25 °C, 98% for **20**, 96% for **21**; (ii) $LiAlH_4$ (or $LiAlD_4$), THF, 60 °C, 90% for **22**, 91% for **23**.

3. Conclusions

In this article, a convenient short synthesis of enantiopure MEP, a key intermediate of isoprenoid biosynthesis in bacteria and plants, is described. Practically, it embodies facile functional group interconversions starting from an easily

accessible chiron, 2-*C*-hydroxymethyl-D-erythrose acetonide (**9**). The most efficient route described (through **12c**)[36] involves seven steps and produces MEP in an over 37% total yield.[37] Additionally, 1- and 2′-deuterio isotopomers of 2-*C*-methyl-D-erythritol acetonide (**8**) were easily obtained after the appropriate modifications of the synthetic plan. Because of its compactness and the ability to scale up involving multigram quantities, this work represents a highly attractive scheme for the facile preparation of the target molecules. Moreover, the well investigated mono-protections of the 1,4-diol system could be useful in the future for the regioselective preparation of analogous compounds.

4. Experimental

4.1. General

All commercially available grade quality reagents were used without further purification. All solvents were purified by standard procedures before use. Dry solvents were obtained by the literature methods and stored over molecular sieves. All reactions were conducted under a nitrogen atmosphere. All reactions were monitored on commercially available pre-coated TLC plates (layer thickness 0.25 mm) of Kieselgel 60 F_{254}. Compounds were visualized by use of a UV lamp or/and *p*-anisaldehyde ethanolic solution and warming. Column chromatography was performed in the usual way using Merck 60 (40–60 μm) silica gel. NMR spectra were recorded on a 300 MHz spectrometer (^{1}H: 300 MHz, ^{13}C: 75 MHz) in $CDCl_3$, unless otherwise stated. Chemical shifts are given in parts per million and *J* in hertz using solvent or tetramethylsilane as an internal reference. IR spectra were recorded on an FTIR instrument as indicated. Mass spectra were obtained by electro spray technique, positive mode (ES-MS) or MALDI-FTMS.

4.1.1. 2,3-*O*-Isopropylidene-2-*C*-(*p*-toluenesulfonyloxymethyl)-D-erythrofuranose (10). Alcohol **9**[20] (15 g, 79 mmol) was dissolved in dry pyridine (500 mL) and TsCl (19.6 g, 103 mmol) was added in portions. The mixture was stirred for two days at room temperature and then poured in a mixture of CH_2Cl_2 (1 L) and H_2O (500 mL). The aqueous phase was extracted with CH_2Cl_2 (2×300 mL) and the combined organic phases were washed with semi-saturated brine (150 mL) and dried (Na_2SO_4). After removal of the solvents under reduced pressure (below 45 °C), the residual oil was purified by column chromatography on silica gel with a mixture of hexane/EtOAc (4:1 v/v) to give 24.6 g of tosylates **10** (90%) as an oil (mixture of α and β anomers in a ratio of ca. 1:1): FTIR (neat film) 3468, 2988, 2940, 2876, 1598, 1363, 1190, 1176, 1096, 977 cm^{-1}; ^{1}H NMR for the α anomer (300 MHz, $CDCl_3$) δ 7.82 (d, *J*=8.3 Hz, 2H), 7.35 (d, *J*=8.3 Hz, 2H), 5.32 (s, 1H), 4.62 (d, *J*=3.5 Hz, 1H), 4.28 (s, 2H), 4.09 (dd, *J*=11.4, 3.5 Hz, 1H), 3.95 (d, *J*=11.4 Hz, 1H), 2.45 (s, 3H), 1.44 (s, 3H), 1.34 (s, 3H); ^{1}H NMR for the β anomer (300 MHz, $CDCl_3$) δ 7.80 (d, *J*=7.9 Hz, 2H), 7.37 (d, *J*=7.9 Hz, 2H), 4.75 (s, 1H), 4.66 (d, *J*=3.5 Hz, 1H), 4.17 (d, *J*=10.5 Hz, 1H), 4.09 (d, *J*=10.5 Hz, 1H), 3.95 (d, *J*=11.0 Hz, 1H), 3.55 (dd, *J*=11.0, 3.5 Hz, 1H), 2.47 (s, 3H), 1.53 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.5, 144.9, 132.7, 132.1, 130.1, 129.8, 128.0, 127.9, 114.7, 114.5, 102.1, 97.5, 92.2, 86.7, 82.5, 82.0, 72.2, 68.7, 67.9, 67.7, 27.6, 27.5, 27.0, 27.6, 21.6 (2C); HRMS *m/z* 367.0830 [$C_{15}H_{20}O_7SNa$ (M+Na)$^+$ requires 367.0827].

4.1.2. 2-*C*-Chloro-2,3-*O*-isopropylidene-D-erythrofuranose (11). Alcohol **9** (2.9 g, 15 mmol) was dissolved in dry pyridine (50 mL) and TsCl (3.8 g, 20 mmol) was added in portions. The mixture was stirred for 8 h at 60 °C and then worked-up as described for **10**. The residual oil was purified by column chromatography on silica gel with a mixture of hexane/EtOAc (6:1 v/v) to give, in the order of elution, 1.7 g of chloride **11** (54%, mixture of α and β anomers in a ratio of ca. 3:1) and 1.5 g of **10** (29%). Compound **11** (solid): mp 61–62 °C; FTIR (neat film) 3430, 2989, 2940, 2882, 1459, 1431, 1372, 1218, 1155, 1064, 1008, 935, 868, 834, 740 cm^{-1}; ^{1}H NMR for the α anomer (300 MHz, $CDCl_3$) δ 5.39 (d, *J*=2.4 Hz, 1H), 4.65 (d, *J*=3.7 Hz, 1H), 4.15 (dd, *J*=10.4, 3.7 Hz, 1H), 3.96 (d, *J*=10.4 Hz, 1H), 3.90 and 3.83 (ABq, *J*=11.6 Hz, 2H), 3.71 (br s, 1H), 1.50 (s, 3H), 1.49 (s, 3H); ^{1}H NMR for the β anomer (300 MHz, $CDCl_3$) δ 5.07 (d, *J*=12.2 Hz, 1H), 4.74 (d, *J*=3.1 Hz, 1H), 3.98 (d, *J*=11.0 Hz, 1H), 3.85 (ABq, obscured, 2H), 3.63 (dd, *J*=11.0, 3.1 Hz, 1H), 2.18 (br s, 1H), 1.57 (s, 3H), 1.48 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 114.6, 114.4, 102.1, 97.8, 93.9, 89.0, 83.7, 83.1, 72.4, 68.2, 45.1, 43.7, 27.9, 27.6, 27.1, 26.9; HRMS *m/z* 231.0402/233.0373 [$C_8H_{13}ClO_4Na$ (M+Na)$^+$ requires 231.0400/233.0371].

4.1.3. 2,3-*O*-Isopropylidene-2-*C*-methyl-D-erythritol (8). Lactol **10** (14 g, 41 mmol) was dissolved in dry THF (1 L) and $LiAlH_4$ (4.6 g, 121 mmol) was added in portions with vigorous stirring (about 1 h). The resulting suspension was stirred for 10 h at reflux, then poured slowly in EtOAc (1 L), acidified to pH 6 with 10% HCl, and filtered. The filtrate was shaken with a saturated sodium hydrogencarbonate solution (500 mL) for 1 h. The aqueous phase was extracted with EtOAc (3×500 mL) and the combined organic ones were washed with brine (200 mL) and dried (Na_2SO_4). After removal of the solvents under reduced pressure the residual oil was purified by column chromatography on silica gel with a mixture of hexane/EtOAc (2:1 v/v) to give 7.05 g of diol **8** (98%) as a solid: mp 95–96 °C (lit.[22a] 95 °C); $[\alpha]_D^{25}$ −26.2 (*c* 0.4, $CHCl_3$) [lit.[15a] $[\alpha]_D^{25}$ −26.0 (*c* 0.36, $CHCl_3$)]; ^{1}H NMR, and ^{13}C NMR spectra were identical with those reported in the literature;[15a] HRMS *m/z* 199.0947 [$C_8H_{16}O_4Na$ (M+Na)$^+$ requires 199.0946].

4.1.4. General procedure B for the mono-protection of diol 8. NaH 90% (34 mg, 1.25 mmol) was suspended in dry THF (5 mL) and a solution of diol **8** (220 mg, 1.25 mmol) in dry THF (10 mL) was added at room temperature. The mixture was stirred vigorously for the indicated time period, and then a solution of EX (1.25 mmol) in dry THF (10 mL) was added dropwise. After the starting material was consumed the reaction mixture was poured in Et_2O (40 mL). The resulting slurry was washed with a 10% sodium carbonate solution (20 mL), the aqueous phase was extracted with EtOAc (50 mL), and the combined organic phases were dried (Na_2SO_4). The solvents were removed under reduced pressure and the residual oil was purified by column chromatography on silica gel.

4.1.5. General procedure C for the mono-protection of diol 8. Imidazole (272 mg, 4 mmol) and Et_3N (30 μL, 0.2 mmol) were added to a solution of diol **8** (352 mg, 2 mmol) in CH_2Cl_2 (3 mL) at room temperature. Then, silyl chloride (2 mmol) was added and the mixture was left stirring for 72 h. The reaction mixture was diluted with CH_2Cl_2 (25 mL), washed with a saturated aqueous ammonium chloride solution (10 mL) and brine (5 mL), and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel.

4.1.6. 4-*O*-Benzyl-2,3-*O*-isopropylidene-2-*C*-methyl-D-erythritol (12a) and 1-*O*-benzyl-2,3-*O*-isopropylidene-2-*C*-methyl-D-erythritol (13a). *Procedure A*—Diol **8** (110 mg, 0.62 mmol) was dissolved in dry toluene (20 mL), DBTO (175 mg, 0.7 mmol) was added and the resulting suspension was heated for 5 h at reflux in a Dean–Stark apparatus. After cooling at room temperature, TBAI (39 mg, 0.12 mmol) and BnCl (0.09 mL, 0.78 mmol) were added successively and the mixture was refluxed for 12 h. The solvent was removed under reduced pressure and the residual oil was purified by column chromatography with a mixture of hexane/EtOAc (8:1 v/v) to give, in the order of elution, 77 mg of mono-benzylated diol **13a** (47%) and 83 mg of mono-benzylated diol **12a** (50%). *Procedure B*—Reaction time: 24 h. Column chromatography was performed as previously described affording 118 mg of **13a** (25%) and 330 mg **12a** (71%). Compound **12a** (solid): mp 63–64 °C; $[\alpha]_D^{25}$ −19.2 (*c* 1.5, $CHCl_3$); FTIR (neat film) 3460, 2980, 2930, 2881, 1499, 1455, 1380, 1217, 1088, 1022, 752 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34–7.27 (m, 5H), 4.61 (d, *J*=11.8 Hz, 1H), 4.55 (d, *J*=11.8 Hz, 1H), 4.07 (t, *J*=5.5 Hz, 1H), 3.73 (dd, *J*=10.3, 5.5 Hz, 1H), 3.67 (dd, *J*=10.3, 5.5 Hz, 1H), 3.45 (d, *J*=6.1 Hz, 2H), 2.34 (br t, *J*=6.1 Hz, 1H), 1.46 (s, 3H), 1.41 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.4, 128.4, 127.8, 127.7, 107.9, 81.9, 81.3, 73.7, 67.5, 65.2, 28.1, 26.5, 22.2; HRMS *m/z* 289.1416 [$C_{15}H_{22}O_4Na$ $(M+Na)^+$ requires 289.1416]. Compound **13a** (solid): mp 81–82 °C; $[\alpha]_D^{25}$ −14.6 (*c* 0.7, $CHCl_3$); FTIR (neat film) 3264, 3174, 2981, 2913, 2862, 1480, 1453, 1356, 1213, 1113, 1038, 736 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36–7.29 (m, 5H), 4.53 (s, 2H), 3.98 (t, *J*=6.6 Hz, 1H), 3.84–3.71 (m, 2H), 3.59 (d, *J*=8.8 Hz, 1H), 3.19 (d, *J*=8.8 Hz, 1H), 2.80 (br s, 1H), 1.42 (s, 3H), 1.37 (br s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.2, 128.5, 128.0, 127.8, 107.7, 82.3, 80.8, 73.9, 72.5, 60.9, 28.3, 26.4, 23.6; HRMS *m/z* 289.1417 [$C_{15}H_{22}O_4Na$ $(M+Na)^+$ requires 289.1416].

4.1.7. 1-*O*-Benzyl-2,3-*O*-isopropylidene-2-*C*-methyl-D-erythritol (13a) from 18a or 18b. Silyl ether **18a** or **18b** (0.53 mmol) was dissolved in dry THF (3 mL) and TBAF (1 M in THF, 0.6 mL, 0.6 mmol) was added at room temperature. The reaction mixture was stirred for 6 h and then quenched with the addition of a saturated ammonium chloride solution (5 mL). It was extracted with EtOAc (2× 10 mL) and the combined organic phases were washed with brine (5 mL) and dried (Na_2SO_4). The solvents were removed under reduced pressure and the residual oil was purified by column chromatography on silica gel with a mixture of hexane/EtOAc (5:1 v/v) to give alcohol **13a** [140 mg from **18a** (100%) or 138 mg from **18b** (98%)].

4.1.8. 4-*O*-(*t*-Butyldimethylsilyl)-2,3-*O*-isopropylidene-2-*C*-methyl-D-erythritol (12b) and 1-*O*-(*t*-butyldimethylsilyl)-2,3-*O*-isopropylidene-2-*C*-methyl-D-erythritol (13b). *Procedure B*—Reaction time: 45 min. Column chromatography was performed with a mixture of hexane/EtOAc (25:1 v/v) affording, in the order of elution, 174 mg of mono-silylated diol **13b** (48%) and 178 mg of mono-silylated diol **12b** (49%). *Procedure C*—Column chromatography was performed as previously described affording, 85 mg of **13b** (15%) and 425 mg of **12b** (73%). Compound **12b** (oil): $[\alpha]_D^{25}$ −19.8 (*c* 2.3, $CHCl_3$); FTIR (neat film) 3478, 2978, 2930, 2857, 1464, 1371, 1254, 1094, 838 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.93–3.86 (m, 3H), 3.61 (d, *J*=11.6 Hz, 1H), 3.44 (d, *J*=11.6 Hz, 1H), 2.79 (br s, 1H), 1.42 (s, 3H), 1.39 (s, 3H), 1.37 (s, 3H), 0.91 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 107.7, 82.3, 82.1, 65.3, 60.9, 28.3, 26.4, 25.7, 22.9, 18.2, −0.1; HRMS *m/z* 313.1810 [$C_{14}H_{30}O_4SiNa$ $(M+Na)^+$ requires 313.1811]. Compound **13b** (solid): mp 42–43 °C; $[\alpha]_D^{25}$ −19.0 (*c* 1.2, $CHCl_3$); FTIR (neat film) 3495, 2985, 2956, 2932, 2859, 1472, 1371, 1254, 1217, 1096, 839, 777 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.98 (t, *J*=6.4 Hz, 1H), 3.83 (br s, 2H), 3.74 (d, *J*=9.8 Hz, 1H), 3.25 (d, *J*=9.8 Hz, 1H), 2.98 (br s, 1H), 1.42 (s, 3H), 1.39 (s, 3H), 1.38 (s, 3H), 0.91 (s, 9H), 0.11 (s, 3H), 0.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 107.4, 82.4, 81.5, 65.4, 60.9, 28.3, 26.3, 25.7, 23.1, 18.0, −5.8; HRMS *m/z* 313.1809 [$C_{14}H_{30}O_4SiNa$ $(M+Na)^+$ requires 313.1811].

4.1.9. 1-*O*-(*t*-Butyldimethylsilyl)-2,3-*O*-isopropylidene-2-*C*-methyl-D-erythritol (13b) from 18. Benzyl ether **16** (140 mg, 0.37 mmol) was dissolved in MeOH (5 mL). A catalytic amount of 5% Pd/C was added and the mixture was hydrogenated with H_2 for 4 h at atmospheric pressure. Then, it was filtered through a short pad of Celite®. Removal of the solvent under reduced pressure afforded 100 mg of pure alcohol **13b** (93%).

4.1.10. 4-*O*-(*t*-Butyldiphenylsilyl)-2,3-*O*-isopropylidene-2-*C*-methyl-D-erythritol (12c) and 1-*O*-(*t*-butyldiphenylsilyl)-2,3-*O*-isopropylidene-2-*C*-methyl-D-erythritol (13c). *Procedure B*—Reaction time: 24 h. Column chromatography was performed with a mixture of hexane/EtOAc (15:1 v/v) affording 200 mg of pure mono-silylated diol **12c** and 245 mg of a 1:1 mixture of **12c** and **13c** (combined yield 86%, ratio of ca. 2.6:1). *Procedure C*—Column chromatography was performed as previously described affording 740 mg of **12c** (89%). Compound **12c** (oil): $[\alpha]_D^{25}$ −9.9 (*c* 1.2, $CHCl_3$); FTIR (neat film) 3489, 3072, 3050, 2931, 2858, 1473, 1463, 1428, 1371, 1216, 1113, 999, 823, 702 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.67 (t, *J*=12.2 Hz, 4H), 7.47–7.36 (m, 6H), 3.98–3.82 (m, 3H), 3.55 (br s, 2H), 2.41 (br s, 1H), 1.41 (s, 3H), 1.38 (s, 3H), 1.36 (s, 3H), 1.07 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.6, 132.7, 130.0, 127.8, 107.9, 82.3, 82.2, 65.3, 61.7, 28.2, 26.8, 26.6, 22.8, 19.2; HRMS *m/z* 437.2121 [$C_{24}H_{34}O_4SiNa$ $(M+Na)^+$ requires 437.2124]. Compound **13c**: ^1H NMR (300 MHz, $CDCl_3$) δ 7.69–7.65 (4H, obscured), 7.47–7.36 (6H, obscured), 4.02 (br t, *J*= 5.5 Hz, 1H), 3.98–3.85 (1H, obscured), 3.82 (d, *J*=7.3 Hz, 1H), 3.76 (d, *J*=9.8 Hz, 1H), 3.24 (d, *J*=9.8 Hz, 1H), 2.74 (br s, 1H), 1.34 (s, 3H), 1.30 (s, 3H), 1.26 (s, 3H), 1.08 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.8, 132.7, 130.0,

127.8, 107.6, 82.9, 81.6, 65.8, 61.3, 28.3, 27.0, 26.4, 23.1, 19.3.

4.1.11. 4-*O*-*p*-Methoxybenzyl-2,3-*O*-isopropylidene-2-*C*-methyl-D-erythritol (12d) and 1-*O*-*p*-methoxybenzyl-2,3-*O*-isopropylidene-2-*C*-methyl-D-erythritol (13d). *Procedure B*—Reaction time: 48 h. Column chromatography was performed with a mixture of hexane/EtOAc (10:1 v/v) affording, in the order of elution, 90 mg of mono-benzylated diol **13d** (24%) and 235 mg of mono-benzylated diol **12d** (63%). Compound **12d** (oil): $[\alpha]_D^{25}$ −13.9 (*c* 1.1, $CHCl_3$); FTIR (neat film) 3479, 2985, 2934, 2873, 1614, 1586, 1515, 1464, 1372, 1248, 1215, 1091, 1000, 930, 850, 820 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.25 (d, *J*=8.0 Hz, 2H), 6.88 (d, *J*=8.0 Hz, 2H), 4.55 and 4.50 (ABq, *J*=11.6 Hz, 2H), 4.05 (dd, *J*=6.1, 4.9 Hz, 1H), 3.80 (s, 3H), 3.67 (dd, *J*=5.5, 2.4 Hz, 2H), 3.44 (s, 2H), 2.54 (br s, 1H), 1.45 (s, 3H), 1.39 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.4, 130.8, 130.0, 113.9, 108.0, 82.0, 81.3, 73.5, 67.1, 65.3, 55.2, 28.2, 26.5, 22.2; HRMS *m/z* 319.1523 [$C_{16}H_{24}O_5Na$ (M+Na)$^+$ requires 319.1521]. Compound **13d** (oil): $[\alpha]_D^{25}$ −10.0 (*c* 1.0, $CHCl_3$); FTIR (neat film) 3486, 2985, 2934, 2868, 1613, 1586, 1514, 1457, 1372, 1248, 1216, 1096, 1036, 848, 820 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, *J*=8.5 Hz, 2H), 6.88 (d, *J*=8.5 Hz, 2H), 4.46 (s, 2H), 3.97 (br t, *J*=6.7 Hz, 1H), 3.84–3.70 (m, 2H), 3.81 (s, 3H), 3.57 (d, *J*=9.2 Hz, 1H), 3.16 (d, *J*=9.2 Hz, 1H), 2.86 (br s, 1H), 1.40 (s, 3H), 1.37 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.6, 129.6, 129.2, 114.0, 107.7, 82.2, 80.9, 73.5, 72.2, 60.9, 55.3, 28.3, 26.5, 23.8; HRMS *m/z* 319.1522 [$C_{16}H_{24}O_5Na$ (M+Na)$^+$ requires 319.1521].

4.1.12. 1-*O*-Acetyl-4-*O*-(*t*-butyldimethylsilyl)-2,3-*O*-isopropylidene-2-*C*-methyl-D-erythritol (14). Alcohol **12b** (145 mg, 0.5 mmol) and Et_3N (0.14 mL, 1 mmol) were dissolved in dry CH_2Cl_2 (2.5 mL) at 0 °C. Ac_2O (0.08 mL, 0.8 mmol) was added and the mixture was stirred for 3 h while warming to room temperature. Then, it was poured in brine (5 mL) and the aqueous phase was extracted with CH_2Cl_2 (2×5 mL). The combined organic phases were dried (Na_2SO_4) and the solvents were removed under reduced pressure. The sticky residue was purified by column chromatography on silica gel with a mixture of hexane/EtOAc (5:1 v/v) to give 163 mg of acetate **14** (98%) as an oil: $[\alpha]_D^{25}$ −16.2 (*c* 2.5, $CHCl_3$); FTIR (neat film) 2985, 2956, 2932, 2885, 2858, 1747, 1464, 1373, 1252, 1217, 1097, 839, 778 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.09 (d, *J*=11.0 Hz, 1H), 4.05 (d, *J*=11.0 Hz, 1H), 3.95 (dd, *J*=7.1, 5.6 Hz, 1H), 3.86 (d, *J*=10.4, 5.6 Hz, 1H), 3.74 (dd, *J*=10.4, 7.1 Hz, 1H), 2.10 (s, 3H), 1.43 (s, 3H), 1.39 (s, 3H), 1.36 (s, 3H), 0.90 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 108.3, 82.8, 80.3, 66.4, 60.9, 29.7, 28.0, 26.6, 25.8, 22.7, 21.0, −5.4, −5.6; HRMS *m/z* 355.1915 [$C_{16}H_{32}O_5SiNa$ (M+Na)$^+$ requires 355.1917].

4.1.13. 4-*O*-Acetyl-1-*O*-(*t*-butyldimethylsilyl)-2,3-*O*-isopropylidene-2-*C*-methyl-D-erythritol (15). According to the preceding procedure, alcohol **13b** (100 mg, 0.34 mmol), gave 110 mg of acetate **15** (97%) as an oil: $[\alpha]_D^{25}$ +9.5 (*c* 1.0, $CHCl_3$); FTIR (neat film) 2986, 2956, 2932, 2859, 1745, 1472, 1464, 1372, 1238, 1218, 1099, 842, 777 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.52 (dd, *J*=11.6, 1.8 Hz, 1H), 4.08 (dd, *J*=11.6, 8.5 Hz, 1H), 4.00 (dd, *J*=8.5, 1.8 Hz, 1H), 3.61 (d, *J*=9.8 Hz, 1H), 3.27 (d, *J*=9.8 Hz, 1H), 2.08 (s, 3H), 1.41 (s, 3H), 1.37 (s, 3H), 1.32 (s, 3H), 0.88 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.8, 108.2, 81.3, 81.2, 65.2, 63.4, 28.4, 26.5, 25.7, 21.9, 20.9, 18.0, −5.7, −5.8; HRMS *m/z* 355.1918 [$C_{16}H_{32}O_5SiNa$ (M+Na)$^+$ requires 355.1917].

4.1.14. 4-*O*-Benzyl-1-*O*-(*t*-butyldimethylsilyl)-2,3-*O*-isopropylidene-2-*C*-methyl-D-erythritol (16). Alcohol **12a** (120 mg, 0.45 mmol) was dissolved in dry CH_2Cl_2 (2.5 mL). Imidazole (60 mg, 0.9 mmol) and a solution of TBSCl (81 mg, 0.54 mmol) in dry CH_2Cl_2 (1 mL) were successively added at room temperature. The reaction mixture was stirred for 12 h, and then poured in a saturated sodium carbonate solution (5 mL). It was extracted with CH_2Cl_2 (2×5 mL), the combined organic phases were washed with brine (5 mL), and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residual oil was purified by column chromatography on silica gel with a mixture of hexane/EtOAc (8:1 v/v) to give 162 mg of silyl derivative **16** (94%) as an oil: $[\alpha]_D^{25}$ −8.4 (*c* 1.5, $CHCl_3$); FTIR (neat film) 2984, 2954, 2931, 2857, 1742, 1455, 1371, 1251, 1096, 838, 778 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.26–7.19 (m, 5H), 4.61 (d, *J*=12.3 Hz, 1H), 4.42 (d, *J*=12.3 Hz, 1H), 3.96 (dd, *J*=8.8, 2.9 Hz, 1H), 3.66 (dd, *J*=9.2, 2.9 Hz, 1H), 3.55–3.47 (m, 2H), 3.08 (d, *J*=10.1 Hz, 1H), 1.34 (s, 3H), 1.30 (s, 3H), 1.18 (s, 3H), 0.73 (s, 9H), −0.09 (s, 3H), −0.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.0, 128.3, 127.8, 127.5, 107.8, 82.5, 81.0, 73.5, 68.6, 65.2, 28.4, 26.4, 25.7, 21.8, 17.9, −5.9, −6.0; HRMS *m/z* 403.2281 [$C_{21}H_{36}O_4SiNa$ (M+Na)$^+$ requires 403.2281].

4.1.15. 1-*O*-(*t*-Butyldimethylsilyl)-2,3-*O*-isopropylidene-2-*C*-methyl-D-erythritol 4-dibenzyl phosphate (17). A solution of $(BnO)_3P$[38] (550 mg, 1.56 mmol) in dry CH_2Cl_2 (2 mL) was cooled to −10 °C and I_2 (370 mg, 1.46 mmol) was added. The mixture was stirred for 5 min at the same temperature, warmed slowly (1 h) to room temperature while it was decolorized and re-cooled to 0 °C. Then, a solution of alcohol **13b** (377 mg, 1.3 mmol) and pyridine (0.35 mL, 4.2 mmol) in dry CH_2Cl_2 (2 mL) was added dropwise and the mixture was stirred for 30 min at the same temperature. After addition of Et_2O (20 mL) the resulting mixture was successively washed with a 25% sodium hydrogencarbonate solution (2×5 mL) and brine (10 mL). The organic phase was dried (Na_2SO_4), the solvents were removed under reduced pressure, and the residual oil was purified by column chromatography on silica gel with a mixture of hexane/EtOAc (5:1 v/v) to give 660 mg of phosphate **17** (92%) as an oil: $[\alpha]_D^{25}$ +2.5 (*c* 10.0, $CHCl_3$); FTIR (neat film) 3437, 2984, 2955, 2931, 2885, 2858, 1498, 1457, 1372, 1252, 1216, 1097, 1019, 844, 777, 737, 697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34 (br s, 10H), 5.06 (br d, *J*=7.0 Hz, 4H), 4.37–4.31 (m, 1H), 4.19–4.11 (m, 1H), 4.00 (d, *J*=9.2 Hz, 1H), 3.54 (d, *J*=10.1 Hz, 1H), 3.17 (d, *J*=10.1 Hz, 1H), 1.39 (s, 3H), 1.33 (s, 3H), 1.25 (s, 3H), 0.85 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.2 (br), 128.51, 128.45, 128.0, 108.2, 82.2 (d, $^3J_{CP}$=7.0 Hz), 81.1, 69.2 (m), 66.6 (d, $^2J_{CP}$=7.0 Hz), 65.2, 28.4, 26.5, 25.8, 21.9, 18.0, −5.65, −5.78; HRMS *m/z* 574.2417 [$C_{28}H_{43}O_7PSiNa$ (M+Na)$^+$ requires 573.2413].

4.1.16. 2,3-*O*-Isopropylidene-2-*C*-methyl-D-erythritol 4-dibenzyl phosphate (7). A solution of silyl ether **19** (100 mg, 0.18 mmol) in dry THF (5 mL) was cooled to −10 °C and then a mixture of AcOH (0.14 mL, 0.24 mmol) and TBAF (1 M in THF, 0.24 mL, 0.24 mmol) was added dropwise. The mixture was stirred for 15 min at the same temperature and then warmed to room temperature over 3 h. EtOAc (20 mL) was added and a saturated ammonium chloride solution was used to adjust pH to 6. The organic phase was washed with brine, dried (Na_2SO_4) and the solvents were removed under reduced pressure. The residual oil was purified by column chromatography on silica gel with a mixture of hexane/EtOAc (3:1 v/v) to give 75 mg of alcohol **7** (96%) as an oil: ^{1}H NMR and ^{13}C NMR spectra were identical with those reported in the literature;[15a] HRMS *m/z* 459.1545 [$C_{22}H_{29}O_7PNa$ $(M+Na)^+$ requires 459.1549].

4.1.17. 1-*O*-Benzyl-4-*O*-(*t*-butyldimethylsilyl)-2,3-*O*-isopropylidene-2-*C*-methyl-D-erythritol (18a). NaH 90% (18 mg, 0.7 mmol) was suspended in dry THF (3 mL) and a solution of alcohol **12b** (165 mg, 0.57 mmol) in dry THF (2 mL) was added at room temperature. The mixture was stirred vigorously for 1 h, and then a solution of BnBr (0.12 mL, 1 mmol) in dry THF (2 mL) was added dropwise. After 24 h the mixture was poured in Et_2O (25 mL). The organic phase was washed with a 10% sodium carbonate solution (10 mL), the aqueous one was extracted with EtOAc (25 mL), and the combined organic phases were dried (Na_2SO_4). The solvents were removed under reduced pressure and the residual oil was purified by column chromatography on silica gel with a mixture of hexane/EtOAc (8:1 v/v) to give 205 mg of benzyl derivative **18a** (94%) as an oil: $[\alpha]_D^{25}$ −11.4 (*c* 3.4, $CHCl_3$); FTIR (neat film) 2984, 2955, 2931, 2858, 1472, 1370, 1252, 1095, 847, 777 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35–7.28 (m, 5H), 4.56 (d, *J*=12.2 Hz, 1H), 4.51 (d, *J*=12.2 Hz, 1H), 3.91 (t, *J*=5.8 Hz, 1H), 3.86–3.78 (m, 2H), 3.43 (d, *J*=9.8 Hz, 1H), 3.33 (d, *J*=9.8 Hz, 1H), 1.42 (s, 3H), 1.38 (s, 3H), 1.37 (s, 3H), 0.87 (s, 9H), 0.05 (s, 3H), 0.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.3, 128.3, 128.1, 127.6, 107.8, 83.5, 81.1, 73.5, 72.8, 61.4, 28.2, 28.2, 26.6, 25.8, 22.8, 18.2, −5.4, −5.5; HRMS *m/z* 403.2282 [$C_{21}H_{36}O_4SiNa$ $(M+Na)^+$ requires 403.2281].

4.1.18. 1-*O*-Benzyl-4-*O*-(*t*-butyldiphenylsilyl)-2,3-*O*-isopropylidene-2-*C*-methyl-D-erythritol (18b). According to the preceding procedure, alcohol **12c** (200 mg, 0.48 mmol), gave 220 mg of benzyl derivative **18b** (91%) as an oil: $[\alpha]_D^{25}$ −5.6 (*c* 0.9, $CHCl_3$); FTIR (neat film) 3071, 2932, 2858, 1590, 1472, 1455, 1428, 1372, 1216, 1112, 1000, 823, 738, 701 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71–7.64 (m, 4H), 7.44–7.32 (m, 7H), 7.27–7.20 (m, 4H), 4.45 (d, *J*=12.2 Hz, 1H), 4.40 (d, *J*=12.2 Hz, 1H), 3.94 (t, *J*=6.1 Hz, 1H), 3.85 (d, *J*=6.1 Hz, 2H), 3.38 (d, *J*=9.2 Hz, 1H), 3.27 (d, *J*=9.2 Hz, 1H), 1.39 (s, 3H), 1.36 (s, 3H), 1.31 (s, 3H), 1.04 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.2, 135.6, 133.3, 129.7, 128.0, 127.8, 127.7, 127.6, 107.9, 83.4, 81.1, 73.4, 72.7, 62.2, 28.2, 26.8, 22.7, 19.3, 19.2; HRMS *m/z* 527.2597 [$C_{31}H_{40}O_4SiNa$ $(M+Na)^+$ requires 527.2594].

4.1.19. 1-*O*-Benzyl-2,3-*O*-isopropylidene-2-*C*-methyl-D-erythritol 4-dibenzyl phosphate (19). According to the procedure described for **17**, alcohol **13a** (345 mg, 1.3 mmol) gave 665 mg of phosphate **19** (97%) as an oil: $[\alpha]_D^{25}$ +1.1 (*c* 2.1, $CHCl_3$); FTIR (neat film) 3468, 3028, 2984, 2924, 1497, 1455, 1374, 1281, 1215, 1098, 1016, 887, 737, 697 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34–7.30 (m, 10H), 7.28–7.25 (m, 5H), 5.04 (br d, *J*=7.9 Hz, 4H), 4.46 (d, *J*=12.2 Hz, 1H), 4.41 (d, *J*=12.2 Hz, 1H), 4.32–4.25 (m, 1H), 4.16–4.07 (m, 1H), 3.99 (dd, *J*=8.6, 3.1 Hz, 1H), 3.36 (d, *J*=9.2 Hz, 1H), 3.14 (d, *J*=9.2 Hz, 1H), 1.38 (s, 3H), 1.33 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.8, 135.9 (d, $^3J_{CP}$=7.5 Hz), 128.6, 128.5, 128.4, 128.0, 127.7, 127.6, 108.5, 81.9 (d, $^3J_{CP}$= 6.7 Hz), 80.5, 73.4, 72.4, 69.3 (m), 66.1 (d, $^2J_{CP}$=6.7 Hz), 28.2, 26.6, 22.4; HRMS *m/z* 549.2020 [$C_{29}H_{35}O_7PNa$ $(M+Na)^+$ requires 549.2018].

4.1.20. 2-*C*-Methyl-D-erythritol 4-phosphoric acid (3). This compound was prepared according to a known procedure.[15a] Hydrogenation required slightly longer periods (22–24 h). Alcohol **7** (70 mg, 0.16 mmol) and the corresponding benzylated derivative **19** (100 mg, 0.19 mmol) afforded 20 mg (58%) and 21 mg (52%) of **3**, respectively, as an amorphous solid: $[\alpha]_D^{25}$ +6.2 (*c* 0.1, H_2O) [lit.[16] $[\alpha]_D^{25}$ +6.4 (*c* 0.1, H_2O)]; ^{1}H NMR, ^{13}C NMR, and ^{31}P NMR spectra were identical with those reported in the literature.[15a]

4.1.21. 2,3-*O*-Isopropylidene-2-*C*-(*p*-toluenesulfonyloxymethyl)-D-erythritol (20). $NaBH_4$ (26 mg, 0.7 mmol) was added to a solution of lactol **10** (155 mg, 0.45 mmol) in MeOH (6 mL). The mixture was stirred for 4 h at room temperature, then H_2O was added (30 mL) and AcOH was used in order to adjust pH to 5. The resulting mixture was extracted with EtOAc (2×70 mL) and the combined organic phases were dried (Na_2SO_4). After removal of the solvents under reduced pressure the residual oil was purified by column chromatography on silica gel with a mixture of hexane/EtOAc (5:1 v/v) to give 152 mg of diol **20** (98%) as a solid: mp 55–56 °C; $[\alpha]_D^{25}$ +2.6 (*c* 1.8, $CHCl_3$); FTIR (neat film) 3435, 2987, 2937, 2886, 1598, 1457, 1360, 1218, 1176, 1055, 984, 848, 815, 667 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, *J*=8.3 Hz, 2H), 7.36 (d, *J*=8.3 Hz, 2H), 4.26 (d, *J*=10.5 Hz, 1H), 4.11 (d, *J*=10.5 Hz, 1H), 4.07 (t, *J*=5.7 Hz, 1H), 3.87 (dd, *J*=7.0, 6.2 Hz, 2H), 3.65 (d, *J*=11.9 Hz, 1H), 3.58 (d, *J*=11.9 Hz, 1H), 2.90 (br s, 2H), 2.45 (s, 3H), 1.40 (s, 3H), 1.32 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.2, 134.8, 129.9, 128.0, 109.1, 81.9, 78.1, 70.4, 61.2, 59.9, 28.1, 26.1, 21.6; HRMS *m/z* 369.0986 [$C_{15}H_{22}O_7SNa$ $(M+Na)^+$ requires 369.0984].

4.1.22. [1-^{2}H]2,3-*O*-Isopropylidene-2-*C*-(*p*-toluenesulfonyloxy-methyl)-D-erythritol (21). According to the preceding procedure but using $NaBD_4$ instead of $NaBH_4$, lactol **10** (155 mg, 0.45 mmol) gave 150 mg of diol **21** (96%) as a foam: FTIR (neat film) 3436, 2988, 2936, 1598, 1455, 1360, 1218, 1176, 1096, 1062, 991, 836, 667 cm^{-1}; ^{1}H NMR for the major diastereoisomer (300 MHz, $CDCl_3$) δ 7.80 (d, *J*=8.6 Hz, 2H), 7.36 (d, *J*=8.6 Hz, 2H), 4.26 (d, *J*=11.0 Hz, 1H), 4.10 (d, *J*=11.0 Hz, 1H), 4.07 (t, *J*=6.1 Hz, 1H), 3.92–3.81 (m, 2H), 3.62 (br d, *J*=4.9 Hz, 1H), 3.10 (br s, 2H), 2.45 (s, 3H), 1.40 (s, 3H), 1.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.1, 132.5, 129.9, 128.0, 109.0, 81.8, 78.1, 70.4, 60.9 (t, $^1J_{CD}$=22.5 Hz), 59.9, 28.1, 26.0, 21.6; HRMS *m/z* 370.1045 [$C_{15}H_{21}DO_7SNa$ $(M+Na)^+$ requires 370.1046].

4.1.23. [2′-^{2}H]2,3-*O*-Isopropylidene-2-*C*-methyl-D-erythritol (22). Tosylate **20** (145 mg, 0.42 mmol) was dissolved in dry THF (10 mL) and $LiAlD_4$ (55 mg, 1.3 mmol) was added in portions with vigorous stirring (about 1 h). The resulting suspension was stirred for 10 h at reflux, then poured slowly in EtOAc (30 mL), acidified to pH 5 with 10% HCl, and filtered. The filtrate was shaken with a saturated sodium hydrogencarbonate solution (7 mL). The aqueous phase was extracted with EtOAc (3×30 mL) and the combined organic ones were washed with brine (5 mL) and dried (Na_2SO_4). After removal of the solvents under reduced pressure the residual oil was purified by column chromatography on silica gel with a mixture of hexane/EtOAc (3:1 v/v) to give 67 mg of deuterated diol **22** (90%) as a foam: $[\alpha]_D^{25}$ −13.8 (*c* 0.9, $CHCl_3$); FTIR (neat film) 3245, 2987, 2947, 2875, 1460, 1369, 1215, 1180, 1094, 1050, 1030, 931, 862 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.96 (t, J=5.0 Hz, 1H), 3.89–3.86 (m, 2H), 3.61 (d, J=11.0 Hz, 1H), 3.41 (d, J=11.0 Hz, 1H), 3.01 (br s, 2H), 1.45 (s, 3H), 1.40 (s, 3H), 1.35 (t, J=1.8 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 107.8, 82.5, 81.6, 65.2, 60.1, 28.2, 26.5, 22.3 (t, $^1J_{CD}$=19.1 Hz); HRMS *m/z* 200.1007 [$C_8H_{15}DO_4Na$ $(M+Na)^+$ requires 200.1008].

4.1.24. [1-^{2}H]2,3-*O*-Isopropylidene-2-*C*-methyl-D-erythritol (23). According to the preceding procedure but using $LiAlH_4$ instead of $LiAlD_4$, tosylate **21** (120 mg, 0.35 mmol) gave 56 mg of deuterated diol **23** (91%) as a foam: FTIR (neat film) 3247, 2986, 2929, 2874, 1448, 1369, 1218, 1191, 1105, 1035, 932, 872 cm^{-1}; ^1H NMR for the major diastereoisomer (300 MHz, $CDCl_3$) δ 3.96 (t, J=4.9 Hz, 1H), 3.89–3.85 (m, 2H), 3.59 (br s, 1H), 2.73 (br s, 2H), 1.45 (s, 3H), 1.40 (s, 3H), 1.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 107.8, 82.5, 81.6, 64.9 (t, $^1J_{CD}$=18.0 Hz), 60.1, 28.2, 26.6, 22.5; HRMS *m/z* 200.1007 [$C_8H_{15}DO_4Na$ $(M+Na)^+$ requires 200.1008].

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