Synthetic Studies on Azaspiracid: Synthesis of Key Intermediate for the Construction of the FGHI Ring System

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Abstract: A highly stereoselective and convergent approach for the key intermediate of the FGHI ring system of azaspiracid is described. The synthesis features the desymmetrization strategy for the construction of the C27–C33 fragment, Masamune–Roush coupling conditions for the C33–C34 bond formation, and Sharpless asymmetric dihydroxylation as the key steps. One more important feature of this synthetic route is that we can synthesize other enantiomers of the FGHI ring system by changing asymmetric hydroboration conditions and valerolactone.

Key words: desymmetrization, Masamune–Roush coupling conditions, Sharpless asymmetric dihydroxylation, asymmetric hydroboration

The azaspiracids are the causative agents of human poisonings associated with the consumption of shellfish that were first recognized in the Netherlands in 1995.[1] Yasumoto and co-workers isolated AZA1 from the mussel *Mitilus edulis* from Killary Harbor, Ireland and reported its structure (Figure 1).[2] The structure proposed by Yasumoto and co-workers was revised and established by a total synthesis by Nicolaou and co-workers.[3] Up to now five azapiracids (AZA1–AZA5) have been isolated and their structures have been elucidated by extensive NMR studies and FABMS–MS experiments.[4] The other azapiracids (AZA6–AZA11) have been detected using a combination of liquid chromatography and multi-tandem mass spectrometry (LC–MS^n).[5] The unusual complex molecular assembly and fascinating biological activity of these natural toxins have attracted considerable interest among synthetic chemists.[6] All the azaspiracids (AZA1–AZA11) have similarity in the C27–C40 domain. The synthesis of the C26–C40 fragment has been reported by the Nicolaou,[6f,l,t,6w–y] Forsyth,[6b,c,h,z] and Sasaki groups.[6n] Still there is a scope for the efficient synthetic strategies and approaches to address the complex natural product.

Our ongoing research on the synthesis of biologically active molecules by desymmetrization strategy, and the azaspiro system encouraged us to synthesize the C27–C40 fragment of the proposed azaspiracid **1**. Our synthesis features desymmetrization strategy, Masamune–Roush coupling conditions,[7] and Sharpless asymmetric dihydroxylation.[8]

The retrosynthetic analysis is based on a convergent approach as outlined in Scheme 1. We envisioned the attachment of the C26 aldehyde **4** to the C27 acetylene **3**, and double intramolecular hetero-Michael addition[6e,h,z] reaction for the FG ring formation. The C27 acetylene would be obtained by sequential formation of the H and I rings from the acetylene **5**, which in turn could be obtained from coupling of aldehyde **6** and ketophosphonate **7**. The aldehyde **6** could be obtained from the desymmetrization strategy and the ketophosphonate **7** could be obtained from (*R*)-valerolactone.

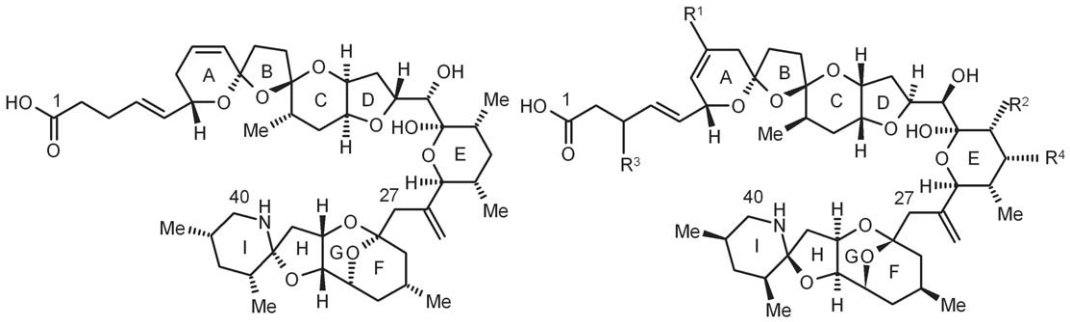

Figure 1 Proposed and revised structures of azaspiracid. R^1 = H, Me; R^2 = H, Me; R^3 = H, OH; R^4 = H, OH.

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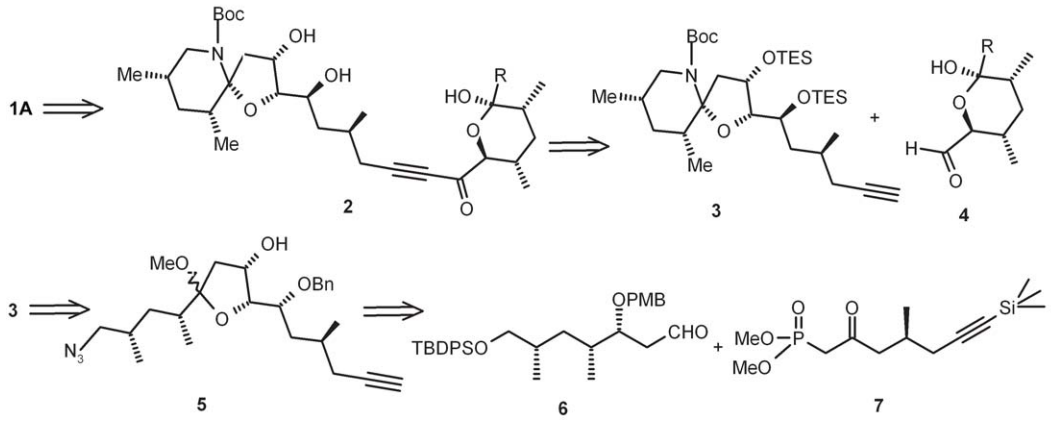
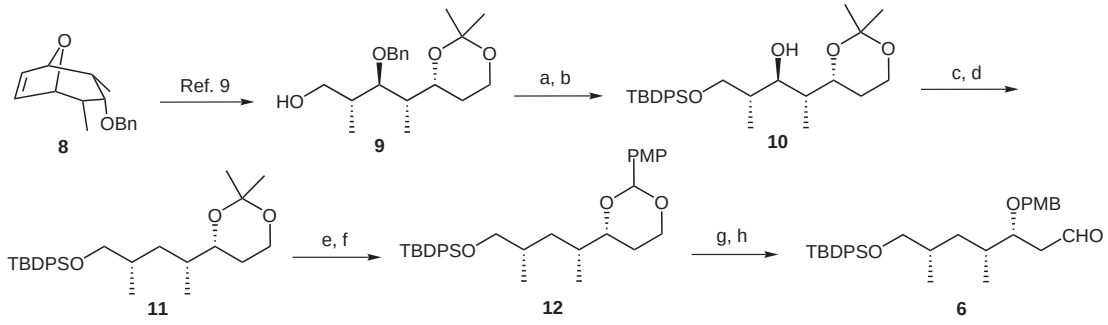


Scheme 1 Retrosynthetic analysis.

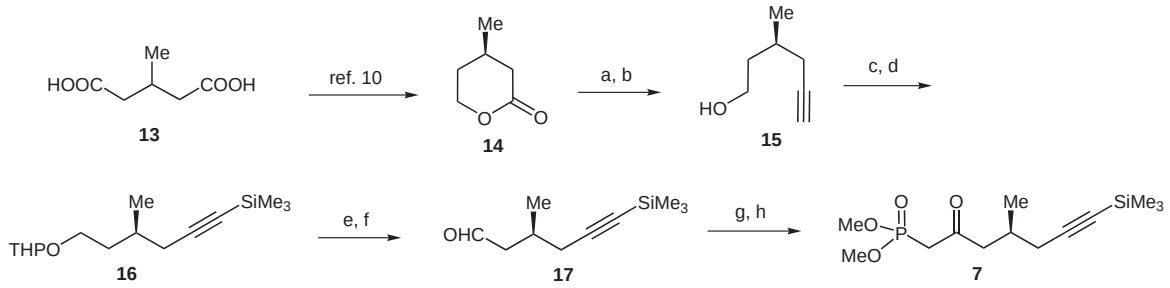
The synthesis of aldehyde **6** began with the precursor **8**, which was prepared earlier in our lab by desymmetrization strategy and utilized in the synthesis of rifamycin, fragments of (+)-discodermolide, fragment of scytophycin C, prelactone-B, (+)-membrenone-C and its 7-epimer, crocacin-C.[9] Compound **8** was converted into **9** as detailed earlier; further deprotection of the benzyl group by Li in liquid ammonia provided a diol, which was selectively protected with TBDPS-Cl to obtain **10**. The secondary hydroxyl group was converted into the xanthate ester and reduced with *n*-Bu_3SnH to give the compound **11**. Deprotection of acetonide and treatment with *para*-methoxybenzaldehyde dimethyl acetal yielded the compound **12**. Treatment of **12** with DIBAL-H yielded the mono protected diol, which on oxidation with 2-iodoxybenzoic acid (IBX) afforded the aldehyde **6** (Scheme 2).

The synthesis of ketophosphonate **7** started with 3-methylglutaric acid. Resolution of 3-methylglutaric acid monomethyl ester with cinchonidine followed by reduction of acid, and lactonization afforded **14**.[10] Dichloro olefination of lactone **14** with CCl_4 and triphenylphosphine (TPP) followed by reductive opening of the resulting enol ether with Li sand gave the alkyne **15**.[11] The hydroxyl group of the alkyne was protected as its THP ether and the alkyne was treated with TMS chloride to furnish compound **16**. Deprotection of THP ether followed by IBX oxidation gave the aldehyde **17**. Treatment of the aldehyde with lithium anion of methyldimethylphosphonate provided β-hydroxyphosphonate, which was subjected to oxidation with Dess–Martin periodinane to afford β-ketophosphonate **7**[12] (Scheme 3).

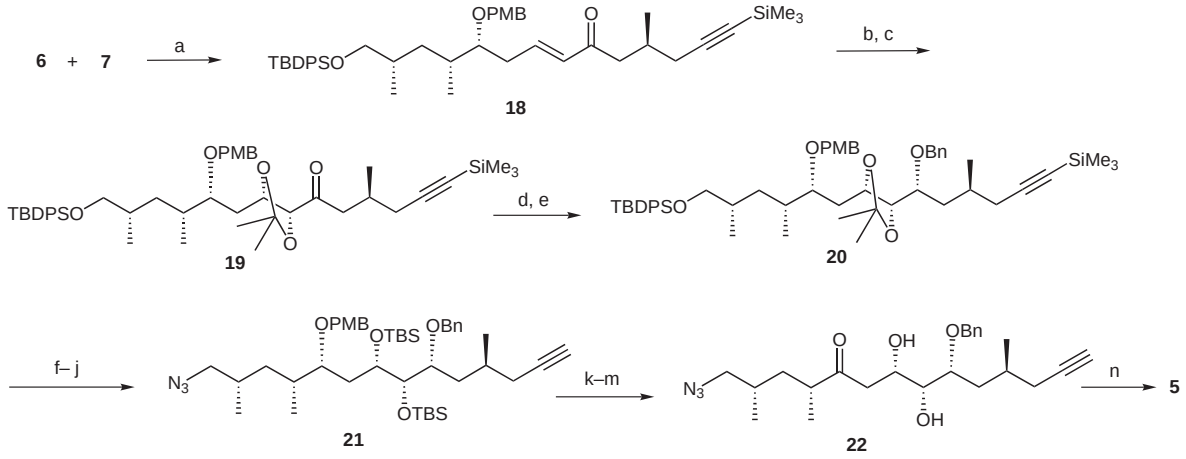
Aldehyde **6** and ketophosphonate **7** were coupled using Masamune–Roush coupling conditions[7] to afford enone **18**,[13] which was subjected to Sharpless asymmetric dihydroxylation[8] with AD-mix α to give a 95:5 diastereomeric mixture of diols (92% yield), and further protected as its acetonide **19**.[14] The stereoselective reduction of the keto functionality of **19** using various reagents afforded the undesired *R* isomer predominantly. With K-selectride, the *R* isomer was obtained exclusively, and the newly formed stereogenic center was conformed by NMR studies of its (*R*)- and (*S*)-MPA esters. We then decided to invert the stereochemistry of the carbinol carbon after the formation of the spirocycle. The hydroxyl group was protected as its benzyl ether **20**.[15] Deprotection of the TBDPS ether and TMS groups by using TBAF, followed by conversion of the resulting hydroxyl group into the azide via methanesulfonate and deprotection of the acetonide with CSA afforded the corresponding diol. Protecting the diol as its diTBDMS ether using TBSOTf gave **21**,[16] which on



Scheme 2 *Reagents and conditions*: (a) Li, liquid NH_3, THF, –78 °C; (b) TBDPS-Cl, imidazole, CH_2Cl_2, 0 °C to r.t., 95% (two steps); (c) CS_2, NaH, MeI, THF, 0 °C to r.t.; (d) *n*-Bu_3SnH, AIBN, toluene, 100 °C, 90% (two steps); (e) PPTS, MeOH, r.t.; (f) *p*-$MeOC_6H_4CH(OMe)_2$, cat. PPTS, CH_2Cl_2, 0 °C–r.t., 81% (two steps); (g) DIBAL-H, CH_2Cl_2, –78 °C; (h) IBX, DMSO, CH_2Cl_2, r.t., 92% (two steps).



Scheme 3 *Reagents and conditions*: (a) TPP, CCl_4, THF, reflux; (b) Li sand, THF, reflux, 85% (two steps); (c) 2,3-dihydropyran (DHP), cat. PPTS, CH_2Cl_2, 0 °C–r.t.; (d) TMS-Cl, *n*-BuLi, THF, –78 °C, 88% (two steps); (e) PPTS, MeOH, 0 °C–r.t.; (f) IBX, DMSO, CH_2Cl_2, r.t., 93% (two steps); (g) *n*-BuLi–MeP(O)$(OMe)_2$, –78 °C; (h) Dess–Martin periodinane, $NaHCO_3$, 0 °C–r.t., 81% (two steps).



Scheme 4 *Reagents and conditions*: (a) *i*-Pr_2NEt, LiCl, MeCN, r.t., 96%; (b) AD-mix α, $MeSO_2NH_2$, $NaHCO_3$, *t*-BuOH–H_2O (1:1), 0 °C, 92%; (c) 2,2-DMP, cat. PPTS, CH_2Cl_2, 0 °C–r.t., 95%; (d) K-selectride, THF, –78 °C; (e) NaHMDS, BnBr, THF–DMF (2:1), 0 °C, 81% (two steps); (f) TBAF, THF, 0 °C to r.t.; (g) $MeSO_2Cl$, Et_3N, CH_2Cl_2, 0 °C; (h) NaN_3, DMF, 90 °C, 93% (three steps); (i) CSA, MeOH, 0 °C to r.t.; (j) TBSOTf, 2,6-lutidine, 0 °C, 81% (two steps); (k) DDQ, CH_2Cl_2–H_2O (19:1), 0 & deg;C; (l) Dess–Martin periodinane, $NaHCO_3$, CH_2Cl_2, 0 °C to r.t.; (m) TBAF–AcOH (5:1), THF, 0 °C to r.t., 87% (three steps); (n) cat. PPTS, MeOH, r.t., quant.

treatment with DDQ led to PMB deprotection to furnish the alcohol which on oxidation using Dess–Martin reagent gave the corresponding ketone. Deprotection of the TBDMS ethers using TBAF–acetic acid (5:1) gave **22**.[17] This was then subjected to ketal formation by PPTS in methanol yielding a 1:4 mixture of isomers **5**[18] (Scheme 4).

In conclusion, we have developed a highly convergent synthetic route towards the FGHI ring domain of azaspiracids (AZA1–AZA11). All the stereogenic centers were obtained through desymmetrization strategy (which our group has utilized to synthesize a number of natural products), Sharpless asymmetric dihydroxylation, and Masamune–Roush coupling conditions yielding exclusively the *E* olefin. Further studies towards the total synthesis of azaspiracids are currently underway and will be reported in due course.

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(13) **Analytical Data for Compound 18**:
Liquid; $[\alpha]_D^{25}$ –20.18 (*c* = 2.0, $CHCl_3$). IR (Neat): 2958, 2172, 1671, 1613, 1513, 1462, 1427, 1249, 1172, 1110, 1036, 843 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.13 (s, 9 H), 0.85 (d, *J* = 6.7 Hz, 3 H), 0.89 (m, 1 H), 0.94 (d, *J* = 6.6 Hz, 3 H), 0.98 (d, *J* = 6.2 Hz, 3 H), 1.04 (s, 9 H), 1.49–1.61 (m, 1 H), 1.64–1.78 (m, 2 H), 2.14–2.45 (m, 6 H), 2.55–2.65 (m, 1 H), 3.25–3.32 (m, 1 H), 3.37 (dd, *J* = 6.4, 9.8 Hz, 1 H), 3.45–3.52 (m, 1 H), 3.76 (s, 3 H), 4.33 (q, *J* = 11.3, 16.6 Hz, 2 H), 6.06 (d, *J* = 15.8 Hz, 1 H), 6.66–6.78 (m, 1 H), 6.75 (d, *J* = 8.6 Hz, 2 H), 7.09 (d, *J* = 8.6 Hz, 2 H), 7.29–7.42 (m, 6 H), 7.59–7.65 (m, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 0.1, 15.6, 18.1, 19.2, 19.5, 26.8, 26.9, 28.8, 33.3, 33.5, 34.5, 36.4, 45.6, 55.1, 68.7, 71.6, 81.2, 86.2, 105.2, 113.6, 127.5, 129.2, 129.5, 130.5, 132.1, 133.8, 135.5, 144.7, 159.0, 199.4. HRMS (ESI): *m*/*z* $[M + NH_4]^+$ calcd for $C_{44}H_{62}O_4Si_2$: 728.4530; found: 728.4501.

(14) **Analytical Data for Compound 19**:
Liquid; $[\alpha]_D^{25}$ –2.584 (*c* = 0.6, $CHCl_3$). IR (Neat): 2958, 2931, 2172, 1714, 1610, 1513, 1462, 1374, 1301, 1249, 1169, 1082, 1034, 844, 758, 703, cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.12 (s, 9 H), 0.85 (d, *J* = 6.7 Hz, 3 H), 0.97 (d, *J* = 4.5 Hz, 6 H), 1.05 (s, 9 H), 1.30–1.39 (m, 1 H), 1.36 (s, 3 H), 1.40 (s, 3 H), 1.48–1.62 (m, 2 H), 1.68–1.90 (m, 3 H), 2.12–2.27 (m, 3 H), 2.35 (dd, *J* = 6.0, 18.1 Hz, 1 H), 2.74 (dd, *J* = 6.0, 18.1 Hz, 1 H), 3.29–3.47 (m, 2 H), 3.48–3.58 (m, 1 H), 3.76 (s, 3 H), 3.85 (d, *J* = 7.5 Hz, 1 H), 3.96–4.10 (m, 1 H), 4.24 (d, *J* = 11.3 Hz, 1 H), 4.37 (d, *J* = 11.3 Hz, 1 H), 6.74 (d, *J* = 9.0 Hz, 2 H), 7.08 (d, *J* = 8.3 Hz, 2 H), 7.64 (m, 6 H), 7.60–7.68 (d, *J* = 6.7 Hz, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 0.1, 15.8, 18.4, 19.2, 19.4, 26.2, 26.6, 26.8, 27.3, 33.2, 33.4, 35.3, 35.8, 44.0, 55.2, 68.7, 71.7, 75.3, 79.6, 85.5, 86.2, 105.1, 109.9, 113.6, 127.5, 129.1, 129.4, 131.0, 133.9, 135.6, 158.9, 208.9. HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{47}H_{68}O_6Si_2$: 807.4452; found: 807.4474.

(15) **Analytical Data for Compound 20**:
Viscous liquid; $[\alpha]_D^{25}$ –21.804 (*c* = 0.6, $CHCl_3$). IR (KBr): 794, 1071, 1248, 1513, 2172, 2958 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 0.12 (s, 9 H), 0.78–0.86 (d, *J* = 6.7 Hz, 3 H), 0.87–0.93 (d, *J* = 6.7 Hz, 3 H), 0.94–1.00 (d, *J* = 6.0 Hz, 3 H), 1.04 (s, 10 H), 1.21–1.39 (m, 1 H), 1.33 (s, 3 H), 1.35 (s, 3 H), 1.40–1.88 (m, 7 H), 1.99–2.10 (dd, *J* = 6.7, 16.6 Hz, 1 H), 2.12–2.22 (dd, *J* = 5.2, 16.6 Hz, 1 H), 3.31–3.40 (dd, *J* = 6.7, 9.8 Hz, 1 H), 3.42–3.56 (m, 3 H), 3.58–3.65 (dd, *J* = 3.7, 8.3 Hz, 1 H), 3.73 (s, 3 H), 4.01–4.14 (m, 1 H), 4.24–4.32 (d, *J* = 10.5 Hz, 1 H), 4.34–4.42 (d, *J* = 11.3 Hz, 1 H), 4.48–4.56 (d, *J* = 12.0 Hz, 1 H), 4.58–4.65 (d, *J* = 11.3 Hz, 1 H), 6.64–6.71 (d, *J* = 8.3 Hz, 2 H), 7.03–7.10 (d, *J* = 8.3 Hz, 2 H), 7.17–7.27 (m, 5 H), 7.29–7.41 (m, 6 H), 7.59–7.68 (d, *J* = 7.5 Hz, 4 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 0.1, 15.7, 18.5, 18.8, 19.2, 26.8, 27.0, 27.5, 27.7, 28.8, 33.4, 33.7, 35.8, 36.1, 37.1, 55.1, 68.7, 72.2, 72.4, 74.0, 75.9, 79.9, 80.0, 82.9, 85.7, 99.9, 105.8, 108.2, 113.5, 127.3, 127.5, 127.7, 128.2, 129.0, 129.4, 131.2, 133.9, 135.5, 138.5, 158.8. HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{54}H_{76}O_6Si_2$: 899.5078; found: 899.5051.

(16) **Analytical Data for Compound 21**:
Viscous liquid; $[\alpha]_D^{25}$ –15.098 (*c* = 0.25, $CHCl_3$). IR (Neat): 3310, 2950, 2885, 2097, 1736, 1612, 1513, 1463, 1362, 1247, 1081, 837, 773, 632 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.01 (s, 3 H), 0.02 (s, 3 H), 0.06 (s, 3 H), 0.07 (s, 3 H), 0.74 (d, *J* = 6.5 Hz, 3 H), 0.88 (s, 9 H), 0.92 (s, 9 H), 0.94 (d, *J* = 6.5 Hz, 3 H), 0.97 (d, *J* = 6.5 Hz, 3 H), 0.85–1.08 (m, 3 H), 1.40–1.55 (m, 2 H), 1.66–1.91 (m, 4 H), 1.94–2.06 (m, 1 H), 2.07–2.17 (m, 2 H), 2.90 (dd, *J* = 7.3, 11.7 Hz, 1 H), 3.08–3.17 (m, 1 H), 3.33–3.41 (m, 1 H), 3.52–3.58 (m, 1 H), 3.67–3.75 (m, 1 H), 3.79 (s, 3 H), 3.93 (dd, *J* = 3.6, 10.2

Hz, 1 H), 4.25 (d, *J* = 10.2 Hz, 1 H), 4.51 (d, *J* = 10.9 Hz, 1 H), 4.62 (d, *J* = 11.7 Hz, 1 H), 4.69 (d, *J* = 12.4 Hz, 1 H), 6.79 (d, *J* = 8.7 Hz, 2 H), 7.17 (d, *J* = 8.7 Hz, 2 H), 7.23–7.31 (m, 5 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = –4.7, –4.5, –4.2, –3.1, 16.6, 17.9, 18.9, 19.2, 25.6, 25.9, 26.7, 28.7, 31.3, 31.4, 35.2, 38.6, 55.2, 57.4, 69.3, 70.4, 71.7, 71.9, 75.7, 77.8, 80.3, 83.0, 113.5, 120.4, 127.0, 127.3, 128.1, 128.7, 131.5, 139.5, 158.8. HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{44}H_{73}N_3O_5Si_2$: 802.4986; found: 802.4968.

(17) **Analytical data for Compound 22**:
Liquid; $[\alpha]_D^{25}$ –47.136 (*c* = 1.1, $CHCl_3$). IR (Neat): 3417, 2119, 1618, 1389, 1204, 772 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.95 (d, *J* = 6.5 Hz, 3 H), 1.06 (d, *J* = 6.5 Hz, 3 H), 1.09 (d, *J* = 6.5 Hz, 3 H), 1.23–1.36 (m, 2 H), 1.45–1.71 (m, 3 H), 1.74–2.05 (m, 3 H), 2.18 (dd, *J* = 2.1, 5.8 Hz, 2 H), 2.61 (m, 1 H), 2.68 (d, *J* = 5.8 Hz, 2 H), 3.07–3.21 (m, 2 H), 3.40 (m, 1 H), 3.64–3.71 (m, 1 H), 3.74 (s, 0.5 H), 3.85 (s, 0.5 H), 4.07–4.15 (m, 1 H), 4.52 (d, *J* = 11.7 Hz, 1 H), 4.68 (d, *J* = 11.7 Hz, 1 H), 7.27–7.41 (m, 5 H). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.0, 17.8, 19.7, 25.9, 28.8, 31.4, 36.2, 37.0, 44.3, 44.5, 57.6, 68.3, 69.7, 71.9, 73.8, 78.6, 82.5, 127.9, 128.2, 128.5, 137.8, 213.9. HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{24}H_{35}N_3O_4$: 452.2525; found: 452.2512.

(18) **Analytical data for Compound 5 (Major Diastereomer)**:
Liquid; $[\alpha]_D^{25}$ –18.801 (*c* = 0.6, $CHCl_3$). IR (Neat): 3418, 2925, 2097, 1665, 1622, 1553, 1527, 1383, 1111, 616 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.92 (d, *J* = 7.1 Hz, 3 H), 0.99 (d, *J* = 6.2 Hz, 3 H), 1.01 (d, *J* = 7.1 Hz, 3 H), 1.39 (s, 1 H), 1.54–1.73 (m, 3 H), 1.77–2.05 (m, 4 H), 2.07–2.23 (m, 4 H), 2.55 (d, *J* = 7.1 Hz, 1 H), 3.07 (dd, *J* = 6.2, 11.6 Hz, 1 H), 3.18 (s, 3 H), 3.24 (dd, *J* = 6.2, 11.6 Hz, 1 H), 3.85–3.91 (m, 1 H), 3.95 (dd, *J* = 3.5, 6.2 Hz, 1 H), 4.37–4.44 (m, 1 H), 4.65 (d, *J* = 11.6 Hz, 1 H), 4.77 (d, *J* = 11.6 Hz, 1 H), 7.27–7.40 (m, 5 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 16.3, 18.8, 19.2, 26.2, 28.7, 32.1, 32.4, 36.9, 37.0, 43.3, 47.7, 57.5, 69.6, 72.4, 72.5, 76.2, 82.8, 83.2, 111.2, 127.6, 127.9, 128.3, 138.5. HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{25}H_{37}N_3O_4$: 466.2681; found: 466.2680.