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Rapid Assembly of Structurally Defined and Highly Functionalized Conjugated Dienes via Tethered Enyne Metathesis

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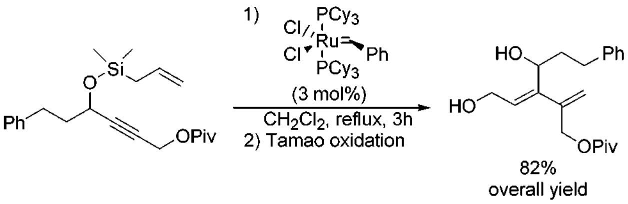
ABSTRACT



Conjugated dienes are versatile building blocks in organic synthesis, and the development of new methods for their synthesis remains an important topic in modern synthetic organic chemistry. We describe here an expedient synthesis of highly functionalized conjugated dienes through sequential silicon-tethered ring-closing enyne metathesis mediated by Grubbs' Ru carbene catalysts and Tamao oxidation. Notable attributes of this methodology include short synthetic manipulations and the structural complexity it confers on the resulting diene moiety.

Conjugated dienes are versatile building blocks in organic synthesis as exemplified by their dominance in the Diels−Alder reaction and most of its variants.[1] There exists a plethora of synthetic methods for conjugated dienes,[2] with prototypical approaches employing base-induced elimination from allylic and homoallylic halides or halide equivalents, double elimination from suitably substituted dihalide substrates, or the Wittig-type olefination of α,β-unsaturated carbonyl compounds. However, for many practical applications, the control of both the regio- and the stereochemistry of the diene moiety has to be rigorously exercised. Cross coupling of vinylic species utilizing an appropriate organometallic catalyst has proven more effective in controlling diene stereochemistry and has been extensively used in organic synthesis.[3] However, the preparation of the prerequisite vinyl halides/triflates (Heck),[4] vinylstannanes (Stille),[5] organoboranes (Suzuki),[6] and alkenylzincs (Negishi)[7] often involves tedious multistep manipulation of air-sensitive and, in the case of organostannanes, toxic compounds.

The rapidly emerging olefin metathesis reaction has found many spectacular applications in organic synthesis.[8] In particular, diene ring-closing metathesis (RCM) and cross olefin metathesis mediated by transition metal carbene complexes have evolved into powerful tools for the formation

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[1] (a) Fringuelli, F.; Taticchi, A. *Dienes in the Diels−Alder Reaction*; Wiley: New York, 1990. (b) Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*; Pergamon: Oxford, 1990.

[2] (a) Norman, J. F. In *Modern Synthetic Methods*; Scheffold, R., Ed.; Wiley: Chichester, 1983; Vol. 3, pp 139−171. (b) Larock, R. C. *Comprehensive Organic Transformations*; VCH Publishers: New York, 1989; pp 241−262.

[3] (a) *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998. (b) Tsuji, J. *Transition Metal Reagents and Catalysts, Innovation in Organic Synthesis*; Wiley: Chichester, 2000.

[4] For recent reviews on the Heck reaction, see: (a) Heck, R. F. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: New York, 1991; Vol. 4, Chapter 4.3. (b) Bräse, S.; de Meijere, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; Chapter 3. (c) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3009−3066.

[5] Stille, J. K. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 508−524. (b) Mitchell, T. N. *Synthesis* **1992**, 803−815. (c) Mitchell, T. N. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; Chapter 4.

[6] For recent reviews, see: (a) Niyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Suzuki, A. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; Chapter 2.

[7] (a) Negishi, E.; Liu, F. in *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 1998; Chapter 1. For examples of diene synthesis via coupling of vinyl halides with organoaluminium and zirconium compounds, see: (b) Baba, S.; Negishi, E. *J. Am. Chem. Soc.* **1976**, *98*, 6729−6731. (c) Negishi, E.; Okukado, N.; King, A. O.; Van Horn, D. E.; Spiegel, B. I. *J. Am. Chem. Soc.* **1978**, *100*, 2254−2256.

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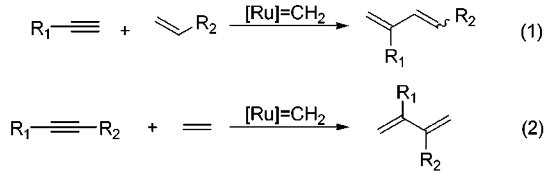
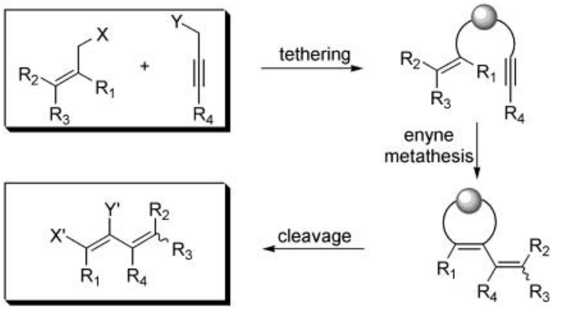
of carbon−carbon double bonds over the past 10 years. Despite its great synthetic utility, the related alkene−alkyne metathesis has been much less explored.[9−11] Whereas enyne RCM has been shown to be a versatile strategy for the synthesis of cyclic dienes,[9] its intermolecular variant, the cross alkene−alkyne metathesis, is limited to only a few cases with less demanding substrates: the cross metatheses of terminal alkynes and terminal alkenes (eq 1, Scheme 1)[10] and of internal alkynes and ethylene (eq 2),[11] furnishing 1,3- and 2,3-disubstitued dienes, respectively. To date, the synthesis of tri- and tetrasubstituted acyclic dienes by alkene−alkyne metathesis has not been rigorously established due to the difficulty encountered in the simultaneous control of their chemo-, regio-, and stereoselectivity.[12]

Scheme 1



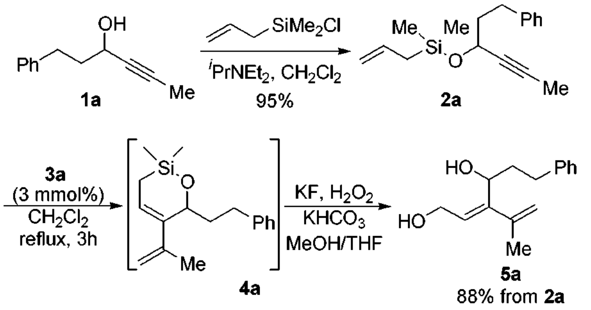
To overcome the above-mentioned limitations of alkene−alkyne metathesis, we chose to apply the principle of the temporary connection methodology[13,14] as a means to facilitate the alkene−alkyne metathesis and to provide regio- and stereochemical control. Specifically, it is expected that tethering of an alkene and an alkyne with an appropriate linker followed by enyne RCM[9] and tether cleavage would provide ready access to highly substituted acyclic conjugated dienes with predetermined regio- and, preferably, stereochemistry (Scheme 2). Even a simplified scenario of Scheme 2 wherein a terminal alkene ($R_1 = R_2 = R_3 = H$) is tethered to an internal alkyne would yield after cleavage of the tether a *trisubstituted diene with complete regio- and stereochemical control*.

Scheme 2



As exemplified in Scheme 3 and summarized in Table 1, our strategy was successfully implemented with a number of silicon-tethered[15] enyne substrates leading to the formation of a variety of highly functionalized dienes. Thus, treatment of the tethered enyne **2a**, prepared from the commercially available allylchlorodimethylsilane and propargyl alcohol **1a**, as shown in Scheme 3, with Grubbs catalyst **3a**[16] (Figure 1)

Scheme 3



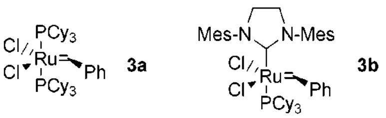


Figure 1. Grubbs Ru catalysts.

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(8) Leading reviews on olefin metathesis: (a) Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2036−2056. (b) Fürstner, A. *Top. Organomet. Chem.* **1998**, *1*, 1−231. (c) Armstrong, S. K. *J. Chem. Soc., Perkin Trans. 1* **1998**, 371−388. (d) Grubbs, R. H.; Chang, S. *Tetrahedron* **1998**, *54*, 4413−4445. (e) Pandit, U. K.; Overleeft, H. S.; Borer, B. C.; Bieräugel, H. *Eur. J. Org. Chem.* **1999**, 959−968. (f) Phillips, A. J.; Abell, A. D. *Aldrichimica Acta* **1999**, *32*, 75−90.

(9) For leading references on ring-closing enyne metathesis, see: (a) Kinoshita, A.; Mori, M. *J. Org. Chem.* **1996**, *61*, 8356−8357 (b) Kinoshita, A.; Mori, M. *Synlett* **1997**, 1020−1022. (c) Mori, M.; Sakakibara, N.; Kinoshita, A. *J. Org. Chem.* **1998**, *63*, 6082−6083. (d) Mori, M.; Kitamura, T.; Sakakibara, N.; Sato, Y. *Org. Lett.* **2000**, *2*, 543−545. (e) Heerding, D. A.; Takata, D. T.; Kwon, C.; Huffman, W. F. Samanen, J. *Tetrahedron Lett.* **1998**, *39*, 6815−6818. (f) Ackermann, L.; Bruneau, C.; Dixneuf, P. H. *Synlett* **2001**, 397−399. For examples of tandem dienyne metathesis, see: (g) Kim, S.-H.; Zuercher, W. J.; Bowden, N. B.; Grubbs, R. H. *J. Org. Chem.* **1996**, *61*, 1073−1081. (h) Renaud, J.; Graf, C.-D.; Oberer, L. *Angew. Chem., Int. Ed.* **2000**, *39*, 3101−3104. (i) Smulik, J. A.; Diver, S. T. *Tetrahedron Lett.* **2001**, *42*, 171−174.

(10) Stragies, R.; Schuster, M.; Blechert, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2518−2560. (b) Schürer, S. C.; Blechert, S. *Comm. Commun.* **1999**, 1203−1204. (c) Schürer, S. C.; Blechert, S. *Tetrahedron Lett.* **1999**, *40*, 1877. (c) Smulik, J. A.; Diver, S. T. *Org. Lett.* **2000**, *2*, 2271−2274.

(11) (a) Kinoshita, A.; Mori, M. *J. Am. Chem. Soc.* **1997**, *119*, 12388−12389. (b) Kinoshita, A.; Sakakibara, N.; Mori, M. *Tetrahedron* **1999**, *55*, 8155−8167.

(12) For example, the cross coupling shown below gave a complex mixture of products, see: Stragies, R.; Voigtmann, U.; Blechert, S. *Tetrahedron Lett.* **2000**, *41*, 5465−5468.

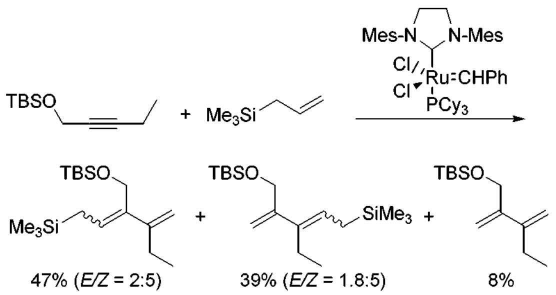
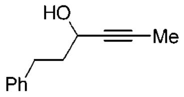
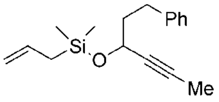
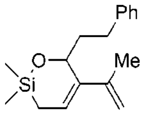
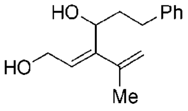
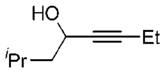
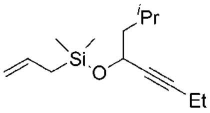
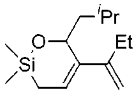
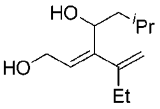
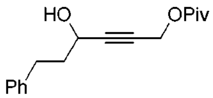
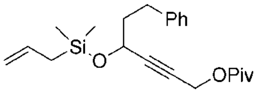
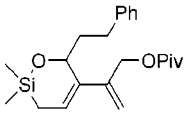
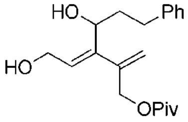
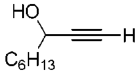
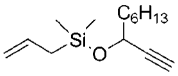
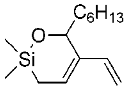
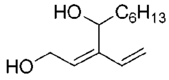
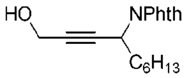
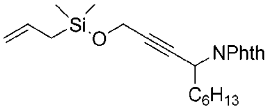
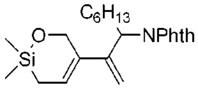
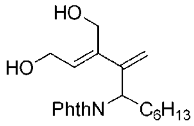
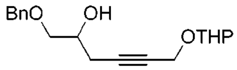
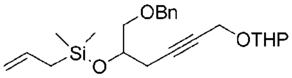
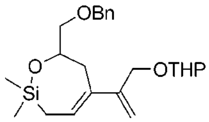
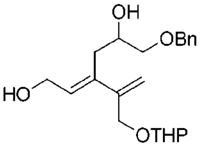
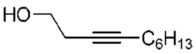
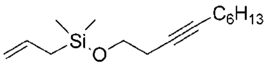
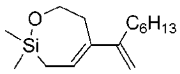
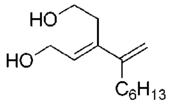
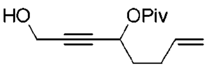
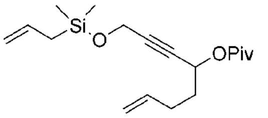
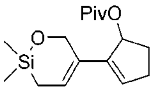
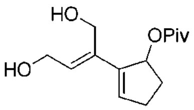


Table 1. Synthesis of Functionalized Dienes via Silicon-Tethered Enyne Metathesis

entry	alkyne	tethered enyne	catalyst	conditions[a]	tethered diene	product (yield[b])
1	 **1a**	 **2a**	**3a** (3 mol%)	45 °C, 3 h	 **4a**	 **5a** (88%)
2[c]	 **1b**	 **2b**	**3a** (3 mol%)	45 °C, 12 h	 **4b**	 **5b** (86%)
3	 **1c**	 **2c**	**3a** (3 mol%)	45 °C, 3 h	 **4c**	 **5c** (82%)
4[c,d]	 **1d**	 **2d**	**3a** (3 mol%)	25 °C, 16 h with CH$_2$=CH$_2$	 **4d**	 **5d** (87%)
5[c,d]	 **1e**	 **2e**	**3a** (4 mol%)	25°C, 23 h with CH$_2$=CH$_2$	 **4e**	 **5e** (68%)
6[c]	 **1f**	 **2f**	**3b** (1 mol%)	45 °C, 12 h	 **4f**	 **5f** (73%)
7	 **1g**	 **2g**	**3b** (1 mol%)	45 °C, 12 h	 **4g**	 **5g** (87%)
8[e]	 **1h**	 **2h**	**3a** (3 mol%)	45 °C, 12 h	 **4h**	 **5h** (70%)

[a] Unless otherwise noted, RCM was carried out at a concentration of in 0.025 M in CH$_2$Cl$_2$ under an Ar atmosphere. [b] Isolated yield. [c] The concentration of the reaction was 0.05 M. [d] Ethylene was supplied under balloon pressure. [e] The concentration of the reaction was 0.005 M.

(3 mol %) in CH$_2$Cl$_2$ (0.025 M) at reflux gave cleanly the tethered product **4a** which, after oxidative cleavage with H$_2$O$_2$ as described by Tamao et al.,[17] afforded diene **5a** in 88% overall yield from **2a** after purification by flash chromatography on silica gel.[18]

Table 1 lists the results with other substrates bearing a diverse array of substituents on the alkyne. Enyne **2b** (entry 2) with an isobutyl group present at the propargylic position exhibited decreased reactivity relative to that of **2a**, and its RCM required a longer reaction time (12 h) and a higher concentration in order for the reaction to go to completion. The ester group in enyne **2c** (entry 3) did not cause any retardation and the RCM of **2c** proceeded uneventfully, furnishing the highly oxygenated diene **5c** in high yield after

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(13) Stork, G.; Suh, H. S.; Kim, G. *J. Am. Chem. Soc.* **1991**, *113*, 7054−7056.

(14) For recent reviews, see: (a) Bols, M.; Skrydstrup, T. *Chem. Rev.* **1995**, *95*, 1253−1277. (b) *Templated Organic Synthesis*; Diederich, F., Stang, P. J., Eds.; Wiley-VCH: Weinheim, 2000.

tether cleavage. Substrates derived from a terminal alkyne (entry 4) or an alkyne containing a hindered phthalimido group (entry 5) experienced diminished reactivity, and the use of ethylene gas was found to be crucial to attain complete conversion.[19] RCM of enynes **2f** (entry 6) and **2g** (entry 7) leading to the formation of seven-membered tethered dienes did not go to completion with catalyst **3a**, but the use of the more active catalyst **3b**[20] resulted in high conversions in both cases. Finally, a tandem ene−yne−ene metathesis[9g−i] was achieved with substrate **2h** (entry 8) which provided the tetrasubstituted diene **5h** in high yield after tether cleavage when the reaction was run under high dilution conditions.

While we have shown that the tethered enyne RCM−oxidative cleavage methodology can provide an efficient access to highly functionalized acyclic dienes, preliminary studies have established that the silicon-tethered diene intermediates can serve as excellent substrates for highly stereoselective Diels−Alder reactions.[21]

Acknowledgment. This research was supported by Northern Illinois University.

Supporting Information Available: NMR (^{1}H and ^{13}C) and characterization data for compounds **2a−h** and **5a−h**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) For examples of silicon-tethered ring-closing diene metathesis, see: (a) Chang, S.; Grubbs, R. H. *Tetrahedron* **1997**, *27*, 4757−4760. (b) Meyer, C.; Cossy, J. *Tetrahedron Lett.* **1997**, *38*, 7861. (c) Cassidy, J. H.; Marsden, S. P.; Stemp, G. *Synlett* **1997**, 1411−1413. (d) Taylor, R. E.; Engelhardt, C.; Schmitt, M. J.; Yuan, H. *J. Am. Chem. Soc.* **2001**, *123*, 2964−2969. For related examples, see: (e) Evans, P. A.; Murthy, V. S. *J. Org. Chem.* **1998**, *63*, 6768−6769. (f) Hoye, T. R.; Promo, M. A. *Tetrahedron Lett*. **1999**, *40*, 1429. (g) Briot, A.; Bujard, M.; Gouverneur, V.; Nolan, S. P.; Mioskowski, C. *Org. Lett.* **2000**, *2*, 1517−1519. (h) Yao, Q. *Angew. Chem., Int. Ed.* **2000**, *39*, 3896−3898. (i) Boitea, J. G.; Van de Weghe, P.; Eustche, J. *Tetrahedron Lett.* **2001**, *42*, 239−242.

(16) Schwab, P.; Grubbs, R. H.; Ziller, J. W. *J. Am. Chem. Soc.* **1996,** *119*, 100−110.

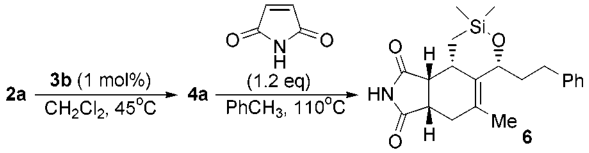
(17) Tamao, K.; Ishida, N.; Kumada, M. *Org. Synth.* **1990**, *69*, 96−105.

(18) **Representative experimental procedures for enyne RCM and Tamao oxidation of tethered diene product** (entry 1, Table 1): To a solution of **2a** (136 mg, 0.50 mmol) in CH_2Cl_2 (0.025 M) was added Grubbs catalyst **3a** (12 mg, 3 mol %), and the reaction mixture was heated to reflux under Ar. After 3 h, the reaction was cooled to rt and concentrated to dryness under vacuum. Examination of the crude reaction mixture by ^{1}H NMR indicated complete consumption of **3a** with clean and essentially quantitative formation of the tethered diene **4a**. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.14 (3H, s), 0.29(3H, s), 1.41−1.49 (2H, m), 1.76−1.95 (2H, m), 1.86 (3H, s), 2.71(1H, ddd, $J = 6.8, 10.2, 13.7$ Hz), 2.87 (1H, ddd, $J = 4.6, 10.4, 13.7$ Hz), 4.70−4.85 (1H, m), 4.73 (1H, s), 4.78 (1H, m), 4.80 (1H, s), 6.05 (1H, dd, $J = 4.6, 7.4$ Hz), 7.16−7.30 (5H, m). Crude **4a** was then dissolved in MeOH/THF (5 mL/5 mL) and treated with KF (145 mg, 2.5 mmol) and $KHCO_3$ (125 mg, 1.25 mmol) followed by H_2O_2 (30%, 0.56 mL, 5 mmol). After stirring at rt for 48 h, TLC indicated complete consumption of the starting material and the reaction mixture was poured into water and extracted with EtOAc (3% × 20 mL). The combined organic extracts were washed with 5% $Na_2S_2O_4$ and brine, dried (Na_2SO_4), and evaporated. Flash chromatography on silica gel (EtOAc/hexane 1:1) gave diene **5a** (102 mg, 88%) as a thick hygroscopic oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.87−2.10 (2H, m), 1.90 (3H, s), 2.69 (1H, m), 2.81 (1H, m), 4.29 (1H, dd, $J = 6.8, 13.4$ Hz), 4.35 (1H, dd, $J = 6.6, 13.4$ Hz), 4.63 (1H, dd, $J = 4.5, 8.8$ Hz), 4.95 (1H, s), 4.96 (1H, s), 5.78 (1H, t, $J = 6.7$ Hz), 7.16−7.34 (5H, m). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 22.88, 32.44, 37.85, 58.70, 69.85, 113.82, 125.93, 127.73, 128.41, 128.46, 141.62, 143.22, 145.87. Anal. Calcd for $C_{15}H_{20}O_2{\cdot}0.2H_2O$: C, 76.36; H, 8.72. Found: C, 76.67; H, 8.78.

(19) For a discussion of the effect of ethylene gas in ring-closing enyne metathesis, see ref 9c.

(20) Scholl, M.; Ding, S.; Lee, C. W.; Grubbs, R. H. *Org. Lett.* **1999**, *1*, 953−956.

(21) For example, treatment of crude **4a** with maleiimide in toluene at reflux led to the formation of the Diels−Alder adduct **6** shown below, which was isolated in 68−70% yield as a single diastereomer and whose stereochemistry was established by conformational analysis of its fused tricyclic structure on the basis of ^{1}H NMR data and NOESY experiments.



Data for **6**. ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 0.14 (3H, s), 0.17 (3H, s), 0.85 (1H, dd, $J = 5.7, 15.2$ Hz), 1.52−1.58 (1H, m), 1.66 (3H, d, $J = 1.6$ Hz), 1.88−1.99 (2H, m), 2.27 (1H, dd, $J = 6.7, 14.7$ Hz), 2.48−2.52 (1H, m), 2.56 (1H, dd, $J = 1.7, 14.7$ Hz), 2.60−2.71 (2H, m), 2.97 (1H, dd, $J = 6.1, 8.9$ Hz), 3.09 (1H, ddd, $J = 1.7, 6.6, 8.9$ Hz), 4.75 (1H, dd, $J = 5.8, 9.0$ Hz), 7.16−7.28 (5H, m), 8.11 (1H, s). ^{13}C NMR ($CDCl_3$, 125 MHz) δ: −0.90, 1.62, 11.55, 19.41, 31.25, 32.32, 33.97, 39.69, 41.53, 47.79, 71.85, 125.79, 128.36, 130.10, 134.47, 141.56, 178.53, 179.36. Anal. Calcd for $C_{21}H_{27}NO_{23}Si$: C, 68.26, H, 7.36., N, 7.39. Found: C, 68.10; H, 7.55; N. 3.83.