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Concise asymmetric syntheses of the (+)-2-*C*-methyltetritol isomers

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ABSTRACT

Two brief and facile syntheses of the title compounds have been developed using the diastereocontrolled addition of organometallics to a (*R*)-cyclohexylideneglyceraldehyde-derived ketone as the key steps. The addition of vinylmagnesium bromide to the ketone gave a 1:1 diastereomeric mixture of separable tertiary alcohols, which were converted to the target erythri- and threitols. On the other hand, the reaction of a dithianyl anion with the ketone gave only the single stereoisomer of a tertiary alcohol, which was converted to erythritol.

1. Introduction

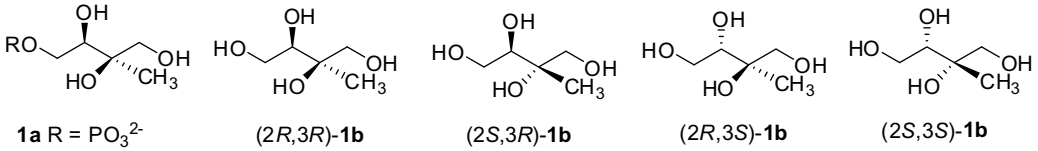
Isoprenoid compounds constitute one of the most chemically diverse families in nature, and are commonly biosynthesized via the intermediacy of isopentenyl pyrophosphate (IPP) and dimethylallyl pyrophosphate (DMAPP) as key intermediates.[1] Over the last few years, independent studies have accumulated evidence for the existence of a mevalonate-independent or methylerythritol phosphate pathway (MIP/MEP) for the biosynthesis of terpenoids in gram-negative bacteria, algae, and plant chloroplasts.[2,3] This new pathway involves the participation of branched isoprenoid precursors, such as 2-*C*-methyl-D-erythritol-4-phosphate **1a**, derived from the condensation of pyruvate and glyceraldehyde-3-phosphate via 1-deoxy-D-xylulose-5-phosphate. The MIP steps for the biosynthesis[4] of terpenoids that involve (+)-2-methylerythritol **1b** as a putative intermediate is of current interest. However, the role of **1b**, as well as the remaining steps of the MIP sequence, is still to be fully clarified. Isotopic experiments have demonstrated a very low incorporation of the tetrol **1b** in the quinones of *Escherichia coli*, suggesting that other compounds may actually be involved in the biosynthetic process. Tetrol (2*S*,3*R*)-**1b** was also isolated from *Convolvulus glomeratus*,[5a] *Liriodendron tulipifera*,[5b] and *Ferula sinaica*, while (2*R*,3*R*)-**1b** was found in *Phlox sublata*.[5d] The chemical structures of **1a** and **1b** are shown in Figure 1.

Since the MEP pathway is absent in animal cells, new opportunities have become available to develop herbicides and drugs against pathogenic bacteria and the malaria parasite.[6a–e] MEP has also been identified as a critical metabolite in the development of the parasite responsible for malaria, *Plasmodium falciparum*.[7] Furthermore, the large amounts of 2-*C*-methyltetritols, present in the air above the Amazonian rain forest, are claimed to be a consequence of the photooxidation of isoprene.[8]

Accordingly, it has become crucial to have a facile access to all the stereomers of **1b**. Most of the known syntheses of **1a**[9a–d] and **1b**[10a–e] are based on asymmetric epoxidation/hydroxylation of suitable substrates, or utilize carbohydrate precursors. More recently, a chemo-enzymatic synthesis[10d] as well as a chemical synthesis using a chiral hydrazone auxiliary[10e] has been reported for all the stereomers of **1b**. Herein, we report a new asymmetric synthesis of **1b** using the known[11] glyceraldehyde derivative **2** as a chiral template.

2. Results and discussion

Our recent strategy on the enantioselective synthesis of tertiary carbinols[12a] and its application[12b] to the syntheses of (*R*)-mevalonolactone and (*S*)-oxybutynin led us to consider the route for the synthesis of the stereomers of **1b**. In those studies, we found that



1a R = PO_3^{2-} (2*R*,3*R*)-**1b** (2*S*,3*R*)-**1b** (2*R*,3*S*)-**1b** (2*S*,3*S*)-**1b**

Figure 1.

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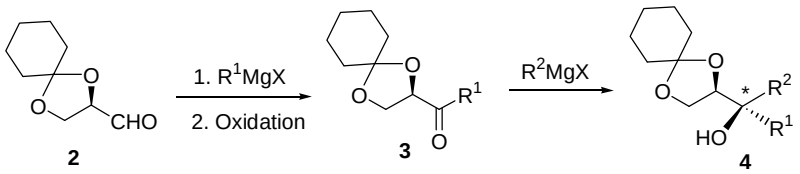


Scheme 1.

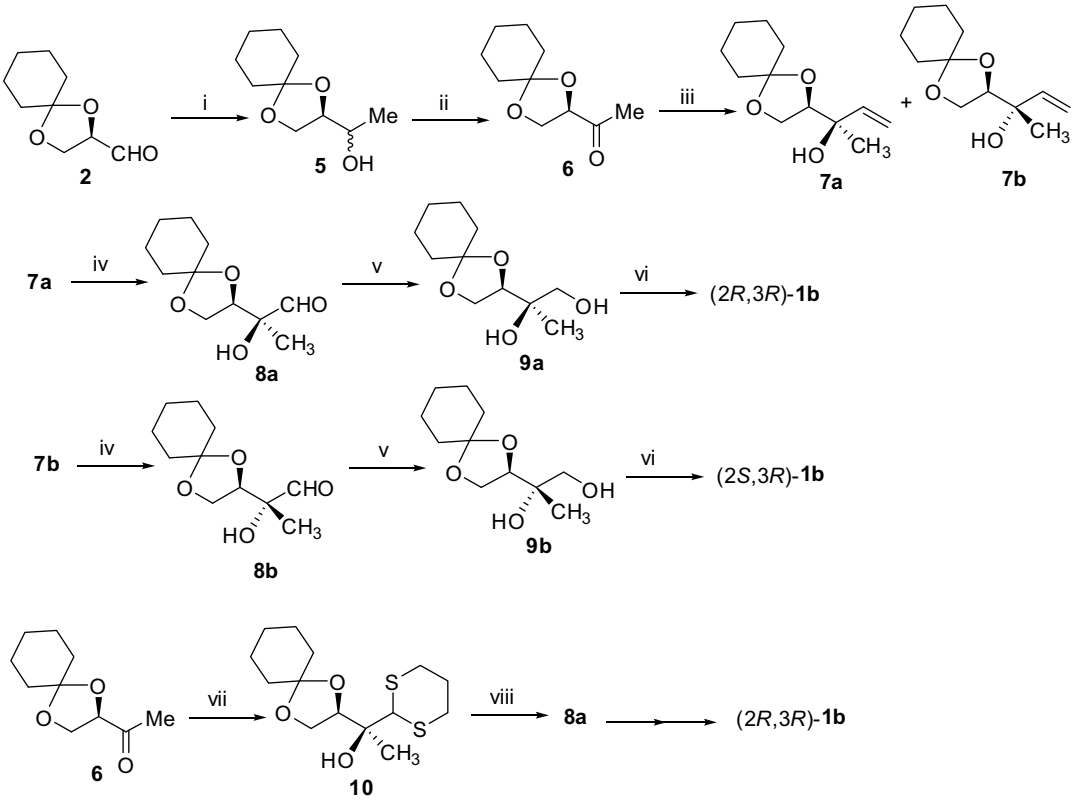
the addition of different Grignard reagents to ketones **3** derived from **2** proceeds with excellent stereoselectivity (Scheme 1). Furthermore, by altering the sequence of the addition of the required Grignard reagents, we could synthesize the *syn*- as well as *anti*-isomers of the tertiary carbinols **4**.

For the synthesis (Scheme 2), aldehyde **2** was reacted with MeMgI to give alcohol **5** as a diastereomeric mixture. Without separating the individual stereomers, carbinol **5** was oxidized with buffered-pyridinium chlorochromate (PCC) to furnish the known[12a] ketone **6**. Upon reaction with vinylmagnesium bromide, this gave the diastereomeric alcohols **7a** and **7b** in a 51:49 ratio. The result was consistent with our earlier observations, wherein the reaction of ketone **6** with alkenylmagnesium bromides was found to proceed with poor diastereoselectivity. After separation by column chromatography, alcohol **7a** was subjected to reductive ozonolysis with O_3/Ph_3P in CH_2Cl_2 to afford aldehyde **8a**. Its reduction with lithium aluminum hydride (LAH) furnished **9a**, which after acidic hydrolysis gave (2*R*,3*R*)-**1b**. Likewise, alcohol **7b** was converted to (2*S*,3*R*)-**1b**. Overall, we have developed a short synthesis of the target compounds using inexpensive reagents, and operationally simple reaction conditions. Although the synthesis was non-selective, the method is well suited for the designated target compound, which is required in all possible isomers. Due to the presence of two stereocenters, there are four possible stereoisomers for **1b**. Herein, we report the efficacy of the method for the synthesis of two of the stereomers of **1b**. However, given that (*S*)-**2** is easily amenable from L-ascorbic acid,[13] the other isomers of **1b** can also be synthesized following our route.

Having completed the above synthesis, we ventured toward a better enantioselective route for **1b**. The addition of alkyl or cycloalkyl Grignard reagents to the glyceraldehyde-derived ketones had been previously found[12a] to furnish enantiomerically pure tertiary alcohols. As a result, we reacted ketone **6** with the 1,3-dithiane anion, generated with ^{t}BuOK in THF. According to our expectation, this produced *syn*-**10** as the sole product. Treatment of **10** with MeI/$CaCO_3$ in aqueous MeCN furnished aldehyde **8a**, which was conveniently converted to (2*R*,3*R*)-**1b**, as above.

3. Conclusion

The development of simple and efficient strategies is a highly desirable goal for organic synthesis. Despite impressive progress,[14a] this remains a very dynamic and challenging area in asymmetric synthesis.[14b,c] The most practical methods are aimed at producing target compounds via reliable routes, utilizing inexpensive and readily available materials. To this end, we have been able to devise, by far the simplest strategy for the synthesis of the



Scheme 2. Reagents and conditions: (i) MeMgI/Et_2O (84%); (ii) PCC/NaOAc/CH_2Cl_2 (86%); (iii) vinylmagnesium bromide/THF (88%); (iv) $O_3/CH_2Cl_2/-78$ °C; Ph_3P (81% for **8a**, 84% for **8b**); (v) LAH/Et_2O (91% for **9a**, 86% for **9b**); (vi) aqueous TFA/CH_2Cl_2 (89% for **1a**, 91% for **1b**); (vii) 1,3-dithiane/^{t}BuOK/THF (72%); (viii) MeI/$CaCO_3$/MeCN–H_2O (4:1) (88%).

target compounds under operationally simple conditions, using inexpensive and readily available reagents/starting materials. Interestingly, the poor diastereoselectivity of the first method was responsible to furnish the erythritol and threitol stereomers in appreciable quantities. On the other hand, the most notable features of the second route was the complete stereocontrol in the organometallic addition to the ketone, providing the required tertiary carbinol as a single diastereomer, and in turn, 2-*C*-methylerythritol.

4. Experimental

4.1. General experimental details

All chemicals (Fluka and Lancanster) were used as received. The other reagents were of AR grade. All anhydrous reactions were carried out under an Ar atmosphere using freshly dried solvents. Unless otherwise mentioned, the organic extracts were dried over anhydrous Na_2SO_4. The IR spectra as thin films were scanned with a Jasco model A-202 FT-IR spectrophotometer. The ^{1}H NMR (200 MHz) and ^{13}C NMR (50 MHz) spectra were recorded with a Bruker AC-200 spectrometer. The optical rotations were recorded with a Jasco DIP 360 digital polarimeter.

4.2. (2*S*/*R*,3*R*)-3,4-Cyclohexanedioxybutan-2-ol 5[12a]

To a well stirred suspension of MeMgI [prepared from Mg (1.73 g, 0.072 mol) and MeI (8.52 g, 0.06 mol)] in diethyl ether (80 mL) was added compound **2** (2.50 g, 0.015 mol) in diethyl ether (25 mL), and the mixture was stirred until the completion of the reaction (cf. TLC, ~4 h). The reaction mixture was quenched with aqueous 10% NH_4Cl. The mixture was filtered and concentrated in vacuo. The residue was dissolved in diethyl ether. The organic layer was washed with water, brine, and dried. Solvent removal in vacuo and column chromatography of the residue afforded the alcohol **5**. Yield: 2.30 (84%); colorless oil; $[\alpha]_D^{22} = +2.4$ (*c* 1.21, $CHCl_3$); IR: 3380, 1478 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.12 (d, *J* = 6.6 Hz, 3H), 1.23–1.39 (m, 4H), 1.57–1.61 (m, 6H), 2.05 (br, 1H), 3.62–3.68 (m, 1H), 3.84–4.03 (m, 3H); ^{13}C NMR: δ 18.4, 18.5, 23.5, 23.7, 24.9, 34.5, 34.6, 35.9, 36.1, 64.6, 65.4, 67.0, 68.6, 78.9, 79.8, 109.3, 109.8.

4.3. (3*R*)-3,4-Cyclohexanedioxybutan-2-one 6[12a]

To a cooled (0 °C) and stirred suspension of PCC (3.48 g, 16.13 mmol) and NaOAc (0.130 g, 1.61 mmol) in CH_2Cl_2 (30 mL) was added the alcohol **5** (2.0 g, 10.75 mmol) in one portion. After stirring for 3 h, the reaction mixture was diluted with diethyl ether (30 mL) and the supernatant was passed through a pad of silica gel (2″ × 1). Removal of solvent in vacuo followed by column chromatography of the residue (silica gel, 0–10% EtOAc/hexane) furnished pure **6**. Yield: 1.70 g (86%); colorless oil; $[\alpha]_D^{22} = +32.0$ (*c* 1.62, $CHCl_3$); IR: 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.42–1.57 (m, 10H), 2.25 (s, 3H), 3.93–4.00 (m, 1H), 4.13–4.21 (m, 1H), 4.32–4.42 (m, 1H); ^{13}C NMR: δ 23.5, 23.7, 24.8, 26.1, 34.3, 35.5, 65.8, 79.9, 111.4, 208.4.

4.4. (3*R*/*S*,4*R*)-4,5-Cyclohexanedioxy-3-methylpent-1-en-3-ol 7a/7b

To a cooled (0 °C) and stirred solution of **6** (1.70 g, 9.24 mmol) in THF (mL) was injected vinylmagnesium bromide (13.86 mmol, 1.0 M in THF). After stirring for 4 h at 0 °C, the reaction was worked up as above, and the crude product was subjected to column chromatography (silica gel, 0–10% EtOAc/hexane) to furnish pure **7a** and **7b** (combined yield: 1.72 g, 88%). Compound **7a**: colorless oil; $[\alpha]_D^{22} = +11.3$ (*c* 1.12, $CHCl_3$); IR: 3475, 3087, 1643 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.23–1.38 (m containing a s at δ 1.30, 5H), 1.42–1.62 (m, 8H), 2.18 (s, 1H), 3.73–4.00 (m, 3H), 5.08–5.35 (m, 2H), 5.72–5.86 (m, 1H); ^{13}C NMR: δ 23.6, 23.8, 25.0, 25.2, 34.6, 35.8, 64.6, 72.3, 80.6, 109.9, 114.2, 140.1. Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 68.03; H, 9.58. Compound **7b**: colorless oil; $[\alpha]_D^{22} = +20.6$ (*c* 1.04, $CHCl_3$); IR: 3452, 3086, 1640 cm^{-1}; ^{1}H NMR: δ 1.24 (s, 3H), 1.28–1.61 (m, 10H), 2.06 (s, 1H), 3.79–3.90 (m, 1H), 3.95–4.16 (m, 2H), 5.11–5.36 (m, 2H), 5.87–6.00 (m, 1H); ^{13}C NMR: δ 23.2, 23.6, 23.8, 25.0, 34.6, 35.8, 64.7, 72.5, 80.6, 109.9, 113.5, 142.0. Anal. Calcd for $C_{12}H_{20}O_3$: C, 67.89; H, 9.50. Found: C, 67.72; H, 9.65.

4.5. (2*S*,3*R*)-3,4-Cyclohexanedioxy-2-methyl-2-hydroxybutanal 8a

Ozone was bubbled through a cooled (−78 °C) solution of **7a** (0.800 g, 3.77 mmol) in CH_2Cl_2 (20 mL) until the solution turned blue. After 0.5 h, the excess O_3 was removed by purging with N_2 (gas), the mixture treated with Ph_3P (2.0 g, 7.55 mmol), and stirred for 16 h at room temperature. Most of the solvent was removed in vacuo, and the residue was dissolved in hexane and chromatographed (silica gel, 0–10% EtOAc/hexane) to furnish pure **8a**. Yield: 0.654 g (81%); colorless oil; $[\alpha]_D^{22} = +16.05$ (*c* 1.52, $CHCl_3$); IR: 3439, 2775, 1732 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.26–1.40 (m containing a s at δ 1.32, 5H), 1.56–1.63 (m, 8H), 2.19 (s, 1H), 3.90–4.08 (m, 3H), 9.69 (s, 1H); ^{13}C NMR: δ 23.5, 23.8, 24.9, 33.8, 35.6, 64.1, 77.3, 78.3, 110.6, 203.5. Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.48; H, 8.45.

4.6. (2*R*,3*R*)-3,4-Cyclohexanedioxy-2-methylbutane-1,2-diol 9a

To a cooled (−5 °C) and stirred suspension of LAH (0.060 g, 1.58 mmol) in diethyl ether (20 mL) was added **8a** (0.650 g, 3.04 mmol) in diethyl ether (10 mL). After stirring the mixture for 3 h at room temperature, the excess hydride was decomposed with aqueous saturated Na_2SO_4, the ether layer was decanted, and the solid residue extracted with the same solvent. Concentration of the organic extract in vacuo afforded pure **9a**. Yield: 0.597 (91%); white solid; mp: 110 °C; $[\alpha]_D^{22} = +11.6$ (*c* 1.02, $CHCl_3$); IR: 3402 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.16 (s, 3H), 1.24–1.40 (m, 2H), 1.56–1.65 (m, 8H), 2.18 (s, 1H), 3.45 (d, *J* = 11.4 Hz, 1H), 3.74 (d, *J* = 11.4 Hz, 1H), 3.83–3.90 (m, 1H), 3.97–4.12 (m, 2H); ^{13}C NMR: δ 19.7, 23.6, 23.9, 25.1, 34.2, 35.9, 64.6, 67.3, 72.6, 78.4, 109.6. Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 61.24; H, 9.42.

4.7. (2*R*,3*R*)-2-Methylbutane-1,2,3,4-tetrol 1b

A mixture of **9a** (0.216 g, 1.0 mmol) and 80% aqueous TFA (0.3 mL) in CH_2Cl_2 (25 mL) was stirred at 0 °C until the completion of the reaction (cf. 3.5 h). The reaction mixture was concentrated in vacuo, the residue taken in MeOH, and subjected to preparative TLC to obtain pure **1b**. Yield: 0.120 g (89%); $[\alpha]_D^{22} = +11.19$ (*c* 1.41, MeOH), [lit.[10e] $[\alpha]_D^{20} = +13$ (*c* = 0.5, MeOH)]; IR: 3427 cm^{-1}; ^{1}H NMR (MeOH-*d*^{4}): δ 1.14 (s, 3H), 3.39–3.48 (m, 1H), 3.60–3.77 (m, 4H); ^{13}C NMR: δ 19.4, 61.7, 66.8, 73.5, 74.5.

4.8. (2*R*,3*R*)-3,4-Cyclohexanedioxy-2-methyl-2-hydroxybutanal 8b

Colourless oil; $[\alpha]_D^{22} = +18.1$ (*c* 1.14, $CHCl_3$); IR: 3455, 2780, 1733 cm^{-1}; ^{1}H NMR ($CDCl_3$): δ 1.16–1.40 (m containing a s at δ 1.27, 5H), 1.62–1.77 (m, 8H), 2.07 (s, 1H), 3.83–3.88 (m, 1H), 3.91–4.16 (m, 1H), 4.24–4.30 (m, 1H), 9.65 (s, 1H); ^{13}C NMR: δ

18.6, 23.3, 23.5, 24.7, 34.0, 35.2, 63.7, 76.4, 77.1, 110.3, 202.6. Anal. Calcd for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.51; H, 8.55.

4.9. (2*S*,3*R*)-3,4-Cyclohexanedioxy-2-methylbutane-1,2-diol 9b

Thick liquid; $[\alpha]_D^{22} = +12.8$ (*c* 1.72, $CHCl_3$); IR: 3433 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.04 (s, 3H), 1.32–1.44 (m, 2H), 1.47–1.65 (m, 8H), 2.26 (s, 1H), 3.42 (d, J = 11.4 Hz, 1H), 3.72 (d, J = 11.4 Hz, 1H), 3.91–4.11 (m, 3H); ^{13}C NMR: δ 19.7, 23.6, 23.8, 24.9, 34.6, 35.5, 64.3, 68.3, 71.4, 79.4 109.8. Anal. Calcd for $C_{11}H_{20}O_4$: C, 61.09; H, 9.32. Found: C, 60.92; H, 9.38.

4.10. (2*S*,3*R*)-2-Methylbutane-1,2,3,4-tetrol 1b

$[\alpha]_D^{22} = +15.0$ (*c* 1.44, MeOH), [lit.[10e] $[\alpha]_D^{20} = +16.5$ (*c* 0.5, MeOH)]; IR: 3443 cm^{-1}; ^1H NMR (MeOH-d_4): δ 1.21 (s, 3H), 3.48–3.60 (m, 2H), 3.65–3.78 (m, 3H); ^{13}C NMR (MeOH-d_4): δ 19.5, 61.8, 66.4, 73.5, 75.2.

4.11. (2*S*,3*R*)-3,4-Cyclohexanedioxy-2-methyl-2-(1′,3′-propanediyldithio)butan-2-ol 10

To a cooled (0 °C) and stirred suspension of ^{t}BuOK (0.370 g, 3.3 mmol) in anhydrous THF (10 mL) was injected 1,3-dithiane (0.396 g, 3.3 mmol) in anhydrous THF (5 mL). After stirring for 0.5 h, compound **6** (0.552 g, 3.0 mmol) in anhydrous THF (5 mL) was injected into the reaction mixture. After stirring for 3 h at 0 °C, the mixture was poured in ice-cold H_2O, and extracted with diethyl ether. The ether layer was washed with H_2O and brine, and dried. Removal of the solvent was followed by column chromatography (silica gel, 0–10% EtOAc/hexane) to give pure **10**. Yield: 0.657 (72%); pale yellow oil; $[\alpha]_D^{22} = +12.45$ (*c* 2.86, $CHCl_3$); IR: 3472, 1280 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.21–1.40 (m containing a s at δ 1.24, 5H), 1.49 (s, 1H), 1.62–1.77 (m, 8H), 2.04–2.11 (m, 2H), 2.83–2.92 (m, 4H), 3.89–4.08 (m, 2H), 4.18 (s, 1H), 4.24–4.30 (m, 1H); ^{13}C NMR: δ 19.3, 23.7, 25.1, 25.8, 30.6, 34.6, 35.8, 50.2, 56.6, 64.4, 74.3, 78.6, 109.8. Anal. Calcd for $C_{14}H_{24}O_3S_2$: C, 55.23; H, 7.95; S, 21.06. Found: C, 55.42; H, 7.81; S, 21.24.

4.12. (2*S*,3*R*)-3,4-Cyclohexanedioxy-2-methyl-2-hydroxybutanal 8a

To a stirred solution of **10** (0.650 g, 2.14 mmol) in 4:1 MeCN–H_2O (25 mL) were added MeI (3.04 g, 21.4 mol) and $CaCO_3$ (1.07 g, 10.7 mol). The reaction mixture was stirred for 24 h at room temperature, treated with H_2O (30 mL) and diethyl ether (60 mL), and further stirred for 1 h. The organic layer was separated, and the aqueous portion was extracted with diethyl ether. The combined organic extracts were washed with H_2O and brine, and dried. Removal of solvent followed by column chromatography (silica gel, 0–10% EtOAc/hexane) of the residue furnished pure **8a**. Yield: 0.402 g (88%).

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