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Efficient syntheses of ^{13}C-labelled erythromycin biosynthetic intermediates. 2: (2*S*,3*S*,4*S*,5*R*,6*R*,7*R*)-3,6,7-trihydroxy-2,4,6-trimethyl[1-^{13}C]nonan-5-olide and *S*-2-acetylaminoethyl (2*R*,3*S*,4*S*,5*R*,6*S*,7*R*)-3,5,6,7-tetrahydroxy-2,4,6-trimethyl[1-^{13}C]nonanethioate

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The ^{13}C-labelled putative erythromycin biosynthetic intermediates, ((2*S*,3*S*,4*S*,5*R*,6*R*,7*R*)-3,6,7-trihydroxy-2,4,6-trimethyl[1-^{13}C]nonan-5-olide and *S*-2-acetylaminoethyl (2*R*,3*S*,4*S*,5*R*,6*S*,7*R*)-3,5,6,7-tetrahydroxy-2,4,6-trimethyl[1-^{13}C]nonanethioate), which would be useful for the investigation of the chain elongation mechanism in erythromycin biosynthesis, were efficiently synthesized via aldol condensation of aldehyde derived from (2*S*,3*R*,4*R*,5*R*)-*tert*-butyldimethylsilyloxy-5-3,4-*O*-isopropylidene-2,4-dimethylheptanol, which was obtained in our previous work on erythromycin A synthesis, and sodium [1-^{13}C]propionate (after conversion to ester).

Keywords: ^{13}C-labelling synthesis; erythromycin biosynthetic intermediate; sodium [1-^{13}C]propionate

Introduction

Erythromycin A, a 14-membered macrolide antibiotic produced by *Saccharopolyspora erythraea*, is widely used in clinical medicine. Cane *et al.* obtained much information about the chain elongation process in the erythromycin biosynthetic pathways from feeding experiments with ^{2}H-, ^{13}C- and/or ^{18}O-labelled compounds in *S. erythraea*.[1–5] In addition, groups led by Leadlay and Katz have employed a genetic approach to study the biosynthesis of 6-deoxyerythronolide B, the first biosynthetic macrolide intermediate of erythromycin A, in *S. erythraea*.[6–9] We are interested in the biosynthetic pathways to 6-deoxyerythronolide B, especially the chain elongation mechanism in erythromycin biosynthesis. In this connection, we have reported an efficient ^{13}C-labelling synthesis of the triketide *S*-2-acetylaminoethyl (2*R*,3*R*,4*R*,5*R*)-3,5-diacetoxy-2,4-dimethyl-4-([^{13}C]methoxy)heptanethioate, which we have proposed to be an erythromycin biosynthetic intermediate.[10]

Here, we describe the efficient ^{13}C-labelling synthesis of two more polyketides, which are putative erythromycin biosynthetic intermediates, as a continuation of our previous work.[10]

Results and discussion

Strategy for ^{13}C-labelling of synthesis of the putative erythromycin biosynthetic intermediates

Although syntheses of biosynthetic intermediates of erythromycin have been reported,[11] the routes are complex and unsuitable for efficient ^{13}C-labelling. Therefore, we planned to develop a more efficient synthetic strategy to obtain the ^{13}C-labelled compounds by utilizing optically active synthetic

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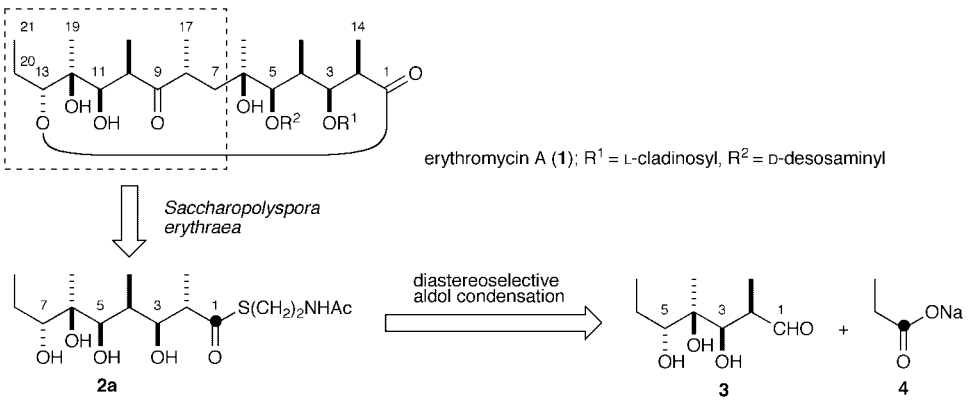
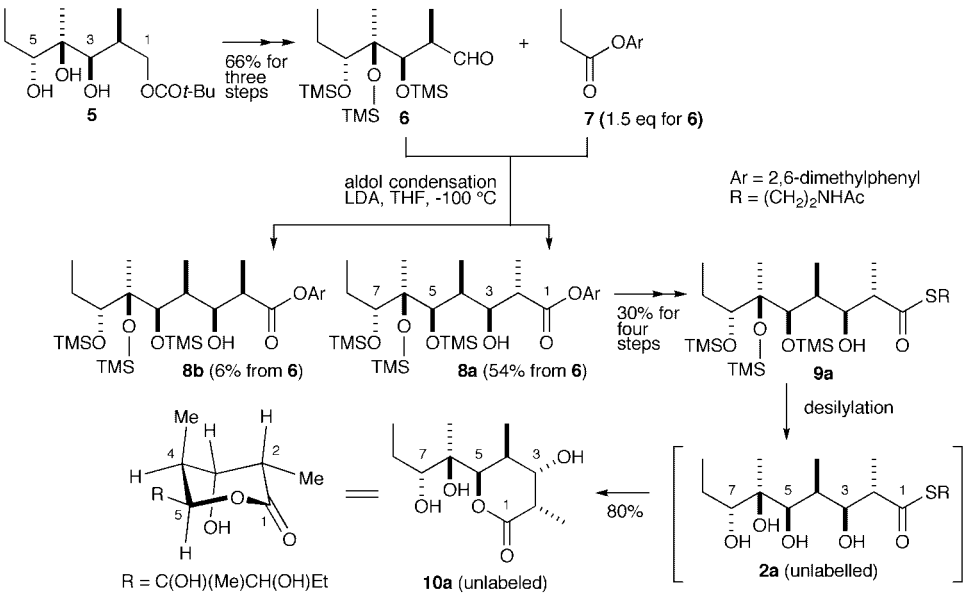
intermediates obtained in our previous work.[12,13] We have already described an efficient ^{13}C-labelling synthesis of the putative erythromycin biosynthetic intermediate, *S*-2-acetylaminoethyl (2*R*,3*R*,4*R*,5*R*)-3,5-diacetoxy-2,4-dimethyl-4-([^{13}C]methoxy)heptanethioate.[10]

As we have previously obtained several aldehydes such as **3**,[12,13] whose absolute configurations are identical to the C-10–C-13 asymmetric carbon atoms of erythromycin A (**1**), here we attempted to synthesize **2a**, which is equivalent to the C-7–C-21 segment of **1** (inside the dotted square in Scheme 1), as a ^{13}C-labelled putative erythromycin biosynthetic intermediate. The basic strategy for synthesis of **2a** was to employ diastereoselective aldol condensation of an aldehyde such as **3** with sodium [1-^{13}C]propionate (**4**) (after conversion to the ester).

As shown in Scheme 2,[14] we prepared aldehyde **6** from ester **5** obtained in our previous work[12] via silylation with trimethylsilyl trifluoromethanesulfonate (TMSOTf), diisobutylaluminum hydride (DIBAL-H) reduction, and pyridium dichromate oxidation in a 66% overall yield. As diastereoselective aldol condensation of an aldehyde branched at C-2 with ester predominantly affords the 3,4-*syn*-product according to the Felkin–Anh model,[15–17] we chose the propionic acid ester, which should predominantly afford the 2,3-*anti*-product on diastereoselective aldol condensation with **6** having C-2-β-Me, in order to obtain the product having the same absolute configuration as C-8 of **1**. As Heathcock's ester **7** has been reported to predominantly afford the 2,3-*anti*-product on diastereoselective aldol condensation with aldehyde,[18] the diastereoselective aldol condensation of aldehydes **6** and **7** was carried out in the presence of LDA at -100°C for 30 min. This reaction predominantly afforded **8a** in a 54% yield from **6** with the **8a**/**8b** ratio of 9:1, as expected.[19] Thioester **9a** was obtained from **8a** via silylation with TMSOTf, DIBAL-H reduction, oxidation with ruthenium (IV) oxide, and thioesterification with 2-acetylaminoethanethiol in a 30% overall yield. The desilylation of **9a** with hydrogen fluoride/pyridine did not afford **2a** (unlabelled), but generated the δ-lactone **10a** (unlabelled)[20] in an 80% yield, analogously to the result in our previous paper.[10] That is, the chair form of **10a** (unlabelled) shown in Scheme 2 might be the lowest-energy chair conformation, as the C-2–Me and C-5–C(OH)(Me)CH(OH)Et moieties can adopt equatorial positions.



Scheme 1. Strategy for synthesis of ^{13}C-labelled putative erythromycin biosynthetic intermediate **2a** from **3** and **4**.



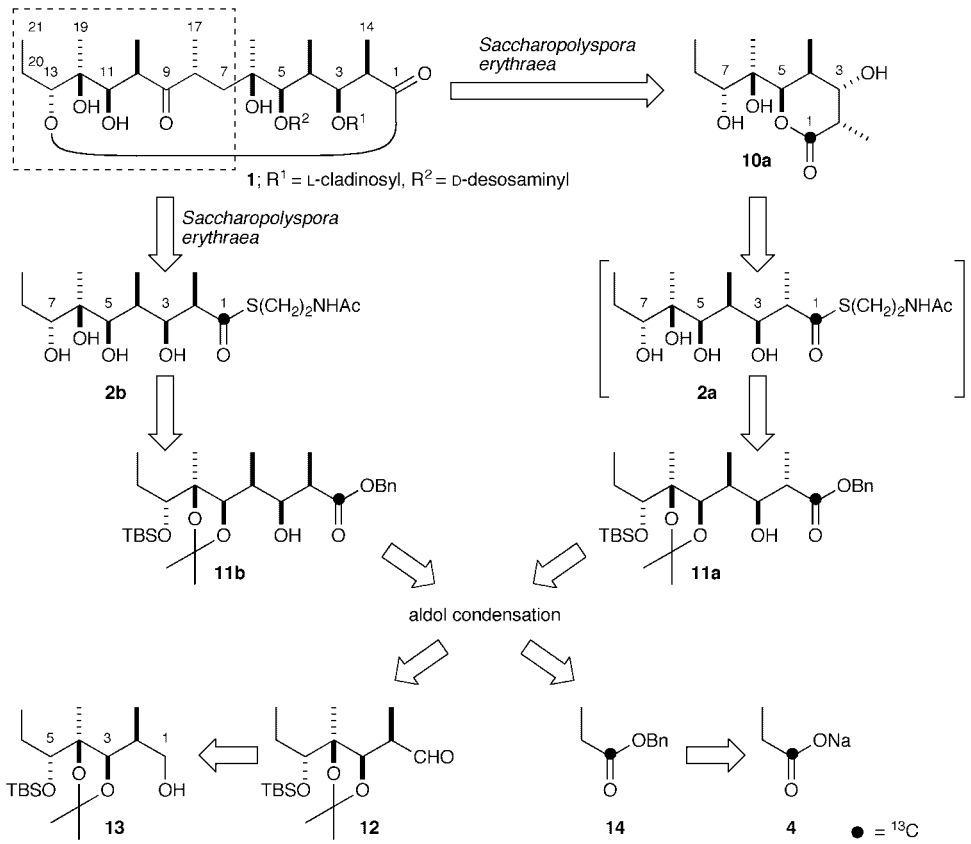
Scheme 2. Synthesis of **2a** (unlabelled) from **5** and **7**.

Thus, **10a** (unlabelled) might be generated from **9a** through the attack of the 5-hydroxyl oxygen on the carbonyl carbon with elimination of 2-acetylaminoethanethioxyl after desilylation. Therefore, as the synthesis of **2a** (unlabelled) appeared to be difficult, we considered the synthesis of **10a** as an alternative. Moreover, as shown in Scheme 3, we attempted to synthesize the tetraol and thioester **2b**, even though **2b** has the opposite absolute configuration at C-8 of **1**. We thought that the δ-lactone might not be generated from **2b** after desilylation, owing to 1,3-diaxial interaction between C-2-Me and C-4-Me. Thus, **2a**, which can be derived from **10a**, and **2b** should be obtainable from esters **11a** and **11b**, respectively. Further, **11a** and **11b** should be obtainable by aldol condensation of aldehyde **12** having C-2-*β*-Me derived from alcohol **13** (obtained in our previous work[12]), with benzyl ester **14** derived from sodium [1-^{13}C]propionate (**4**).

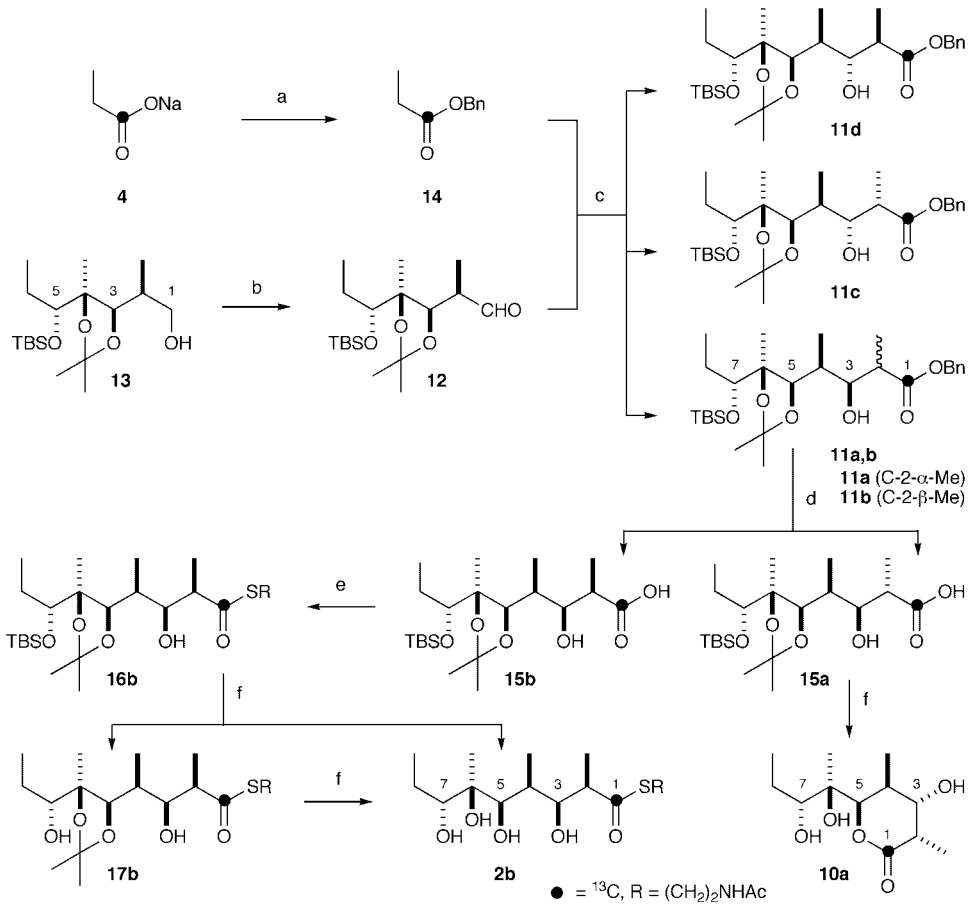
Synthesis of the putative erythromycin biosynthetic intermediates

As shown in Scheme 4, [1-^{13}C]propionyl chloride was prepared from sodium [1-^{13}C]propionate (**4**) treated with phthaloyl chloride under an argon atmosphere at 150°C for 1.5 h on the basis of the methods described in a previous paper.[4] Although esterification of benzyl alcohol with **4** was carried out by using benzyl alcohol and **4** (unlabelled) in the presence of *n*-butyllithium under an argon atmosphere at −78°C for 40 min in the Evans method,[21] ester **14** (unlabelled)[22] was obtained in only a 62% yield from **4** (unlabelled). However, esterification of benzyl alcohol with **4** in the presence of Et_3N under an argon atmosphere at room temperature for 30 min gave ester **14** in a 79% yield from **4**. Oxidation of alcohol **13** with pyridinium dichromate (PDC) in the presence of zeolite (MS-4A)[23] gave aldehyde **12** at room temperature for 1.5 h in a 92% yield. The aldol condensation of **12** and **14** in the presence of LDA under an argon atmosphere at −78°C for 30 min gave a mixture of products. The mixture could be separated by silica gel chromatography to afford a product (6% yield), a mixture (67% yield) of two inseparable products in equal quantity, based on the ^{1}H NMR spectrum, and another product (18% yield). These results indicate that all four products were diastereomers (**11a**, **11b**, **11c**, and **11d**) with regard to the newly generated asymmetric carbon atoms at C-2 and C-3.

The absolute configurations at C-2 and C-3 of these four products were determined by the consideration of both the Zimmerman–Traxler and the Felkin–Anh models for this aldol condensation and the analysis of the ^{1}H NMR spectra of the four products (unlabelled), which were separately synthesized from **12** and **14** (unlabelled), and their derivatives. Firstly, **14** treated with LDA might be transformed to (*E*)- and (*Z*)-enolates of **14** in similar amounts. On the basis of the Zimmerman–Traxler model, the aldol condensation with (*E*)-enolate predominantly affords the 2,3-*anti*-product, whereas that with (*Z*)-enolate predominantly affords the 2,3-*syn*-product. Therefore, the aldol condensation with **12** having C-2-*β*-Me was examined. In the case of the (*E*)-enolate of **14**, the major product was the 2,3-*anti*-3,4-*syn*-product **11a** (2*S*,3*S*) and the minor product was the 2,3-*anti*-3,4-*anti*-product **11d** (2*R*,3*R*), as predicted by the Felkin–Anh model. In the case of the (*Z*)-enolate of **14**, the major product was the 2,3-*syn*-3,4-*syn*-product **11b** (2*R*,3*S*) and the minor product was

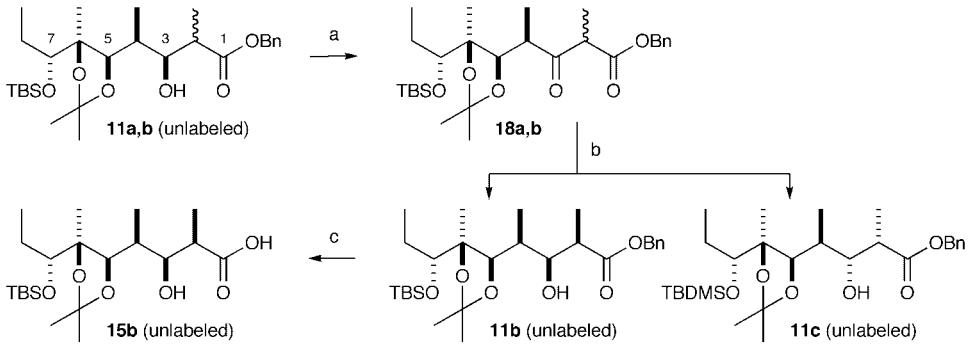


Scheme 3. Strategy for syntheses of ^{13}C-labelled putative erythromycin biosynthetic intermediates **2b** and **10a** from **4** and **13**.



Reaction conditions for syntheses of **2b** and **10a** from **4** and **13**: (a) 1) phthaloyl chloride, 150 °C, 1.5 h; 2) $PhCH_2OH$, Et_3N, CH_2Cl_2, rt, 30 min, 79% for two steps; (b) PDC, MS-4A, CH_2Cl_2, rt, 1.5 h, 92%; (c) LDA, THF, -78 °C, 30 min, 67% (**11a,b**), 6% (**11c**), and 18% (**11d**); (d) H_2, Pd on C, MeOH, rt, 2 h, 45% (**15a**) and 45% (**15b**); (e) $HS(CH_2)_2NHAc$, $(PhO)_2P(O)N_3$, Et_3N, DMF, rt, 19 h, 93%; (f) 48% HF/CH_3CN (1:9), rt, 73% (**2b** from **16b** for 8 h) and 14% (**17b** from **16b**); 61% (**2b** from **17b** for 7 h); 50% (**10a** from **15a** for 6 h).

Scheme 4



Reaction conditions for syntheses of **11b** (unlabeled), **11c** (unlabeled), and **15b** (unlabeled) from **11a,b** (unlabeled) for determination of absolute configuration of **11a**, **11b**, **11c**, and **11d**: (a) DMSO, $(CF_3CO)_2O$, Et_3N, CH_2Cl_2, -78 °C, 30 min, 81%; (b) $Zn(BH_4)_2$, Et_2O, 0 °C, 2.5 h, 35% (**11b** (unlabeled)) and 45% (**11c** (unlabeled)); (c) H_2, Pd on C, MeOH, rt, 2 h, 90%.

Scheme 5

the 2,3-*syn*-3,4-*anti*-product **11c** (2*S*,3*R*), as predicted. Our unpublished ^{1}H NMR data for similar compounds indicated that the 3,4-*anti*-form showed $J_{2,3} = 2$–4 Hz and the 3,4-*syn*-form showed $J_{2,3} = 9$–10 Hz, irrespective of the absolute configuration at C-2. The values of $J_{2,3} = 8.8$, 8.9, 9.0, and 9.6 Hz in the ^{1}H NMR spectrum of the mixture of two inseparable unlabelled products, obtained from aldol condensation of **12** and **14** (unlabelled), led us to postulate that these products were **11a** (unlabelled) and **11b** (unlabelled), i.e. the 3,4-*syn*-form. Thus, we designated this mixture as **11a,b** (unlabelled), and we similarly designated the

mixture of two inseparable products obtained from the aldol condensation of **12** and **14** as **11a,b**. On the other hand, the values of $J_{2,3}$ = 3.4, 3.5 Hz and $J_{2,3}$ = 1.7, 4.9 Hz in the ^{1}H NMR spectra of the two minor unlabelled products led us to postulate that these products were **11c** (unlabelled) and **11d** (unlabelled), i.e. the 3,4-*anti*-form. Further, as shown in Scheme 5, Swern oxidation[24] of the 3-hydroxy ester **11a,b** (unlabelled) with DMSO, trifluoroacetic anhydride, and Et_3N under an argon atmosphere at −78°C for 30 min gave the 3-oxo ester **18a,b** in an 81% yield. Zinc borohydride ($Zn(BH_4)_2$) reduction of 3-oxo ester affords the 2,3-*syn*-product,[25] and its application (argon atmosphere, 0°C, 2.5 h) to **18a,b** gave the 2,3-*syn*-3-hydroxy esters **11b** (unlabelled), which was identified on the basis of $J_{2,3}$ = 8.8, 8.9 Hz in its ^{1}H NMR spectrum, and **11c** (unlabelled), which was identified on the basis of $J_{2,3}$ = 3.4, 3.5 Hz, in 35 and 45% yields, respectively. By comparison of the ^{1}H NMR spectra of the two minor unlabelled products, which were generated from **12** and **14** (unlabelled), with the ^{1}H NMR spectrum of **11c** (unlabelled), which was synthesized via Swern oxidation and $Zn(BH_4)_2$ reduction of **11a,b** (unlabelled), these two minor unlabelled products were identified as **11c** (unlabelled) and **11d** (unlabelled). Moreover, as shown in Scheme 4, the hydrogenolysis of **11a,b** on palladium–carbon at room temperature for 2 h afforded two acids that were separable by silica gel chromatography, **15a** and **15b**, in a 45% yield. By comparison of the ^{1}H NMR spectra of the two acids **15a** (unlabelled) and **15b** (unlabelled) prepared from **11a,b** (unlabelled) by hydrogenolysis with that of **15b** (unlabelled), which was prepared from hydrogenolysis of **11b** (unlabelled) synthesized via Swern oxidation and zinc borohydride reduction of **11a,b** (unlabelled), the absolute configurations of the two acids could be identified. Consequently, we had established the absolute configuration of all four products generated from the aldol condensation of **12** and **14**. As shown in Scheme 4, the product obtained in a 6% yield was identified as **11c**, that obtained in a 67% yield was identified as a mixture of **11a** and **11b** in equal quantity, and that obtained in an 18% yield was identified as **11d**.

Deprotection and cyclization of **15a** in a 48% HF/CH_3CN (1:9) at room temperature for 6 h directly gave the desired δ-lactone **10a** in a 50% yield. Thioesterification[4,26] of **15b** with 2-acetylaminoethanethiol in DMF in the presence of diphenylphosphonyl azide and Et_3N at room temperature for 19 h gave the thioester **16b** in a 93% yield. Finally, deprotection of **16b** in 48% HF/CH_3CN (1:9) at room temperature for 8 h gave the diol **17b** (14% yield) and the tetraol **2b** (73% yield), and repeated reaction of recovered **17b** gave further **2b** in a 61% yield. Finally, the desired **2b** was obtained from **15b** in a 76% overall yield. Thus, we had obtained the desired ^{13}C-labelled putative erythromycin biosynthetic intermediates **10a** and **2b**.

Experimental

Materials and instruments

Sodium [1-^{13}C]propionate (**4**) (99 atom% ^{13}C) was purchased from Cambridge Isotope Laboratories. (2*S*,3*R*,4*R*,5*R*)-*tert*-Butyldimethylsilyloxy-5-3,4-*O*-isopropylidene-2,4-dimethylheptanol (**2**) (>95% e.e.) synthesized in our previous work[12] was used. All other chemicals were of analytical grade and commercially available. ^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL GX-400, GX-500, or GSX-400 (^{1}H: 400 or 500 MHz and ^{13}C: 100 MHz) spectrometer. IR spectra were recorded on a Jasco VALORA-III FT-IR spectrometer. MS spectra were obtained with a JEOL JMS-DX-302 spectrometer.

Benzyl [1-^{13}C]propionate (14)

Sodium [1-^{13}C]propionate (**4**) (1 g, 10.4 mmol) and phthaloyl chloride (2 ml, 13.9 mmol) were mixed and heated at 150°C for 1.5 h under an argon atmosphere. The resulting [1-^{13}C]propionyl chloride was distilled into dry CH_2Cl_2 (2 ml). To a solution of benzyl alcohol (1.3 ml, 12.6 mmol) and Et_3N (7 ml, 50.2 mmol) in dry CH_2Cl_2 (2 ml) was added dropwise the above solution of [1-^{13}C]propionyl chloride in dry CH_2Cl_2 under an argon atmosphere at 0°C, and the whole was stirred for 30 min at room temperature. The reaction mixture was diluted with Et_2O, and washed with 10% HCl, sat. $NaHCO_3$ aq., and brine, dried over anhydrous $MgSO_4$ and evaporated. Chromatography of the crude product on silica gel with Et_2O/hexane (2:1) gave **14** (1.35 g, 79%), ^{1}H NMR ($CDCl_3$) δ: 1.17 (dt, 3H, $^3J_{1H13C}$ = 5.5 Hz, J = 7.6 Hz, 3-$\underline{H}_3$), 2.39 (quintet, 2H, J = 7.6 Hz, 2-$\underline{H}_2$), 5.12 (d, 2H, $^3J_{1H13C}$ = 3.1 Hz, phenyl-C$\underline{H}_2$), 7.35 (m, 5H, phenyl-$\underline{H}_5$); ^{13}C NMR ($CDCl_3$) δ: 174.3 (1-^{13}C); FAB-MS (glycerol) *m/z*: 166 (MH^+).

(2*R*,3*R*,4*R*,5*R*)-5-*tert*-Butyldimethylsilyloxy-3,4-*O*-isopropylidene-2,4-dimethylheptanal (12)

To a solution of (2*S*,3*R*,4*R*,5*R*)-*tert*-butyldimethylsilyloxy-5-3,4-*O*-isopropylidene-2,4-dimethylheptanol (**13**) (4.17 g, 12.0 mmol) in dry CH_2Cl_2 (20 ml) was added zeolite (MS-4A, 9.2 g) at room temperature. To this suspension was added PDC (9.2 g, 24.5 mmol) at 0°C, and the whole was stirred for 1.5 h at room temperature. The reaction mixture was diluted with Et_2O and filtered through Florisil and Celite. Repeated elution with Et_2O gave **12** (3.83 g, 92%), ^{1}H NMR ($CDCl_3$) δ: 0.07 (s, 3H, isopropylidene-C$\underline{H}_3$), 0.10 (s, 3H, isopropylidene-C$\underline{H}_3$), 0.89 (s, 9H, SiC(C$\underline{H}_3$)$_3$), 0.98 (t, 3H, J = 7.6 Hz, 7-$\underline{H}_3$), 1.16 (s, 3H, 4-C$\underline{H}_3$), 1.24 (d, 3H, J = 7.3 Hz, 2-C$\underline{H}_3$), 1.37 (s, 3H, SiC$\underline{H}_3$), 1.40 (s, 3H, SiC$\underline{H}_3$), 1.48 (m, 1H, 6-$\underline{H}$), 1.79 (m, 1H, 6-$\underline{H}$), 2.73 (m, 1H, 2-$\underline{H}$), 3.59 (t, 1H, J = 5.6 Hz, 5-$\underline{H}$), 4.35 (d, 1H, J = 5.9 Hz, 3-$\underline{H}$), 9.64 (d, 1H, J = 2.5 Hz, 1-$\underline{H}$).

Benzyl (2*S*,3*S*,4*S*,5*R*,6*R*,7*R*)- and benzyl (2*R*,3*S*,4*S*,5*R*,6*R*,7*R*)-7-*tert*-butyldimethylsilyloxy-3-hydroxy-5,6-*O*-isopropylidene-2,4,6-trimethyl[1-^{13}C]nonanoate (11a,b), (2*S*,3*R*,4*S*,5*R*,6*R*,7*R*) (11c) and (2*R*,3*R*,4*S*,5*R*,6*R*,7*R*) (11d)

To a solution of diisopropylamine (1.3 ml, 9.28 mmol) in dry THF (12 ml) was added dropwise *n*-butyllithium (1.4 M in hexane, 5.9 ml, 8.26 mmol) at −78°C under an argon atmosphere, and the mixture was stirred for 5 min at 0°C. To this solution was added dropwise a solution of **14** (1.35 g, 8.18 mmol) in dry THF (5 ml) at −78°C, and the solution was stirred for 30 min. To this solution was added dropwise a solution of **12** (3.83 g, 11.1 mmol) in dry THF (5 ml) at −78°C, and the whole was stirred for 30 min at this temperature. The reaction was quenched with sat. NH_4Cl aq. and extracted with Et_2O. The combined extract was washed with brine, dried over anhydrous $MgSO_4$, and evaporated. Chromatography of the crude product on silica gel with Et_2O/hexane (1:4) gave **11c** (259 mg, 6%) and **11a,b** (2.80 g, 67%), and further elution with Et_2O:hexane (1:2) gave **11d** (739 mg, 18%), data of **11a,b**; ^{1}H NMR ($CDCl_3$) δ: 0.08 (s, 3H, isopropylidene-C$\underline{H}_3$), 0.08 (s, 3H, isopropylidene-C$\underline{H}_3$), 0.90 (s, 9H, SiC(C$\underline{H}_3$)$_3$), 0.94 (t, 3H, J = 7.5 Hz, 9-$\underline{H}_3$), 1.01 (d, 3H, J = 7.0 Hz, 4-C$\underline{H}_3$), 1.30 (dd, 3H, $^3J_{1H13C}$ = 5.0 Hz, J = 6.9 Hz, 2-C$\underline{H}_3$),

1.34 (s, 3H, 6-C$\underline{H}_3$), 1.39 (s, 3H, SiC$\underline{H}_3$), 1.58 (s, 3H, SiC$\underline{H}_3$), 1.66, (m, 1H, 8-$\underline{H}$), 1.80 (m, 1H, 4-$\underline{H}$), 2.68 (m, 1H, 2-$\underline{H}$), 3.54 (dd, 1H, J = 4.6, 6.4 Hz, 7-$\underline{H}$), 3.82 (d, 1H, J = 9.2 Hz, 3-$\underline{H}$), 4.04 (d, 1H, J = 3.4 Hz, 5-$\underline{H}$), 5.09 (m, 2H, phenyl-C$\underline{H}_2$), 7.35 (m, 5H, phenyl-$\underline{H}_5$); ^{13}C NMR ($CDCl_3$) δ: 174.6 (1-^{13}C); FAB-MS (glycerol) *m/z*: 510 (MH^+), data of **11a,b** (unlabelled); ^{1}H NMR ($CDCl_3$) δ: 0.08 (s, 3H, isopropylidene-C$\underline{H}_3$), 0.09 (s, 3H, isopropylidene-C$\underline{H}_3$), 0.90 (s, 9H, SiC(C$\underline{H}_3$)$_3$), 0.95 (t, 3H, J = 7.6 Hz, 9-$\underline{H}_3$), 1.01 (d, 3H, J = 6.8 Hz, 4-C$\underline{H}_3$), 1.02 (d, 3H, J = 7.2 Hz, 4-C$\underline{H}_3$), 1.10 (s, 3H, 6-C$\underline{H}_3$), 1.30 (d, 3H, J = 6.8 Hz, 2-C$\underline{H}_3$), 1.33 (s, 3H, SiC$\underline{H}_3$), 1.39 (s, 3H, SiC$\underline{H}_3$), 1.48 (m, 1H, 8-$\underline{H}$), 1.67 (m, 1H, 8-$\underline{H}$), 1.79 (m, 1H, 4-$\underline{H}$), 1.97 (m, 1H, 4-$\underline{H}$), 2.67 (dq, 1H, J = 6.8, 9.0 Hz, 2-$\underline{H}$), 2.83 (dq, 1H, J = 6.8, 8.8 Hz, 2-$\underline{H}$), 3.54 (t, 1H, J = 5.5 Hz, 7-$\underline{H}$), 3.59 (t, 1H, J = 5.5 Hz, 7-$\underline{H}$), 3.82 (dd, 1H, J = 2.1, 8.9 Hz, 3-$\underline{H}$), 3.96 (dd, 1H, J = 1.6, 9.6 Hz, 3-$\underline{H}$), 4.04 (d, 1H, J = 3.4 Hz, 5-$\underline{H}$), 4.05 (d, 1H, J = 3.9 Hz, 5-$\underline{H}$), 5.10 (m, 2H, phenyl-C$\underline{H}_2$), 7.34 (m, 5H, phenyl-$\underline{H}_5$), data of **11c** (unlabelled); ^{1}H NMR ($CDCl_3$) δ: 0.07 (s, 3H, isopropylidene-C$\underline{H}_3$), 0.10 (s, 3H, isopropylidene-C$\underline{H}_3$), 0.90 (s, 9H, SiC(C$\underline{H}_3$)$_3$), 0.96 (t, 3H, J = 7.4 Hz, 9-$\underline{H}_3$), 0.96 (d, 3H, J = 6.8 Hz, 4-C$\underline{H}_3$), 1.19 (s, 3H, 6-C$\underline{H}_3$), 1.20 (d, 3H, J = 8.1 Hz, 2-C$\underline{H}_3$), 1.34 (s, 3H, SiC$\underline{H}_3$), 1.41 (s, 3H, SiC$\underline{H}_3$), 1.70 (m, 1H, 8-$\underline{H}$), 1.84 (m, 1H, 4-$\underline{H}$), 2.74 (dq, 1H, J = 3.4, 7.3 Hz, 2-$\underline{H}$), 3.57 (t, 1H, J = 5.4 Hz, 7-$\underline{H}$), 3.89 (dd, 1H, J = 3.5, 8.5 Hz, 3-$\underline{H}$), 4.39 (s, 1H, 5-$\underline{H}$), 5.08 (m, 2H, phenyl-C$\underline{H}_2$), 7.35 (m, 5H, phenyl-$\underline{H}_5$), data of **11d** (unlabelled); ^{1}H NMR ($CDCl_3$) δ: 0.07 (s, 6H, 2 × isopropylidene-C$\underline{H}_3$), 0.90 (s, 9H, SiC(C$\underline{H}_3$)$_3$), 0.98 (t, 3H, J = 7.5 Hz, 9-$\underline{H}_3$), 1.10 (d, 3H, J = 9.8 Hz, 4-C$\underline{H}_3$), 1.10 (s, 3H, 6-C$\underline{H}_3$), 1.33 (s, 3H, SiC$\underline{H}_3$), 1.34 (d, 3H, J = 11.2 Hz, 2-C$\underline{H}_3$), 1.41 (s, 3H, SiC$\underline{H}_3$), 1.76 (m, 1H, 8-$\underline{H}$), 2.02 (m, 1H, 4-$\underline{H}$), 2.67 (dq, 1H, J = 1.7, 7.3 Hz, 2-$\underline{H}$), 3.55 (t, 1H, J = 5.4 Hz, 7-$\underline{H}$), 3.60 (d, 1H, J = 4.9 Hz, 3-$\underline{H}$), 3.90 (d, 1H, J = 4.2 Hz, 5-$\underline{H}$), 5.10 (m, 2H, phenyl-C$\underline{H}_2$), 7.35 (m, 5H, phenyl-$\underline{H}_5$).

(2*S*,3*S*,4*S*,5*R*,6*R*,7*R*)-7-*tert*-Butyldimethylsilyloxy-3-hydroxy-5,6-*O*-isopropylidene-2,4,6-trimethyl[1-^{13}C]nonanoic acid (15a) and (2*R*,3*S*,4*S*,5*R*,6*R*,7*R*) (15b)

To a solution of **11a,b** (4.88 g, 9.57 mmol) in MeOH (50 ml) was added 10% palladium–carbon (500 mg), and the mixture was stirred for 2 h at room temperature under a hydrogen atmosphere. The reaction mixture was filtered through a Celite pad and evaporated. Chromatography of the crude product on silica gel with AcOEt/hexane (1:1) gave **15b** (1.8 g, 45%) and further elution with $CHCl_3$:MeOH (10:1) gave **15a** (1.8 g, 45%), data of **15a**; ^{1}H NMR ($CDCl_3$) δ: 0.07 (s, 3H, isopropylidene-C$\underline{H}_3$), 0.09 (s, 3H, isopropylidene-C$\underline{H}_3$), 0.89 (s, 9H, SiC(C$\underline{H}_3$)$_3$), 0.98 (t, 3H, J = 7.5 Hz, 9-$\underline{H}_3$), 1.03 (d, 3H, J = 6.7 Hz, 4-C$\underline{H}_3$), 1.21 (s, 3H, 6-C$\underline{H}_3$), 1.25 (dd, 3H, $^3J_{1H13C}$ = 4.9 Hz, J = 7.0 Hz, 2-C$\underline{H}_3$), 1.35 (s, 3H, SiC$\underline{H}_3$), 1.43 (s, 3H, SiC$\underline{H}_3$), 1.78, (m, 1H, 8-$\underline{H}$), 2.02 (br, 1H, 4-$\underline{H}$), 2.56 (br, 1H, 2-$\underline{H}$), 3.50 (br, 1H, 7-$\underline{H}$), 3.90 (br, 1H, 3-$\underline{H}$), 4.12 (br, 1H, 5-$\underline{H}$); ^{13}C NMR ($CDCl_3$) δ: 177.5 (1-^{13}C); FAB-MS (glycerol) *m/z*: 420 (MH^+), data of **15b**; ^{1}H NMR ($CDCl_3$) δ: 0.08 (s, 3H, isopropylidene-C$\underline{H}_3$), 0.09 (s, 3H, isopropylidene-C$\underline{H}_3$), 0.89 (s, 9H, SiC(C$\underline{H}_3$)$_3$), 0.97 (t, 3H, J = 7.6 Hz, 9-$\underline{H}_3$), 1.05 (d, 3H, J = 6.7 Hz, 4-C$\underline{H}_3$), 1.20 (s, 3H, 6-C$\underline{H}_3$), 1.28 (dd, 3H, $^3J_{1H13C}$ = 4.9 Hz, J = 7.0 Hz, 2-C$\underline{H}_3$), 1.36 (s, 3H, SiC$\underline{H}_3$), 1.43 (s, 3H, SiC$\underline{H}_3$), 1.43, (m, 1H, 8-$\underline{H}$), 1.75 (m, 1H, 8-$\underline{H}$), 2.01 (m, 1H, 4-$\underline{H}$), 2.71 (q, 1H, J = 7.3 Hz, 2-$\underline{H}$), 3.57 (t, 1H, J = 5.5 Hz, 7-$\underline{H}$), 3.94 (m, 1H, 3-$\underline{H}$), 4.08 (d, 1H, J = 2.4 Hz, 5-$\underline{H}$); ^{13}C NMR ($CDCl_3$) δ: 177.5 (1-^{13}C); FAB-MS (glycerol) *m/z*: 420 (MH^+), data of **15b** (unlabelled); ^{1}H NMR ($CDCl_3$) δ: 0.08 (s, 3H, isopropylidene-C$\underline{H}_3$), 0.09 (s, 3H, isopropylidene-C$\underline{H}_3$), 0.88 (s, 9H, SiC(C$\underline{H}_3$)$_3$), 0.98 (t, 3H, J = 7.6 Hz, 9-$\underline{H}_3$), 1.02 (d, 3H, J = 6.4 Hz, 4-C$\underline{H}_3$), 1.20 (s, 3H, 6-C$\underline{H}_3$), 1.28 (d, 3H J = 6.4 Hz, 2-C$\underline{H}_3$), 1.36 (s, 3H, SiC$\underline{H}_3$), 1.41 (s, 3H, SiC$\underline{H}_3$), 1.43, (m, 1H, 8-$\underline{H}$), 1.78 (m, 1H, 8-$\underline{H}$), 2.01 (br, 1H, 4-$\underline{H}$), 2.57 (br, 1H, 2-$\underline{H}$), 3.56 (br, 1H, 7-$\underline{H}$), 3.92 (br, 1H, 3-$\underline{H}$), 4.03 (br, 1H, 5-$\underline{H}$).

(2*S*,3*S*,4*S*,5*R*,6*R*,7*R*)-3,6,7-Trihydroxy-2,4,6-trimethyl[1-^{13}C]-nonan-5-olide (10a)

A solution of **15a** (389 mg, 0.927 mmol) in 48% HF/CH_3CN (1:9, 9.5 ml) was stirred for 6 h at room temperature, then added dropwise to a suspension of $NaHCO_3$ in CH_2Cl_2, and the whole was stirred for 30 min at room temperature. To this suspension was added anhydrous $MgSO_4$ and the whole was stirred for 30 min at room temperature. The suspension was filtered and the filtrate was evaporated. Chromatography of the crude product on silica gel with AcOEt/hexane (2:1) gave **10a** (114 mg, 50%), ^{1}H NMR ($CDCl_3$) δ: 1.08 (t, 3H, J = 7.3 Hz, 9-$\underline{H}_3$), 1.13 (s, 3H, 6-C$\underline{H}_3$), 1.18 (d, 3H, J = 7.3 Hz, 4-C$\underline{H}_3$), 1.33 (dd, 3H, $^3J_{1H13C}$ = 5.0 Hz, J = 7.2 Hz, 2-C$\underline{H}_3$), 1.40 (m, 1H, 8-$\underline{H}$), 1.72 (m, 1H, 8-$\underline{H}$), 2.22 (m, 1H, 4-$\underline{H}$), 2.72 (ddt, 1H, $^2J_{1H13C}$ = 15.2 Hz, J = 3.7, 7.6 Hz, 2-$\underline{H}$), 3.40 (dt, 1H, J = 1.8, 11.0 Hz, 7-$\underline{H}$), 3.88 (dt, 1H, J = 3.7, 11.9 Hz, 3-$\underline{H}$), 4.97 (d, 1H, J = 2.8 Hz, 5-$\underline{H}$); ^{13}C NMR ($CDCl_3$) δ: 174.1 (1-^{13}C); IR ($CHCl_3$) cm^{-1}: 3447, 2973, 2938, 1685, 1457, 1382, 1331, 1160, 1115, 979; FAB-MS (glycerol) *m/z*: 248 (MH^+).

S-2-Acetylaminoethyl (2*R*,3*S*,4*S*,5*R*,6*R*,7*R*)-7-*tert*-butyldimethylsilyloxy-3-hydroxy-5,6-*O*-isopropylidene-2,4,6-trimethyl[1-^{13}C]nonanethioate (16b)

To a solution of **15b** (588 mg, 1.40 mmol) and 2-acetylaminoethanethiol (1.53 g, 12.8 mmol) in DMF (800 μl) was added diphenylphosphonyl azide (900 μl, 4.19 mmol) under an argon atmosphere. To this solution was added Et_3N (1.2 ml, 8.61 mmol) at 0°C, and the whole was stirred for 19 h at room temperature. The reaction mixture was quenched with sat. NH_4Cl aq. and extracted with Et_2O. The combined extract was washed with 10% Na_2CO_3 aq. and brine, dried over anhydrous $MgSO_4$, and evaporated. Chromatography of the crude product on silica gel with AcOEt/hexane (2:1) gave **16b** (861 mg, 93%), ^{1}H NMR ($CDCl_3$) δ: 0.09 (s, 3H, isopropylidene-C$\underline{H}_3$), 0.10 (s, 3H, isopropylidene-C$\underline{H}_3$), 0.91 (s, 9H, SiC(C$\underline{H}_3$)$_3$), 0.97 (t, 3H, J = 7.6 Hz, 9-$\underline{H}_3$), 1.06 (d, 3H, J = 7.0 Hz, 4-C$\underline{H}_3$), 1.17 (s, 3H, 6-C$\underline{H}_3$), 1.32 (dd, 3H, $^3J_{1H13C}$ = 5.4 Hz, J = 6.7 Hz, 2-C$\underline{H}_3$), 1.34 (s, 3H, SiC$\underline{H}_3$), 1.41 (s, 3H, SiC$\underline{H}_3$), 1.41, (m, 1H, 8-$\underline{H}$), 1.73 (m, 1H, 8-$\underline{H}$), 1.87 (m, 1H, 4-$\underline{H}$), 1.97 (s, 3H, COC$\underline{H}_3$), 2.87 (m, 1H, 2-$\underline{H}$), 2.95 (m, 1H, SC$\underline{H}$), 3.06 (m, 1H, SC$\underline{H}$), 3.42 (m, 2H, SC$\underline{H}_2$C$\underline{H}_2$), 3.56 (dt, 1H, J = 4.9, 5.8 Hz, 7-$\underline{H}$), 3.88 (d, 1H, J = 7.6 Hz, 3-$\underline{H}$), 4.04 (d, 1H, J = 3.4 Hz, 5-$\underline{H}$), 5.75 (br, 1H, N$\underline{H}$); ^{13}C NMR ($CDCl_3$) δ: 202.3 (1-^{13}C); FAB-MS (glycerol) *m/z*: 521 (MH^+).

S-2-Acetylaminoethyl (2*R*,3*S*,4*S*,5*R*,6*R*,7*R*)-3,7-dihydroxy-5,6-*O*-isopropylidene-2,4,6-trimethyl[1-^{13}C]nonanethioate (16b) and *S*-2-acetylaminoethyl (2*R*,3*S*,4*S*,5*R*,6*R*,7*R*)-3,5,6,7-tetrahydroxy-2,4,6-trimethyl[1-^{13}C]nonanethioate (7b)

A solution of **16b** (441 mg, 0.847 mmol) in 48% HF/CH_3CN (1:9, 10 ml) was stirred for 8 h at room temperature, then added dropwise to a suspension of $NaHCO_3$ in CH_2Cl_2, and the whole was stirred for 30 min at room temperature. To this suspension was added anhydrous $MgSO_4$ and the whole was stirred for 30 min at room temperature. The suspension was filtered and the filtrate was evaporated. Chromatography of the crude

product on silica gel with $CHCl_3$/MeOH (30:1) gave **17b** (47 mg, 14%), and further elution with $CHCl_3$:MeOH (7:1) gave **2b** (227 mg, 73%). **17b** (279 mg, 0.688 mmol) was transformed to **2b** (155 mg, 61%) for 7 h by the same procedure, data of **2b**; ^{1}H NMR ($CDCl_3$) δ: 1.06 (t, 3H, J = 7.3 Hz, 9-H$_3$), 1.06 (s, 3H, 6-CH$_3$), 1.12 (d, 3H, J = 7.0 Hz, 4-CH$_3$), 1.31 (dd, 3H, $^3J_{1H13C}$ = 5.5 Hz, J = 6.7 Hz, 2-CH$_3$), 1.44 (m, 1H, 8-H), 1.59 (m, 1H, 8-H), 1.83 (m, 1H, 4-H), 1.97 (s, 3H, COCH$_3$), 2.90 (m, 1H, 2-H), 3.02 (q, 2H, SCH$_2$), 3.34 (dd, 1H, J = 1.8, 10.7 Hz, 7-H), 3.44 (m, 2H, SCH$_2$CH$_2$), 4.04 (d, 1H, J = 1.8 Hz, 5-H), 5.88 (br, 1H, NH); ^{13}C NMR ($CDCl_3$) δ: 202.9 (1-^{13}C); IR ($CHCl_3$) cm^{-1}: 3447, 3007, 2978, 2937, 2879, 1656, 1529, 1456, 1375, 1093, 1045, 974, 960, 924; FAB-MS (glycerol) m/z: 367 (MH^+), data of **17b**; ^{1}H NMR ($CDCl_3$) δ: 1.03 (t, 3H, J = 7.3 Hz, 9-H$_3$), 1.08 (d, 3H, J = 7.0 Hz, 4-CH$_3$), 1.14 (s, 3H, 6-CH$_3$), 1.32 (s, 6H, 2 × isopropylidene-CH$_3$), 1.35 (br, 3H, 2-CH$_3$), 1.67 (br, 2H, 8-H$_2$), 2.90 (m, 1H, 2-H), 3.02 (m, 2H, SCH$_2$), 3.41 (m, 1H, 7-H), 3.44 (m, 2H, SCH$_2$CH$_2$), 3.99 (d, 1H, J = 5.2 Hz, 5-H), 4.22 (m, 1H, 3-H), 5.84 (br, 1H, NH).

11b (unlabelled) and 11c (unlabelled) from 11a,b (unlabelled) via 18a,b, and 15b (unlabelled) from 11b (unlabelled)

To a solution of DMSO (180 μl, 2.54 mmol) in dry CH_2Cl_2 (4 ml) was added trifluoroacetic anhydride (240 μl, 1.70 mmol) at −78°C under an argon atmosphere, and the mixture was stirred for 15 min. To this solution was added a solution of **11a,b** (unlabelled) (440 mg, 0.865 mmol) in dry CH_2Cl_2 (2 ml) at −78°C, and the whole was stirred for 20 min. To this solution was added Et_3N (540 μl, 3.87 mmol), and the whole was stirred for 30 min. The reaction was quenched with sat. NH_4Cl aq. and extracted with Et_2O. The combined extract was washed with brine, dried over anhydrous $MgSO_4$, and evaporated. Chromatography of the crude product on silica gel with Et_2O/hexane (1:20) gave benzyl (2*RS*,4*S*,5*R*,6*R*,7*R*)-7-*tert*-butyldimethylsilyloxy-5,6-*O*-isopropylidene-3-oxo-2,4,6-trimethylnonanoate (**18a,b**) (354 mg, 81%). To a solution of **18a,b** (135 mg, 0.266 mmol) in dry Et_2O (3.3 ml) was added $Zn(BH_4)_2$ (0.2 M in Et_2O, 3.3 ml, 0.66 mmol) at 0°C under an argon atmosphere, and the mixture was stirred for 2.5 h. The reaction was quenched with water (170 μl) at 0°C, and the whole was stirred for 15 min. To this suspension was added sat. NH_4Cl aq. (170 μl) at room temperature, and the whole was stirred for 30 min. This solution was dried over anhydrous $MgSO_4$ with stirring for 30 min and filtered, and the filtrate was evaporated. Chromatography of the crude product on silica gel with Et_2O/hexane (1:10) gave **11c** (unlabelled) (61 mg, 45%) and **11b** (unlabelled) (47 mg, 35%), data of **11b** (unlabelled); ^{1}H NMR ($CDCl_3$) δ: 0.08 (s, 3H, isopropylidene-CH$_3$), 0.08 (s, 3H, isopropylidene-CH$_3$), 0.89 (s, 9H, SiC(CH$_3$)$_3$), 0.95 (t, 3H, J = 7.6 Hz, 9-H$_3$), 1.01 (d, 3H, J = 6.8 Hz, 4-CH$_3$), 1.09 (s, 3H, 6-CH$_3$), 1.30 (d, 3H, J = 6.8 Hz, 2-CH$_3$), 1.33 (s, 3H, SiCH$_3$), 1.39 (s, 3H, SiCH$_3$), 1.65 (m, 2H, 8-H$_2$), 1.79 (m, 1H, 4-H), 2.68 (dq, 1H, J = 6.8, 8.8 Hz, 2-H), 3.54 (dd, 1H, J = 4.6, 6.1 Hz, 7-H), 3.82 (dd, 1H, J = 1.8, 8.9 Hz, 3-H), 4.04 (d, 1H, J = 3.2 Hz, 5-H), 5.10 (m, 2H, phenyl-CH$_2$), 7.36 (m, 5H, phenyl-H$_5$), data of **11c** (unlabelled); ^{1}H NMR ($CDCl_3$) δ: 0.07 (s, 3H, isopropylidene-CH$_3$), 0.10 (s, 3H, isopropylidene-CH$_3$), 0.90 (s, 9H, SiC(CH$_3$)$_3$), 0.96 (t, 3H, J = 7.4 Hz, 9-H$_3$), 0.96 (d, 3H, J = 6.8 Hz, 4-CH$_3$), 1.19 (s, 3H, 6-CH$_3$), 1.20 (d, 3H, J = 8.1 Hz, 2-CH$_3$), 1.34 (s, 3H, SiCH$_3$), 1.41 (s, 3H, SiCH$_3$), 1.70 (m, 2H, 8-H$_2$), 1.84 (m, 1H, 4-H), 2.74 (dq, 1H, J = 3.4, 7.3 Hz, 2-H), 3.57 (t, 1H, J = 5.4 Hz, 7-H), 3.89 (dd, 1H, J = 3.5, 8.5 Hz, 3-H), 4.39 (s, 1H, 5-H), 5.08 (m, 2H, phenyl-CH$_2$), 7.35 (m, 5H, phenyl-H$_5$).

11b (unlabelled) was transformed to **15b** (unlabelled) via the above-mentioned procedure, data of **15b** (unlabelled); ^{1}H NMR ($CDCl_3$) δ: 0.08 (s, 3H, isopropylidene-CH$_3$), 0.09 (s, 3H, isopropylidene-CH$_3$), 0.88 (s, 9H, SiC(CH$_3$)$_3$), 0.98 (t, 3H, J = 7.6 Hz, 9-H$_3$), 1.02 (d, 3H, J = 6.4 Hz, 4-CH$_3$), 1.20 (s, 3H, 6-CH$_3$), 1.28 (d, 3H, J = 6.4 Hz, 2-CH$_3$), 1.36 (s, 3H, SiCH$_3$), 1.41 (s, 3H, SiCH$_3$), 1.43, (m, 1H, 8-H), 1.78 (m, 1H, 8-H), 2.01 (br, 1H, 4-H), 2.57 (br, 1H, 2-H), 3.56 (br, 1H, 7-H), 3.92 (br, 1H, 3-H), 4.03 (br, 1H, 5-H).

Conclusion

We efficiently synthesized ^{13}C-labelled putative erythromycin biosynthetic intermediates, **10a** and **2b**, via aldol condensation of aldehyde derived from the optically active synthetic intermediate **13** (obtained in our previous work for erythromycin A synthesis) and benzyl ester **14** derived from sodium [1-^{13}C]propionate (**4**) for investigations on the biosynthesis of erythromycin.

Supplementary electronic material for this paper is available in Wiley Interscience at http://www.interscience.wiley.com/jpages/1099–1034/suppmat/

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[14] The experiments shown in Scheme 2 are described in the supplemental data.
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[19] ^{1}H NMR ($CDCl_3$) data of **8a**; δ: 0.14 (s, 9H, Si(CH$_3$)$_3$), 0.15 (s, 9H, Si(CH$_3$)$_3$), 0.17 (s, 9H, Si(CH$_3$)$_3$), 0.91 (d, 3H, J = 7.1 Hz, 4-CH$_3$), 0.92 (t, 3H, J = 7.6 Hz, 9-H$_3$), 1.23 (s, 3H, 6-CH$_3$), 1.31 (d, 3H, J = 7.1 Hz, 2-CH$_3$), 1.44 (m, 1H, 8-H), 1.56 (m, 1H, 8-H), 2.07 (m, 1H, 4-H), 2.18 (s,

6H, Ph(CH_3)$_2$), 2.66 (d, 1H, J = 10.3 Hz, 3-OH), 2.85 (dq, 1H, J = 7.1, 9.5 Hz, 2-H), 3.49 (dd, 1H, J = 2.2, 9.5 Hz, 7-H), 3.80 (d, 1H, J = 3.2 Hz, 5-H), 3.93 (d, 1H, J = 10.0 Hz, 3-H), 7.04 (s, 3H, phenyl-H_3), that of **8b**; δ: 0.11 (s, 9H, Si(CH_3)$_3$), 0.12 (s, 9H, Si(CH_3)$_3$), 0.16 (s, 9H, Si(CH_3)$_3$), 0.85 (t, 3H, J = 7.3 Hz, 9-H_3), 0.94 (d, 3H, J = 6.8 Hz, 4-CH_3), 1.20 (s, 3H, 6-CH_3), 1.48 (m, 2H, 8-H_2), 1.54 (d, 3H, J = 7.3 Hz, 2-CH_3), 1.89 (m, 1H, 4-H), 2.15 (s, 6H, Ph(CH_3)$_2$), 3.00 (d, 1H, J = 10.3 Hz, 3-OH), 3.09 (dq, 1H, J = 7.3, 9.0 Hz, 2-H), 3.33 (dd, 1H, J = 3.2, 9.3 Hz, 3-H), 3.44 (t, 1H, J = 6.3 Hz, 7-H), 4.15 (d, 1H, J = 3.2 Hz, 5-H), 7.04 (s, 3H, phenyl-H_3).

[20] ^{1}H NMR ($CDCl_3$) data of **10a** (unlabelled); δ: 1.08 (t, 3H, J = 7.3 Hz, 9-H_3), 1.13 (s, 3H, 6-CH_3), 1.18 (d, 3H, J = 7.3 Hz, 4-CH_3), 1.33 (d, 3H, J = 7.2 Hz, 2-CH_3), 1.40 (m, 1H, 8-H), 1.72 (m, 1H, 8-H), 2.22 (m, 1H, 4-H), 2.72 (dt, 1H, J = 3.7, 7.6 Hz, 2-H), 3.40 (dt, 1H, J = 1.8, 11.0 Hz, 7-H), 3.88 (dt, 1H, J = 3.7, 11.9 Hz, 3-H), 4.97 (d, 1H, J = 2.8 Hz, 5-H).

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