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CONCISE FORMATION OF SPIROCYCLIC COMPOUNDS FOR MARINE PHYCOTOXINS

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Abstract – The stereoselective construction of azaspiro[5.6]dodecenone skeletons by the chiral BOX/copper-mediated Diels-Alder reaction is described. The cycloaddition reaction of α-methylene caprolactams and functionalized dienes allows the concise formation of spirocyclic structures of marine phycotoxins, such as pinnatoxin and spirolide.

INTRODUCTION

Marine phycotoxins containing a spirocyclic imine unit belong to an emerging class of fast-acting toxins responsible for incidents of shellfish toxicity. The phycotoxins, such as pinnatoxin,[1] spirolide,[2] and gymnodimine,[3] were initially known as strong neurotoxins, and later they were demonstrated to bind to nicotinic acetylcholine receptors (nAChRs) with high affinity and behave as competitive AChR antagonists (Figure 1).[4-6] Since naturally occurring amino ketone compounds generated by the hydrolysis of the corresponding cyclic imines are inactive, the cyclic imine unit plays an important role for the effective binding to nAChRs.[7] Pinnatoxin and spirolide possess the characteristic macrocyclic structures with a spirocyclic imine unit and a bisspiroacetal unit. In addition to their potent biological activities, the complex molecular architectures make them challenging synthetic targets. As such, a number of efforts has been made in the synthesis of pinnatoxin,[8,9] spirolide,[10,11] and gymnodimine[12] as well as their analogues.[13] Previous our efforts to form the spirocyclic unit focused on an asymmetric Diels-Alder reaction mediated by a chiral BOX/copper complex, which was developed by Evans and co-workers (Scheme 1).[14] The Diels-Alder reaction of an α-methylene caprolactam and a diene in the presence of *t*BuBOX copper complex affords the desired spirocyclic compound with excellent *exo*-selectivity as well

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Dedicated with respect to Dr. Masakatsu Shibasaki on the occasion of his 70th birthday

as high enantioselectivity.[15] Although this methodology appeared in the literatures,[12a-b,16] its successful utilization for constructing the spirocyclic units of pinnatoxin and spirolide had never been reported. Herein we disclose the application of the cycloaddition reaction to the construction of the spirocyclic core structures of **1** and **2**.

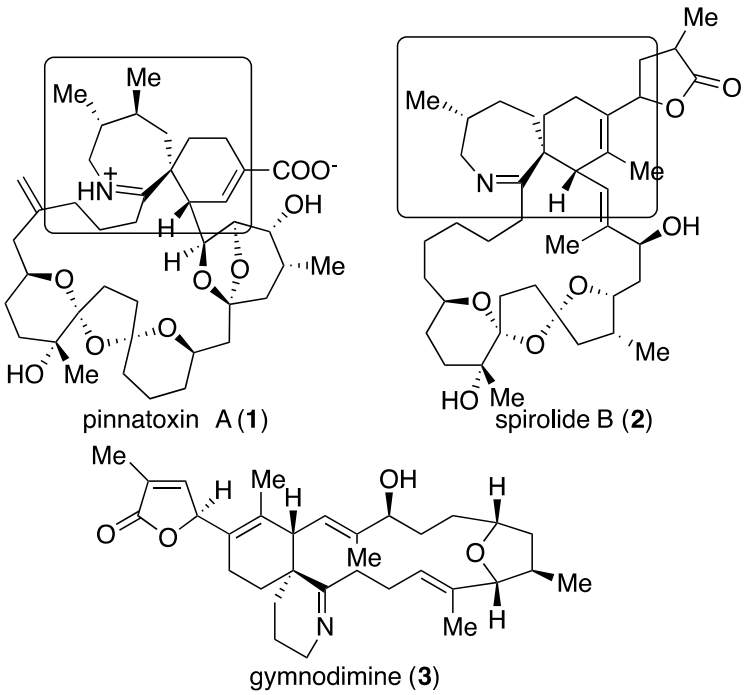
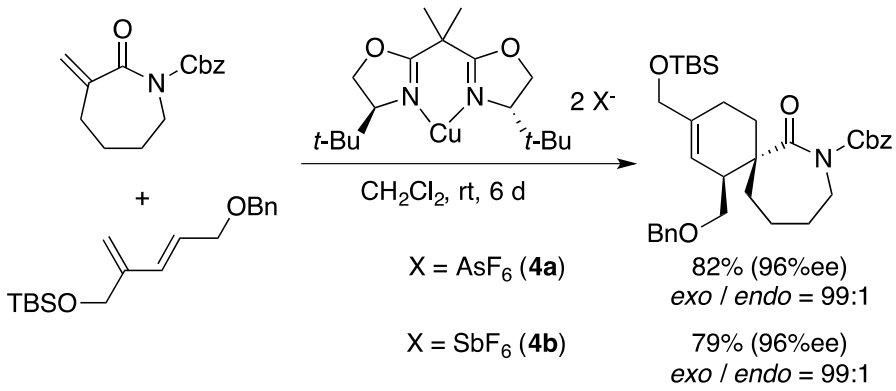


Figure 1

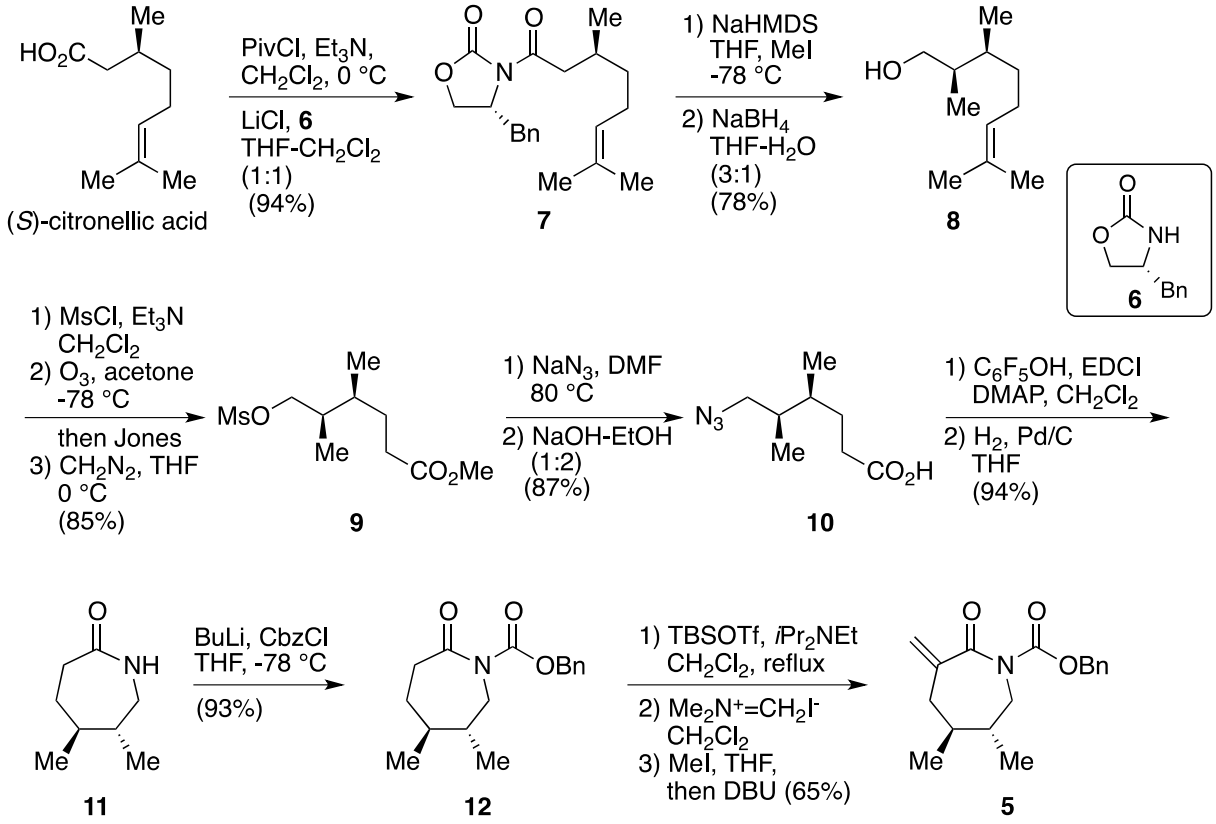


Scheme 1

RESULTS AND DISCUSSION

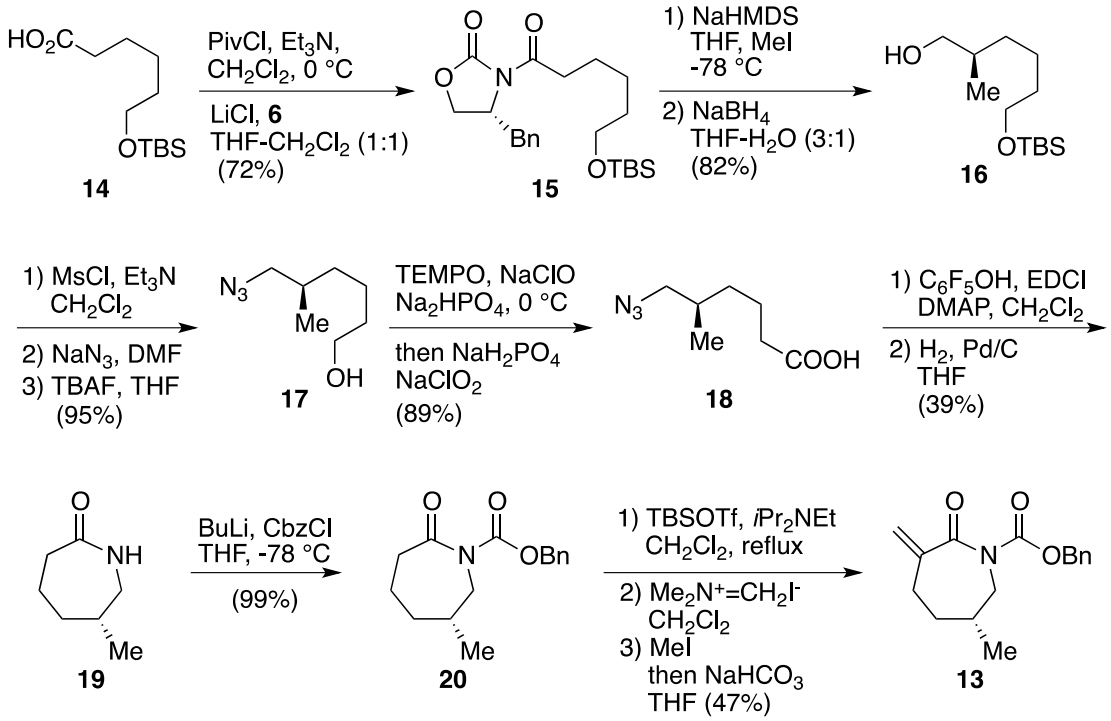
At first, 4,5-dimethylcaprolactam **5**, a promising dienophile for the synthesis of pinnatoxin, was prepared by the sequence of reactions outlined in Scheme 2. The chiral auxiliary, (*S*)-benzyloxazolidone (**6**) was introduced to (*S*)-citronellic acid to give amide **7** in 96% yield. Stereoselective methylation of **7**[17] followed by reduction[18] generated alcohol **8** in 78% yield. After mesylation of the primary alcohol,

ozonolysis, followed by oxidative treatment afforded the carboxylic acid, which was esterified to compound **9** in 88% yield for 3 steps. Mesylate **9** was then converted to carboxylic acid **10** by azidation and saponification in 93% yield. The resulting acid **10** was esterified with pentafluorophenol in the presence of EDCI to furnish the corresponding activated ester quantitatively. When the activated ester was hydrogenated with Pd/C, reduction of the azide group and spontaneous formation of an azepinone ring readily proceeded to give lactam **11** in 94% yield.[19] The Cbz protection of **11** afforded compound **12** in 93% yield. The α-methylenation[20] of **12** was accomplished a three-step sequence involving formation of the TBS enol ether, Mannich reaction with Eschenmoser's salt, and elimination to give compound **5** in 65% yield.



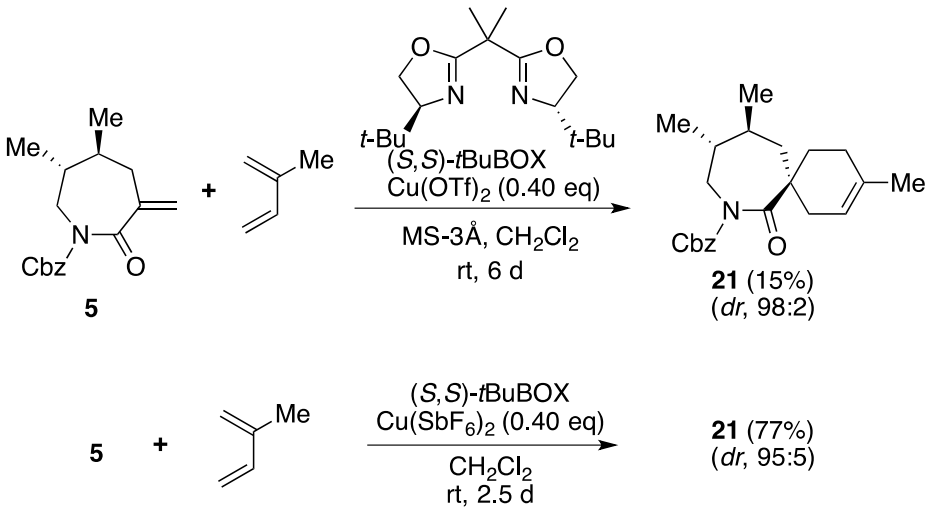
Scheme 2

Similarly, 4-methylcaprolactam **13**, a dienophile for the synthesis of spirolide B, was derived from siloxycaproic acid **14**[21] (Scheme 3). Amidation of **14** with chiral auxiliary **6** gave **15** in 72% yield, which was subjected to methylation and reduction to afford alcohol **16** in 81% yield. After conversion of **16** to azide **17**, TEMPO oxidation[22] of **17** furnished carboxylic acid **18** in good yield. The lactam formation from **18** generated **19** in 39% yield. Cbz protection of **19** and subsequent α-methylation of **20** furnished the desired dienophile **13** in 47% yield.



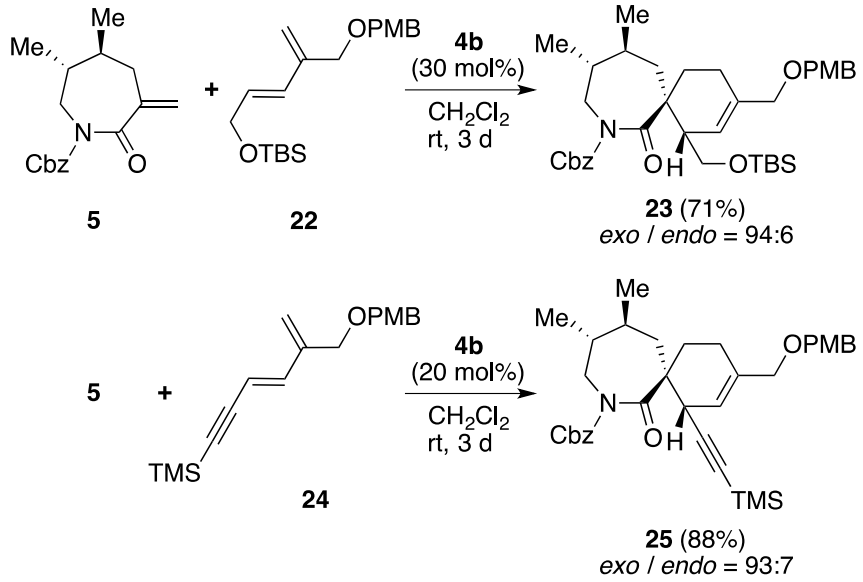
Scheme 3

With chiral lactams in hand, the copper-catalyzed Diels-Alder reaction was explored (Scheme 4). The cycloaddition of dimethylcaprolactam **5** and isoprene in the presence of *t*BuBOX/Cu(OTf)$_2$ complex proceeded slowly to afford spirocyclic product **21** in 15% yield.[23] On the other hand, when *t*BuBOX/Cu(SbF$_6$)$_2$ (**4b**) was employed, **21** was obtained in 77% yield with high diastereomeric ratio. Based on the results, we next examined the cycloaddition of **5** and some 4-substituted 2,4-pentadienes towards the synthesis of the spirocyclic core of pinnatoxin.



Scheme 4

The Diels-Alder reaction of **5** and **22**[24] employing (*S*,*S*)-*t*BuBOX/copper complex **4b** (40 mol%) led to the formation of spirocyclic product **23** in 71% yield with high *exo*-selectivity (Scheme 5).[25] Furthermore, reaction of **5** and dieneyne **24** in the presence of 20 mol% of **4b** produced compound **25** in excellent yield with good *exo*-selectivity. The carbamate lactam, such as **5** would be applicable to the asymmetric construction of a spirocyclic system due to the nature of its locked *s*-cis conformation. It could support the proposal of the *s*-cis conformation of the dienophile in the activated complex. Notably, the *exo*-selectivity was observed in both cases. The C-2 substituent of the diene would have severe interaction against the copper ligand complex in TS-2 in the plausible transition structure (Figure 2). In addition, as Roush[26a] and other groups reported, the Diels-Alder reaction of conformationally rigid cyclic cisoid dienophiles, such as α-methylene-lactones, with cyclopentadiene proceeds with *exo*-selectivity explained by Berson's dipole moment hypotheses.[27]



Scheme 5

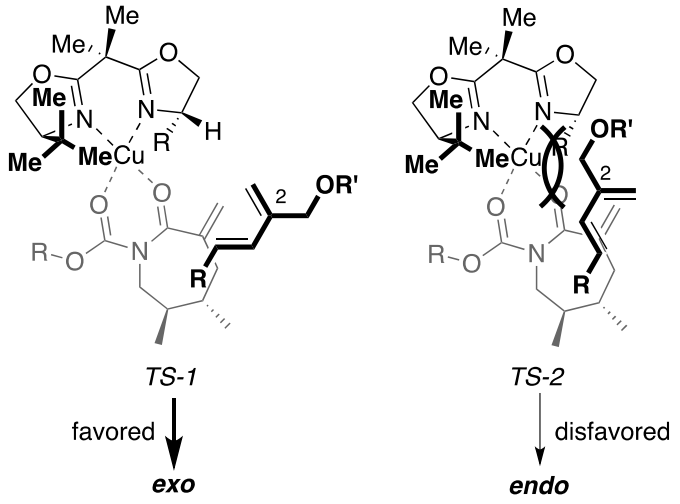
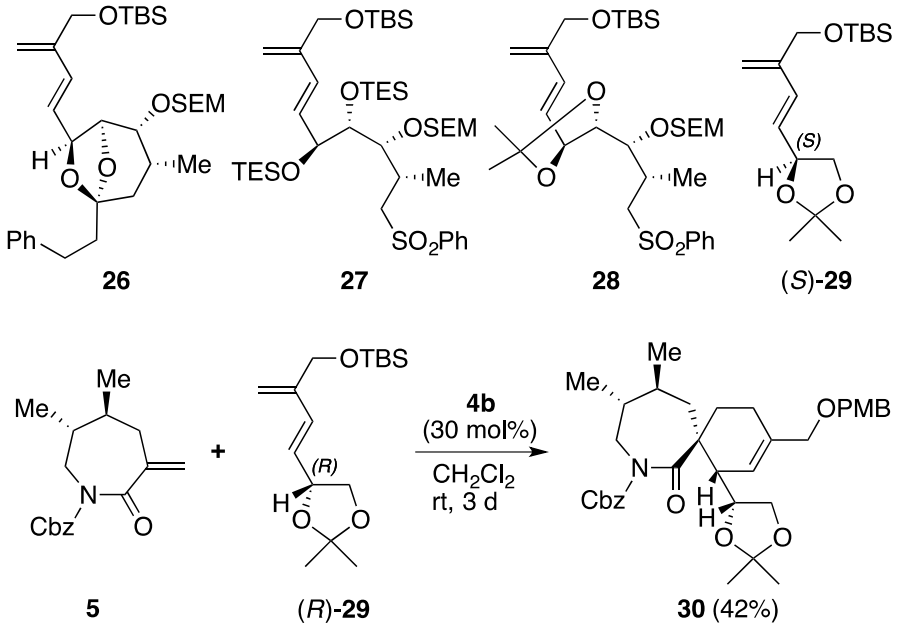


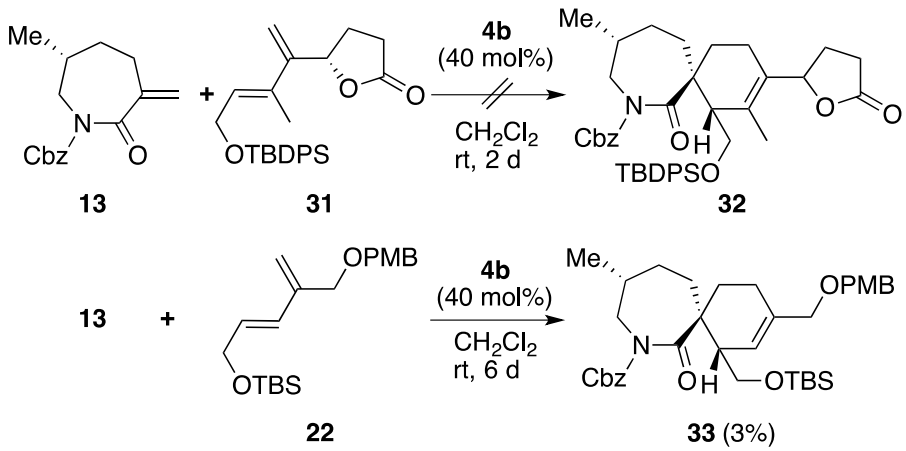
Figure 2

Encouraged by the results, we then investigated the Diels-Alder reactions of highly functionalized dienes. However, the reactions of **5** and **26-29**[28] did not produce any cycloaddition adduct (Scheme 6). Notably, (*S*)-**29** was unaffected under the condition, while (*R*)-**29** underwent the cycloaddition to generate adduct **30** in moderate yield. This result clearly shows that *S*-configuration of the diene is mismatched for the Diels-Alder reaction mediated by (*S,S*)-*t*BuBOX complex **4b**.



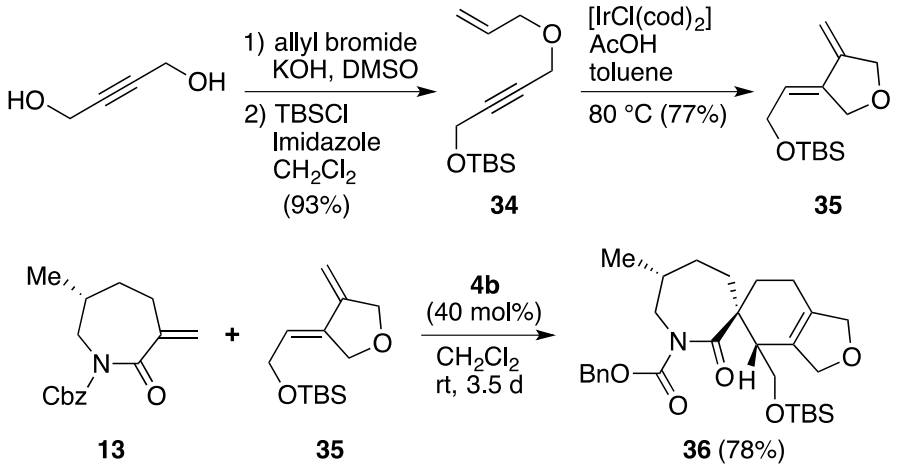
Scheme 6

We next turned our attention to the formation of the spirocyclic unit of spirolide. Unexpectedly, the Diels-Alder reaction of 4-methylcaprolactam **13** with diene **31**[15a] resulted in no reaction and the cycloaddition of **13** and diene **22** produced the desired product in only 3% yield (Scheme 7). The reactions under the thermal conditions also failed. It is not clear why **13** has poor reactivity against **22** under the *t*BuBOX/copper-mediated conditions.



Scheme 7

Considering these results, we explored to use the diene fixed to a cisoid conformation, which would be preferable to the cycloaddition reaction. The cisoid diene **35** was readily prepared from 2-butyn-1,4-ol[29] in 3 steps through an Ir-catalyzed cyclization reported by Chatani and Murai (Scheme 8).[30] Gratifyingly, it was found that Diels-Alder reaction of **13** and diene **35**, utilizing **4b**, furnished the desired cycloadduct **36** in 78% yield as a single diastereomer. To our knowledge, it is the first case for the construction of the spirocyclic unit for spirolide B by a chiral copper-mediated Diels-Alder reaction.



Scheme 8

In conclusion, we have developed a concise formation of the spirocyclic compounds by chiral copper-mediated Diels-Alder reaction. The present method would be useful for the stereoselective assembly of the spirocyclic core structure of pinnatoxin and spirolide. Further exploration of this chemistry is underway in our laboratory.

EXPERIMENTAL

Where appropriate, reactions were performed in flame-dried glassware under argon atmosphere. All extracts were dried over $MgSO_4$ and concentrated by rotary evaporation below 30 °C at 25 Torr unless otherwise noted. Commercial reagents and solvents were used as supplied with following exceptions. *N,N*-Dimethylformamide (DMF), dimethyl sulfoxide (DMSO), dichloromethane (CH_2Cl_2), toluene, and triethylamine (NEt_3) were distilled from CaH_2. Column chromatography was performed using silica gel (particle size 100-210 μm (regular), 40-50 μm (flash). Optical rotations were recorded on digital polarimeter at ambient temperature. Infrared spectra (FTIR) were measured on a Fourier transform infrared spectrometer. ^1H NMR (300 and 400 MHz) and ^{13}C NMR (75 and 100 MHz) spectra were measured using $CDCl_3$, or C_6D_6 as solvent, and chemical shifts are reported as δ values in ppm based on internal $CHCl_3$ (7.26 ppm, ^1H; 77.0 ppm, ^{13}C), C_6D_6 (7.13 ppm, ^1H; 128.6 ppm, ^{13}C). Mass (MS) and high resolution mass (HRMS) spectra were taken in EI or FAB mode.

[(3*S*)-3,7-Dimethyl-6-octenoyl]-(4'*R*)-benzyl-2'-oxazolidinone (7). To a solution of (*S*)-(-)-citronellic acid (7.67 g, 45.1 mmol) in CH_2Cl_2 (400 mL) were added Et_3N (16.0 mL, 0.115 mol) and PivCl (6.0 mL, 48.8 mmol) at 0 °C. After stirring at the same temperature for 3 min, LiCl (3.83 g, 90.5 mmol) and (4*R*)-(+)-4-benzyl-2-oxazolidinone **6** (8.80 g, 49.7 mmol) in THF (200 mL) were added, and the mixture was stirred at 21 °C for 3 h. To the mixture was added **6** (0.58 g, 3.3 mmol) again, and stirring was continued for 1.5 h. The reaction mixture was diluted with 0.5 M aqueous NaOH (500 mL), and extracted with Et_2O (3 x 30 mL), dried, and concentrated. The residue was purified flash chromatography (SiO_2, hexane–AcOEt, 8:1 to 5:1) gave oxazolidinone **7** (14.1 g, 94%); colorless oil; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 1.01 (3H, d, *J* = 6.9 Hz), 1.17-1.32 (1H, m), 1.37-1.49 (1H, m), 1.60 (3H, s), 1.68 (3H, s), 1.94-2.15 (3H, m,) 2.75 (1H, dd, *J* = 9.7, 13.4 Hz), 2.85-2.88 (2H, m), 3.32 (1H, dd, *J* = 3.3, 13.4 Hz), 4.13-4.21 (2H, m), 4.64-4.72 (1H, m), 5.08-5.13 (1H, m), 7.21-7.36 (5H, m); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 17.6, 19.6, 25.4, 25.7, 29.3, 36.7, 37.9, 42.4, 55.2, 66.0, 124.3, 127.3, 128.9, 129.4, 131.5, 135.3, 153.4, 172.8; IR (neat) 2963, 2919, 2855, 1781, 1705, 1694, 1605, 1481, 1447, 1384, 1351, 1305, 1207, 1102, 1079, 1051, 1023, 998, 744, 701 cm^{-1}; MS (EI) *m/z* 152, 178, 329 (M^+).

[(2*R*,3*S*)-2,3,7-Trimethyl-6-octenoyl]-(4'*R*)-benzyl-2'-oxazolidinone. To a solution of **7** (14.0 g, 42.6 mmol) in THF (300 mL) was added NaHMDS (47.0 mL, 1.0 M solution in THF, 47.0 mmol) at -78 °C. After stirring 45 min, MeI (13.0 mL, 209 mmol) was added, and the stirring was continued at the same temperature for 4.5 h. The reaction was quenched by saturated NH_4Cl (300 mL) and saturated $Na_2S_2O_3$ (100 mL). The mixture was extracted with Et_2O (3 x 300 mL), dried, and concentrated. The residue was purified flash chromatography (SiO_2, hexane–AcOEt, 30:1) gave methyl product (13.1 g, 90%); colorless oil; $[\alpha]_D^{26}$ -85.0 (*c* 0.92, $CHCl_3$); ^{1}H-NMR (C_6D_6, 300 MHz) δ 0.95 (3H, d, *J* = 6.8 Hz), 1.21 (3H, d, *J* = 6.8 Hz), 1.29-1.41 (1H, m), 1.59 (3H, s), 1.54-1.67 (1H, m), 1.69 (3H, s), 2.04-2.21 (3H, m), 2.26 (1H, dd, *J* = 9.6, 13.4 Hz), 2.99 (1H, dd, *J* = 3.1, 13.4 Hz), 3.11 (1H, dd, *J* = 8.3, 9.0 Hz), 3.42 (1H, dd, *J* = 2.4, 9.0 Hz), 4.02 (1H, dq, *J* = 6.6, 6.8 Hz), 4.12-4.23 (1H, m), 5.24-5.32 (1H, m), 6.83-6.88 (2H, m), 6.99-7.07 (3H, m); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 12.7, 15.0, 17.6, 25.6, 25.7, 34.7, 35.4, 37.7, 42.1, 55.4, 65.8, 124.3, 127.2, 128.8, 129.4, 131.3, 135.3, 152.9, 176.9; IR (neat) 2968, 2920, 1782, 1694, 1605, 1481, 1449, 1385, 1350, 1289, 1209, 1103, 1076, 1050, 1016, 969, 832, 747, 702 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{21}H_{29}NO_3$ (M^+) 343.2147, found 343.2154.

(2*R*,3*S*)-2,3,7-Trimethyl-6-octen-1-ol (8). To a suspension of $NaBH_4$ (5.75g, 152 mmol) in water (100 mL) was added a solution of methyl product (13.1 g, 38.0 mmol) in THF (300 mL) at 23 °C. After stirring of the mixture at the same temperature for 1.5 d, the reaction mixture was diluted with brine (150 mL), extracted with Et_2O (2 x 150 mL) and CH_2Cl_2 (3 x 200 mL), dried, and concentrated. The residue was purified flash chromatography (SiO_2, hexane–AcOEt, 10:1 to 1:2) to give the alcohol **8** (5.61 g, 87%); colorless oil; $[\alpha]_D^{26}$ -8.9 (*c* 0.90, $CHCl_3$); ^{1}H-NMR (C_6D_6, 300 MHz) δ 0.80 (3H, d, *J* = 6.2 Hz), 0.82 (3H,

d, *J* = 6.6 Hz), 1.14-1.41 (3H, m), 1.61 (3H, s), 1.67 (3H, s), 1.58-1.74 (2H, m), 1.88-2.06 (2H, m), 3.41-3.61 (2H, m), 5.07-5.14 (1H, m); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 131.3, 124.7, 66.9, 39.5, 35.0, 32.9, 25.9, 25.7, 17.6, 14.3, 11.3; IR (neat) 3337, 2963, 2920, 2877, 1447, 1380, 1116, 1037, 829 cm^{-1}; HRMS (FD) *m/z* calcd for $C_{11}H_{22}O$ (M^+) 170.1661, found 170.1660.

(6*S*,7*R*)-7-Methanesulfonyloxy-2,6,7-trimethyl-6-octene. To a solution of **8** (10.5 g, 61.7 mmol) in CH_2Cl_2 (434 mL) at 0 °C were added Et_3N (32.8 mL, 235 mmol) and MsCl (9.6 mL, 124 mmol) at 0 °C. The reaction mixture was stirred at rt for 15 h. The reaction mixture was diluted with aqueous NH_4Cl (400 mL), extracted with Et_2O (4 x 400 mL), dried, and concentrated. The residue was purified flash chromatography (SiO_2, hexane–AcOEt, 8:1) afforded a mesylate (14.7 g, 59.2 mmol, 96%); pale yellow oil; $[\alpha]_D^{20}$ -11.3 (*c* 1.11, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.83 (3H, d, *J* = 6.8 Hz), 0.89 (3H, d, *J* = 6.8 Hz), 1.14-1.27 (1H, m), 1.29-1.43 (1H, m), 1.61 (3H, s), 1.53-1.67 (1H, m), 1.69 (3H, d, *J* = 1.1 Hz), 1.87-2.07 (3H, m), 3.00 (3H, s), 4.04 (1H, dd, *J* = 7.3, 9.5 Hz), 4.14 (1H, dd, *J* = 6.6, 9.5 Hz), 5.05-5.12 (1H, m); IR (neat) 2966, 2919, 1453, 1357, 1176, 958, 843 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{12}H_{24}O_3S$ (M^+) 248.1446, found 248.1453.

(4*S*,5*R*)-4,5-Dimethyl-6-methanesulfonyloxyhexanoic acid. To a solution of mesylate (14.7 g, 59.1 mmol) in acetone (335 mL) at -78 °C was bubbled O_3 gas (O_2 containing ca. 3% O_3). After stirring at the same temperature for 2 h, N_2 gas was bubbled for 20 min, and Jones reagent (44.1 mL, a 2.68 M solution in acetone, 118 mmol) was added at -78 °C. The reaction mixture was warmed to rt, and stirred for 2 h. The reaction was quenched by 2-propanol (4 mL). The resulting suspension was filtered through a Celite pad and $MgSO_4$, and the filtrate was concentrated. The residue was purified by flash chromatography (SiO_2, hexane–AcOEt, 2:1 to 1:3) to afford the carboxylic acid (7.29 g, 97%); colorless oil; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.86 (3H, d, *J* = 6.8 Hz), 0.91 (3H, d, *J* = 7.0 Hz), 1.48-1.58 (1H, m), 1.62-1.78 (2H, m), 1.90-2.00 (1H, m), 2.28-2.47 (2H, m), 3.01 (3H, s), 4.07 (1H, dd, *J* = 6.8, 9.7 Hz), 4.13 (1H, dd, *J* = 7.0, 9.7 Hz); IR (neat) ν_{max} 3306, 3027, 2967, 2943, 1709, 1352, 1174, 958, 845 cm^{-1}; HRMS (FD) *m/z* calcd for $C_9H_{19}O_5S$ [$(M+H)^+$] 239.0939, found: 239.0937.

Methyl (4*S*,5*R*)-4,5-dimethyl-6-methanesulfonyloxyhexanoate (9). To a solution of the carboxylic acid (7.21 g, 30.3 mmol) in THF (100 mL) was added a solution of diazomethane in Et_2O dropwise at 0 °C until the solution persisted in yellow color. The mixture was stirred at the same temperature for 30 min and concentrated. The residue was purified by flash chromatography (SiO_2, hexane–AcOEt, 3:1) to give methyl ester **9** (6.92 g, 91%); colorless oil; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.84 (3H, d, *J* = 6.6 Hz), 0.90 (3H, d, *J* = 7.0 Hz), 1.47-1.57 (1H, m), 1.60-1.76 (2H, m), 1.90-2.00 (1H, m), 2.24-2.41 (2H, m), 3.01 (3H, s), 3.63 (3H, s), 4.06 (1H, dd, *J* = 7.0, 9.7 Hz), 4.13 (1H, dd, *J* = 6.8, 9.7 Hz); IR (neat) 3024, 2964, 2884, 1736, 1458, 1439, 1355, 1264, 1174, 1115, 959, 844, 749 cm^{-1}; HRMS (EI) *m/z* calcd for $C_9H_{17}O_4S$ [$(M-OMe)^+$] 221.0847, found 221.0850.

Methyl (4*S*,5*R*)-6-azido-4,5-dimethylhexanoate. To a solution of **9** (6.88 g, 27.2 mmol) in DMF (100 mL) was added NaN_3 (6.22 g, 95.7 mmol). The mixture was stirred at 80 °C for 7 h and cooled to 22 °C. To the reaction mixture was added brine (100 mL) and the aqueous layer was extracted with hexane (3 x 100 mL), dried, and concentrated. The residue was purified flash chromatography (SiO_2, hexane–AcOEt, 20:1) furnished azide (5.29 g, 98%); pale yellow oil; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.81 (3H, d, *J* = 6.6 Hz), 0.87 (3H, d, *J* = 6.8 Hz), 1.46-1.78 (4H, m), 2.21-2.40 (2H, m), 3.15 (1H, dd, *J* = 7.3, 12.1 Hz), 3.24 (1H, dd, *J* = 7.0, 12.1 Hz), 3.68 (3H, s); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 174.0, 55.9, 51.5, 36.8, 33.8, 32.1, 29.7, 13.8, 12.7; IR (neat) 2963, 2879, 2098, 1740, 1438, 1384, 1264, 1173, 1111, 1023 cm^{-1}; HRMS (FD) *m/z* calcd for $C_9H_{18}N_3O_2$ [$(M+H)^+$] 200.1386, found: 200.1384.

(4*S*,5*R*)-6-Azido-4,5-dimethylhexanoic acid (10). To a solution of the azide (5.22 g, 28.2 mmol) in EtOH (60 mL) was added 1.0 M NaOH (30 mL) at 0 °C. After stirring at 22 °C for 8 h, the reaction was quenched by 1.0 M HCl until the solution was adjusted to pH 3.0 at 0 °C, and the aqueous layer was extracted with Et_2O (3 x 80 mL), dried, and concentrated. The residue was purified flash chromatography (SiO_2, hexane–AcOEt, 5:1 to 3:1) gave carboxylic acid **10** (4.65 g, 89%); colorless oil; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.83 (3H, d, *J* = 6.6 Hz), 0.88 (3H, d, *J* = 7.0 Hz), 1.47-1.79 (4H, m), 2.38 (2H, ddd, *J* = 6.2, 9.2, 9.4 Hz), 3.16 (1H, dd, *J* = 7.2, 12.1 Hz), 3.25 (1H, dd, *J* = 6.8, 12.1 Hz); IR (neat) 2966, 2919, 1453, 1357, 1176, 958, 843 cm^{-1}; HRMS (FD) *m/z* calcd for $C_8H_{16}N_3O_2$ [$(M+H)^+$] 186.1232, found 186.1231.

Pentafluorophenyl (4*S*,5*R*)-6-azido-4,5-dimethylhexanoate. To a solution of EDCI (33.0 mg, 0.172 mmol) and DMAP (cat.) in CH_2Cl_2 (0.5 mL) was added a solution of **10** (16.5 mg, 89.1 mmol) and pentafluorophenol (34.6 mg, 0.188 mmol) in CH_2Cl_2 (1.5 mL) at 0 °C. After stirring at 21 °C for 3 h, the reaction mixture was diluted with saturated NH_4Cl (2 mL) at 0 °C, and aqueous layer was extracted with Et_2O (3 x 2 mL), dried, and concentrated. The residue was purified flash chromatography (SiO_2, hexane–AcOEt = 30:1) afforded pentafluorophenyl ester (31.3 mg, 100%); pale yellow oil; ^{1}H-NMR ($CDCl_3$ 300 MHz) δ 0.88 (3H, d, *J* = 6.6 Hz), 0.90 (3H, d, *J* = 6.8 Hz), 1.57-1.91 (4H, m), 2.57-2.78 (2H, m), 3.19 (1H, dd, *J* = 7.2, 12.1 Hz), 3.26 (1H, dd, *J* = 6.8, 12.1 Hz); IR (neat) 2968, 2933, 2881, 2100, 1791, 1523, 1467, 1447, 1385, 1271, 1224, 1088, 1001 cm^{-1}; HRMS (FD) *m/z* calcd for $C_{14}H_{15}N_3O_2F_5$ [$(M+H)^+$] 352.1076, found 352.1075.

(5*S*,6*R*)-5,6-Dimethylhexahydro-2-azepinone (11). A suspension of pentafluorophenyl ester (30.0 mg, 85.4 mmol) and 10% Pd-C in THF (2 mL) was stirred under H_2 atmosphere at 21 °C for 14.5 h. The reaction mixture was filtered through a Celite pad, and the filtrate was concentrated. The residue was purified by flash chromatography (SiO_2, hexane–AcOEt, 3:1) to give lactam **11** (11.4 mg, 94%); white needles; mp 96-97 °C; $[\alpha]_D^{24}$ -18.1 (*c* 0.54, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.95 (3H, d, *J* = 6.4 Hz), 1.00 (3H, d, *J* = 5.9 Hz), 1.26-1.49 (3H, m), 1.79-1.88 (1H, m), 2.43-2.49 (2H, m), 3.03-3.09 (2H, m), 5.70 (1H, brs); ^{13}C-NMR ($CDCl_3$, 100 MHz) δ 18.2, 20.9, 30.6, 34.4, 40.2, 41.5, 48.1, 178.8; IR

(KBr) 3237, 3097, 2955, 2926, 2900, 2875, 1661, 1489, 1441, 1417, 1381, 1222, 1126, 1073, 820, 790, 480 cm^{-1}; HRMS (EI) *m/z* calcd for $C_8H_{15}NO$ (M^+) 141.1154, found 141.1159.

(5*S*,6*R*)-*N*-Benzyloxycarbonyl-5,6-dimethylhexahydro-2-azepinone (12). To a solution of **11** (202 mg, 1.43 mmol) in THF (15 mL) was added *n*BuLi (1.60 M solution in hexane, 0.9 mL, 1.44 mmol) at -78 °C. After stirring at the same temperature for 30 min, CbzCl (240 mL, 1.60 mmol) was added, and the mixture was stirred at the same temperature for 3 h. The reaction mixture was diluted with saturated NH_4Cl (15 mL), and extracted with Et_2O (3 x 20 mL), dried, and concentrated. The residue was purified flash chromatography (SiO_2, hexane–AcOEt, 5:1) gave cbz product **12** (366 mg, 93%); colorless oil; $[\alpha]_D^{11}$ -99.4 (*c* 0.85, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.97 (3H, d, *J* = 2.6 Hz), 0.99 (3H, d, *J* = 3.9 Hz), 1.17-1.56 (3H, m), 1.88 (1H, dddd, *J* = 2.2, 2.6, 7.7, 14.3 Hz), 2.63 (1H, ddd, *J* = 2.2, 7.7, 15.2 Hz), 2.74 (1H, ddd, *J* = 2.6, 10.9, 15.2 Hz), 3.36 (1H, dd, *J* = 8.7, 15.3 Hz), 3.99 (1H, dd, *J* = 0.3, 15.3 Hz), 5.25 (1H, d, *J* = 12.5 Hz), 5.30 (1H, d, *J* = 12.5 Hz), 7.44-7.27 (5H, m); IR (neat) 3070, 3034, 2958, 2927, 2877, 1773, 1715, 1497, 1458, 1378, 1352, 1291, 1254, 1223, 1187, 1159, 1101, 1076, 1056, 1025, 983, 897, 777, 738, 698 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{16}H_{21}NO_3$ (M^+) 275.1521, found: 275.1521.

(5*S*,6*R*)-*N*-Benzyloxycarbony-2-*tert*-butyldimethylsilyloxy-5,6-dimethyltetrahydroazepine. To a solution of **12** (348 mg, 1.26 mmol) in CH_2Cl_2 (10 mL) were added *i*Pr_2NEt (0.65 mL, 3.73 mmol) and TBSOTf (0.43 mL, 1.87 mmol) at 0 °C. The reaction mixture was refluxed for 15 h. The reaction was quenched by saturated $NaHCO_3$ (10 mL) at 0 °C, and the aqueous layer was extracted with hexane (3 x 15 mL). The residue was dried over $MgSO_4$, concentrated *in vacuo*, and purified flash chromatography (SiO_2, hexane–AcOEt, 30:1, 1% Et_3N) gave the silyl enol ether (434 mg, 88%); pale yellow oil; ^{1}H-NMR (C_6D_6, 300 MHz) δ 0.15 (6H, s), 0.72 (3H, d, *J* = 6.1 Hz), 0.74 (3H, d, *J* = 6.8 Hz), 0.97 (9H, s), 0.85-1.01 (1H, m), 1.36-1.52 (1H, m), 1.68-1.90 (2H, m), 4.00 (1H, brs), 4.69 (2H, brs), 5.15 (1H, d, *J* = 12.1 Hz), 5.20 (1H, d, *J* = 12.1 Hz), 7.01-7.33 (5H, m); IR (neat) 3034, 2955, 2930, 2888, 2858, 1714, 1676, 1456, 1398, 1335, 1258, 1190, 1150, 1100, 1040, 901, 841, 784, 697, 672 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{22}H_{35}NO_3Si$ (M^+) 389.2386, found: 389.2385.

(5*S*,6*R*)-*N*-Benzyloxycarbonyl-5,6-dimethyl-3-methenylpentahydro-2-azepinone (5). To a suspension of Eschenmoser's salt (279 mg, 1.51 mmol) in CH_2Cl_2 (10 mL) was added a solution of silyl enol ether (427 mg, 1.10 mmol) in CH_2Cl_2 (5 mL) at 23 °C. The reaction mixture was stirred at the same temperature for 2 h. The reaction was quenched by 1.0 M NH_3 (15 mL), and the aqueous layer was extracted with EtOAc (4 x 25 mL). Drying over $MgSO_4$ and concentration *in vacuo* gave a crude amine 428 mg as pale yellow oil.

To a solution of the crude amine (428 mg) THF (10 mL) was added MeI (0.7 mL, 11.2 mmol). The reaction mixture was stirred at 22 °C for 13 h in the dark, and concentrated *in vacuo*. To a suspension of the residue in THF (10 mL) was added DBU (0.33 mL, 2.21 mmol) at 0 °C. After stirring at 22 °C for 21

h, the reaction was quenched by saturated NH_4Cl (10 mL) at 0 °C, and the aqueous layer was extracted with Et_2O (3 x 20 mL). The residue was dried over $MgSO_4$, concentration *in vacuo*, and flash chromatography (SiO_2, hexane–AcOEt, 10:1) afforded α,β-unsaturated lactam **5** (234 mg, 74%); colorless oil; $[\alpha]_D^{20}$ -92.8 (*c* 0.90, $CHCl_3$); ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.96 (3H, d, *J* = 6.4 Hz), 1.01 (3H, d, *J* = 6.2 Hz), 1.37-1.51 (2H, m), 2.14 (1H, dd, *J* = 9.4, 13.8 Hz), 2.49 (1H, dd, *J* = 2.9, 14.3 Hz), 3.28 (1H, dd, *J* = 8.4, 15.0 Hz), 3.90 (1H, dd, *J* = 1.5, 15.0 Hz), 5.26 (1H, d, *J* = 12.5 Hz), 5.32 (1H, d, *J* = 12.5 Hz), 5.42 (1H, d, *J* = 1.0 Hz), 5.85 (1H, d, *J* = 1.3 Hz), 7.27-7.45 (5H, m); IR (neat) 3416, 3034, 2959, 2931, 2878, 1767, 1711, 1455, 1379, 1353, 1273, 1189, 1079, 1008, 904, 788, 737, 697 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{17}H_{21}NO_3$ (M^+) 287.1521, found: 287.1518.

(6-*tert*-Butyldimethylsiloxyhexanoyl)-(4'*R*)-benzyl-2'-oxazolidinone (15). To a solution of **14** (15.4 g, 63.0 mmol) in CH_2Cl_2 (157 mL) were added Et_3N (24 mL, 73.0 mmol) and pivaloyl chloride (24 mL, 176 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min, a solution of LiCl (6.29 g, 125 mmol), prepared by drying at 200 °C for 2 h, and (*R*)-benzyloxazolidinone (14.5 g, 81.9 mmol) in THF (157 mL) was added, and stirring was continued at rt for 4.5 h. The mixture was diluted with saturated $NaHCO_3$ (200 mL), and extracted with Et_2O (200 mL x 3). Drying over $MgSO_4$, concentration *in vacuo*, and flash chromatography (SiO_2, hexane–AcOEt, 20:1) gave **15** (18.4 g, 45.0 mmol, 72%); $[\alpha]_D^{22}$ -36.0 (*c* 1.01, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.05 (6H, s), 0.89 (9H, s), 1.41-1.47 (2H, m), 1.52-1.61 (2H, m), 1.67-1.75 (2H, m), 2.76 (1H, dd, *J* = 9.6, 13.6 Hz), 2.88-3.00 (2H, m), 3.30 (1H, dd, *J* = 3.2, 13.2 Hz), 3.62 (2H, t, *J* = 6.0 Hz), 4.14-4.22 (2H, m), 4.64-4.69 (1H, m), 7.19-7.34 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.2, 18.5, 24.3, 25.3, 26.1, 32.6, 35.7, 38.1, 55.3, 63.1, 66.3, 128.4, 129.4, 129.7, 135.4, 153.4, 173.2; IR (neat) 2942, 1787, 1492, 1089 cm^{-1}; MS (EI) *m/z* 362 (100), 405 (M^+); HRMS (EI) calcd for $C_{22}H_{35}NO_4Si$ (M^+) 405.2336, found 405.2339.

(2*R*)-(6-*tert*-Butyldimethylsiloxy-2-methylhexanoyl)-(4'*R*)-benzyl-2'-oxazolidinone. To a solution of **15** (18.4 g, 45.0 mmol) in THF (450 mL) was added NaHMDS (1.0 M THF, 49.5 mL, 49.5 mmol) at -78 °C. After stirring for 1 h, MeI (13.7 mL, 224 mmol) was added and stirring was continued for 2 h. The reaction was quenched by saturated NH_4Cl (500 mL) and extracted with Et_2O (400 mL x 3). Drying over $MgSO_4$, concentration *in vacuo*, and the flash chromatography (SiO_2, hexane–AcOEt, 10:1) gave methyl product (17.1 g, 40.8 mmol, 91%); colorless oil; $[\alpha]_D^{22}$ -44.4 (*c* 1.44, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.03 (6H, s), 0.88 (9H, s), 1.22 (3H, d, *J* = 6.9 Hz), 1.34-1.38 (2H, m), 1.40-1.52 (2H, m), 1.70-1.77 (2H, m), 2.76 (1H, dd, *J* = 9.9 Hz, 13.0 Hz), 3.26 (1H, dd, *J* = 3.0, 13.0 Hz), 3.59 (2H, t, *J* = 6.3 Hz), 3.71 (1H, d, *J* = 6.6 Hz), 4.11-4.22 (2H, m), 4.63-4.70 (1H, m), 7.20-7.36 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.2, 17.4, 18.4, 23.6, 26.0, 32.9, 33.0, 37.7, 37.9, 55.4, 63.0, 66.0, 127.6, 129.0, 129.5, 135.4, 153.1, 177.3; IR (neat) 3752, 2940, 2861, 1712, 1535, 1463, 1251, 1101, 838, 777 cm^{-1}; MS (EI) *m/z* 419 (M^+); HRMS (EI) calcd for $C_{23}H_{37}NO_4Si$ (M^+) 419.2492, found 419.2480.

(*R*)-6-*tert*-Butyldimethylsiloxy-2-methylhexan-1-ol (16). To a suspension of $NaBH_4$ (252 mg, 6.60 mmol) in water (3 mL) was added a solution of methyl compound (465 mg, 1.18 mmol) in THF (9 mL), and the mixture was stirred at rt for 26 h. The reaction mixture was diluted with saturated NH_4Cl (10 mL), and extracted with Et_2O (10 mL x 3). Drying over $MgSO_4$, concentrated *in vacuo*, and the residue was purified by flash chromatography (SiO_2, hexane–AcOEt, 10:1) to give the alcohol **16** (245 mg, 0.99 mmol, 90%); colorless oil; $[\alpha]_D^{23}$ +6.4 (*c* 1.10, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.05 (6H, s), 0.89 (9H, s), 0.90 (3H, d, *J* = 4.5 Hz), 1.07-1.18 (1H, m), 1.24-1.33 (2H, m), 1.36-1.43 (2H, m), 1.46-1.62 (2H, m), 3.42 (1H, t, *J* = 6.0 Hz), 3.50 (1H, t, *J* = 6.0 Hz), 3.61 (2H, t, *J* = 6.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.1, 16.7, 18.5, 23.3, 26.1, 33.0, 33.2, 35.9, 63.2, 68.4; IR (neat) 3347, 2935, 2861, 1461, 1251, 1099, 1043, 840, 777 cm^{-1}; MS (FAB) *m/z* 247; HRMS (FAB) calcd for $C_{13}H_{31}O_2Si$ $[(M+H)^+]$ 247.2119, found 247.2106.

(*R*)-6-*tert*-Butyldimethylsiloxy-2-methylhexylmethanesulfonate. To a solution of **16** (351 mg, 1.42 mmol) in CH_2Cl_2 (14.2 mL) were added Et_3N (0.60 mL, 4.26 mmol) and MsCl (0.16 mL, 21.3 mmol). The mixture was stirred at rt for 1 h. The mixture was diluted with brine (15 mL), and extracted with Et_2O (20 mL x 2). Drying over $MgSO_4$, concentration *in vacuo*, and the flash chromatography (SiO_2, hexane–AcOEt = 4:1) afforded mesylate (451 mg, 1.39 mmol, 98%); pale yellow oil; $[\alpha]_D^{24}$ +0.2 (*c* 0.88, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.05 (6H, s), 0.84 (9H, s), 0.94 (3H, d, *J* = 6.6 Hz), 1.16-1.53 (6H, m), 1.88 (1H, q, *J* = 6.6 Hz), 2.55 (3H, s), 3.56 (2H, t, *J* = 6.0 Hz), 3.95-4.06 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.0, 16.2, 18.9, 22.8, 25.8, 32.4, 32.7, 32.9, 37.0, 62.7, 74.3; IR (neat) 3226, 2711, 1745, 1689, 1644, 1525, 970 cm^{-1}; MS (EI) *m/z* 150 (100), 325 $[(M+H)^+]$; HRMS (EI) calcd for $C_{14}H_{33}O_4SSi$ $[(M+H)^+]$ 325.1869, found 325.1862.

(*R*)-1-Azido-6-*tert*-butyldimethylsiloxy-2-methylhexane. To a solution of mesylate (451 mg, 1.39 mmol) in DMF (14 mL) was added NaN_3 (136 mg, 2.10 mmol), and the mixture was stirred at 80 °C for 10 h. The reaction mixture was diluted brine (15 mL) at 0 °C, and extracted with hexane (20 mL x 3). Drying over $MgSO_4$, concentration *in vacuo*, and flash chromatography (SiO_2, hexane-EtOAc = 20:1) furnished azide (364 mg, 1.34 mmol, 97%); pale yellow oil; $[\alpha]_D^{22}$ +2.0 (*c* 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.05 (6H, s), 0.89 (9H, s), 0.95 (3H, d, *J* = 6.6 Hz), 1.08-1.60 (1H, m), 1.70-1.76 (1H, m), 3.07-3.24 (2H, m), 3.61 (2H, t, *J* = 6.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.1, 17.8, 18.5, 23.2, 26.1, 33.1, 33.7, 34.0, 57.9, 63.1; IR (neat) 2935, 2861, 2098, 1463, 1386, 1255, 1101, 1008, 950, 840, 775 cm^{-1}; MS (FAB) *m/z* 272 (M^++H); HRMS (FAB) calcd for $C_{13}H_{30}N_3OSi$ $[(M+H)^+]$ 272.2159, found 272.2159.

(*R*)-5-(Azidomethyl)hexan-1-ol (17). To a solution of azide (364 mg, 1.34 mmol) in THF (13.4 mL) was added TBAF (1.0 M solution in THF, 2.01 mL, 2.01 mmol) at 0 °C, and the mixture was stirred at rt for 1.5 h. The reaction mixture was diluted with saturated $NaHCO_3$ (15 mL) and extracted with Et_2O (20 mL

x 3). Drying over $MgSO_4$, concentration *in vacuo*, and flash chromatography (SiO_2, hexane–AcOEt, 5:1) gave **17** (300.4 mg, 1.34 mmol, 100%); yellow oil; $[\alpha]_D^{22}$ +3.9 (*c* 1.22, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (3H, d, *J* = 6.9 Hz), 1.10-1.82 (7H, m), 2.04 (1H, t, *J* = 6.9 Hz), 3.09-3.24 (2H, m), 3.66 (2H, t, *J* = 6.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 62.8, 57.8, 34.0, 33.7, 33.0, 23.2, 17.7; IR (neat) 3421, 2927, 2097, 1681, 1455, 1290, 948 cm^{-1}.

(*R*)-6-Azido-5-methylhexanoic acid (18). To a solution of alcohol **17** (3.60 g, 22.9 mmol) in AcOEt (229 mL) were added TEMPO (179 mg, 1.15 mmol), aqueous Na_2HPO_4 (0.4 mol, l, 36 mL), and aqueous NaOCl (>5 %, 42 mL, 34.3 mmol), and the mixture was stirred for 1 h. To the mixture were then added aqueous NaH_2PO_4 (0.5 g / 10 mL, 36 mL) and $NaClO_2$ (3.09 g, 34.3 mmol) at 0 °C, and stirring was continued at rt for 3.5 h. The reaction mixture was diluted with brine (200 mL) and extracted with AcOEt (200 mL x 3), washed with saturated $Na_2S_2O_3$ (150 mL). Drying over $MgSO_4$, concentration *in vacuo*, and flash chromatography (SiO_2, hexane–AcOEt, 5:1) afforded **18** (3.50 g, 20.3 mmol, 89%); yellow oil; $[\alpha]_D^{24}$ +5.3 (*c* 1.10, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.97 (3H, d, *J* = 6.9 Hz), 1.19-1.28 (2H, m), 1.40-1.52 (2H, m), 1.59-1.77 (1H, m), 3.11-3.25 (2H, m), 3.36 (2H, t, *J* = 7.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.6, 22.1, 33.5, 33.5, 34.2, 57.8, 179.9; IR (neat) ν_{max} 2929, 2669, 1708, 1454, 1417, 1278, 1106, 941, 767 cm^{-1}; MS (FAB) *m/z* 172.2 (100) (M^++H); HRMS (FAB) calcd for $C_7H_{14}N_3O_2$ (M^++H) 172.1086, found 172.1087.

(*R*)-Pentafluorophenyl 6-azido-5-methylhexanoate. To a solution of EDCI (251 mL, 1.31 mmol) and DMAP (10.6 mg, 0.0880 mmol) in CH_2Cl_2 (5 mL) were added a solution of **18** (150 mg, 0.874 mmol) in CH_2Cl_2 (1.7 mL) and pentafluorophenol (242 mg, 1.31 mmol) in CH_2Cl_2 (1.7 mL), and the mixture was stirred at rt for 4 h. The reaction mixture was diluted with saturated NH_4Cl (10 mL) at 0 °C, and extracted with Et_2O (20 x 2 mL). Drying over $MgSO_4$, concentration *in vacuo*, and flash chromatography (SiO_2, hexane) afforded pentafluorophenyl ester (188 mg, 0.552 mmol, 63%); pale yellow oil; $[\alpha]_D^{22}$ +5.7 (*c* 1.11, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.00 (3H, d, *J* = 6.6 Hz), 1.22-1.35 (2H, m), 1.48-1.58 (1H, m), 1.69-1.90 (2H, m), 2.68 (2H, t, *J* = 7.2 Hz), 3.20 (2H, t, *J* = 5.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.4, 22.2, 33.2, 33.3, 33.4, 57.6, 136.6, 139.3, 139.2, 141.1, 169.1; IR (neat) ν_{max} 2931, 2100, 1789, 1519, 1461, 1369, 1280, 1087, 998, 879 cm^{-1}; MS (EI) *m/z* 154 (100), 337 (M^+). HRMS (EI) calcd for $C_{13}H_{13}F_5N_3O_2$ (M^++H) 338.0928, found 338.0917.

(*R*)-6-Methylazepan-2-one (19). A suspension of pentafluorophenyl ester (5.80 g, 17.2 mmol) and 10% Pd-C (0.91g, 0.86 mmol) in THF (688 mL) was stirred under H_2 atmosphere at rt for 22 h. The mixture was filtered through a Celite pad, and the filtrate was concentrated *in vacuo*. The residue was purified by flash chromatography (SiO_2, hexane–EtOAc, 1:1 to EtOAc) gave lactam **19** (1.34 g, 10.7 mmol, 62%); needles; mp 100-102 °C; $[\alpha]_D^{24}$ -20.2 (*c* 0.65, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.92 (3H, d, *J* = 6.9

Hz), 1.31-1.39 (1H, m), 1.53-1.75 (1H, m), 1.75-1.99 (3H, m), 2.45 (2H, dd, *J* = 4.2, 7.8 Hz), 3.03 (2H, t, *J* = 5.4 Hz), 5.83 (1H, br);^{13}C NMR (100 MHz, $CDCl_3$) δ 19.4, 22.2, 34.3, 36.7, 39.8, 49.0, 178.9; IR (neat) ν_{max} 3438, 2921, 2063, 1654, 1448, 1315, 1226, 1118, 763 cm^{-1}; MS (EI) *m/z* 127 (100) (M^+); HRMS (EI) calcd for $C_7H_{13}NO$ 127.0997, found 127.0987.

(*R*)-Benzyl 6-methyl-2-oxoazepane-1-carboxylate (20). To a solution of **19** (11.9 g, 9.4 mmol) in THF (94 mL) was added *n*BuLi (1.58 M solution in hexane, 7.15 mL, 11.3 mmol) at -78 °C, and stirred for 30 min. To the mixture was added CbzCl (1.72 mL, 11.7 mmol), and stirring was continued at that temperature for 3 h. The reaction mixture was diluted with saturated NH_4Cl (100 mL), and extracted with CH_2Cl_2 (150 mL x 3). Drying over $MgSO_4$, concentration *in vacuo*, and flash chromatography (SiO_2, hexane–AcOEt, 5:1) afforded **20** (2.02 g, 9.3 mmol, 99%); colorless oil; $[\alpha]_D^{24}$ -62.6 (*c* 0.95, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (3H, d, *J* = 6.9 Hz), 1.25-1.35 (1H, m), 1.62-1.84 (2H, m), 1.84-1.92 (2H, m), 2.66 (2H, t, *J* = 4.8 Hz), 3.36 (1H, dd, *J* = 8.7, 15.0 Hz), 3.98 (1H, d, *J* = 15.0 Hz), 5.28 (2H, s), 7.31-7.44 (5H, m), ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.1, 22.0, 33.5, 37.1, 39.0, 51.7, 68.3, 127.6, 128.0, 128.3, 135.3, 154.2, 175.2; IR (neat) 3735, 2925, 1764, 1708, 1455, 1376, 1278, 1774 cm^{-1}; MS (EI) *m/z* 261 (M^+).

(*R*)-Benzyl 6-methyl-3-methylene-2-oxoazepane-1-carboxylate (13). To a solution of **20** (100 mg, 0.383 mmol) in CH_2Cl_2 (3.8 mL) were added *i*Pr_2EtN (0.175 mL, 7.65 mmol) and TBSOTf (0.24 mL, 0.765 mmol), and the mixture was refluxed for 3 h. The reaction mixture was diluted with saturated $NaHCO_3$ (5 mL) and extracted with hexane (10 mL x 3). Drying over $MgSO_4$, concentration *in vacuo*, and flash chromatography (SiO_2, hexane–AcOEt, 50:1, 1% Et_3N) afforded silyl ether (134 mg, 0.356 mmol, 93%); colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.06 (6H, s), 0.82-1.02 (13H, m), 1.60-1.72 (1H, m), 1.72-1.82 (1H, m), 1.90-2.10 (2H, m), 2.52 (1H, brs), 3.90 (1H, brs), 4.74 (1H, t, *J* = 6.0 Hz), 5.16 (2H, s), 7.31-7.35 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.2, 18.1, 19.5, 25.6, 33.8, 35.1, 53.3, 68.4, 77.9, 101.2, 126.9, 127.9, 128.1, 128.4, 132.5, 177.9; IR (neat) 2937, 1716, 1671, 1594, 1396, 1336, 1247, 1178, 1089, 840 cm^{-1}.

To a suspension of Eschenmoser's salt (620 mg, 1.79 mmol) in CH_2Cl_2 (10 mL) was added a solution of silyl enol ether (560 mL, 1.49 mmol) in CH_2Cl_2 (5 mL) and the mixture was stirred at rt for 11 h. To the mixture was diluted with 1.0 M NH_3 (12 mL) and extracted with AcOEt (15 mL x 3). Drying over $MgSO_4$ and concentration *in vacuo* gave a crude amine (623 mg) as pale yellow oil.

To a solution of the crude amine (623 mg) was added MeI (5.0 mL, 59.6 mmol), and the mixture was stirred at rt for 42 h in the dark, and concentrated in *vacuo*. The residue was dissolved in THF (15 mL), and stirred at rt for 42 h. To the mixture was added $NaHCO_3$ (1.25 g, 14.9 mmol), and stirring was continued for 49 h. The mixture was diluted with saturated NH_4Cl (12 mL), and extracted with Et_2O (15 mL x 3). Drying over $MgSO_4$, concentration *in vacuo*, and flash chromatography (SiO_2, hexane–AcOEt,

5:1 to $CHCl_3$–MeOH, 20:1) afforded **13** (203.8 mg, 0.75 mmol, 50%); $[\alpha]_D^{24}$ -76.4 (*c* 0.67, EtOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.93 (3H, d, *J* = 6.8 Hz), 1.29-1.42 (1H, m), 1.80-1.97 (2H, m), 2.28-2.37 (1H, m), 2.53 (1H, dq, *J* = 3.3, 14.4 Hz), 3.18 (1H, dd, *J* = 9.0, 15.0 Hz), 3.94 (1H, d, *J* = 14.4 Hz), 5.26 (1H, d, *J* = 12.7 Hz), 5.32 (1H, d, *J* = 12.7 Hz), 5.43 (1H, s), 5.82 (1H, s), 7.45-7.30 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 18.7, 31.0, 33.2, 374.2, 51.9, 68.3, 123.9, 127.7, 128.1, 128.5, 135.6, 146.4, 154.2, 172.2; IR (neat) 2929, 1764, 1712, 1452, 1378, 1274, 1158, 1081, 1012, 782 cm^{-1}; MS (EI) *m/z* 91 (100), 273 (M^+); HRMS (EI) calcd for $C_{16}H_{19}NO_3$ 273.1365, found 273.1348.

(6*R*,10*R*,11*S*)-3,10,11-Trimethyl-8-benzyloxycarbonyl-10,11-dimethyl-8-azaspiro[5.6]dodec-2-en-7-one (21): colorless oil; $[\alpha]_D^{25}$ -50.4 (*c* 0.24, $CHCl_3$); ^{1}H-NMR (C_6D_6, 400 MHz) δ 0.64 (3H, d, *J* = 6.9 Hz), 0.80 (3H, d, *J* = 6.8 Hz), 1.03-0.93 (1H, m), 1.21-1.05 (2H, m), 1.35 (1H, d, *J* = 12.7 Hz), 1.54 (3H, s), 1.57-1.46 (1H, m), 1.87-1.71 (2H, m), 1.90-1.87 (1H, m), 2.02 (1H, ddd, *J* = 6.1, 9.5, 13.2 Hz), 2.77-2.68 (1H, m), 3.41 (1H, dd, *J* = 5.9, 15.1 Hz), 3.68 (1H, dd, *J* = 2.9, 15.1 Hz), 5.16 (1H, d, *J* = 12.7 Hz), 5.22 (1H, d, *J* = 12.7 Hz), 5.26-5.23 (1H, m), 7.05-6.99 (1H, m), 7.14-7.08 (2H, m), 7.40-7.37 (2H, m); ^{13}C-NMR (C_6D_6, 100 MHz) δ 17.7, 21.8, 23.2, 27.3, 32.4, 34.1, 35.0, 40.3, 40.9, 46.7, 49.2, 68.2, 119.0, 127.7, 128.0, 128.2, 128.5, 132.7, 155.9, 179.8; IR (neat) 2959, 2925, 1711, 1447, 1379, 1271, 1202, 1161, 1081, 989 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{22}H_{29}NO_3$ (M^+) 355.2147, found 355.2146.

(*E*)-1-(*tert*-Butyldimethylsiloxy)-4-(4-methoxybenzyloxymethyl)penta-2,4-diene (22): a colorless oil; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 0.08 (6H, s), 0.80 (9H, s), 3.81 (3H, s), 4.16 (2H, s), 4.24 (2H, dd, *J* = 1.5, 5.6 Hz), 4.45 (2H, s), 5.15 (1H, brs), 5.23 (1H, brs), 5.88 (1H, dt, *J* =16.0, 5.0 Hz), 6.28 (1H, d, *J* =16.0 Hz), 6.80 (2H, d, *J* = 8.1 Hz), 7.19 (2H, d, *J* = 8.1 Hz).

(*E*)-(5-(4-Methoxybenzyloxymethyl)-1-(trimethylsilyl)hexa-3,5-dien-1-yne (24): colorless oil; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.19 (9H, s), 3.81 (3H, s), 4.12 (2H, s), 4.42 (2H, s), 5.27 (1H, s), 5.32 (1H, s), 5.80 (1H, d, *J* = 16.5 Hz), 6.67 (1H, d, *J* = 16.5 Hz), 6.88 (2H, d, *J* = 8.8 Hz), 7.25 (2H, d, *J* = 8.8 Hz); IR ν_{max} (neat) 2958, 1613, 1464, 1442, 1366, 1151, 1082 cm^{-1}.

(1*R*,3*R*,4*R*,5*R*,6*S*)-7-[3-(*tert*-Butyldimethylsiloxymethyl)-buta-1,3-dienyl]-4-[2-(trimethylsilyl)ethoxy-methoxy]-3-methyl-1-(2-phenylethyl)dioxabicyclo[3.2.1]octane (26): colorless oil; $[\alpha]_D^{24}$ +43.1 (*c* 0.65, $CHCl_3$); ^{1}H-NMR (C_6D_6, 300 MHz) δ 7.21-7.03 (5H, m), 6.53 (1H, d, *J* = 16.2 Hz), 5.91 (1H, dd, *J* = 5.4, 16.2 Hz), 5.32 (1H, s), 5.05 (1H, s), 4.79 (1H, d, *J* = 7.0 Hz), 4.69-4.61 (3H, m), 4.30 (2H, s), 3.87 (1H, dt, *J* = 8.6, 9.4 Hz), 3.66 (1H, dt, *J* = 8.6, 9.4 Hz), 3.55-3.53 (1H, m), 3.12-2.95 (2H, m), 2.53-2.37 (1H, m), 2.24-2.10 (2H, m), 1.67 (1H, dd, *J* = 11.6, 12.8 Hz), 1.58 (1H, dd, *J* = 6.2, 12.8 Hz), 1.04-0.92 (5H, m), 0.99 (9H, s), 0.06 (6H, s), 0.00 (9H, s); IR (neat) ν_{max} 2953, 2928, 2857, 1466, 1378, 1251, 1101, 1056, 1033, 837 cm^{-1}; HRMS (EI) calcd for $C_{32}H_{54}O_5Si_2$ (M^+): 574.3510, found 574.3509.

(8*R*,9*R*,10*S*,*E*)-2,2,16,16,17,17-Hexamethyl-13-methylene-8-((*S*)-1-phenylsulfonylpropan-2-yl)-9,10-bis(triethylsiloxy)-5,7,15-trioxa-2,16-disilaoctadec-11-ene (27): colorless oil; ^{1}H-NMR ($CDCl_3$, 300

MHz) δ 0.00 (9H, s), 0.08 (6H, s), 0.48-0.58 (12H, M), 0.85-0.92 (29H, m), 1.23 (3H, d, *J* = 6.8 Hz), 2.35-2.56 (1H, m), 2.97 (1H, dd, *J* = 10.5, 14.4 Hz), 3.48-3.56 (2H, m), 3.63-3.72 (2H, m), 3.80-3.91 (2H, m), 4.29 (2H, s), 4.57 (1H, d, *J* = 6.6 Hz), 4.63 (1H, d, *J* = 6.6 Hz), 5.08 (1H, brs), 5.34 (1H, brs), 5.44 (1H, dd, *J* = 15.9, 8.1 Hz), 6.10 (1H, d, *J* = 15.9 Hz), 6.10 (1H, d, *J* = 15.9 Hz), 7.51-7.65 (3H, m), 7.89-7.92 (2H, m); IR (neat) ν_{max} 3066, 2736, 1612, 1462, 1413, 1306, 1249, 1189, 1104, 970, 939, 897, 743, 689 cm^{-1}.

(*E*)-1-*tert*-Butyldimethylsiloxy-4-((4*S*,5*S*)-2,2-dimethyl-5-((1*R*,2*S*)-2-methyl-3-phenylsulfonyl-1-((2-(trimethylsilyl)ethoxy)methoxy)propyl)-1,3-dioxolan-4-yl)-2-methylenebut-3-ene (28): colorless oil; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.00 (9H, s), 0.07-0.09 (6H, s), 0.84-0.91 (11H, m), 1.17 (3H, d, *J* = 7.0 Hz), 1.29 (3H, s), 1.42 (3H, s), 2.52-2.67 (1H, m), 3.06 (1H, dd, *J* = 14.5, 8.3 Hz), 3.39-3.64 (4H, m), 4.10 (1H, dd, *J* = 8.4, 6.1 Hz), 4.30 (2H, s), 4.48 (1H, d, *J* = 6.8 Hz), 4.53 (1H, d, *J* = 6.8 Hz), 4.60 (1H, dd, *J* = 8.4, 7.7 Hz), 5.11 (1H, brs), 5.32 (1H, brs), 5.60 (1H, dd, *J* = 16.3, 7.7 Hz), 6.27 (1H, d , *J* = 16.3 Hz), 7.53-7.67 (3H, m), 7.91-7.93 (2H, m).

(*R*,*E*)-1-*tert*-Butyldimethylsiloxy-4-(2,2-dimethyl-1,3-dioxolan-4-yl)-2-methylenebut-3-en-1-ol (29): colorless oil; ^{1}H-NMR ($CDCl_3$, 300 MHz) δ 0.13 (6H, s), 0.92 (9H, s), 1.40 (3H, s), 1.44 (3H, s), 3.60 (1H, t, *J* = 8.3 Hz), 4.10 (1H, dd, *J* = 6.3, 8.3 Hz), 4.32 (2H, s), 4.52 (1H, q, *J* = 6.8 Hz), 5.13 (1H, s), 5.35 (1H, s), 5.60 (1H, dd, *J* = 7.8, 16.1 Hz), 6.34 (1H, d, *J* = 16.1 Hz); IR (neat) ν_{max} 2986, 2930, 2958, 1749, 1613, 1472, 1462, 1379, 1370, 1252, 1157, 1115, 1061, 1028, 1006, 965, 939, 902, 836, 776, 668 cm^{-1}.

Preparation of [Cu((*S*,*S*)-*t*BuBOX)]Cl_2. The mixture of (*S,S*)-*t*BuBOX (1.0 g, 3.4 mmol) in CH_2Cl_2 (13.6 mL) was stirred at rt for 3 h. Concentration of the reaction mixture afforded Cu((*S,S*)-*t*BuBOX)]Cl_2·CH_2Cl_2 (1.46 g) as green solid.

Preparation of [Cu((S,S)-*t*BuBOX)]$(SbF_6)_2$ (4b). A flask was charged with MS-3A (100 mg) prepared by heating at 200 °C for 3 h, [Cu((*S,S*)-*t*BuBOX)]Cl_2·CH_2Cl_2 (525 mg, 1.0 mmol) and $AgSbF_6$ (705 mg, 2.1 mmol) in a glove box under N_2 atmosphere, and CH_2Cl_2 (6 mL) was added to the mixture. After stirring at rt for 3 h in the dark, the mixture was centrifuged at 1000 rpm for 3 min and the resulting green supernatant was used for the asymmetric Diels-Alder reaction as 0.167 M solution of **4b** in CH_2Cl_2.

(1*S*,6*R*,10*R*,11*S*)-8-Benzyloxycarbonyl-1-(*tert*-butyldimethylsiloxymethyl)-3-(4-methoxybenzyloxy-methyl)-10,11-dimethyl-8-azaspiro[5.6]dodec-2-en-7-one (23). To a solution of dienophile **5** (736 mg, 2.56 mmol) and diene **22** (892 mg, 2.56 mmol) in CH_2Cl_2 (10 mL) was added **4b** (0.167 M solution in hexane, 6.0 mL, 1.0 mmol) at -78 °C. After 10 min, the mixture was gradually allowed to rt, and stirring was continued for 72 h. The reaction mixture was directly subjected to short column chromatography (SiO_2, hexane–AcOEt = 4:1) to remove copper reagent, and the eluent was concentration. The residue was purified by chromatography (SiO_2, hexane–AcOEt, 10:1 to 4:1) to afford spirocyclic product **23** (1.15 g,

71%); colorless oil; $[\alpha]_D^{23}$ +55.0 (*c* 0.18, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 0.05 (3H, s), 0.08 (3H, s), 0.89 (9H, s), 0.97 (3H, d, *J* = 6.6 Hz), 0.98 (3H, d, *J* = 4.8 Hz), 1.19-1.42 (3H, m), 1.57 (1H, d, *J* = 14.0 Hz), 1.75 (1H, dt, *J* = 12.3, 9.6 Hz), 1.97 (1H, dt, *J* = 12.3, 3.9 Hz), 2.10-2.15 (2H, m), 3.32 (1H, d, *J* = 9.0 Hz), 3.35 (1H, d, *J* = 9.0 Hz), 3.71-3.82 (2H, m), 3.80 (3H, s), 3.91 (2H, brs), 4.00 (1H, d, *J* = 15.0 Hz), 4.38 (2H, s), 5.23 (1H, d, *J* = 12.3 Hz), 5.28 (1H, d, *J* = 12.3 Hz), 5.75 (1H, brs), 6.84-6.89 (2H, m), 7.23-7.43 (7H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.5, -5.2, 17.3, 18.3, 20.8, 23.1, 25.9, 33.3, 34.9, 36.2, 40.5, 46.2, 48.3, 49.4, 55.2, 62.9, 68.5, 71.1, 73.8, 113.7, 125.0, 128.0, 128.1, 128.4, 129.3, 130.5, 133.6, 135.6, 155.6, 159.1, 177.4; IR (neat) 2289, 2254, 1685, 1612, 1586, 1513, 1462, 1448, 1349, 1249, 1169, 1081, 911, 837, 776, 734, 595 cm^{-1}; HRMS (FAB) calcd for (M^++H) 636.3721, found 636.3732.

(1*S*,6*R*,10*R*,11*S*)-8-Benzyloxycarbonyl-3-((4-methoxybenzyloxymethyl)-10,11-dimethyl-1-(trimethylsilylethynyl)-8-azaspiro[5.6]dodec-2-en-7-one (25): colorless oil; $[\alpha]_D^{23}$ +9.0 (*c* 1.1, $CHCl_3$); ^1H-NMR ($CDCl_3$, 300 MHz) δ 0.11 (9H, s), 0.95 (3H, d, *J* = 6.6 Hz), 0.97 (3H, d, *J* = 6.0 Hz), 1.26-1.32 (1H, m), 1.41 (1H, dd, *J* = 14.4, 11.1 Hz), 1.62-1.70 (2H, m), 1.78 (1H, d, *J* = 14.4, 11.1 Hz), 1.98 (1H, dt, *J* = 13.2, 3.9 Hz), 2.11-2.13 (2H, m), 3.75 (1H, dd, *J* = 15.0, 3.0 Hz), 3.80 (3H, s), 3.87 (2H, s), 4.00 (1H, dd, *J* = 15.0, 2.4 Hz), 4.08 (1H, brs), 4.37 (2H, s), 5.25 (2H, s), 5.58 (1H, brs), 6.88 (2H, d, *J* = 8.6 Hz), 7.25 (2H, d, *J* = 8.6 Hz), 7.30-7.42 (5H, m); IR (neat) 3400, 2959, 2871, 2170, 1960, 1880, 1767, 1716, 1612, 1513, 1456, 1376, 1335, 1303, 1249, 1207, 1172, 1145, 1086, 1036, 991, 923, 842, 758 cm^{-1}.

(1*S*,6*R*,10*R*,11*S*)-1-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-8-benzyloxycarbonyl-3-(4-methoxybenzyloxymethyl)-10,11-dimethyl-8-azaspiro[5.6]dodec-2-en-7-one (30): colorless oil; ^1H-NMR ($CDCl_3$, 300 MHz) δ 0.07 (6H, s), 0.91 (9H, s), 0.91-0.95 (6H, m), 1.27 (3H, s), 1.38 (3H, s), 1.66-1.76 (1H, m), 1.98-2.11 (2H, m), 3.21 (1H, brs), 3.66 (1H, t, *J* = 8.1 Hz), 3.79 (1H, d, *J* = 15.0 Hz), 3.93-4.13 (4H, m); 4.32 (1H, t, *J* = 7.0 Hz), 5.24 (1H, d, *J* = 12.5 Hz), 5.29 (1H, d, *J* = 12.5 Hz), 5.60 (1H, brs), 7.29-7.43 (5H, m); IR (neat) 2930, 1763, 1720, 1498, 1456, 1378, 1335, 1212, 1086, 926, 836, 758, 697, 666 cm^{-1}.

(1*S*,6*R*,10*R*)-8-Benzyloxycarbonyl-1-(*tert*-butyldimethylsiloxymethyl)-3-(4-methoxybenzyloxymethyl)-10-methyl-8-azaspiro[5.6]dodec-2-en-7-one (33): colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 0.00 (6H, d, *J* = 0.8 Hz), 0.85 (9H, s), 0.93 (3H, d, *J* = 6.4 Hz), 1.32-1.47 (2H, m), 1.72-2.14 (7H, m), 3.47-3.73 (4H, m), 3.80 (3H, s), 3.85 (2H, s), 4.36 (2H, s), 5.17 (1H, d, *J* = 12.8 Hz), 5.26 (1H, d, *J* = 12.8 Hz), 5.58 (1H, s, 1H), 6.87 (2H, d, *J* = 8.4 Hz), 7.24 (2H, d, *J* = 8.4 Hz, 2H), 7.28-7.38 (5H, m); IR (neat) 2942, 2859, 1714, 1612, 1511, 1461, 1378, 1253, 1089, 840, 777 cm^{-1}; MS (EI) *m/z* 121 (100), 487 (M^+); HRMS (EI) calcd for $C_{28}H_{45}NO_4Si$ (M^+) 487.3118, found 487.3113.

4-Allyloxy-1-*tert*-butyldimethylsiloxybut-2-yn (34). To a solution of KOH (6.47 g, 115 mmol) in DMSO (57 mL) was added 2-butyne-1,4-diol (9.94 g, 115 mmol) and allyl bromide (2 mL, 23.1 mmol) at rt. After stirring at rt for 12 h, the mixture was diluted with 6 M HCl at 0 °C, extracted with CH_2Cl_2, dried and concentrated. The residue was diluted with Et_2O, and washed with H_2O (40 mL). The residue was

subjected to the chromatography to give allyl ether (2.74 g, 27.7 mmol, 94%).

To a solution of the above-mentioned allyl ether (1.0 g, 7.93 mmol) in CH_2Cl_2 (80 mL) were added imidazole (1.62 g, 23.8 mmol) and TBSCl (11.9 mmol) at 0 °C. The mixture was stirred at rt for 12 h, and the mixture was diluted with saturated NH_4Cl (80 mL), extracted with Et_2O (100 mL x 3), dried, and concentrated. The residue was purified flash chromatography (SiO_2, hexane–AcOEt = 100:1 to 20:1) gave **34** (2.29 g, quant); colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.13 (6H, s), 0.90 (9H, s), 4.05 (2H, td, *J* = 1.2, 5.7 Hz), 4.19 (2H, t, *J* = 1.5 Hz), 4.36 (2H, t, *J* = 1.8 Hz), 5.25 (2H, dddd, *J* = 1.5, 3.3, 13.2, 18.9 Hz), 5.97-5.84 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ -5.0, 18.4, 25.9, 51.6, 57.7, 70.5, 80.7, 85.0, 117.6, 134.0; IR (neat) 2940, 2857, 1461, 1357, 1255, 1130, 1081, 927, 838 cm^{-1}; MS (EI) *m/z* 75 (100), 240 (M^+); HRMS (EI) calcd for $C_{13}H_{25}O_2Si$ (M^+) 240.1545, found 240.1521.

(*Z*)-3-(2-*tert*-Butyldimethylsiloxyethylidene)-4-methylenetetrahydrofuran (35). To a solution of $[IrCl(cod)]_2$ in toluene (5 mL) were added AcOH (19 □L) and a solution of **34** (500 mg, 2.08 mmol) in toluene (5 mL), and the mixture was stirred at 80 °C for 10 min. The reaction was quenched by saturated $NaHCO_3$ (10 mL), and the mixture was extracted with Et_2O (20 x 3), dried, and concentration. The residue was purified by chromatography (SiO_2, hexane–AcOEt, 30:1) to afford spirocyclic product **35** (383 mg, 1.59 mmol, 77%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.13 (6H, s), 0.90 (9H, s), 4.22 (2H, d, *J* = 5.7 Hz), 4.42 (2H, t, *J* = 2.4 Hz), 4.51 (2H, d, *J* = 2.1 Hz), 4.90 (1H, s), 5.35 (2H, t, *J* = 2.7 Hz), 5.90-5.96 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.2, 18.4, 26.0, 61.5, 70.5, 72.3, 101.4, 118.8, 136.6, 144.7; IR (neat) 2942, 2854, 1637, 1465, 1378, 1255, 1083, 1033, 927, 836, 777 cm^{-1}; MS (EI) *m/z* 75 (100), 240 (M^+); HRMS (EI) calcd for $C_{13}H_{24}O_2Si$ (M^+) 240.1546, found 240.1516.

(3*S*,4'*S*,6*R*)-1-Benzyloxycarbonyl-4'-(*tert*-butyldimethylsiloxymethyl)-6-methyl-1',4',6',7'-tetra-hydro-3'H-spiro[azepane-3,5'-isobenzofuran]-2-one (36): colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ -0.01 (s, 6H), 0.84 (s, 9H), 0.97 (3H, d, *J* = 6.9 Hz), 1.38-1.53 (2H, m), 1.69-2.11 (7H, m), 3.12 (1H, brs) 3.42 (1H, dd, *J* = 8.7, 14.4 Hz), 3.51 (1H, dd, *J* = 7.5, 9.8 Hz), 3.67 (1H, dd, *J* = 5.4, 9.8 Hz), 3.79 (1H, dd, *J* = 2.7, 13.8 Hz), 4.22-4.30 (1H, m), 4.20-4.69 (3H, m), 5.11 (1H, d, *J* = 12.7 Hz), 5.28 (1H, d, *J* = 12.7 Hz), 7.27-7.38 (5H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ -5.4, 18.3, 19.4, 26.0, 30.6, 30.7, 31.4, 36.5, 43.4, 43.5, 50.3, 51.4, 62.5, 68.2, 77.0, 77.1, 127.7, 128.0, 128.4, 131.2, 131.6, 135.9, 155.2, 181.9; IR (neat) 2942, 2856, 1714, 1461, 1378, 1265, 1193, 1087, 840, 777 cm^{-1}; MS (EI) *m/z* 353 (100), 513 (M^+); HRMS (EI) calcd for $C_{29}H_{43}NO_5Si$ (M^+) 513.2910, found 513.2896.

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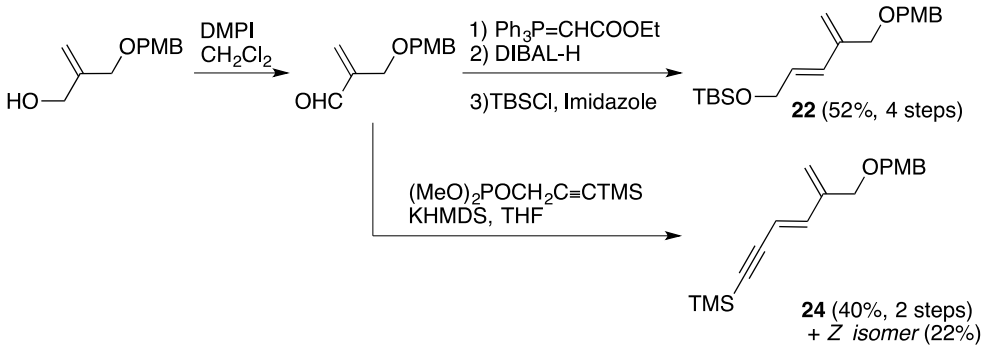
23. When (*R*,*R*)-*t*BuBOX was employed for the reaction of **5** and isoprene, a diastereomer at spirocyclic carbon was produced. This result shows that the chirality of the copper complex would be responsible for controlling enantioselectivity in the cycloaddition rather than the *vic*-dimethyl chiral center on the lactam.
24. Dienes **22** and **24** were prepared from the known alcohol (S.-J. Min and S. J. Danishefsky, *Angew. Chem. Int. Ed.*, 2007, **46**, 2199) as shown below.



25. All Diels-Alder adducts were characterized by NMR spectroscopy. The stereochemstries of the products were carefully determined by NOESY of themselves and Kusumi method of their derivatives: for Kusumi method, see; Y. Nagai and T. Kusumi, *Tetrahedron Lett.*, 1995, **36**, 1853.
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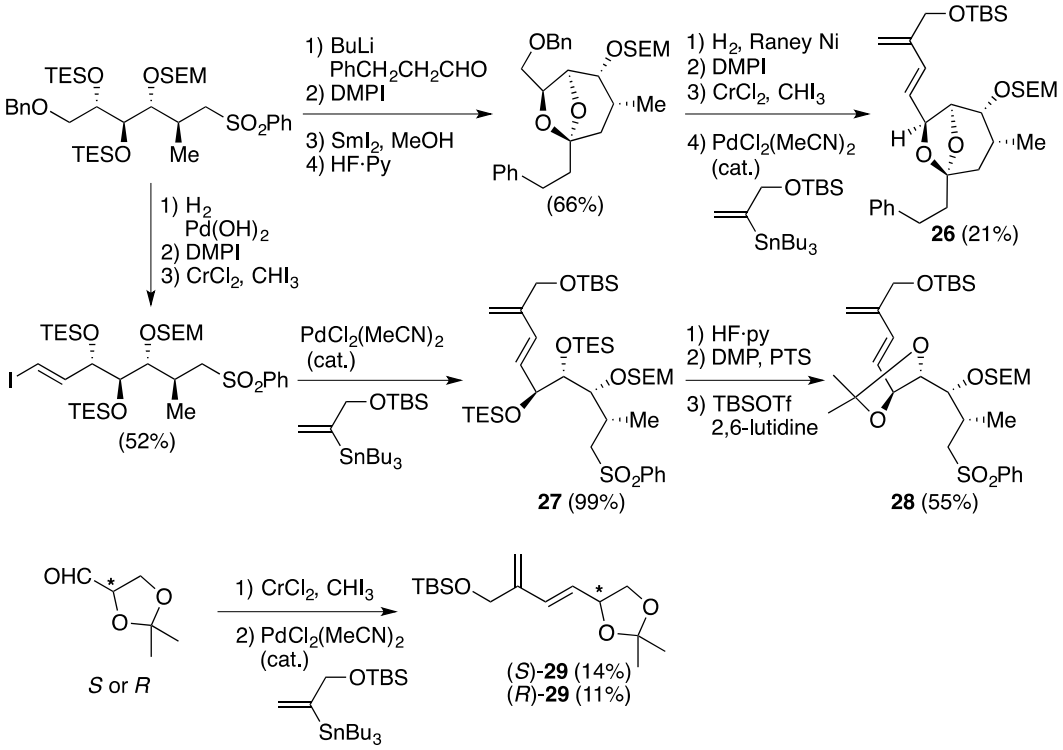
28. Functionalized dienes **26-29** were prepared as shown below.



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