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# Synthesis of the spiro fused β-lactone-γ-lactam segment of oxazolomycin

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**Abstract**—An effective synthetic strategy for construction of the novel spiro-bicyclic β-lactone-γ-lactam system present in oxazolomycin has been demonstrated. The 3,4-disubstituted pyrrolidine ring system was constructed via an Evans aldol reaction. The spiro-β-lactone ring was elaborated from a *gem*-hydroxymethyl moiety that was successfully installed by an aldol followed by a crossed Cannizzaro reaction.


Oxazolomycin (**1**) and neooxazolomycin (**2**) were isolated from the strain of *Streptomyces* sp. KBFP-2025.[1] These drew initial attention for their strong antibacterial and anticancer activities.[2] Later studies revealed their exceptional ability to suppress replication of vaccinia, herpes simplex virus type-1, and influenza A virus in both human and chicken cells.[3] Unique structural features of oxazolomycin are a triene moiety (*Z*,*Z*,*E*) attached to an oxazole ring, a diene system (*E*,*E*), and a spiro-bicyclic β-lactone-γ-lactam subunit (Fig. 1). Their fascinating biology allied with their structural complexity and novelty of the backbone has resulted in several groups dedicating efforts toward the synthesis of these molecules. Hitherto, the total synthesis of **1** has not been accomplished. Most studies have focused on the left and middle segments;[4] a simple model of the spiro-bicyclic system of **1** has been reported by Taylor and Papillon.[5] Additional research needs to be pursued to install the requisite functionalities on the pyrrolidine ring and modulate their behavior while forming the spiro-bicyclic β-lactone-γ-lactam system.

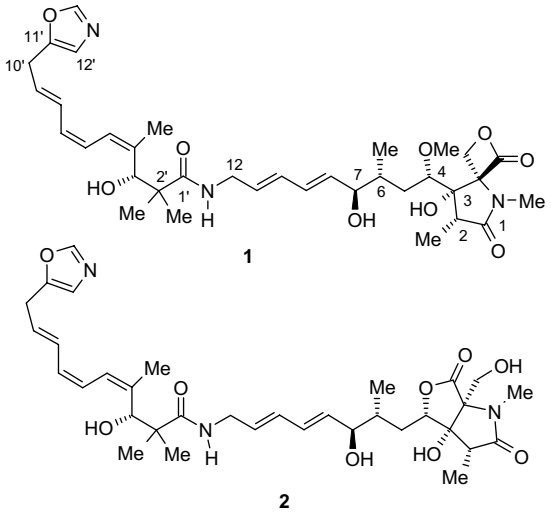


**Figure 1.** Oxazolomycin (**1**) and neooxazolomycin (**2**).

Oxazolomycin (**1**) can be envisioned as an assembly of three intermediates A–C (Fig. 2) representing the left, middle, and right segments. The critical coupling between B and C could be mediated by a Wittig reaction. Subsequent Sharpless asymmetric dihydroxylation with an appropriate chiral auxiliary would ensure installation of the two hydroxyl groups present at C-3 and C-4 in oxazolomycin. Described in this article is a synthetic strategy for segment C via successful adoption of an Evans' aldol reaction followed by further elaboration to the 3,4-disubstituted-prolinol intermediate. In order to construct the spiro-bicyclic β-lactone ring system, we utilized an aldol reaction followed by a crossed

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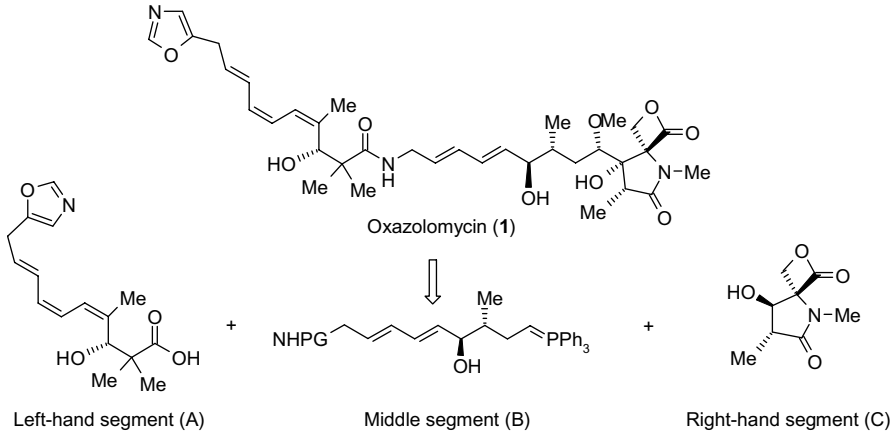
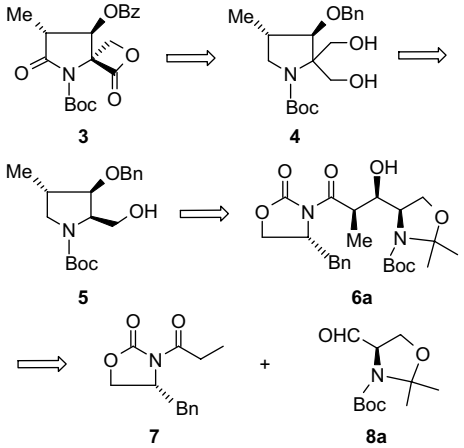


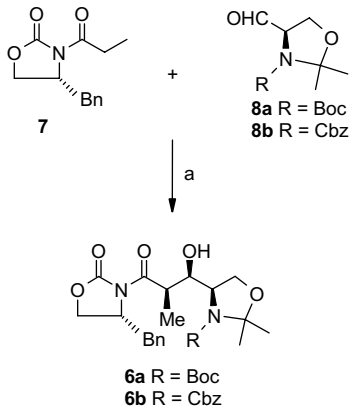

**Figure 2.** Retrosynthesis of oxazolomycin (**1**).

Cannizzaro reaction to install the *gem*-hydroxymethyl derivative. The β-lactone ring could be appropriately derived from this (Scheme 1).

Our first concern was the Evans' aldol[6] reaction between the (*R*)-oxazolidinone[7] derivative (**7**) and (*R*)-Garner's aldehyde[8] (**8a**) using Crimmins' modified method.[9] It was reported that this aldol reaction with $TiCl_4$ catalysis ensures a higher diastereomeric excess. In our case, the chirality present in both the substrates would have either a complementary or an opposing effect on the course of the aldol reaction. The reaction was carried out in the presence of $TiCl_4$ (1.0 equiv) and DIPEA (2.5 equiv) at 0 °C, to give *syn*-**6a** as the sole product (Scheme 2). Much to our delight, **6a** crystallized out in 82% yield after column chromatography. Spectroscopic and elemental data supported the structure of **6a**;[10] a single crystal X-ray study (CCDC 603757)[11] conclusively proved the (Fig. 3) stereochemical assignments. Similarly, the structure of **6b** (CCDC 603758)[11] was confirmed by single crystal X-ray crystallography (Fig. 4). The aldol product **6a** on reductive hydrolysis[12] with lithium borohydride generated the primary alcohol **9**. The protection and deprotection sequence, shown in




**Scheme 1.** Retrosynthetic analysis of spiro fused β-lactone-γ-lactam segment (**3**).




**Scheme 2.** Reagents and conditions: (a) $TiCl_4$, DIPEA, $CH_2Cl_2$, 0 °C, 82%.

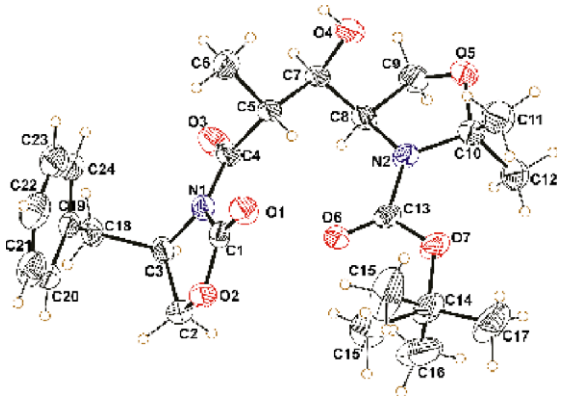


**Figure 3.** ORTEP diagram of **6a**.

Scheme 3, furnished tosylate **12** via intermediates **10** and **11**. Exposure of **12** to *p*-TSA-MeOH gave the appropriately substituted pyrrolidine derivative[13] **5** (Scheme 3) by deprotection of the isopropylidene group followed by ring closure.

We next turned our attention to introducing the *gem*-hydroxymethyl group at C-2. We planned to use an aldol reaction followed by a crossed Cannizzaro reac-

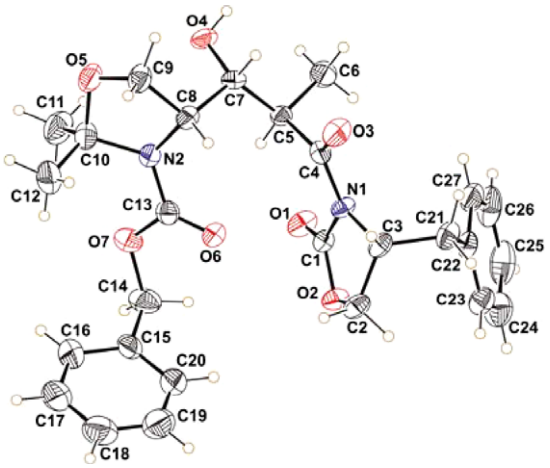
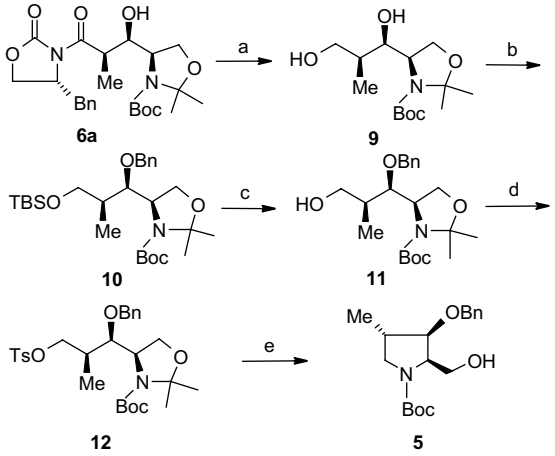


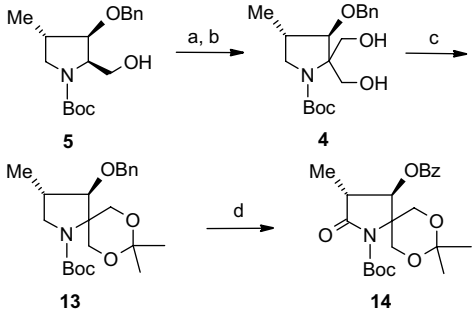

**Figure 4.** ORTEP diagram of **6b**.



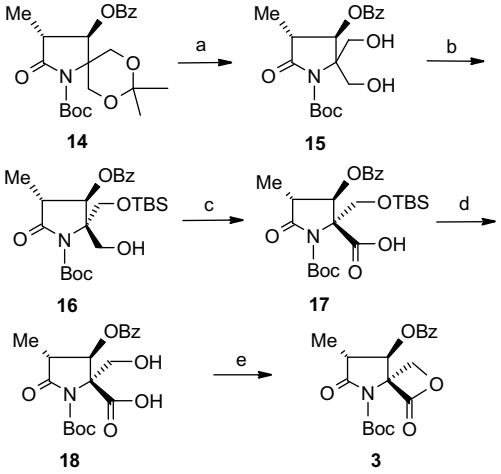

**Scheme 3.** Reagents and conditions: (a) LiCl, $NaBH_4$, EtOH: THF (2:1), rt, 75%; (b) (i) TBDMSCl, $Et_3N$, DMAP (cat.), $CH_2Cl_2$, rt, 82%; (ii) NaH, BnBr, DMF, 0 °C, 91%; (c) TBAF, THF, rt, 89%; (d) TsCl, $Et_3N$, $CH_2Cl_2$, rt, 97%; (e) *p*-TSA, MeOH, rt, 63%.

tion[14] at C-2. Prior to performing this key reaction, compound **5** was first oxidized with IBX–DMSO–THF[15] and the corresponding aldehyde treated with formaldehyde in the presence of 2 M NaOH solution to furnish the *gem*-dihydroxymethyl derivative **4**. The structure of **4**[16] was supported by spectroscopic and elemental data. To secure the pyrrolidinone benzoate[17] derivative **14**, diol **4** was first protected as the isopropylidene[18] derivative **13**, and subsequently oxidized selectively with $RuO_4$ as per the literature protocol.[19] The $^1H$ and $^{13}C$ NMR, IR and elemental analysis confirmed the structure of **14**[20] (Scheme 4).

Our next endeavor was to construct the β-lactone ring. The isopropylidene group of **14** was cleaved and the resulting *gem*-hydroxymethyl derivative **15** was selectively protected with a TBS-group.[21] The structure of the mono-protected TBS-derivative[22] **16** was proposed on the basis of steric hindrance of the adjacent β-OBz group and substantiated by NOESY experiments. The free β-hydroxymethyl group was oxidized with ruthenium tetroxide to acid **17**,[23,24] and the TBS group was




**Scheme 4.** Reagents and conditions: (a) IBX, DMSO, THF, rt; (b) HCHO, 2 M NaOH, THF:$H_2O$ (7:1), rt (55%, two steps); (c) DMP, *p*-TSA, rt, 85%; (d) $RuCl_3$, $NaIO_4$ (aq), EtOAc, rt, 82%.




**Scheme 5.** Reagents and conditions: (a) *p*-TSA, MeOH, rt, 86%; (b) TBSCl, imidazole, $CH_2Cl_2$, rt, 82%; (c) $RuCl_3$, $NaIO_4$ (aq), EtOAc, rt, 86%; (d) AcOH, THF, $H_2O$, rt, 77%; (e) TPP, DEAD, THF, −78 °C-rt, 88%.

removed using aqueous acetic acid in THF to furnish the hydroxy acid derivative[25] **18**. This was finally lactonized under Mitsunobu[5,26] conditions (TPP and DEAD at −78 °C-rt) to provide the spiro-bicyclic β-lactone-γ-lactam fragment **3**. The characteristic IR absorption at 1841 $cm^{-1}$ for the carbonyl stretching frequency verified

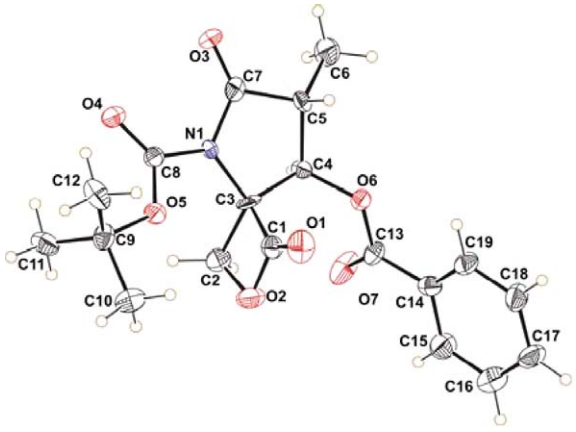



**Figure 5.** ORTEP diagram of **3**.

formation of the β-lactone (Scheme 5). The $^{1}H$, $^{13}C$ NMR, and elemental analysis of **3**[27] were in agreement with the assigned structure. Unambiguous proof of the stereochemistry was obtained from single crystal X-ray crystallography (CCDC 603759) (Fig. 5).[11]

In conclusion, we have demonstrated a strategy to install a spiro fused β-lactone-γ-lactam ring possessing 3,4-substituted functional groups using an aldol reaction, followed by a crossed Cannizzaro reaction. Ruthenium tetroxide mediated oxidation on an already installed pyrrolidine ring system led to improved yields in γ-lactam formation.

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10. Analytical and spectral data of compound **6a**. Mp 127–128 °C; $[\alpha]_D^{25}$ −6.6 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$): 1688, 1781 $cm^{-1}$; $^{1}H$ NMR ($CDCl_3$, 200 MHz): $\delta$ 1.34 (d, 3H, $J = 6.8$ Hz), 1.45 (s, 9H), 1.49 (s, 3H), 1.59 (s, 3H), 2.77 (dd, 1H, $J = 9.7$, 13.4 Hz), 3.15 (d, 1H, $J = 5.2$ Hz), 3.28 (dd, 1H, $J = 3.4$, 13.4 Hz), 3.60 (quintet, 1H, $J$= 6.8 Hz), 3.99 (dd, 2H, $J = 5.2$, 10.4 Hz), 4.07 (dd, 1H, $J = 1.5$, 9.2 Hz), 4.14 (dd, 1H, $J = 2.5$, 8.8 Hz), 4.24 (dd, 2H, $J = 7.4$, 9.2 Hz), 4.74 (m, 1H), 7.24 (m, 5H); $^{13}C$ NMR ($CDCl_3$, 50 MHz): $\delta$ 12.7, 24.0, 26.8, 28.3, 38.2, 41.4, 55.4, 58.5, 66.2, 75.1, 81.0, 94.4, 127.2, 128.8, 129.4, 135.5, 153.2, 154.7, 175.2; Anal. Calcd for $C_{24}H_{34}N_2O_7$: C, 62.32; H, 7.41; N, 6.06%; Found: C, 62.31; H, 7.49, N; 6.08%.
11. Crystallographic data for the structures in this letter have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 603757 for **6a**, CCDC 603758 for **6b**, and CCDC 603759 for **3**. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44 0 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
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13. Analytical and spectral data of compound **5**. $[\alpha]_D^{25}$ +31.4 (*c* 1.25, $CHCl_3$); IR ($CHCl_3$): 1684 $cm^{-1}$; $^{1}H$ NMR ($CDCl_3$, 200 MHz): $\delta$ 1.01 (d, 3H, $J = 6.8$ Hz), 1.46 (s, 9H), 2.30 (quintet, 1H, $J = 6.8$ Hz), 2.92 (dd, 1H, $J = 7.8$, 10.7 Hz), 3.55 (dd, 1H, $J = 7.8$, 10.7 Hz), 3.60–3.80 (m, 2H), 3.92 (dt, 1H, $J = 2.4$, 11.7 Hz), 4.12 (m, 1H), 4.54 (d, 1H, $J = 11.5$ Hz), 4.61 (d, 1H, $J = 11.5$ Hz), 7.34 (s, 5H); $^{13}C$ NMR ($CDCl_3$, 50 MHz): $\delta$ 15.6, 28.3, 36.2, 50.8, 60.4, 63.4, 72.5, 80.1, 83.8, 127.7, 127.8, 128.4, 137.4, 156.4; Anal. Calcd for $C_{18}H_{27}NO_4$: C, 67.26; H, 8.47; N, 4.36%; Found: C, 67.26; H, 8.53; N, 4.36%.
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16. Analytical and spectral data of compound **4**. $[\alpha]_D^{25}$ +15.0 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$): 1665, 3436 $cm^{-1}$; $^{1}H$ NMR ($CDCl_3$, 200 MHz): $\delta$ 1.08 (d, 3H, $J = 6.4$ Hz), 1.46 (s, 9H), 2.22–2.44 (m, 1H), 2.80 (t, 1H, $J = 10.6$ Hz), 3.45 (d, 1H, $J = 9.2$ Hz), 3.64 (dd, 1H, $J = 8.9$, 10.6 Hz), 3.77 (d, 1H, $J = 11.8$ Hz), 3.85–4.10 (m, 3H), 4.71 (s, 2H), 7.34 (br s, 5H); $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ 16.0, 28.3, 36.0, 51.5, 62.5, 65.6, 68.9, 74.5, 80.5, 88.7, 127.9, 128.1, 128.5, 137.5, 155.8; Anal. Calcd for $C_{19}H_{29}NO_5$: C, 64.93; H, 8.32; N, 3.99%; Found: C, 64.76; H, 8.37; N, 4.12%.
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20. Analytical and spectral data of compound **14**. Mp 73.1 °C (re-crystallized from ethyl acetate/hexane): $[\alpha]_D^{25}$ −33.0 (*c* 1.0, $CHCl_3$); IR ($CHCl_3$): 1725, 1743, 1783 $cm^{-1}$; $^{1}H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 1.24 (s, 3H), 1.46 (d, 3H, $J = 7.8$ Hz), 1.52 (s, 3H), 1.58 (s, 9H), 2.70 (dq, 1H, $J$ = 4.0, 7.8, 11.5 Hz), 3.65 (d, 1H, $J = 11.3$ Hz), 4.11 (d, 1H, $J = 11.3$ Hz), 4.64 (t, 2H, $J = 11.3$ Hz), 5.60 (d, 1H, $J$ = 4.0 Hz), 7.45 (t, 2H, $J = 7.5$ Hz), 7.58 (t, 1H, $J = 7.5$ Hz), 8.06 (d, 2H, $J = 7.5$ Hz); $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ 15.3, 20.1, 27.2, 28.0, 43.7, 59.5, 61.9, 64.0, 75.2, 84.4, 98.8, 128.5, 129.6, 129.8, 133.3, 150.1, 165.5, 174.5; Anal. Calcd for $C_{22}H_{29}NO_7$: C, 62.99; H, 6.97; N, 3.34%; Found: C, 63.18; H, 6.98; N, 3.47%.

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22. Analytical and spectral data of compound **16**. $[\alpha]_D^{25}$ −14.3 (*c* 1.0, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 0.04 (s, 3H), 0.09 (s, 3H), 0.88 (s, 9H), 1.32 (d, 3H, $J = 7.3$ Hz), 1.56 (s, 9H), 2.86–2.94 (m, 1H), 3.65 (d, 1H, $J = 10.3$ Hz), 3.90 (d, 1H, $J = 11.8$ Hz), 4.10 (d, 1H, $J = 10.3$ Hz), 4.13 (d, 1H, $J = 11.8$ Hz), 5.63 (d, 1H, $J = 8.8$ Hz), 7.47 (t, 2H, $J = 7.5$ Hz), 7.60 (m, 1H), 8.04 (m, 2H); $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ −5.6, −5.5, 13.9, 18.3, 25.8, 25.9, 26.2, 42.9, 61.1, 61.6, 69.6, 75.2, 83.7, 128.7, 129.4, 129.8, 151.3, 165.6, 173.3; Anal. Calcd for $C_{25}H_{39}NO_7Si$: C, 60.82; H, 7.96; N, 2.84%; Found: C, 60.95; H, 7.87; N, 2.97%.
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24. Analytical and spectral data of compound **17**. $[\alpha]_D^{25}$ +9.1 (*c* 1.7, $CHCl_3$); $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 0.05 (s, 3H), 0.10 (s, 3H), 0.86 (s, 9H), 1.34 (d, 3H, $J = 7.2$ Hz), 1.50 (s, 9H), 2.93 (m, 1H), 4.06 (d, 1H, $J = 10.6$ Hz), 4.34 (d, 1H, $J = 10.6$ Hz), 5.66 (d, 1H, $J = 8.0$ Hz), 7.37 (m, 2H), 7.48 (m, 1H), 7.97 (m, 2H), 8.37 (br s, 1H); $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ −5.6, −5.5, 13.4, 18.1, 25.7, 27.9, 42.7, 61.2, 70.7, 74.1, 84.1, 128.5, 128.8, 129.7, 130.2, 133.5, 133.7, 149.2, 165.5, 172.9, 173.0; Anal. Calcd for $C_{25}H_{37}NO_8Si$: C, 59.15; H, 7.35; N, 2.76%; Found: C, 59.34; H, 7.24; N, 2.92%.
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27. Analytical and spectral data of compound **3**. $[\alpha]_D^{25}$ +35.0 (*c* 1.1, $CHCl_3$); IR ($CHCl_3$): 1720, 1728, 1794, 1841 $cm^{-1}$; $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 1.37 (d, 3H, $J = 7.3$ Hz), 1.58 (s, 9H), 2.99 (quintet, 1H, $J = 7.3$ Hz), 4.54 (d, 1H, $J = 5.4$ Hz), 4.86 (d, 1H, $J = 5.4$ Hz), 5.63 (d, 1H, $J = 6.3$ Hz), 7.48 (t, 2H, $J = 7.5$ Hz), 7.61 (m, 1H), 8.08 (m, 2H); $^{13}C$ NMR ($CDCl_3$, 100 MHz): $\delta$ 13.4, 27.8, 43.0, 69.0, 74.4, 76.6, 86.4, 128.1, 128.5, 128.7, 130.1, 134.1, 148.3, 165.7, 165.9, 171.5; Anal. Calcd for $C_{19}H_{21}NO_7$: C, 60.79; H, 5.64; N, 3.73%; Found: C, 60.84; H, 5.75; N, 3.92%.