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Note

Synthesis of [*N-methyl*-^{13}C]clarithromycin

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Summary

We describe a simple synthesis of [*N-methyl*-^{13}C]clarithromycin (**3**) via the *N*-desmethylation of clarithromycin. Copyright © 2004 John Wiley & Sons, Ltd.

Key Words: [*N-methyl*-^{13}C]clarithromycin; *N*-demethylation; reductive amino-methylation; [^{13}C]formaldehyde

Introduction

Clarithromycin (**1**) is a semisynthetic macrolide antibiotic with a broad antibacterial spectrum against gram-positive and some kinds of gram-negative bacteria.[1] It inhibits ribosomal protein synthesis. We present a simple synthesis of [*N-methyl*-^{13}C]clarithromycin, which is expected to be useful for studies of its metabolism and interactions with other drugs.

Results and discussion

N-Desmethylation of clarithromycin (**1**) with iodine (1 eq.) under light (Scheme 1) gave mono-*N*-des-methylclarithromycin **(2)**[2] in 73.6%. Di-*N*-desmethylation was not observed even when excess iodine was used under the same conditions. ^{13}C-Methylation was performed by reductive amino-methylation with [^{13}C]formaldehyde in the presence of palladium black under a hydrogen atmosphere to give [*N-methyl*-^{13}C]clarithromycin (**3**)[3] in 90.3% yield.

The ^{13}C-NMR spectrum is shown in Figure 1. The enriched signal at 40.3 ppm, assigned to the *N*-methyl group, confirmed the successful regioselective ^{13}C-labeling of clarithromycin.

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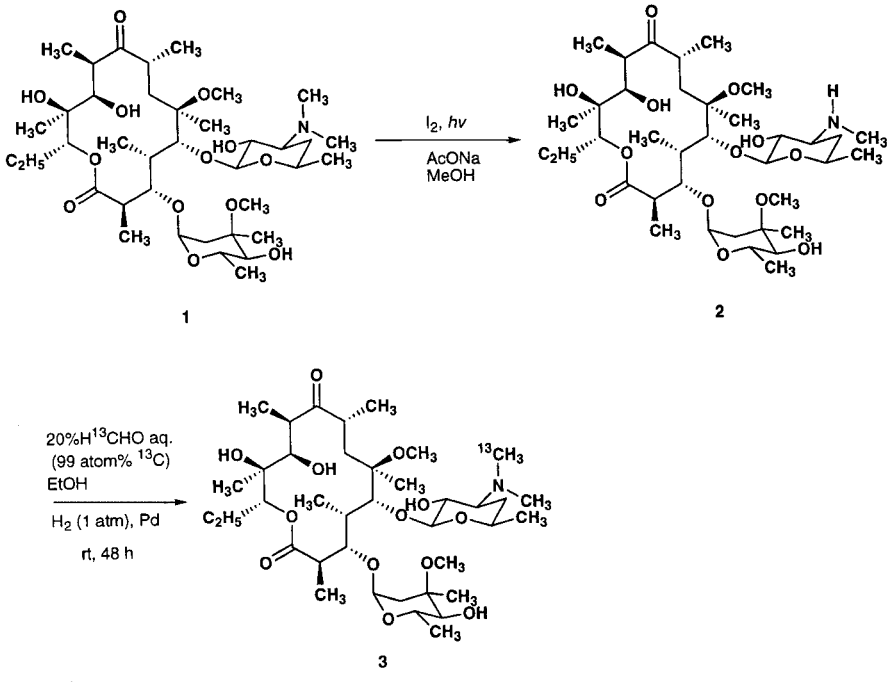

Scheme 1.

Experimental

Materials

A 20% aqueous solution of [^{13}C]formaldehyde (99 atom% ^{13}C) was purchased from Isotec Inc. Palladium black was purchased from Kojima Chemical Co., Ltd. Other chemicals were of analytical grade.

Instruments

Melting point determinations were carried on a Yanaco micro-melting point apparatus, Model MP; values are uncorrected. ^{1}H-NMR (300 MHz) and ^{13}C-NMR (75.4 MHz) spectra were recorded on a Varian Gemini 2000 spectrometer. EI-MS spectra were obtained on a JMS-700 spectrometer.

N-des-Methylclarithromycin

Clarithromycin (2.02 g, 2.7 mmol) was added to methanol (20 ml), then sodium acetate (1.21 g, 14.8 mmol), iodine (776 mg, 2.7 mmol) and water (0.8 ml) were added sequentially. The mixture was exposed to two incandescent lamps (100 W) and stirred for 4 day. The reaction was quenched with sat. sodium bicarbonate and sat. sodium thiosulfate. The mixture was evaporated to 1/5 of its initial volume. Dichloromethane (70 ml) was added and the solution was

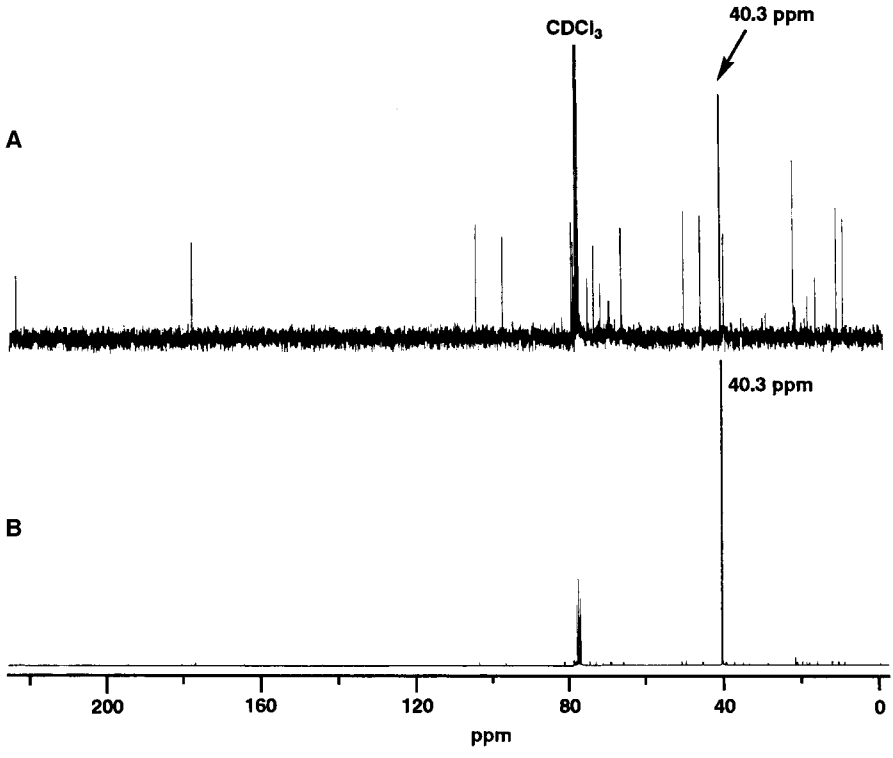

Figure 1. ^{13}C-NMR spectra of clarithromycins. (A) unlabeled clarithromycin and (B) [*N-methyl*-^{13}C]clarithromycin

washed with sat. sodium bicarbonate (60 ml) and water (3 × 60 ml). The organic phase was dried with anhydrous sodium sulfate and evaporated. The residue was chromatographed (chloroform: methanol = 8: 1–1 : 1) to yield 1.46 g (73.6%) of solid *N*-des-methylclarithromycin, m.p. 121–123°C; ^{1}H-NMR ($CDCl_3$) δ: 0.84 (t, J = 7.4 Hz, 3 H), 1.04 (d, J = 7.5 Hz, 3 H), 1.13 (s, 3 H), 1.11–1.15 (m, 6 H), 1.19–1.23 (m, 6 H), 1.26 (s, 3 H), 1.30 (d, J = 6.3 Hz, 3 H), 1.42 (s, 3 H), 1.55–1.69 (m, 2 H), 1.78 (m, 2 H), 1.91–1.96 (m, 3 H), 2.25–2.33 (m, 3 H), 2.42 (s, 3 H), 2.55–2.65 (m, 2 H), 2.87 (m, 1 H), 3.03 (s, 3 H), 3.15 (m, 1 H), 3.26 (d, J = 9.3 Hz, 1 H), 3.32 (s, 3 H), 3.51–3.59 (m,1 H), 3.67 (d, J = 6.9 Hz, 1 H), 3.75–3.78 (m, 2 H), 4.01 (m, 1 H), 4.42 (d, J = 7.4 Hz, 1 H), 4.92 (d, J = 4.1 Hz, 1 H), 5.06 (dd, J = 2.2, 11.0 Hz, 1 H); ^{13}C-NMR ($CDCl_3$) δ: 9.62, 10.62, 12.32, 15.99, 16.06, 18.03, 18.71, 19.72, 21.09, 21.25, 21.50, 33.11, 34.91, 37.27, 37.31, 39.01, 39.31, 45.09, 45.12, 49.44, 50.62, 60.30, 65.72, 68.47, 69.09, 72.74, 74.24, 74.95, 76.70, 77.89, 78.33, 78.38, 81.17, 96.08, 102.30, 175.55, 220.70; EI-MS m/z (rel. int. %): 733 (M^+, 3), 701 (11), 648 (13), 341 (15), 157 (21), 144 (100), 127 (20), 115 (25), 102 (28), 83 (16); HR-MS: Calcd. for $C_{37}H_{67}NO_{13}$: 733.4612, found: 733.4618 (M^+).

[N-methyl-^{13}C]clarithromycin

N-des-Methylclarithromycin (200 mg, 0.267 mmol) was dissolved in absolute methanol (9 ml) in a 50 ml flask. To this, palladium black (72 mg, 0.677 mmol) and a 20% aqueous solution of [^{13}C]formaldehyde (0.077 ml, 0.490 mmol) were added. The reaction mixture was stirred with hydrogen (1 atm, at rt) for 24 h. The catalyst was removed from the reaction mixture by filtration through Celite. The filtrate was evaporated to dryness under reduced pressure. The residue was crystallized from chloroform-hexane to give [*N-methyl*-^{13}C]clarithromycin (180.5 mg, 0.241 mmol) in 90.3% yield, m.p. 207–210°C; ^{1}H-NMR ($CDCl_3$) δ: 0.84 (t, $J = 7.4$ Hz, 3 H), 1.08–1.14 (m, 6 H), 1.12 (s, 3 H), 1.19–1.24 (m, 6 H), 1.25 (s, 3 H), 1.31 (d, $J = 6.0$ Hz, 3 H), 1.40 (s, 3 H), 1.56 (d, $J = 4.5$ Hz, 1 H), 1.61–1.74 (m, 4 H), 1.81–1.96 (m, 3 H), 2.24 (s, 1 H), 2.30 (d, $J = 4.9$ Hz, 3 H), 2.30 (d, $J = 133.5$ Hz, 3 H), 2.37 (d, $J = 15.4$ Hz, 1 H), 2.56–2.62 (m, 1 H), 2.89 (t, $J = 7.5$ Hz, 2 H), 2.99–3.05 (m, 2 H), 3.04 (s, 3 H), 3.20 (m, 2 H), 3.33 (s, 3 H), 3.44–3.54 (m, 1 H), 3.67 (d, $J = 7.1$ Hz, 1 H), 3.76–3.78 (m, 2 H), 3.96–4.06 (m, 1 H), 3.98 (s, 1 H), 4.44 (d, $J = 7.4$ Hz, 1 H), 4.93 (d, $J = 4.7$ Hz, 1 H), 5.05 (dd, $J = 2.2$, 11.1 Hz, 1 H); ^{13}C-NMR ($CDCl_3$) δ : 9.09, 10.65, 12.34, 15.98, 16.02, 18.05, 18.75, 19.79, 21.04, 21.52, 28.58, 33.30, 34.91, 37.22, 39.24, 39.35, 40.29, 45.08, 45.28, 49.50, 50.65, 65.59, 65.71, 68.77, 69.05, 70.97, 72.67, 74.25, 77.19, 77.97, 78.39, 80.76, 96.07, 102.80, 175.78, 220.94; EI-MS *m/z* (rel. int. %): 748 (M^+, 3), 676 (12), 663 (10), 341 (15), 188 (19), 172 (96), 159 (100), 157 (21), 127 (20), 115 (32), 99 (24), 83 (20); HR-MS : Calcd. for $C_{37}\ ^{13}C_1H_{69}NO_{13}$: 748.4802, found: 748.4813 (M^+).

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