Synlett H. R. Aitken et al. Letter

A Catalytic Asymmetric Ene Reaction for Direct Preparation of α-Hydroxy 1,4-Diketones as Intermediates in Natural Product Synthesis

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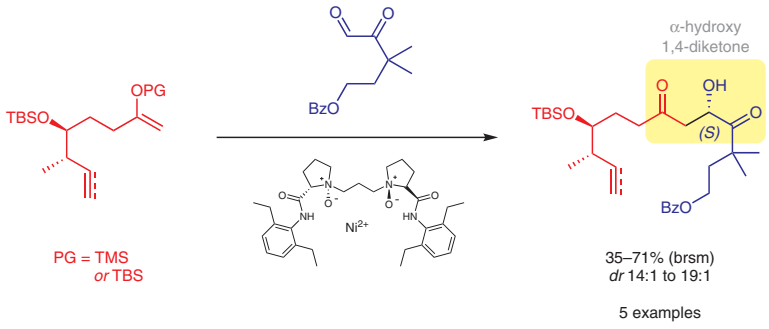

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Abstract Asymmetric access to α-hydroxy-1,4-diketones has been achieved by direct ene coupling of silyl enol ethers with glyoxal electrophiles, mediated by a chiral *N*,*N*′-dioxide–nickel(II) complex catalyst. Successful union of a polyketide silyl enol ether with an α-quaternary glyoxal, generated by dioxirane oxidation of an α-diazo ketone, models a proposed C_5–C_6 disconnection of the polyketide and spirocyclic imine domains of the marine natural product, portimine.

Key words ene reaction, glyoxal, *N*,*N*′-dioxide–nickel(II) complex, natural product synthesis, Leighton crotylation, portimine

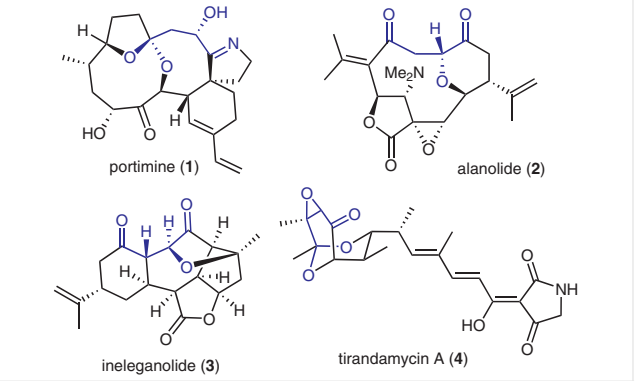

Figure 1 Natural products containing an α-hydroxy-1,4-diketone motif

A wide variety of bioactive natural products contain functionality derived from the α-hydroxy-1,4-diketone moiety (Figure 1). Examples include the caspase activator portimine,[1] the antileukemia agent ineleganolide,[2] and the antibiotic tirandamycin A.[3] Despite the importance of α-hydroxy-1,4-diketones as potential intermediates in the synthesis of these compounds, there are currently no broadly applicable methods for the direct stereoselective preparation of complex examples of this challenging fragment.[4]

In 2011, the Feng group reported a novel asymmetric *N*,*N*′-dioxide–nickel(II) complex for the Mukaiyama aldol reaction of acetophenone-derived silyl enol ethers with simple aryl glyoxal derivatives (Scheme 1, A)[5] achieving good yields and high enantioselectivity. Recent theoretical studies on *N*,*N*′-dioxide–metal complex catalysis by Su and co-workers suggested that aliphatic enol ethers may react via an ene-type mechanism.[6] We became interested in investigating these reactions with a view to extending *N*,*N*′-dioxide-nickel(II) complex catalysis to the asymmetric union of complex, aliphatic substrates that serve as plausible intermediates in natural product synthesis. Specifically, we report herein our investigation into the coupling of silyl enol ether **5** and glyoxal **6**, a plausible model system for the C5–C6 disconnection of the spirocyclic imine algal metabolite, portimine.

The synthesis of the methyl ketone coupling fragment **5** started from ester **9** (Scheme 2) prepared in one step from commercially available ethyl levulinate.[7] Following DIBAL reduction of ester **9**, the crude aldehyde was subjected to second-generation Leighton crotylation conditions using the *in situ* generated chiral silicon complex **14**,[8] to afford alcohol **10** as a single diastereoisomer in excellent yield and enantioselectivity (82%, 94% *ee*). While the standard aqueous acidic workup procedure for ligand recovery proved unsuitable for the sensitive acetal functionality, simple gradient elution of the crude reaction mixture facilitated excellent recovery (≤90%) of the recyclable diaminophenol ligand derived from **14** by chromatography. In order to prepare alkyne **5**, alcohol **10** was protected as the TBS ether, followed by oxidation and then homologation with the Ohira–Bestmann reagent to give **13**.[9,10] Treatment of **13** with Amberlyst 15 sulfonic acid resin then liberated the free ketone **5** in good yield, for use in the key fragment coupling.

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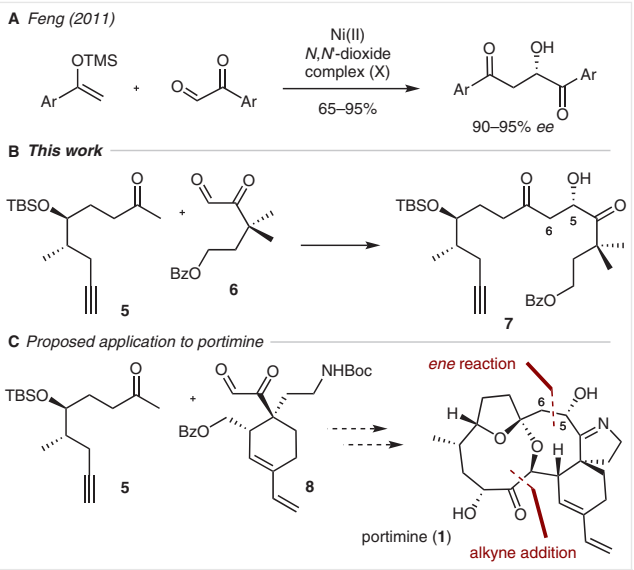
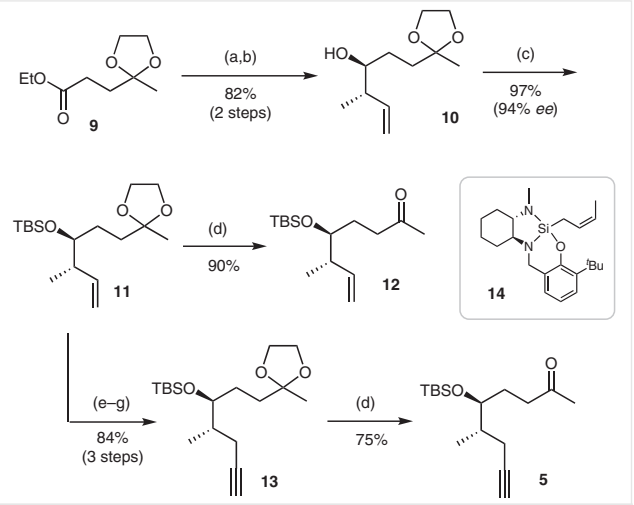
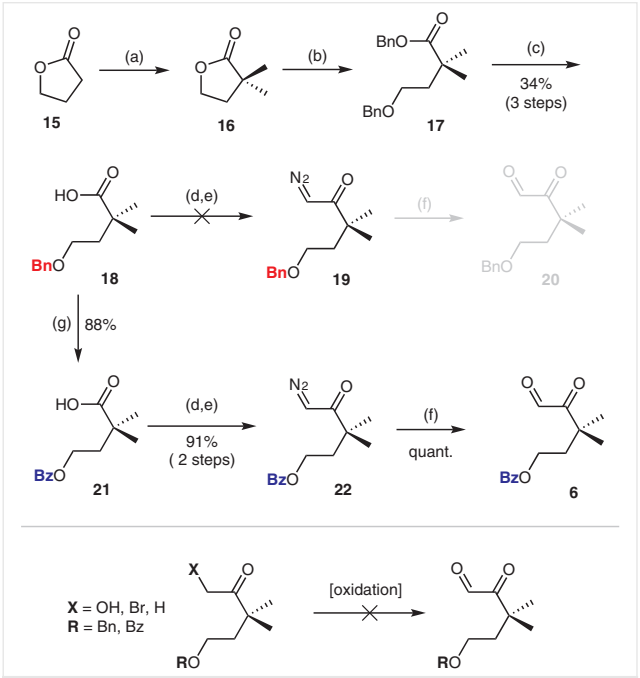


Scheme 1 (A) Feng's nickel(II)-catalyzed aldol reaction; (B) this work; (C) proposed application towards portimine.



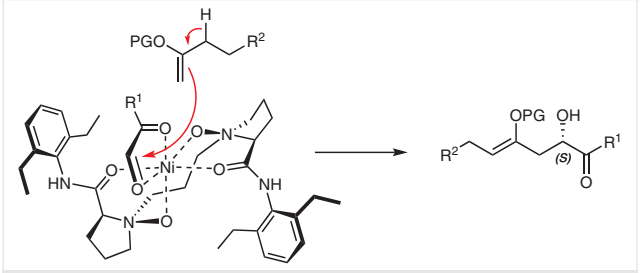
Scheme 2 Synthesis of methyl ketones **5** and **12**. *Reagents and conditions:* (a) DIBAL (1 M in hexane), CH_2Cl_2, 2 h, –78 °C; (b) **14**, THF, 2 h, rt to 0 °C, then TBAF (1 M in THF), Et_2O; (c) TBSOTf, 2,6-lutidine, CH_2Cl_2, 5 min, 0 °C; (d) Amberlyst-15, acetone/CH_2Cl_2 (1:1), 15 h–20 h, rt; (e) 9-BBN dimer, THF, 3.5 h, rt, then NaOH (aq, 3 M), H_2O_2 (30% aq); (f) SO_3·py, DMSO, *i*-Pr_2NEt, CH_2Cl_2, 5 min, 0 °C; (g) K_2CO_3, Ohira–Bestmann reagent, MeOH, 1 h, rt.

Synthesis of glyoxal **6** proceeded from γ-butyrolactone (**15**, Scheme 3). Initially, dimethylation was followed by a ring-opening protection sequence to generate carboxylic acid **18** in moderate yield.[11,12] Surprisingly, attempts to convert carboxylic acid **18** into glyoxal **20** met with failure, due to cleavage of the benzyl ether during preparation of the corresponding acid chloride. To circumvent this issue, the sensitive benzyl ether was submitted to ruthenium-catalyzed oxidation using periodate as the stoichiometric oxidant.[13] The resultant benzoate ester **21** then smoothly underwent conversion into diazoketone **22**. Addition of a solution of DMDO (69 mM in acetone) to **22** successfully resulted in rapid conversion into the desired glyoxal **6**.[14,15] Notably, alternative efforts to prepare glyoxals **6** or **20** by a number of α-ketone oxidation strategies proved unsuccessful, with other processes leading to rapid degradation, or a complex mixture of byproducts (Scheme 3).[16–20]



Scheme 3 Synthesis of glyoxal **6**. *Reagents and conditions:* (a) MeI, NaH (60% *w*/*w* in mineral oil), THF, 3 h, reflux; (b) KOH, BnBr, toluene, 13 h, Dean–Stark reflux; (c) KOH, MeOH/H_2O (2:1), 16 h, reflux; (d) $(COCl)_2$, DMF, CH_2Cl_2, 3 h, rt; (e) $TMSCHN_2$ (2 M in hexane), MeCN, 16 h, rt; (f) dimethyldioxirane (69 mM in acetone), 2 min, rt; (g) $NaIO_4$, $RuCl_3$·xH_2O, EtOAc/H_2O (2:1), 3 h, rt.

Initial investigation of the proposed ene reaction focused on the union of glyoxal **6** and ketone **12**, readily prepared by deprotection of acetal **11** (Scheme 4).



Scheme 4 Favored facial approach for glyoxal ene reaction, as proposed by Feng[4]

In order to carry out the ene reaction (Table 1), ketone **12** was converted into the corresponding TMS enol ether, which was directly used without further purification, for reaction with freshly prepared crude glyoxal **6**.[21] This mixture was treated with the *N*,*N*′-dioxide–nickel(II) complex derived from ligand **23**, to afford small quantities of aldol product **25**, together with large amounts of recovered ketone **12** (Table 1, entry 1). Notably however, the reaction appeared to proceed with good stereoselectivity (*dr* = 11:1), as determined by comparison of the relative integral of the newly formed epimeric hydroxyl proton in the ^{1}H NMR spectrum.

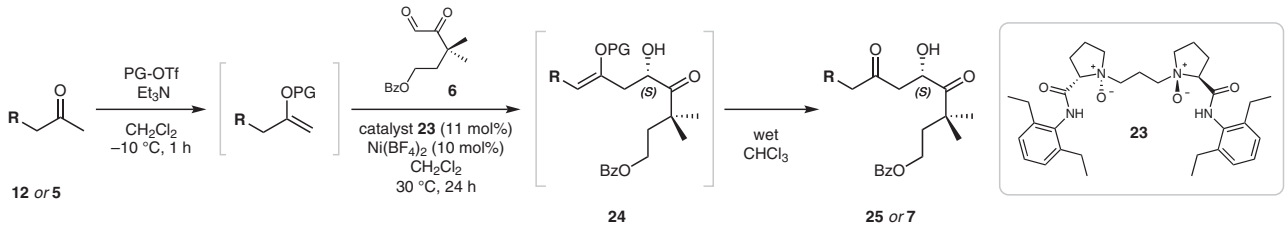
When the more hindered TBS enol ether derivative was employed, coupling proceeded cleanly, affording the ene enol silane product **24**. Stirring this compound in wet chloroform overnight resulted in clean cleavage of the enol silane, leading to the isolation of α-hydroxy-1,4-diketone **25** in 29% yield from ketone **12** (14:1 *dr*, Table 1, entry 2). However, when the reaction sequence was repeated using the more stable TIPS enol ether derivative of **12**, only 19% of α-hydroxy-1,4-diketone **25** was isolated, with competing decomposition of glyoxal **6** observed after prolonged reaction times (Table 1, entry 3).

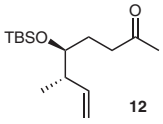
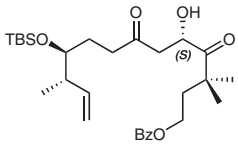
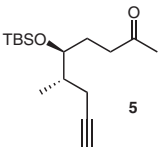
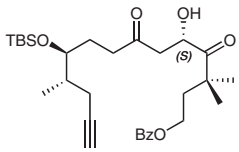
Similar results were obtained using the TBS enol ether of the portimine polyketide fragment **5** (Table 1, entry 4). Due to the inherent instability of glyoxal **6**, it appeared that the efficiency of the ene coupling was most likely limited by its decomposition under the reaction conditions. To test this possibility, the reaction sequence was performed with 3 equivalents of glyoxal **6**, added in three portions over 3 h, which afforded α-hydroxy-1,4-diketone **7** in an improved yield of 32% (71% based on recovered starting material; Table 1, entry 5). In the ene coupling, only minimal concomitant desilylation of intermediate silyl enol ether was observed prior to the reaction workup, suggesting that improved yields could be achieved using an even larger excess of glyoxal.

The absolute stereochemistries of the α-hydroxy-1,4-diketone adducts were determined by analogy with the model proposed by the Feng group for related ene and aldol transformations. In this model a nucleophile undergoes addition to a facially discriminated, activated glyoxal–nickel complex.[4] Accordingly, the newly formed stereocenter of hydroxy dione **7** exists in the *S* configuration (Scheme 4).

In conclusion, an asymmetric ene reaction catalyzed by Feng's *N*,*N*′-dioxide–nickel(II) complex has been applied to the union of ketone **5** and glyoxal **6**, to model to the C_5–C_6 disconnection of portimine.[21] The reaction cleanly afforded the challenging α-hydroxy-1,4-diketone motif with excellent stereocontrol over three steps from ketone **5**. This transformation is the first application of *N*,*N*′-dioxide–nickel(II) catalysis to a target-directed synthetic sequence and

Table 1 Optimization of the N,N′-Dioxide–Nickel(II) Complex Catalyzed Ene Reaction[a]



Entry	Ketone	PG	Product	Yield (%)[b] and *dr*	Recovered SM
1		TMS		21 (11:1)	–[c]
2		TBS		29 (14:1)	17
3[d]	**12**	TIPS	**25**	19 (14:1)	44
4		TBS		12 (>19:1)	48
5[e]	**5**	TBS	**7**	32 (>19:1)	55

[a] Reactions were performed on ketone **5** or **13** (25 mg) with glyoxal **6** (1.3 equiv) unless otherwise noted. Intermediate silanes were not purified before use.
[b] Yield reported over three steps from starting ketone.
[c] Treatment with wet $CHCl_3$ was not performed.
[d] Ene reaction performed for 40 h.
[e] Glyoxal **6** (3 equiv) was added in three portions over 3 h.

represents a significant increase in substrate scope for that methodology.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0037-1610748.

References and Notes

(1) Selwood, A. I.; Wilkins, A. L.; Munday, R.; Shi, F.; Rhodes, L. L.; Holland, P. T. *Tetrahedron Lett.* **2013**, *54*, 4705.
(2) Duh, C.-Y.; Wang, S.-K.; Chia, M.-C.; Chiang, M. Y. *Tetrahedron Lett.* **1999**, *40*, 6033.
(3) Meyer, C. E. *J. Antibiot.* **1971**, *24*, 3.
(4) Some methods for asymmetric synthesis of simple derivatives have been reported: (a) Moles, F. J. N.; Guillena, G.; Nájera, C. *Synlett* **2015**, *26*, 656. (b) Alberg, D. G.; Poulsen, T. B.; Bertelsen, S.; Christensen, K. L.; Birkler, R. D.; Johannsen, M.; Jørgensen, K. A. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3888. (c) Guo, L.; Plietker, B. *Angew. Chem. Int. Ed.* **2019**, *58*, 8346. (d) Richter, C.; Krumey, M.; Klaue, K.; Mahrwald, R. *Eur. J. Org. Chem.* **2016**, 5309.
(5) Zhao, J.; Zheng, K.; Yang, Y.; Shi, J.; Lin, L.; Liu, X.; Feng, X. *Synlett* **2011**, 903.
(6) Wang, J.; Su, Z.; Yang, N.; Hu, C. *J. Org. Chem.* **2016**, *81*, 6444.
(7) Wanner, M. J.; Boots, R. N. A.; Eradus, B.; Gelder, R. D.; van Maarseveen, J. H.; Hiemstra, H. *Org. Lett.* **2009**, *11*, 2579.
(8) Suen, L. M.; Steigerwald, M. L.; Leighton, J. L. *Chem. Sci.* **2013**, *4*, 2413.
(9) Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett* **1996**, 521.
(10) Ohira, S. *Synth. Commun.* **1989**, *19*, 561.
(11) Jägel, J.; Schmauder, A.; Binanzer, M.; Maier, M. E. *Tetrahedron* **2007**, *63*, 13006.
(12) Wilson, Z. E.; Hubert, J. G.; Brimble, M. A. *Eur. J. Org. Chem.* **2011**, 3938.
(13) Schuda, P. F.; Cichowicz, M. B.; Heimann, M. R. *Tetrahedron Lett.* **1983**, *24*, 2.
(14) Ihmels, H.; Maggini, M.; Prato, M.; Scorrano, G. *Tetrahedron Lett.* **1991**, *32*, 6215.
(15) **Preparation of Glyoxal (6)**
To stirred diazoketone **22** (104 mg, 0.400 mmol), dimethyldioxirane (69 mM in acetone, 6.7 mL, 0.466 mmol) was added rapidly. The mixture was vigorously stirred for 2 min, then concentrated under a stream of nitrogen. The resultant crude oil was used in the next step without further purification. An analytical sample gave the following data. IR (film): 2972, 1716, 1452, 1316, 1274, 1113, 1026, 712 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 9.20 (s, 1 H), 7.91–7.86 (m, 2 H), 7.59–7.52 (m, 1 H), 7.47–7.40 (m, 2 H), 4.36 (t, *J* = 6.1 Hz, 2 H), 2.31 (t, *J* = 6.1 Hz, 2 H), 1.35 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 202.3, 188.7, 166.4, 133.3, 129.7, 129.6, 128.6, 61.5, 44.3, 37.8, 24.0. HRMS (ESI): *m/z* $[M + Na]^+$ calcd for $C_{14}H_{16}NaO_4$: 271.0941; found: 271.0935.
(16) Wu, F.; Mandadapu, V.; Day, A. I. *Tetrahedron* **2013**, *69*, 9957.
(17) Kornblum, N.; Frazier, H. W. *J. Am. Chem. Soc.* **1966**, *88*, 865.
(18) Mitschka, R.; Oehldrich, J.; Takahashi, K.; Cook, J. M.; Weiss, U.; Silverton, J. V. *Tetrahedron* **1981**, *37*, 4521.
(19) Kotha, S. S.; Sekar, G. *Tetrahedron Lett.* **2015**, *56*, 6323.
(20) Zhu, Y.-P.; Jia, F.-C.; Liu, M.-C.; Wu, A.-X. *Org. Lett.* **2012**, *14*, 4414.
(21) To a solution of ketone **5** (40 mg, 0.142 mmol) in dichloromethane (1 mL) at –10 °C triethylamine (97 μL, 0.71 mmol) was added, followed by *tert*-butyldimethylsilyl trifluoromethanesulfonate (65 μL, 0.28 mmol). After 1 h the reaction was quenched with saturated aqueous sodium hydrogen carbonate (2 mL) and extracted with dichloromethane (3 × 3 mL). The combined organic layers were dried over sodium sulfate, filtered, concentrated, then dissolved in petroleum ether (10 mL), filtered through a plug of cotton wool and concentrated again, to give the crude silyl enol ether. To a solution of diamine-*N*-dioxide (8.7 mg, 0.015 mmol) in dichloromethane (1 mL) at 30 °C, nickel tetrafluoroborate hexahydrate (4.8 mg, 0.014 mmol) was added, the mixture was stirred vigorously for 30 min, and then concentrated and dried *in vacuo* for 5 h. A solution of freshly prepared crude glyoxal (**6**, ca. 0.142 mmol) and the previously prepared silyl enol ether in dichloromethane (1 mL) was then added, and the mixture warmed to 30 °C. After 2 h, further glyoxal **6** (ca. 0.142 mmol) in dichloromethane (0.5 mL) was added dropwise, followed after a further 2 h by another solution of glyoxal **6** (ca. 0.142 mmol) in dichloromethane (0.5 mL). The reaction was then stirred for 18 h and quenched with aqueous citric acid (0.5 M, 3 mL), stirred for 30 min, and then extracted with dichloromethane (3 × 3 mL). The combined organic layers were washed with brine (6 mL), dried over sodium sulfate, filtered, and concentrated. The resultant oil was allowed to stand in chloroform for 14 h, then concentrated *in vacuo*. Chromatography (petroleum ether/ethyl acetate, 15:1) afforded (**7**, 24 mg, 32%) as a colorless oil and returned starting material ketone (**5**, 22 mg, 55%); $[\alpha]_D^{20}$ 2.2 (*c* 2.4, $CHCl_3$). IR (film): 3480, 2958, 2857, 1716, 1275, 1113, 1027, 837, 776, 713 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 8.01–7.97 (m, 2 H), 7.59–7.53 (m, 1 H), 7.46–7.40 (m, 2 H), 4.90–4.83 (m, 1 H), 4.39–4.27 (m, 2 H), 3.71–3.67 (m, 1 H), 3.60–3.56 (m, 1 H), 2.65–2.57 (m, 2 H), 2.58–2.36 (m, 2 H), 2.28 (ddd, *J* = 16.6, 5.8, 2.6 Hz, 1 H), 2.23–1.98 (m, 3 H), 1.95 (dd, *J* = 3.0, 2.6 Hz, 1 H), 1.80–1.62 (m, 3 H), 1.33 (s, 3 H), 1.33 (s, 3 H), 0.96 (d, *J* = 6.9 Hz, 3 H), 0.88 (s, 9 H), 0.06 (s, 6 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 214.4, 209.4, 166.7, 133.2, 130.3, 129.7, 128.5, 83.9, 73.4, 70.6, 69.2, 61.9, 46.0, 45.8, 40.2, 38.3, 37.9, 26.9, 26.0, 25.4, 24.6, 21.9, 18.2, 14.4, –4.1, –4.4. HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{30}H_{46}NaO_6Si$: 553.2956; found: 553.2957.