# An Efficient Synthesis of de novo Imidates via Aza-Claisen Rearrangements of *N*-Allyl Ynamides

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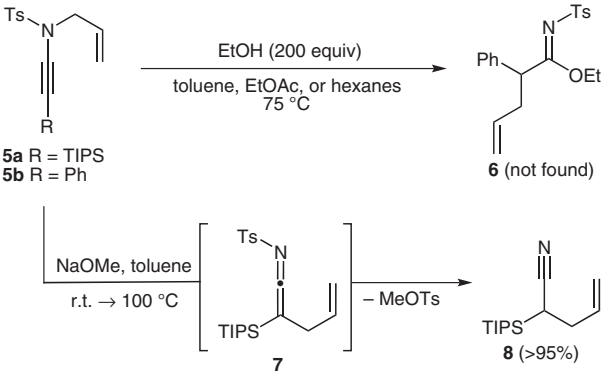
**Abstract:** A novel thermal 3-aza-Claisen rearrangement of *N*-allyl ynamides for the synthesis of α-allyl imidates is described. Also, a sequential aza-Claisen, palladium-catalyzed Overman rearrangement is described for the synthesis of azapin-2-ones.

**Key words:** ynamide, aza-Claisen, imidate, ketenimine, Overman rearrangement

We recently reported the de novo synthesis of pharmacologically useful amidines from *N*-allyl ynamides[1,2] featuring either a Pd-catalyzed[3] N-to-C allyl transfer or unprecedented thermal[3,4] 3-aza-Claisen[5] rearrangement followed by trapping of the in situ generated ketenimine[6] with amine nucleophiles. There has been great interest within the synthetic community on preparing amidines and imidates,[7] most commonly through interception of the ketenimine intermediate produced during a Cu-catalyzed Huisgen [3+2] cycloaddition of azides and alkynes.[8–10] Herein, we describe our efforts at the synthesis of imidates via trapping of ketenimines **3** formed through aza-Claisen rearrangement of ynamides **1** in the presence of alcoholic nucleophiles (Scheme 1).

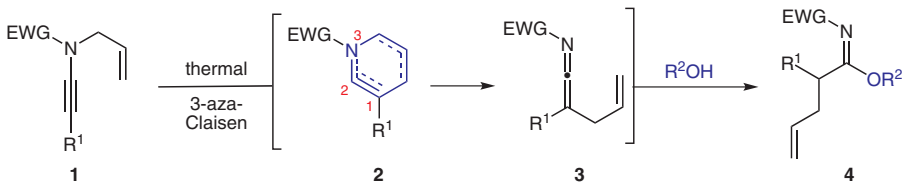
It was quickly discovered that the nucleophilicity of even simple alcohols such as methanol and ethanol was not sufficient to yield imidates **6** despite the alcohols being used in 200-fold excess (Scheme 2)! Furthermore, attempts to trap ketenimine **7** generated from ynamide **5a** with more nucleophilic sodium methoxide led to cleavage of the *N*-toluenesulfonamide protecting group furnishing nitrile **8** in quantitative yield.

Our subsequent attempts to carry out this transformation intramolecularly were also met with difficulty. Alcohol **10** could be prepared by simple TBAF-mediated desilylation of **9**. Upon heating of **10** in toluene, the only isolable products were nitrile **11** formed through a 1,3-sulfonyl[4,11] transfer during the ketenimine intermediate and *p*-toluenesulfonamide, which implies that the aza-Claisen did in fact occur but was not productive towards imidate formation. Alternatively, when **10** was treated with sodium hydride to increase the nucleophilicity of the oxygen and then heated to 80 °C, only enamides **13** and **14** were formed through 5-*exo*-dig and 6-*endo*-dig cyclization onto the ynamide, respectively (Scheme 3). Since this was too nucleophilic for the aza-Claisen to occur, we instead opted to cleave the silyl protecting group of ynamide **9** in situ to trigger the cyclization, however, again only nitrile **12** was found, demonstrating that the 1,3-sulfonyl shift is quite facile.




**Scheme 2** Alkoxide-induced detosylation of the ketenimine

Finally, we found that heating of ynamides **1** in alcoholic solvents in the presence of 4 Å molecular sieves led to imidates **4** in moderate to excellent yields. The reaction conditions tolerated both silyl and aryl-terminated ynamides and showed moderate sensitivity to the electron-withdrawing nature of *N*-sulfonyl protecting group with




**Scheme 1** In situ trapping of a ketenimine intermediate

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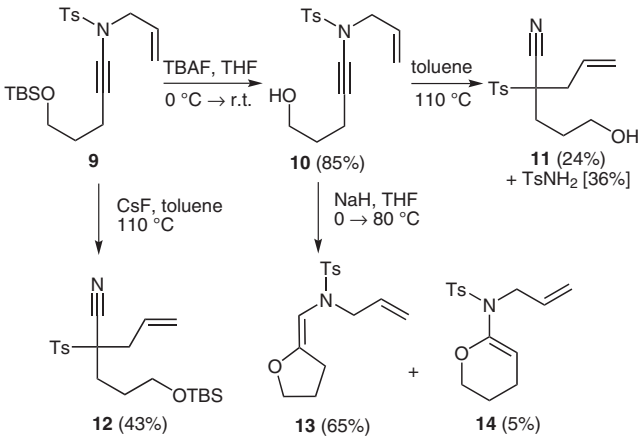



**Scheme 3** Attempts at intramolecular imidate formation

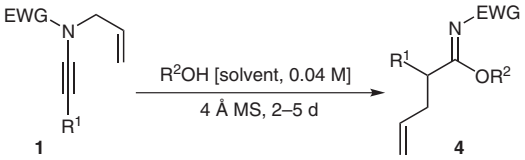
*p*-Ns providing the corresponding imidates in the highest yields due to increased electrophilicity of the ketenimine (Table 1, entries 3 vs. 6 and 4 vs. 7). Notably, there was no reaction observed with *N*-Boc or *N*-Ac ynamides even at temperatures of >140 °C, indicating the strong electronic effect on the initial aza-Claisen rearrangement. There was also a clear sensitivity to steric effects with the use of more sterically hindered nucleophiles giving rise to nitriles through the competing intramolecular 1,3-sulfonyl shift in the ketenimine intermediate when $R^1$ = Ph (Table 1, entries 8 vs. 10). Interestingly, no nitrile formation was observed in the cases where $R^1$ = TIPS, likely due to the increased steric bulk preventing the necessary migration.

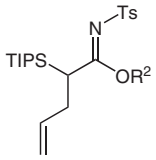
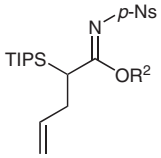
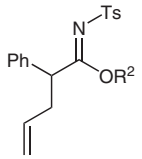
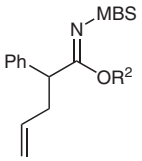
Next, we sought to develop a tandem aza-Claisen–Overman[12] rearrangement, which followed by RCM may be used for the synthesis of useful azapin-2-one scaffolds **17**. Ynamide **5a** underwent reaction with allyl alcohol to yield diallyl imidate **15** in moderate yield. Unfortunately, our attempts at a thermal Overman rearrangement were unsuccessful, as heating of **15** in *n*-decane at 140 °C even for several days resulted in no formation of **16**.

However, to our delight, exposure of **15** to a catalytic amount of $PdCl_2(PhCN)_2$ at room temperature led to [3,3] rearrangement product **16** in >95% yield.[9b] With **16** in hand, efficient ring-closing metathesis[13] was achieved using Grubbs first-generation catalyst to provide azapin-2-one **17**[14] in 90% yield (Scheme 4).

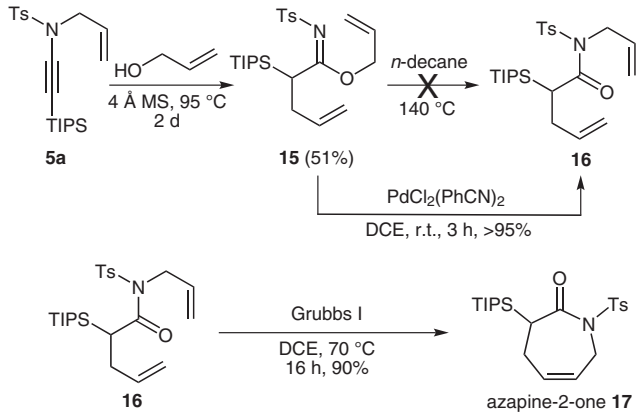
Herein, we have disclosed a novel synthesis of α-allyl imidates via a thermal 3-aza-Claisen rearrangement of

**Table 1** Synthesis of α-Allyl Imidates




| Entry | Alcohol | Temp (°C) | Time (d) | Imidate[a] | Yield (%)[b] |
|---|---|---|---|---|---|
| 1 | MeOH | 75 | 2 |  | **4a** $R^2$ = Me, 81% |
| 2 | EtOH | 75 | 2 | | **4b** $R^2$ = Et, 43% |
| 3 | *i*-PrOH | 90 | 5 | | **4c** $R^2$ = *i*-Pr, 39% |
| 4 | *c*-Pentanol | 110 | 5 | | **4d** $R^2$ = *c*-Pent, 45% |
| 5 | EtOH | 85 | 3 |  | **4e** $R^2$ = Et, 76% |
| 6 | *i*-PrOH | 90 | 4 | | **4f** $R^2$ = *i*-Pr, 76% |
| 7 | *c*-Pentanol | 115 | 4 | | **4g** $R^2$ = *c*-Pent, 71% |
| 8 | MeOH | 75 | 2 |  | **4h** $R^2$ = Me, 95%[c] |
| 9 | EtOH | 75 | 2 | | **4i** $R^2$ = Et, 75% |
| 10 | *i*-PrOH | 75 | 5 | | **4j** $R^2$ = *i*-Pr, 47%[d] |
| 11 | EtOH | 75 | 2 |  | **4k** $R^2$ = Et, 82% |
| 12 | *c*-Pentanol | 75 | 2 | | **4l** $R^2$ = *c*-Pent, 38% |

[a] MBS = *p*-methoxybenzenesulfonyl.
[b] Isolated yields.
[c] No nitrile observed in crude $^1$H NMR.
[d] Estimated nitrile yield by crude $^1$H NMR = 20%.




**Scheme 4** Construction of an azapin-2-one scaffold

*N*-allyl ynamides. We found that it is necessary to use the alcohol as solvent to avoid a competing 1,3-sulfonyl transfer forming nitriles. Also, the use of alkoxides intermolecularly led to efficient desulfonylation, while intramolecularly gave 5-*exo*-dig cyclization of the alkoxide onto the ynamide. In addition, we have demonstrated the use of a sequential 3-aza-Claisen–Overman rearrangement, which followed by ring-closing metathesis may be used to provide access to azapin-2-one scaffolds.

## Acknowledgment

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## References and Notes

(1) For reviews, see: (a) DeKorver, K. A.; Li, H.; Lohse, A. G.; Hayashi, R.; Lu, Z.; Zhang, Y.; Hsung, R. P. *Chem. Rev.* **2010**, *110*, in press. (b) Evano, G.; Coste, A.; Jouvin, K. *Angew. Chem. Int. Ed.* **2010**, *49*, 2840.

(2) For examples in 2010, see: (a) Li, H.; Antoline, J. E.; Yang, J.-H.; Al-Rashid, Z. F.; Hsung, R. P. *New J. Chem.* **2010**, *34*, in press. (b) Kramer, S.; Madsen, J. L. H.; Rottländer, M.; Skrydstrup, T. *Org. Lett.* **2010**, *12*, 2758. (c) Banerjee, B.; Litvinov, D. N.; Kang, J.; Bettale, J. D.; Castle, S. L. *Org. Lett.* **2010**, *12*, 2650. (d) Gourdet, B.; Rudkin, M. E.; Lam, H. W. *Org. Lett.* **2010**, *12*, 2554. (e) Jia, W.; Jiao, N. *Org. Lett.* **2010**, *12*, 2000. (f) Burley, G. A.; Davies, D. L.; Griffith, G. A.; Lee, M.; Singh, K. *J. Org. Chem.* **2010**, *75*, 980. (g) Yamasaki, R.; Terashima, N.; Sotome, I.; Komagawa, S.; Saito, S. *J. Org. Chem.* **2010**, *75*, 480.

(3) Zhang, Y.; DeKorver, K. A.; Lohse, A. G.; Zhang, Y.-S.; Huang, J.; Hsung, R. P. *Org. Lett.* **2009**, *11*, 899.

(4) DeKorver, K. A.; Hsung, R. P.; Lohse, A. G.; Zhang, Y. *Org. Lett.* **2010**, *12*, 1840.

(5) For leading reviews on aza-Claisen rearrangements, see: (a) Majumdar, K. C.; Bhayyacharyya, T.; Chattopadhyay, B.; Nandi, R. K. *Synthesis* **2009**, 2117. (b) Nubbemeyer, U. *Top Curr. Chem.* **2005**, *244*, 149. For some examples of aza-Claisen rearrangements, see: (c) Majumdar, K. C.; Samanta, S.; Chattopadhyay, B.; Nandi, R. K. *Synthesis* **2010**, 863. (d) Cheung, L. L. W.; Yudin, A. K. *Org. Lett.* **2009**, *11*, 1281. (e) Cant, A. A.; Bertrand, G. H. V.; Henderson, J. L.; Roberts, L.; Greaney, M. F. *Angew. Chem. Int. Ed.* **2009**, *48*, 5199.

(6) For reviews on the chemistry of ketenimines, see: (a) Krow, G. R. *Angew. Chem., Int. Ed. Engl.* **1971**, *10*, 435. (b) Gambaryan, N. P. *Usp. Khim.* **1976**, *45*, 1251. (c) Dondoni, A. *Heterocycles* **1980**, *14*, 1547. (d) Barker, M. W.; McHenry, W. E. In *The Chemistry of Ketenes, Allenes and Related Compounds*, Part 2; Patai, S., Ed.; Wiley-Interscience: Chichester, **1980**, 701–720. (e) Alajarin, M.; Vidal, A.; Tovar, F. *Targets Heterocycl. Syst.* **2000**, *4*, 293.

(7) For examples of imidates serving as prodrugs, see: (a) Maryanoff, B. E.; McComsey, D. F.; Costanzo, M. J.; Yabut, S. C.; Lu, T.; Player, M. R.; Giardino, E. C.; Damiano, B. P. *Chem. Biol. Drug. Des.* **2006**, *68*, 29. (b) Poon, S. F.; Stock, N.; Payne, J. E.; McGuire, A. R.; Stearns, B.; Yang, X.; Chen, W.; Munoz, B.; Smith, N. D. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 2259. (c) Bundgaard, H.; Drustrup Larsen, J. *J. Med. Chem.* **1988**, *31*, 2066.

(8) For recent examples of amidine formation, see: (a) Shang, Y.; He, X.; Hu, J.; Wu, J.; Zhang, M.; Yu, S.; Zhang, Q. *Adv. Synth. Catal.* **2009**, *351*, 2709. (b) She, J.; Jiang, Z.; Wang, Y. *Synlett* **2009**, 2023. (c) Yu, R. T.; Rovis, T. *J. Am. Chem. Soc.* **2008**, *130*, 3262. (d) Yoo, E. J.; Ahlquist, M.; Bae, I.; Sharpless, B.; Fokin, V.; Chang, S. *J. Org. Chem.* **2008**, *73*, 5520.

(9) For recent examples of imidate formation, see: (a) Song, W.; Lu, W.; Wang, J.; Lu, P.; Wang, Y. *J. Org. Chem.* **2010**, *75*, 3481. (b) Yoo, E. J.; Park, S. H.; Lee, S. H.; Chang, S. *Org. Lett.* **2009**, *11*, 1155. (c) Yoo, E. J.; Bae, I.; Cho, S. H.; Han, H.; Chang, S. *Org. Lett.* **2006**, *8*, 1347.

(10) For a recent example of α-functionalization of imidates, see: Matsubara, R.; Berthiol, F.; Kobayashi, S. *J. Am. Chem. Soc.* **2008**, *130*, 1804.

(11) For a related 1,3-shift, see: Bendikov, M.; Duong, H. M.; Bolanos, E.; Wudl, F. *Org. Lett.* **2005**, *7*, 783.

(12) (a) For leading references, see: Anderson, C. E.; Overman, L. E. *J. Am. Chem. Soc.* **2003**, *125*, 12412. (b) For a review, see: Overman, L. E. *Acc. Chem. Res.* **1980**, *13*, 218. Also see: (c) Overman, L. E. *J. Am. Chem. Soc.* **1974**, *96*, 597. (d) Overman, L. E. *J. Am. Chem. Soc.* **1976**, *98*, 2901.

(13) Tomooka, K.; Suzuki, M.; Uehara, K.; Shimada, M.; Akiyama, T. *Synlett* **2008**, 2518.

(14) **Selected Experimental Procedures and Characterizations**

**Synthesis of Nitrile 8**

To a stirring solution of ynamide **5a** (75.0 mg, 0.19 mmol) in toluene (2 mL) at r.t. was slowly added freshly prepared NaOMe (31.0 mg, 0.58 mmol). After addition, the reaction mixture was sealed under dry nitrogen and heated to 100 °C for 1 h. Over the course of the reaction, TsOMe was observed to precipitate out of solution and was subsequently removed by filtration of the crude reaction mixture through a plug of Celite™ to afford the pure nitrile **8** (45.6 mg, 0.19 mmol, >95% yield) as a colorless oil.

$R_f$ = 0.45 (hexanes–EtOAc, 4:1). $^1$H NMR (500 MHz, $CDCl_3$): δ = 1.00–1.41 (m, 21 H), 2.05 (dd, 1 H, *J* = 7.5, 4.0 Hz), 2.28–2.34 (m, 1 H), 2.35–2.44 (m, 1 H), 5.14 (d, 1 H, *J* = 10.5 Hz), 5.17 (d, 1 H, *J* = 18.0 Hz), 5.88–5.98 (m, 1 H). $^{13}$C NMR (125 MHz, $CDCl_3$): δ = 11.3, 14.4, 18.9, 31.8, 117.2, 122.7, 136.2. IR (film): 2946 (m), 2869 (m), 2222 (w), 1595 (m), 1377 (m) cm$^{-1}$. MS (APCI): *m/e* (%) = 238 (100) $[M + H]^+$.

**Synthesis of Alcohol 10**

To a stirring solution of ynamide **9** (315.0 mg, 0.77 mmol) in THF (2 mL) at r.t. was slowly added TBAF (0.85 mL, 1.0 M in THF). After 2 h, the solvent was removed via rotary evaporation, and the crude oil was purified by flash silica gel column chromatography [isocratic eluent: hexanes–EtOAc,

1:1] to afford the alcohol **10** (191.0 mg, 0.65 mmol, 85% yield) as a pale yellow oil.
$R_f$ = 0.09 (hexanes–EtOAc = 2:1). $^1$H NMR (500 MHz, $CDCl_3$): δ = 1.52 (br s, 1 H), 1.73 (pent, 2 H, *J* = 6.5 Hz), 2.38 (t, 2 H, *J* = 7.0 Hz), 3.71 (d, 2 H, *J* = 7.0 Hz), 3.91 (d, 2 H, *J* = 7.0 Hz), 5.19 (d, 1 H, *J* = 10.5 Hz), 5.24 (d, 1 H, *J* = 17.5 Hz), 5.72 (ddt, 1 H, *J* = 17.5, 10.5, 7.0 Hz), 7.34 (d, 2 H, *J* = 8.0 Hz), 7.78 (d, 2 H, *J* = 8.0 Hz). $^{13}$C NMR (125 MHz, $CDCl_3$): δ = 15.4, 21.9, 31.8, 54.4, 61.9, 69.9, 73.8, 120.0, 128.0, 130.0, 131.4, 135.0, 144.8. IR (film): 3200 (br s), 2981 (m), 2878 (m), 1644 (m) cm$^{-1}$. MS (APCI): *m/e* (%) = 294 (100) $[M + H]^+$.

**Nitrile 12**

$R_f$ = 0.41 (hexanes–EtOAc, 8:1). $^1$H NMR (400 MHz, $CDCl_3$): δ = 0.02 (s, 6 H), 0.86 (s, 9 H), 1.66–1.85 (m, 2 H), 2.05 (dd, 2 H, *J* = 8.4, 6.8 Hz), 2.48 (s, 3 H), 2.67–2.79 (m, 2 H), 3.59 (t, 2 H, *J* = 6.0 Hz), 5.24 (d, 1 H, *J* = 16.8 Hz), 5.26 (d, 1 H, *J* = 10.0 Hz), 5.82 (ddt, 1 H, *J* = 17.6, 10.0, 7.2 Hz), 7.40 (d, 2 H, *J* = 8.0 Hz), 7.88 (d, 2 H, *J* = 8.4 Hz). $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 5.2, 18.4, 22.0, 26.1, 28.3, 28.7, 36.8, 62.1, 65.8, 116.9, 121.9, 129.8, 130.2, 131.0, 131.7. IR (film): 2929 (m), 2857 (m), 2238 (w), 1596 (m), 1331 (s), 1150 (s) cm$^{-1}$. MS (APCI): *m/e* (%) = 408 (100) $[M + H]^+$, ESI-HRMS: *m/e* calcd for $C_{21}H_{33}NO_3SSiNa$: 430.1843; found: 430.1860.

**Synthesis of Compound 13**

To a solution of ynamide **10** (75.0 mg, 0.26 mmol) in THF (5 mL) at 0 °C was added NaH (19.0 mg, 0.46 mmol, 60% wt/wt in mineral oil). The reaction mixture was warmed to r.t. and stirred for 20 min to allow for complete deprotonation and then sealed under dry nitrogen and heated to 85 °C for 3 h. The reaction mixture was quenched with $H_2O$, and the organic phase was extracted with EtOAc and then dried over $Na_2SO_4$. Removal of the solvent by rotary evaporation and purification by flash silica gel column chromatography (hexanes–EtOAc, 4:1) afforded **13** (50.0 mg, 0.17 mmol, 65% yield) as a colorless oil.

**Compound 13**

$R_f$ = 0.35 (hexanes–EtOAc, 4:1). $^1$H NMR (500 MHz, $CDCl_3$): δ = 1.90 (pent, 2 H, *J* = 9.5 Hz), 2.40 (s, 3 H), 2.49 (td, 2 H, *J* = 9.5, 2.0 Hz), 3.96 (t, 2 H, *J* = 8.0 Hz), 3.97 (d, 2 H, *J* = 8.5 Hz), 4.86 (s, 1 H), 5.06 (dd, 1 H, *J* = 13.0, 2.0 Hz), 5.14 (dd, 1 H, *J* = 20.0, 2.0 Hz), 5.76 (ddt, 1 H, *J* = 20.0, 13.0, 8.5 Hz), 7.26 (d, 2 H, *J* = 9.5 Hz), 7.70 (d, 2 H, *J* = 9.5 Hz). $^{13}$C NMR (125 MHz, $CDCl_3$): δ = 21.8, 24.6, 28.4, 52.3, 72.0, 94.9, 117.6, 127.7, 129.4, 134.1, 136.9, 143.1, 157.4. IR (film): 3055 (m), 2980 (m), 1597 (s), 1337 (s) cm$^{-1}$. MS (APCI): *m/e* (%) = 294 (100) $[M + H]^+$. ESI-HRMS: *m/e* calcd for $C_{15}H_{19}NO_3SNa$: 316.0978; found: 316.0986.

**Compound 14**

$R_f$ = 0.38 (hexanes–EtOAc, 4:1). $^1$H NMR (500 MHz, $CDCl_3$): δ = 1.99 (pent, 2 H, *J* = 7.0 Hz), 2.43 (s, 3 H), 2.80 (td, 2 H, *J* = 8.0, 2.0 Hz), 3.66 (d, 2 H, *J* = 6.5 Hz), 4.16 (t, 2 H, *J* = 6.5 Hz), 4.76 (t, 1 H, *J* = 2.0 Hz), 5.08–5.13 (m, 2 H), 5.70 (ddt, 1 H, *J* = 17.0, 10.0, 6.5 Hz), 7.30 (d, 2 H, *J* = 8.0 Hz), 7.67 (d, 2 H, *J* = 8.5 Hz). $^{13}$C NMR (125 MHz, $CDCl_3$): δ = 21.8, 24.4, 28.1, 54.8, 72.1, 97.8, 119.1, 127.9, 129.8, 133.1, 135.0, 143.5, 166.8. MS (APCI): *m/e* (%) = 294 (20) $[M + H]^+$.

**General Procedure for the Synthesis of Imidates 4a–l**

To a flame-dried vial containing 4 Å MS was added the appropriate ynamide and anhydrous alcohol solvent (0.04 M in ynamide). The reaction mixture was sealed under dry nitrogen and heated to 75–95 °C for 2–5 d. Upon cooling to r.t., the mixture was filtered through a plug of Celite™. Removal of the alcohol solvent in vacuo followed by flash silica gel column chromatography afforded the respective imidate.

**Imidate 4a**

$R_f$ = 0.45 (hexanes–EtOAc, 4:1). $^1$H NMR (500 MHz, $CDCl_3$): δ = 1.15 (d, 9 H, *J* = 7.5 Hz), 1.20 (d, 9 H, *J* = 7.5 Hz), 1.35 (sept, 3 H, *J* = 7.5 Hz), 2.46 (s, 3 H), 2.50 (m, 1 H), 2.62 (ddd, 1 H, *J* = 20.5, 12.5, 8.5 Hz), 3.71 (dd, 1 H, *J* = 3.0, 12.0 Hz), 3.73 (s, 3 H), 4.92 (dd, 1 H, *J* = 10.0, 1.0 Hz), 5.00 (ddt, 1 H, *J* = 17.0, 3.0, 1.5 Hz), 5.73 (dddd, 1 H, *J* = 22.5, 14.0, 8.5, 5.5 Hz), 7.31 (d, 2 H, *J* = 8.0 Hz), 7.86 (d, 2 H, *J* = 8.0 Hz). $^{13}$C NMR (125 MHz, $CDCl_3$): δ = 11.8, 19.1, 19.1, 21.8, 32.6, 34.2, 54.0, 115.8, 126.9, 129.4, 137.5, 140.2, 143.0, 178.4. IR (film): 2948 (m), 2868 (m), 1582 (s), 1288 (s) cm$^{-1}$. MS (APCI): *m/e* (%) = 424 (100) $[M + H]^+$. ESI-HRMS: *m/e* calcd for $C_{22}H_{37}NO_3SSiNa$: 446.2156; found: 446.2161.

**Imidate 4b**

$R_f$ = 0.38 (hexanes–EtOAc, 4:1). $^1$H NMR (500 MHz, $CDCl_3$): δ = 1.11 (d, 9 H, *J* = 7.5 Hz), 1.16 (d, 9 H, *J* = 7.5 Hz), 1.24 (t, 3 H, *J* = 7.0 Hz), 1.31 (sept, 3 H, *J* = 7.5 Hz), 2.41 (s, 3 H), 2.59 (dt, 1 H, *J* = 13.5, 9.0 Hz), 3.64 (dd, 1 H, *J* = 12.5, 3.0 Hz), 4.04–4.17 (m, 2 H), 4.87 (d, 1 H, *J* = 10.0 Hz), 4.95 (d, 1 H, *J* = 16.5 Hz), 5.63–5.73 (m, 1 H), 7.26 (d, 2 H, *J* = 7.5 Hz), 7.80 (d, 2 H, *J* = 8.5 Hz). $^{13}$C NMR (125 MHz, $CDCl_3$): δ = 11.7, 13.9, 19.1, 19.1, 21.7, 32.4, 34.2, 64.2, 115.7, 126.8, 129.3, 137.5, 140.2, 142.8, 177.8. IR (film): 2948 (m), 2871 (m), 1965 (w), 1575 (s), 1289 (s), 1155 (s) cm$^{-1}$. MS (APCI): *m/e* (%) = 438 (100) $[M + H]^+$. ESI-HRMS: *m/e* calcd for $C_{23}H_{39}NO_3SSiNa$: 460.2313; found: 460.2295.

**Imidate 4c**

$R_f$ = 0.19 (hexanes–EtOAc, 15:1). $^1$H NMR (500 MHz, $CDCl_3$): δ = 1.13 (d, 9 H, *J* = 7.5 Hz), 1.14 (d, 3 H, *J* = 6.0 Hz), 1.15 (d, 9 H, *J* = 7.5 Hz), 1.25 (d, 3 H, *J* = 6.0 Hz), 1.31 (sept, 3 H, *J* = 7.5 Hz), 2.41 (s, 3 H), 2.40–2.48 (m, 1 H), 2.57 (dt, 1 H, *J* = 14.0, 8.5 Hz), 2.84 (dd, 1 H, *J* = 12.0, 3.0 Hz), 4.86 (d, 1 H, *J* = 10.0 Hz), 4.96 (dd, 1 H, *J* = 17.0, 1.0 Hz), 5.03 (sept, 1 H, *J* = 6.0 Hz), 5.68 (dddd, 1 H, *J* = 17.0, 10.0, 8.5, 5.5 Hz), 7.26 (d, 2 H, *J* = 8.0 Hz), 7.80 (d, 2 H, *J* = 8.0 Hz). $^{13}$C NMR (125 MHz, $CDCl_3$): δ = 11.8, 19.2, 21.6, 21.7, 21.8, 32.4, 34.4, 71.9, 115.8, 126.8, 129.3, 137.4, 140.4, 142.7, 177.2. IR (film): 2946 (m), 2868 (m), 1570 (s), 1464 (m), 1287 (m), 1153 (s) cm$^{-1}$. MS (APCI): *m/e* (%) = 410 (100) [M – propene + H]$^+$. ESI-HRMS: *m/e* calcd for $C_{24}H_{41}NO_3SSiNa$: 474.2469; found: 474.2446.

**Imidate 4d**

$R_f$ = 0.41 (hexanes–EtOAc, 4:1). $^1$H NMR (500 MHz, $CDCl_3$): δ = 1.12 (d, 9 H, *J* = 9.5 Hz), 1.15 (d, 9 H, *J* = 9.5 Hz), 1.31 (sept, 3 H, *J* = 9.5 Hz), 1.50–1.82 (m, 8 H), 2.41 (s, 3 H), 2.40–2.47 (m, 1 H), 2.55 (dt, 1 H, *J* = 18.0, 10.5 Hz), 3.64 (dd, 1 H, *J* = 15.5, 4.0 Hz), 4.86 (d, 1 H, *J* = 12.5 Hz), 4.94 (d, 1 H, *J* = 21.0 Hz), 5.12–5.16 (m, 1 H), 5.62–5.74 (m, 1 H), 7.25 (d, 2 H, *J* = 10.0 Hz), 7.80 (d, 2 H, *J* = 10.0 Hz). $^{13}$C NMR (125 MHz, $CDCl_3$): δ = 11.8, 19.2, 21.7, 23.8, 24.2, 32.2, 32.9, 34.4, 81.4, 115.6, 126.8, 129.3, 137.6, 140.5, 142.7, 117.5. IR (film): 2946 (m), 2869 (m), 1571 (s), 1463 (w), 1287 (m), 1153 (s) cm$^{-1}$. MS (APCI): *m/e* (%) = 410 (100) [M – cyclopentene + H]$^+$. ESI-HRMS: *m/e* calcd for $C_{26}H_{43}NO_3SSiNa$: 500.2626; found: 500.2618.

**Imidate 4e**

$R_f$ = 0.42 (hexanes–EtOAc, 4:1). $^1$H NMR (500 MHz, $CDCl_3$): δ = 1.12 (d, 9 H, *J* = 9.0 Hz), 1.16 (d, 9 H, *J* = 9.5 Hz), 1.26 (t, 3 H, *J* = 9.0 Hz), 1.32 (sept, 3 H, *J* = 9.5 Hz), 2.44–2.52 (m, 1 H), 2.61 (dt, 1 H, *J* = 17.5, 11.0 Hz), 3.59 (dd, 1 H, *J* = 15.5, 4.0 Hz), 4.05–4.15 (m, 2 H), 4.93 (d, 1 H, *J* = 12.5 Hz), 4.99 (d, 1 H, *J* = 21.0 Hz), 5.71–5.82 (m, 1 H), 8.09 (d, 2 H, *J* = 11.5 Hz), 8.32 (d, 2 H, *J* = 11.5 Hz). $^{13}$C

NMR (125 MHz, $CDCl_3$): δ = 11.8, 13.9, 19.0, 19.1, 33.5, 34.3, 64.8, 116.1, 124.2, 128.0, 137.3, 148.6, 179.5. IR (film): 2943 (w), 2868 (w), 1566 (s), 1531 (s), 1295 (s), 1159 (s) $cm^{-1}$. MS (APCI): *m/e* (%) = 469 (100) $[M + H]^+$. ESI-HRMS: *m/e* calcd for $C_{22}H_{36}N_2O_5SSiNa$: 491.2007; found: 491.2007.

**Imidate 4f**

$R_f$ = 0.27 (hexanes–EtOAc, 15:1). $^1H$ NMR (400 MHz, $CDCl_3$): δ = 1.14 (d, 9 H, *J* = 7.2 Hz), 1.15 (d, 3 H, *J* = 6.4 Hz), 1.17 (d, 9 H, *J* = 7.6 Hz), 1.28 (d, 3 H, *J* = 6.4 Hz), 1.32 (sept, 3 H, *J* = 7.6 Hz), 2.46–2.52 (m, 1 H), 2.60 (dt, 1 H, *J* = 14.4, 8.8 Hz), 3.61 (dd, 1 H, *J* = 12.0, 3.6 Hz), 4.93 (d, 1 H, *J* = 10.0 Hz), 4.96–5.04 (m, 2 H), 5.76 (dddd, 1 H, *J* = 17.0, 10.0, 8.8, 5.2 Hz), 8.10 (d, 2 H, *J* = 9.2 Hz), 8.33 (d, 2 H, *J* = 8.8 Hz). $^{13}C$ NMR (125 MHz, $CDCl_3$): δ = 11.8, 19.1, 19.1, 21.5, 21.8, 33.4, 34.4, 72.9, 116.1, 124.2, 128.0, 137.3, 148.7, 149.9, 178.9. IR (film): 2946 (m), 2869 (m), 1562 (s), 1531 (s), 1349 (s), 1296 (s), 1156 (s) $cm^{-1}$. MS (APCI): *m/e* (%) = 441 (30) $[M – propene + H]^+$. ESI-HRMS: *m/e* calcd for $C_{23}H_{38}N_2O_5SSiNa$: 505.2163; found: 505.2164.

**Imidate 4g**

$R_f$ = 0.36 (hexanes–EtOAc, 10:1). $^1H$ NMR (400 MHz, $CDCl_3$): δ = 1.13 (d, 9 H, *J* = 7.2 Hz), 1.16 (d, 9 H, *J* = 7.6 Hz), 1.33 (sept, 3 H, *J* = 7.6 Hz), 1.50–1.88 (m, 8 H), 2.46–2.51 (m, 1 H), 2.58 (dt, 1 H, *J* = 14.0, 8.4 Hz), 3.60 (dd, 1 H, *J* = 12.0, 3.2 Hz), 4.92 (d, 1 H, *J* = 10.0 Hz), 5.00 (d, 1 H, *J* = 16.8 Hz), 5.09–5.14 (m, 1 H), 5.70–5.82 (m, 1 H), 8.11 (d, 2 H, *J* = 8.4 Hz), 8.33 (d, 2 H, *J* = 8.8 Hz). $^{13}C$ NMR (125 MHz, $CDCl_3$): δ = 11.8, 19.1, 23.8, 24.1, 32.2, 32.9, 33.2, 34.4, 82.2, 116.0, 124.1, 128.0, 137.4, 148.7, 149.9, 179.1. IR (film): 2947 (m), 2871 (m), 1565 (s), 1531 (s), 1349 (s), 1303 (m), 1157 (s) $cm^{-1}$. MS (APCI): *m/e* (%) = 441 (30) $[M – cyclopentene + H]^+$. ESI-HRMS: *m/e* calcd for $C_{25}H_{40}N_2O_5SSiNa$: 531.2320; found: 530.2333.

**Imidate 4h**

$R_f$ = 0.30 (hexanes–EtOAc, 4:1). $^1H$ NMR (400 MHz, $CDCl_3$): δ = 2.43 (s, 3 H), 3.59 (tt, 2 H, *J* = 6.0, 1.2 Hz), 3.69 (s, 3 H), 4.49 (t, 1 H, 6.0 Hz), 5.10 (ddt, 1 H, *J* = 10.4, 2.8, 1.6 Hz), 5.16 (ddt, 1 H, *J* = 17.2, 2.8, 1.6 Hz), 5.72 (ddt, 1 H, *J* = 17.2, 10.4, 6.0), 7.24–7.34 (m, 7 H), 7.76 (d, 2 H, *J* = 8.4 Hz). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 21.6, 41.3, 45.8, 52.2, 117.7, 127.2, 127.3, 128.7, 129.4, 129.8, 133.2, 134.1, 137.1, 143.6, 172.2. IR (film): 3034 (m), 2951 (m), 1735 (s), 1597 (m), 1325 (s) $cm^{-1}$. MS (APCI): *m/e* (%) = 344 (100) $[M + H]^+$. ESI-HRMS: *m/e* calcd for $C_{19}H_{21}NO_3SNa$: 366.1135; found: 366.1150.

**Imidate 4i**

$R_f$ = 0.48 (hexanes–EtOAc, 4:1). $^1H$ NMR (500 MHz, $CDCl_3$): δ = 1.26 (t, 3 H, *J* = 7.0 Hz), 2.41 (s, 3 H), 2.63 (dt, 1 H, *J* = 13.5, 6.5 Hz) 2.83 (dt, 1 H, *J* = 16.5, 8.0 Hz), 4.09 (dq, 1 H, *J* = 11.0, 7.0 Hz), 4.19 (dq, 1 H, *J* = 11.0, 7.0 Hz), 4.98–5.04 (m, 2 H), 5.10 (dd, 1 H, *J* = 17.0, 1.5 Hz), 5.70–5.80 (m, 1 H), 7.23–7.28 (m, 3 H), 7.32 (t, 2 H, *J* = 8.0 Hz), 7.46 (d, 2 H, *J* = 7.5 Hz), 7.77 (d, 2 H, *J* = 8.0 Hz). $^{13}C$ NMR (125 MHz, $CDCl_3$): δ = 13.7, 21.7, 36.0, 37.9, 48.9, 64.6, 117.7, 126.9, 127.8, 128.8, 129.0, 129.5, 134.9, 137.8, 143.3, 174.6. IR (film): 2985 (w), 1592 (s), 1301 (s), 1152 (s) $cm^{-1}$. MS (APCI): *m/e* (%) = 358 (100) $[M + H]^+$. ESI-HRMS: *m/e* calcd for $C_{20}H_{23}NO_3SNa$: 380.1291; found: 380.1287.

**Imidate 4j**

$R_f$ = 0.32 (hexanes–EtOAc, 6:1). $^1H$ NMR (500 MHz, $CDCl_3$): δ = 1.14 (d, 3 H, *J* = 6.0 Hz), 1.25 (d, 3 H, *J* = 6.5 Hz), 2.40 (s, 3 H), 2.59 (dt, 1 H, *J* = 12.5, 5.5 Hz), 2.80 (dt, 1 H, *J* = 14.5, 8.5 Hz), 4.97 (m, 3 H), 5.10 (d, 1 H, *J* = 17.5 Hz), 5.70–5.79 (m, 1 H), 7.22–7.27 (m, 3 H), 7.31 (t, 2 H, *J* = 7.5 Hz), 7.44 (d, 2 H, *J* = 8.0 Hz), 7.75 (d, 2 H, *J* = 8.5 Hz). $^{13}C$ NMR (125 MHz, $CDCl_3$): δ = 21.3, 21.4, 21.7, 38.1, 48.9, 72.5, 117.7, 126.8, 127.7, 128.7, 128.8, 129.5, 134.8, 137.9, 139.7, 143.1, 174.0. IR (film): 2984 (w), 1592 (s), 1302 (s), 1156 (s) $cm^{-1}$. MS (APCI): *m/e* (%) = 330 (100) $[M – propene + H]^+$. ESI-HRMS: *m/e* calcd for $C_{21}H_{25}NO_3SNa$: 394.1448; found: 394.1440.

**Imidate 4k**

$R_f$ = 0.33 (hexanes–EtOAc, 4:1). $^1H$ NMR (500 MHz, $CDCl_3$): δ = 1.25 (t, 3 H, *J* = 7.0 Hz), 2.62 (dt, 1 H, *J* = 13.5, 7.0 Hz), 2.83 (dt, 1 H, *J* = 15.5, 8.5 Hz), 3.84 (s, 3 H), 4.09 (dq, 1 H, *J* = 11.0, 7.0 Hz), 4.18 (dq, 1 H, *J* = 11.0, 7.0 Hz), 4.99–5.04 (m, 2 H), 5.09 (d, 1 H, *J* = 17.0 Hz), 5.70–5.59 (m, 1 H), 6.91 (d, 2 H, *J* = 9.0 Hz), 7.26 (t, 1 H, *J* = 7.5 Hz), 7.32 (d, 2 H, *J* = 7.5 Hz), 7.45 (d, 2 H, *J* = 7.5 Hz), 7.81 (d, 2 H, *J* = 9.0 Hz). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 13.7, 37.9, 48.8, 55.7, 64.8, 114.0, 117.7, 127.7, 128.8, 128.9, 128.9, 133.1, 134.9, 137.8, 162.9, 174.4. IR (film): 2986 (w), 1593 (s), 1499 (m), 1298 (s), 1150 (s) $cm^{-1}$. MS (APCI): *m/e* (%) = 374 (100) $[M + H]^+$. ESI-HRMS: *m/e* calcd for $C_{20}H_{23}NO_4SNa$: 396.1231; found: 396.1240.

**Imidate 4l**

$R_f$ = 0.20 (hexanes–EtOAc, 4:1). $^1H$ NMR (500 MHz, $CDCl_3$): δ = 1.55–1.83 (m, 8 H), 2.59 (dt, 1 H, *J* = 12.5, 6.5 Hz), 2.79 (dt, 1 H, *J* = 17.0, 8.0 Hz), 3.85 (s, 3 H), 4.99 (dd, 1 H, *J* = 9.0, 7.0 Hz), 5.02 (d, 1 H, *J* = 11.0 Hz), 5.09 (dd, 1 H, *J* = 17.0, 1.5 Hz), 5.12–5.17 (m, 1 H), 5.74 (dddd, 1 H, *J* = 17.0, 10.0, 7.5, 5.5 Hz), 6.92 (d, 2 H, *J* = 9.0 Hz), 7.24–7.28 (m, 1 H), 7.31 (t, 2 H, *J* = 7.0 Hz), 7.43 (d, 2 H, *J* = 7.5 Hz), 7.81 (d, 2 H, *J* = 9.0 Hz). $^{13}C$ NMR (125 MHz, $CDCl_3$): δ = 24.0, 32.4, 32.6, 38.0, 48.8, 55.8, 81.8, 114.0, 117.6, 127.7, 128.7, 128.8 128.8, 134.6, 134.9, 137.9, 162.7, 173.9. IR (film): 2968 (w), 2850 (w), 1579 (s), 1294 (s), 1257 (s), 1150 (s) $cm^{-1}$. MS (APCI): *m/e* (%) = 346 (100) $[M – cyclopentene + H]^+$. ESI-HRMS: *m/e* calcd for $C_{23}H_{27}NO_4SNa$: 436.1553; found: 436.1552.

**Imidate 15**

$R_f$ = 0.50 (hexanes–EtOAc, 4:1). $^1H$ NMR (400 MHz, $CDCl_3$): δ = 1.11 (d, 9 H, *J* = 7.6 Hz), 1.17 (d, 9 H, *J* = 7.6 Hz), 1.31 (sept, 3 H, *J* = 7.6 Hz), 2.41 (s, 3 H), 2.43–2.48 (m, 1 H), 2.61 (td, 1 H, *J* = 13.6, 8.8 Hz), 3.67 (dd, 1 H, *J* = 12.0, 3.2 Hz), 4.47 (dd, 1 H, *J* = 12.8, 6.0 Hz), 4.59 (dd, *J* = 12.8, 6.0 Hz), 4.87 (d, 1 H, *J* = 10.0 Hz), 4.95 (d, 1 H, *J* = 17.2 Hz), 5.22 (d, 1 H, *J* = 10.4 Hz), 5.28 (dd, 1 H, *J* = 16.0, 1.2 Hz), 5.63–5.74 (m, 1 H), 5.87 (ddt, 1 H, *J* = 16.8, 10.0, 6.0 Hz), 7.26 (d, 2 H, *J* = 8.0 Hz), 7.80 (d, 2 H, *J* = 8.4 Hz). $^{13}C$ NMR (100 MHz, $CDCl_3$): δ = 11.8, 19.1, 21.7, 32.5, 34.2, 69.1, 115.9, 119.8, 126.8, 126.9, 129.4, 131.6, 137.4, 140.1, 142.9, 177.4 $cm^{-1}$. IR (film): 2943 (m), 2869 (m), 1584 (s), 1302 (m), 1155 (s) $cm^{-1}$. MS (APCI): *m/e* (%) = 450 (100) $[M + H]^+$. ESI-HRMS: *m/e* calcd for $C_{24}H_{39}NO_3SSiNa$: 472.2313; found: 472.2305.

**Synthesis of Amide 16**

To a stirring solution of imidate **15** (35.0 mg, 0.078 mmol) in DCE (0.4 mL) was added $PdCl_2(PhCN)_2$ (1.5 mg, 0.004 mol). The reaction was stirred under a nitrogen atmosphere for 3 h at r.t., and then the solvent was removed by rotary evaporation. The crude residue was purified by flash silica gel column chromatography [isocratic eluent: hexanes–EtOAc, 20:1] to afford the amide **16** (35.0 mg, 0.078 mmol, >95% yield) as a colorless oil.

$R_f$ = 0.50 (hexanes–EtOAc, 4:1). $^1H$ NMR (400 MHz, $CDCl_3$): δ = 1.05 (d, 9 H, *J* = 6.8 Hz), 1.11 (d, 9 H, *J* = 6.8 Hz), 1.13–1.25 (m, 3 H), 2.26 (dd, 1 H, *J* = 11.6, 6.4 Hz), 2.43 (s, 3 H), 2.66 (td, 1 H, *J* = 13.2, 7.2 Hz), 3.00 (br s, 1 H), 4.34 (dd, 1 H, *J* = 16.4, 6.8 Hz), 4.47–4.54 (m, 1 H), 4.69 (d, 1 H, *J* = 10.0 Hz), 4.82 (d, 1 H, *J* = 16.8 Hz), 5.21 (d, 1 H,

$J$ = 10.0 Hz), 5.27 (d, 1 H, $J$ = 17.2 Hz), 5.21–5.37 (m, 1 H), 7.29 (d, 2 H, $J$ = 8.8 Hz), 7.83 (d, 2 H, $J$ = 8.4 Hz). $^{13}$C NMR (100 MHz, $CDCl_3$): δ = 11.8, 18.8, 19.2, 21.8, 34.8, 49.5, 116.0, 119.0, 128.0, 128.8, 129.5, 133.6, 137.4, 144.6, 176.0. IR (film): 2950 (m), 2870 (m), 1678 (s), 1352 (s) cm$^{-1}$. MS (APCI): *m/e* (%) = 450 (100) $[M + H]^+$. ESI-HRMS: *m/e* calcd for $C_{24}H_{39}NO_3SSiNa$: 472.2313; found: 472.2317.

**Synthesis of Azapin-2-one 17**

To a solution of amide **16** (35.0 mg, 0.078 mmol) in DCE was added Grubbs I catalyst (3.2 mg, 0.004 mmol). The reaction vial was flushed with dry nitrogen, sealed, and heated to 70 °C for 16 h. The solvent was removed by rotary evaporation, and the crude residue was purified by flash silica gel column chromatography [isocratic eluent: hexanes–EtOAc, 10:1] to afford azapin-2-one **17** (29.5 mg, 0.070 mmol, 90% yield) as a white solid.

$R_f$ = 0.30 (hexanes–EtOAc, 8:1). Mp 129–130 °C. $^1$H NMR (500 MHz, $CDCl_3$): δ = 0.95 (d, 9 H, $J$ = 7.5 Hz), 0.99 (d, 9 H, $J$ = 7.5 Hz), 1.18 (sept, 3 H, $J$ = 7.5 Hz), 2.28–2.40 (m, 1 H), 2.41 (s, 3 H), 2.41–2.48 (m, 1 H), 2.90 (dd, 1 H, $J$ = 13.0, 2.5 Hz), 4.49 (dt, 1 H, $J$ = 18.0, 3.0 Hz), 4.81 (dd, 1 H, $J$ = 18.0, 8.0 Hz), 5.75–5.79 (m, 1 H), 5.83–5.88 (m, 1 H), 7.26 (d, 2 H, $J$ = 8.0 Hz), 7.83 (d, 2 H, $J$ = 8.0 Hz). $^{13}$C NMR (120 MHz, $CDCl_3$): δ = 11.2, 19.3, 21.8, 28.1, 31.0, 43.1, 123.9, 128.5, 129.3, 133.6, 136.8, 144.3, 175.4. IR (film): 2943 (m), 2866 (m), 1963 (s), 1597 (w), 1350 (s) cm$^{-1}$. MS (APCI): *m/e* (%) = 422 (100) $[M + H]^+$. ESI-HRMS: *m/e* calcd for $C_{22}H_{35}NO_3SSiNa$: 444.2000; found: 444.2000.