

Preparation of clarithromycin. Selective 6-O-methylation of the novel erythromycin A 9-O-(2-pyrimidyl)oxime

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Received 6 November 2006; revised 19 December 2006; accepted 20 December 2006

Available online 23 December 2006

Abstract—A new method for the preparation of clarithromycin is described through the highly regioselective O-methylation at C(6)-OH of the novel derivative 9-pyrimidyloxime erythromycin A. The facile synthesis of 6,11-O-dimethyl- and 6,11,12-O-trimethyl erythromycin A is also reported. These compounds are useful as standards to assess clarithromycin purity in quality control processes.

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The 6-O-alkyl derivatives of erythromycin, namely its methyl derivative clarithromycin (**1**; Fig. 1), are 14-membered macrolide antibiotics which are active in vitro against clinically important gram-positive and gram-negative bacteria.¹ Numerous methods of regioselective alkylation at 6-OH of erythromycin have been described in the literature.² The most important ones comprise the direct protection of the highly reactive OH groups at 2' and 4'' positions and indirect blocking of hydroxyl groups at 11 and 12 positions by derivatiza-

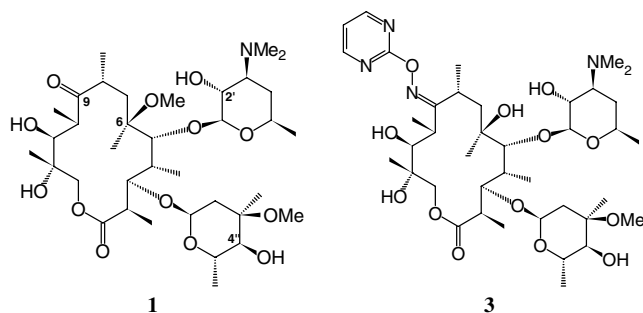


Figure 1. Clarithromycin (**1**) and its pyrimidyloxime precursor (**3**) studied in this work.

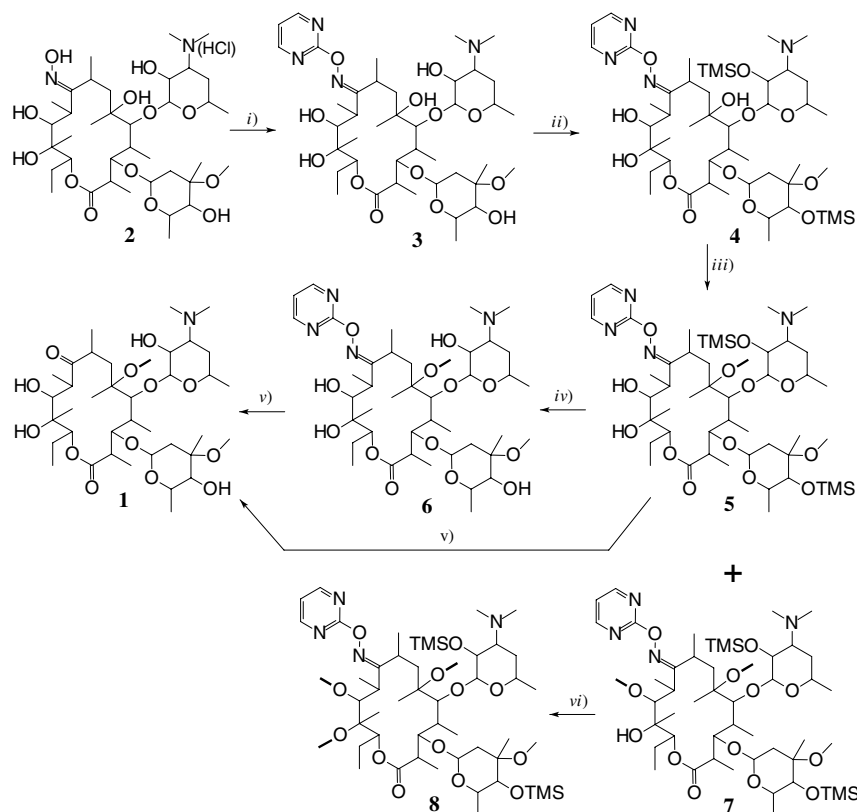
Keywords: Erythromycin; Clarithromycin; Regioselective methylation.

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tion of the 9-carbonyl group via O-substituted oximes bearing relatively bulky substituents.³ We hereby report the synthesis of the novel erythromycin A 9-O-(2-pyrimidyl)oxime and the excellent results concerning the 6-O-methylation of its 2',4''-O-bistrimethylsilyl derivative.⁴

The whole process is outlined in Scheme 1 (the absolute stereochemistry, which is the same as in of Fig. 1, has been omitted for clarity). Derivatization of erythromycin A oxime (**2**) was easily performed in high isolation yields by reaction with 2-chloro-pyrimidine in basic solution.⁵ The corresponding erythromycin A 9-O-(2-pyrimidyl)-oxime (**3**) was quantitatively silylated at 2' and 4'' positions using a mixture of trimethylsilylchloride and trimethylsilyl-imidazole in dichloromethane.⁶

The key methylation at 6-OH was performed on the resulting 2',4''-O-bistrimethylsilyl erythromycin A 9-O-(2-pyrimidyl)oxime (**4**) by reaction with 1.5 equiv of methyl iodide in a solution of 1.5–2.0 equiv of ground potassium hydroxide in DMSO at room temperature.⁷ Deprotection of 2' and 4'' OH groups and 9-carbonyl can be performed stepwise by treatment of **5** with formic acid in water/ethanol leading to 9-O-(2-pyrimidyl)oxime of clarithromycin (**6**) which was then easily transformed into clarithromycin (**1**) by treatment with sodium hydrogen sulfite ethanol/water solution at 80 °C for 6 h. The latter process performed on **5** allowed for the simultaneous deprotection of 2' and 4'' OH groups and 9-carbonyl in a single-pot process.



Scheme 1. Reagents and conditions: (i) *K**t*-BuO/DMF/2-chloro-pyrimidine, 80 °C, 2 h, 93%; (ii) TMS-imidazole/TMSCl/CH₂Cl₂, 0 °C, 2 h, 90%; (iii) KOH/MeI/DMSO (see text), 83%; (iv) HCO₂H/EtOH/H₂O, 97%; (v) EtOH/H₂O/NaSO₃H, 80 °C, 4–6 h, 95%; (vi) NaH/MeI/THF/DMSO (1.25:1), 90%.

Study of the crude clarithromycin obtained by the single-pot deprotection procedure by NMR and HPLC indicated that the major impurity (ca. 10%) was its 11-*O*-methyl derivative. The use of different ratios of base and MeI relative to compound **4** or the usual mixtures of THF/DMSO led to lower conversion ratios and/or higher amounts of **7** (Table 1), precursor of the 11-*O*-methylclarithromycin. The best results were thus obtained in pure DMSO (the presence of water inhibited the reaction) with 1.5–2.0 equiv of base and 1.5 equiv of MeI. In those conditions, full transformation of the starting material was observed and the chemical yield of pure **5** was above 80% when 2 equiv of base was used (Table 1). Further increase of base and methylating agent and/or the use of THF/DMSO mixture raised the amount of **7** which, fortunately, was easily isolated by simple precipitation with acetone from the reaction mixture.⁸ Its crystallization and single-crystal X-ray analysis confirmed its structure as shown in Figure 1.⁹

Compound **6** was also crystallized and its structure solved by X-ray diffraction (Fig. 2). The structures of both compounds **6** and **7** showed the *E* stereochemistry of the pyrimidylloxime group.⁸ It can be seen that the new methyl at C(6)–O lies in **6** at the shielding cone of the pyrimidine. This fact explains the relative low chemical shift (2.7 ppm) shown by the protons of this methyl and suggests that the conformation of the macrolide of **6** in CDCl₃ solution should be similar to that in the solid state. It can also be seen that C(11)–OH in **6** is hardly

Table 1. Molar ratio data (from ¹H NMR) for the transformation of compound **4** into **5** (Scheme 1) concerning recovered starting material (**4**) and by-product 11-*O*-methylclarithromycin (**7**) in various conditions

| KOH/MeI | Solvent | 4 | 7 |
|-----------|--|----------|------------------|
| 0.5/0.5 | THF/DMSO ^a | 1.8 | — |
| 0.75/0.75 | THF/DMSO ^a | 0.6 | 0.2 |
| 1.1/1.1 | THF/DMSO ^a | 0.6 | 0.3 |
| 1.5/1.5 | THF/DMSO ^a | 0.2 | 0.7 |
| 0.75/0.5 | THF/DMSO/H ₂ O ^b | 1.0 | — |
| 0.75/0.5 | THF | 1.0 | — |
| 0.75/0.5 | DMSO | 2.6 | — |
| 1.0/1.0 | DMSO | 1.3 | 0.3 |
| 1.5/1.5 | DMSO | — | 0.1 |
| 2.0/1.5 | DMSO | — | 0.1 ^c |

^a 1.25:1.

^b 1.25:1:0.1.

^c Chemical yield of pure **5** was higher than 80%.

hindered by the pyrimidine ring. Despite this, the dimethylated compound **7** was obtained in relatively low amount in the more polar DMSO, even using 0.5 equiv excess of MeI (cf. Table 1). Other reasons in addition to steric factors have to be at play in controlling the methylation regiochemistry of protected derivatives of erythromycin oxime¹⁰ but this will be the subject of future papers.

The X-ray structure of compound **7** shows that the new methoxyl group at C(11) forces the pyrimidine to stay

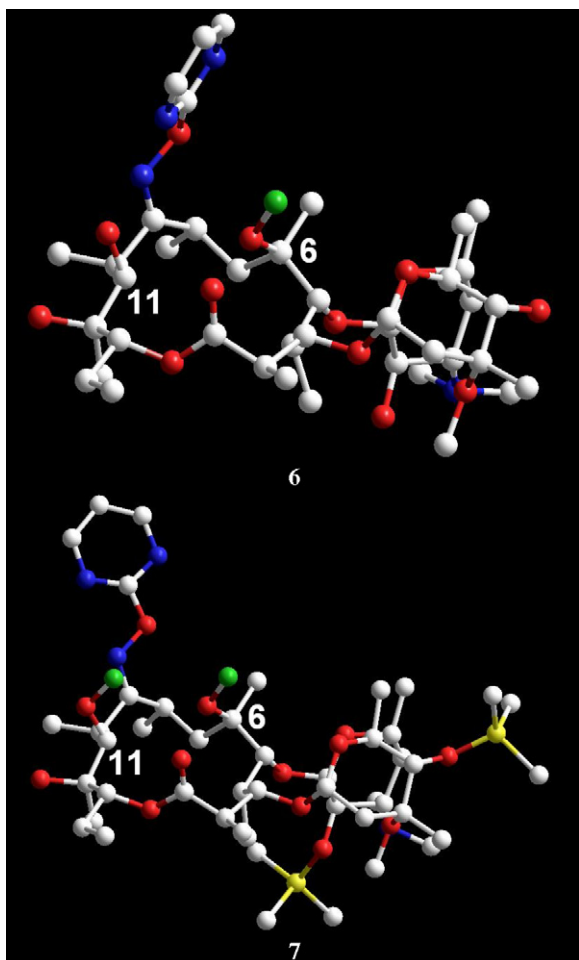


Figure 2. X-ray structures of compounds **6** and **7** [methyl groups at C(6) and C(11) in green].

farther from the macrolide ring than in **6**. This is also seen in solution because the methyl group at C(6)–O suffered a deshielding of 0.3 ppm from **6** to **7**. Finally, compound **7** was easily methylated at C(12)–OH under mild conditions to give the trimethylated product **8**,¹¹ the single-crystal X-ray structure is depicted in Figure 3.⁸

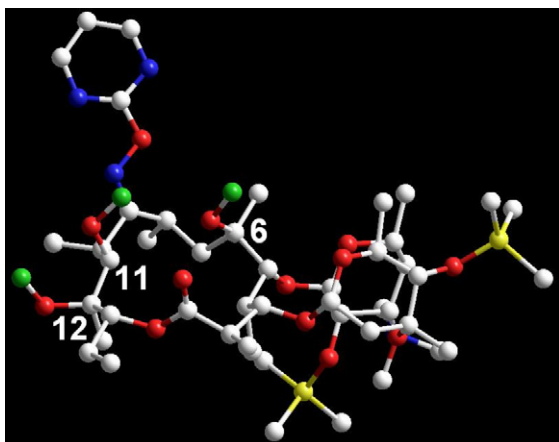


Figure 3. X-ray structure of compound **8** [methyl groups at former hydroxyl groups of C(6), C(11) and C(12) in green].

In conclusion, the pursued objective of developing an original method for clarithromycin synthesis, allowing its high-scale production without infringing any of the existing patents, has been fully and successfully achieved. To this effect, the novel erythromycin A 9-*O*-(2-pyrimidyl)oxime was prepared in very mild terms and high yields from erythromycin A. Conditions were described to attain its regioselective methylation at C(6)–OH and a deprotection protocol was given to obtain clarithromycin in an excellent overall yield which has successfully been scaled up to multi-kilogram amounts. Simultaneous methylation of hydroxyl groups at C(11) and C(6) occurred in mixtures of THF/DMSO with relatively low excess of base and MeI. The dimethylated product was easily methylated again at C(12)–OH, leading to a complete product series which is useful as standards for assessing the quality of clarithromycin samples by HPLC methods or other techniques.¹²

References and notes

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- This work is protected under patent numbers ES2221807 and JP 2005015459.
- Mp 152–154 °C; $[\alpha]_D^{25}$ –144.1 (*c* 0.122, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃) δ (ppm): 8.57 [d, 2H, *J* = 5, C(3Ar)H], 7.02 [t, 1H, *J* = 4.4, C(4Ar)H], 5.17 [dd, 1H, *J* = 2.5, 10.7, C(13)H], 4.86 [d, 1H, *J* = 5, C(1)H], 4.72 (s, 1H, OH), 4.38 [d, 1H, *J* = 7.6, C(1′)C)H], 4.02 [dd, 1H, *J* = 1.2, 9.5, C(3)H], 3.93–3.98 [m, 3H, C(8)H, C(11)H, C(5′′)H], 3.50 [d, 1H, *J* = 7.6, C(5)H], 3.44 [m, 1H, C(5′)H], 3.39 (s ancho, 1H, OH), 3.29 [s, 3H, C(3′′)OCH₃], 3.21 [m, 2H, C(2′)H, OH], 2.96 [t, 1H, *J* = 9.5, C(4′′)H], 2.88 [dc, 1H, *J* = 7.2, 9.1, C(2)H], 2.80 [dc, 1H, *J* = 0.9, 7.2, C(10)H], 2.40 [m, 1H, C(3′)H], 2.34 [d, 1H, *J* = 14.5, C(2′′)H], 2.27 [s, 6H, C(3′)N(CH₃)₂], 2.20 [d, 1H, *J* = 11.3, OH], 2.01 [t, 1H, *J* = 7.6, C(4)H], 1.94 [dc, 1H, *J* = 1.9, 7.6, C(14)H], 1.88 (s ancho, 1H, OH), 1.71 [m, 2H, C(7)H₂], 1.64 [m, 1H, C(4′)H], 1.53 [dd, 1H, *J* = 5.0, 14.5, C(2′′)H], 1.48 [m, 1H, C(14)H], 1.43 [s, 3H, C(6)CH₃], 1.30 [d, 3H, *J* = 6.9, C(10)CH₃], 1.24 [m, 1H, C(4′)H], 1.21 [s, 3H, C(12)CH₃], 1.18 [d, 3H, *J* = 7.5, C(5′′)CH₃], 1.18 [d, 3H, *J* = 7.5, C(5′)CH₃], 1.17 [s, 3H, C(3′′)CH₃], 1.16 [d, 3H, *J* = 7.5, C(2)CH₃], 1.14 [d, 3H, *J* = 7.5, C(8)CH₃], 1.09 [d, 3H, *J* = 7.5, C(4)CH₃], 0.85 [t, 3H, *J* = 6.9, C(15)CH₃]; ¹³C NMR (75 MHz, CDCl₃) δ (ppm): 177.6, 175.3, 165.6, 159.6, 116.4, 103.1, 96.1, 95.3, 83.6, 79.8, 77.9, 76.9, 75.0, 74.4, 72.6, 70.9, 70.0, 68.8, 65.5, 65.4, 49.4, 44.7, 40.2, 39.2, 37.7, 34.9, 34.1, 28.6, 27.9, 26.9, 21.4, 21.3, 21.2, 18.6, 18.5, 16.2, 15.9, 15.0, 13.5, 11.4, 10.6, 9.1.
- Mp 150–152 °C; $[\alpha]_D^{25}$ –131.5 (*c* 0.1, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃) δ (ppm): 8.55 [d, 1H, *J* = 4.8, C(3Ar)H], 6.99 [t, 1H, *J* = 4.8, C(4)H], 5.14 [dd, 1H, *J* = 2.7, 10.5, C(13)H], 4.81 [d, 1H, *J* = 4.9, C(1′′)H], 4.78 (s, 1H, OH), 4.38 [d, 1H, *J* = 7.15, C(1′)H], 4.11–4.21 [m, 2H, C(8)H, C(5′′)H], 3.92–4.02 [m, 2H, C(8)H, C(11)H], 3.57 [m, 1H, C(5′)H], 3.49 [d, 1H, *J* = 8.26, C(5)H], 3.28 [s, 3H, C(3′′)OCH₃], 3.21 (s, 1H, OH), 3.17 [dd, 1H, *J* = 7.3, 9.9, C(2′)H], 3.14 [d, 1H, *J* = 9.1, C(4′′)H], 2.74–2.87 [m,

- 2H, C(2)H, C(10)H], 2.52 [m, 1H, C(3')H], 2.33 [d, 1H, $J = 15.3$, C(2'')H], 2.22 [s, 6H, C(3')N(CH₃)₂], 2.03 (s ancho, 1H, OH), 1.87–2.01 [m, 2H, C(4)H, C(14)H], 1.57–1.73 [m, 3H, C(7)H₂, C(4')H], 1.50 [m, 1H, C(13)H], 1.45 [dd, 1H, $J = 4.9$, 15.0, C(2'')H], 1.42 [s, 3H, C(6)CH₃], 1.31 [d, 1H, $J = 7.2$, C(10)CH₃], 1.25 [s ancho, 1H, C(4')H], 1.22 [s, 3H, C(12)CH₃], 1.15 [d, 3H, $J = 6.9$, C(8)CH₃], 1.14 [d, 3H, $J = 6.9$, C(2)CH₃], 1.12 [s, 3H, C(3'')CH₃], 1.12 [d, 3H, $J = 6.9$, C(5')CH₃], 1.07 [d, 3H, $J = 6$, C(4)CH₃], 1.05 [d, 3H, $J = 6.9$, C(5'')CH₃], 0.87 [t, 3H, $J = 7.1$, C(14)CH₃], 0.10 [s, 9H, C(4'')OSi(CH₃)₃], 0.09 (s, 9H, C(2'')OSi(CH₃)₃); ¹³C NMR (75 MHz, CDCl₃) δ (ppm): 177.1, 176.0, 165.7, 159.5, 116.3, 102.7, 96.5, 81.8, 80.9, 79.3, 77.2, 77.05, 75.3, 74.5, 73.2, 73.1, 70.2, 67.7, 65.2, 65.0, 44.8, 40.9, 40.3, 38.3, 35.8, 34.3, 30.3, 29.7, 28.0, 27.0, 22.1, 21.7, 21.4, 19.2, 18.6, 16.3, 15.5, 14.9, 10.8, 9.6, 1.0, 0.8.
7. Mp 172–174 °C; [α]_D²⁵ –151.65 (*c* 0.1, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃) δ (ppm): 8.56 [d, 2H, $J = 4.8$, C(3Ar)H], 6.97 [t, 1H, $J = 4.8$, C(4Ar)H], 5.19 [dd, 1H, $J = 11.2$, 2.1, C(13)H], 5.09 (s ancho, 1H, OH), 4.84 [d, 1H, $J = 5.1$, C(1'')H], 4.39 [d, 1H, $J = 7.6$, C(1')H], 4.16 [dc, 1H, $J = 6.1$, 9.4, C(5'')H], 3.92 [m, 1H, C(8)H], 3.84 [s, 1H, C(11)H], 3.70 [d, 1H, $J = 10.7$, C(3)H], 3.61 [m, 2H, C(5)H, C(5')H], 3.28 [s, 3H, C(3'')OCH₃], 3.05–3.23 [m, 2H, C(2')H, C(4'')H], 2.86 [dc, 1H, $J = 7.3$, 9.5, C(2)H], 2.74 [s, 4H, C(6)OCH₃, C(10)H], 2.50 [s ancho, 1H, C(3')H], 2.32 [d, 1H, $J = 14.7$, C(2'')H], 2.20 [s, 6H, C(3')N(CH₃)₂], 1.95 [m, 1H, C(14)H], 1.82 [m, 1H, C(4)H], 1.54–1.66 [m, 3H, C(14)H, C(7)H₂], 1.43–1.54 [m, 2H, C(4')H, C(2'')CH], 1.40 [s, 3H, C(6)CH₃], 1.29 [d, 3H, $J = 6.8$, C(10)CH₃], 1.26 [m, 1H, C(4')H], 1.23 [s, 3H, C(3'')CH₃], 1.20 [s, 3H, C(12)CH₃], 1.16 [d, 3H, $J = 6.8$, C(2)CH₃], 1.14 [d, 3H, $J = 6.8$, C(5')CH₃], 1.12 [d, 3H, $J = 6.8$, C(5'')CH₃], 1.11 [d, 3H, $J = 6.8$, C(8)CH₃], 1.04 [d, 3H, $J = 6.8$, C(4)CH₃], 0.84 [t, 3H, $J = 6.9$, C(14)CH₃], 0.10 (s, 9H, C(4'')OSi(CH₃)₃), 0.08 (s, 9H, C(2'')OSi(CH₃)₃). ¹³C NMR (75 MHz, CDCl₃) δ (ppm): 176.1, 175.7, 165.9, 159.5, 116.0, 102.5, 96.2, 81.8, 80.8, 79.0, 77.7, 76.7, 75.3, 74.3, 73.3, 73.1, 70.1, 67.1, 65.2, 65.1, 50.8, 49.6, 45.2, 41.0, 39.2, 37.8, 35.8, 34.1, 31.8, 29.4, 27.8, 22.6, 22.2, 20.4, 19.4, 18.6, 16.3, 16.1, 15.1, 10.6, 9.8, 1.03, 0.84.
8. Mp 190–192 °C; [α]_D²⁵ –125.17 (*c* 0.102, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃) δ (ppm): 8.56 [d, 2H, $J = 4.8$, C(3Ar)H], 6.94 [t, 1H, $J = 4.8$, C(4Ar)H], 5.00 [dd, 1H, $J = 2.3$, 11.0, C(13)H], 4.88 [d, 1H, $J = 5.0$, C(1'')H], 4.43 [d, 1H, $J = 7.2$, C(1')H], 4.21 (dc, 1H, $J = 6.3$, 9.5, C(5'')H), 3.98 [m, 1H, C(8)H], 3.86 [s, 3H, C(11)OCH₃], 3.66–3.73 [m, 2H, C(3)H, C(11)H], 3.59–3.64 [m, 2H, C(5')H, C(12)OH], 3.30 [s, 3H, C(3'')OCH₃], 3.21 [m, 1H, C(5)H], 3.15 [m, 1H, C(2')H], 3.13 [d, 1H, $J = 9.4$, C(4'')H], 3.00 [s, 3H, C(6)OCH₃], 2.93 [dc, 1H, $J = 2.4$, 7.2, C(2)H], 2.77 [m, 1H, C(10)H], 2.51 [m, 1H, C(3')H], 2.35 [d, 1H, $J = 15.1$, C(2'')H], 2.21 [s, 6H, C(3')N(CH₃)₂], 1.91–2.02 [m, 2H, C(4)H, C(14)H], 1.55–1.71 [m, 2H, C(7)H, C(4')CH], 1.45–1.55 [m, 5H, C(6)CH₃, C(14)CH, C(2'')H], 1.35 [d, 3H, $J = 7.4$, C(10)H], 1.05–1.26 [m, 23H, C(2)H₃, C(4)H₃, C(7)H, C(8)H₃, C(12)CH₃, C(4')H, C(5')CH₃, C(3'')CH₃, C(5'')CH₃], 0.83 [t, 3H, $J = 7.7$, C(14)CH₃], 0.13 [s, 9H, C(4'')OSi(CH₃)₃], 0.07 [s, 9H, C(2'')OSi(CH₃)₃]; ¹³C NMR (75 MHz, CDCl₃) δ (ppm): 176.0, 174.5, 166.2, 159.3, 115.6, 102.3, 96.3, 80.7, 79.5, 79.3, 78.2, 78.1, 77.6, 75.7, 73.2, 73.0, 67.0, 65.1, 65.0, 62.3, 50.4, 49.5, 45.1, 38.8, 37.1, 35.8, 35.7, 29.4, 27.9, 22.1, 21.9, 21.6, 20.9, 19.4, 19.3, 17.3, 16.0, 15.4, 10.5, 9.8, 1.2, 0.8.
9. CCDC 626463–626465 contains the supplementary crystallographic data for this Letter. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.
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11. Mp 181–183 °C; [α]_D²⁵ –103.61 (*c* 0.104, CH₂Cl₂); ¹H NMR (500 MHz, CDCl₃) δ (ppm): 8.55 [d, 2H, $J = 4.9$, C(3Ar)H], 6.93 [t, 1H, $J = 4.9$, C(4Ar)H], 5.52 [dd, 1H, $J = 1.7$, 11.6, C(13)H], 4.87 [d, 1H, $J = 4.8$, C(1'')H], 4.38 [d, 1H, $J = 6.9$, C(1')H], 4.23 [dc, 1H, $J = 9.2$, 6.1, C(5'')H₃], 3.44–3.83 [m, 6H, C(3)H, C(8)H, C(5')H, C(11)OCH₃], 3.40 [s, 3H, C(12)OCH₃], 3.29 [s, 3H, C(3'')OCH₃], 2.97–3.23 [m, 7H, C(5)H, C(10)H, C(2')H, C(4'')H, C(6)OCH₃], 2.92 [m, 1H, C(2)H], 2.50 [m, 1H, C(3')H], 2.35 [d, 1H, $J = 14.7$, C(2'')H], 2.20 [s, 6H, C(3')N(CH₃)₂], 1.96 [m, 1H, C(4)H], 1.80 [m, 1H, C(14)H], 1.49–1.71 [m, 4H, C(7)H, C(14)H, C(4')H, C(2'')H], 1.46 (s, 3H, C(6)H₃), 1.37 [d, 4H, $J = 7.7$, C(7)H, C(10)CH₃], 1.21–1.31 [m, 4H, C(4')H, C(5'')CH₃], 1.22 [s, 3H, C(12)CH₃], 1.19 [d, 3H, $J = 6.3$, C(2)CH₃], 1.18 [d, 3H, $J = 7.2$, C(8)CH₃], 1.15 [s, 3H, C(3'')CH₃], 1.14 [d, 3H, $J = 5.3$, C(5')CH₃], 1.07 [d, 3H, $J = 7.2$, C(4)CH₃], 0.86 [t, 3H, $J = 7.4$, C(14)CH₃], 0.13 [s, 9H, C(4'')OSi(CH₃)₃], 0.01 [s, 9H, C(2'')OSi(CH₃)₃]; ¹³C NMR (75 MHz, CDCl₃) δ (ppm): 175.6, 174.9, 165.8, 159.0, 115.3, 102.4, 96.4, 80.9, 80.5, 79.4, 78.3, 75.8, 72.7, 66.8, 64.9, 61.2, 53.3, 50.0, 49.3, 44.9, 40.7, 38.8, 37.2, 35.6, 29.3, 28.2, 21.8, 21.6, 19.4, 19.0, 15.8, 14.3, 10.1, 9.6, 0.6, 0.5.
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