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SYNTHEISIS OF THE ABCD RING SYSTEM OF AZASPIRACID, A MARINE POISON FROM *Mytilus Edulis*

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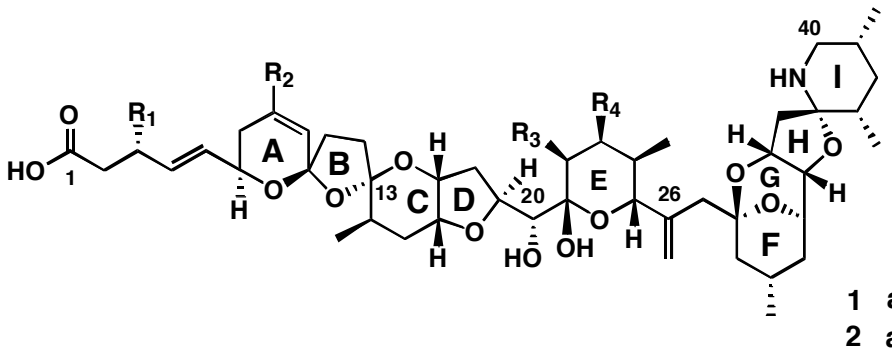
Abstract - Synthesis of the ABCD ring system of azaspiracid (**1**) was accomplished. The bridge system between the B and C rings using a sulfur atom, supported the spiroacetal-construction at the C13 position in the natural form. The stereochemistry was confirmed by the NOE experiments, along with conversion under acidic conditions into the unnatural derivative (**12**).

INTRODUCTION

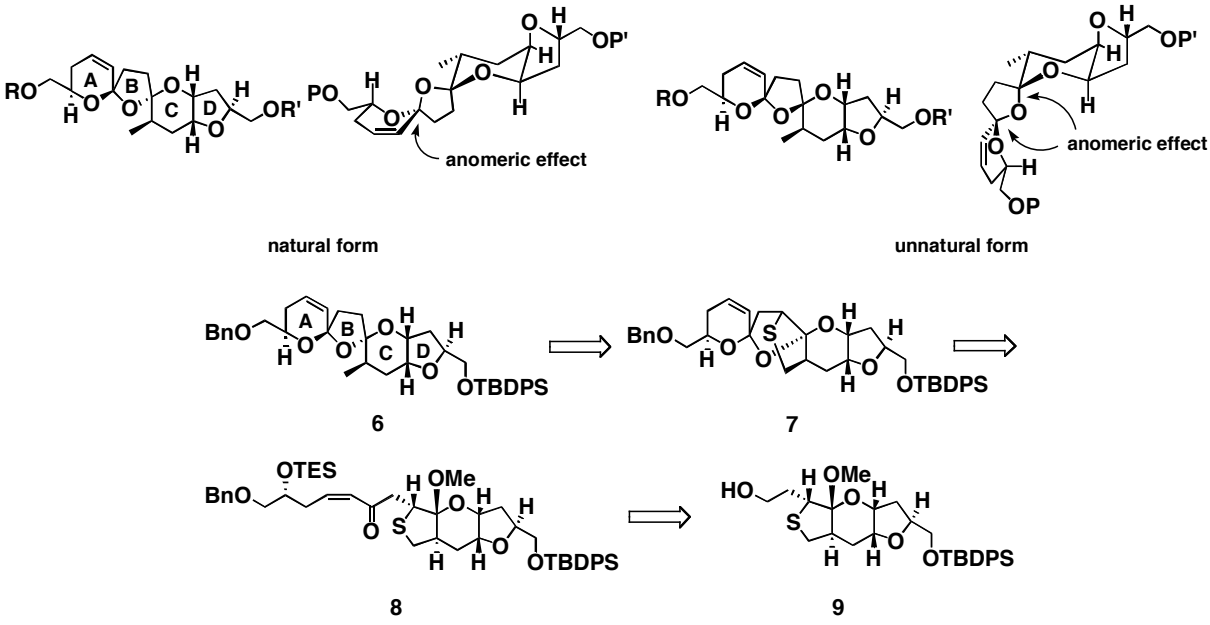
Azaspiracid (**1**), a marine polyether, was isolated from the blue mussel, *Mytilus edulis*, in Killary Harbor, Ireland, as a novel shellfish poison, by Yasumoto and co-workers (Figure 1).[1a] Although five congeners (**1**-**5**) were isolated to date, the absolute configurations and the relative stereochemistry between the C1-C25 and C28-C40 domains have not been uncovered.[1] From the viewpoint of synthetic chemistry,



			R_1	R_2	R_3	R_4
1	**azaspiracid**	:	H	H	Me	H
2	**azaspiracid-2**	:	H	Me	Me	H
3	**azaspiracid-3**	:	H	H	H	H
4	**azaspiracid-4**	:	OH	H	H	H
5	**azaspiracid-5**	:	H	H	H	OH

Figure 1. Azaspiracids.

azaspiracids have an attractive architecture including an azaspiro ring, a 2,9-dioxabicyclo[3.3.1]nonane ring, and trispiro ring units. Although Nicolaou accomplished a total synthesis of the proposed structure of **1** among many synthetic studies,[2] the synthetic sample did not provide complete agreement with the data of natural **1**.[3] Against such background, we started on the synthesis of **1** to determine the complete structure and to disclose the bioactivity.



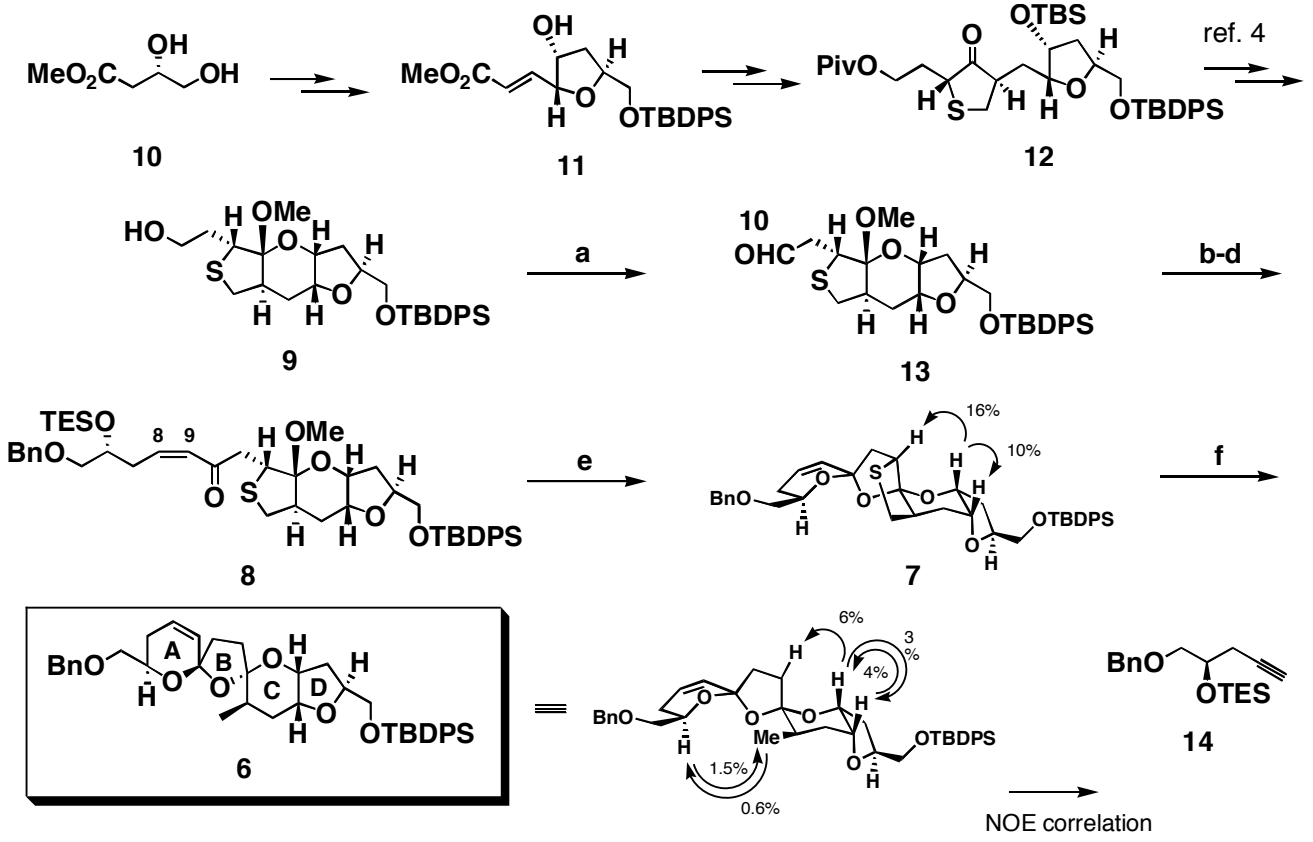
Scheme 1. Structure of the natural and unnatural forms of the ABCD ring system and retrosynthesis for construction of the ABCD ring system.

Toward the total synthesis of **1**, we initiated a synthesis of the ABCD ring systems, as the first target. Although several groups have attempted construction of the ABCD ring system, its successful synthesis has not been reported with the exception of Nicolaou's work.[3] Because the spirocenter (C13) in unnatural form possesses the stereochemistry stabilized by the two anomeric effects (Scheme 1), construction of the natural form by such usual methods as acidic conditions would be impossible.[4b] Thus, we elaborated a new strategy for synthesis of the ABCD ring system including the spirocenter at the C13 position. To produce the spirocenter in the BC ring in the expected manner, a sulfur atom would be introduced to the molecule (Scheme 1).[4] The bridge supported with the sulfur atom would regulate the conformation of synthetic substrates, and a mode of spiroactalization. After construction of the spirocenter, removal of the sulfur atom would afford the desired ABCD ring system (**6**). In our previous paper, we reported a synthesis of the BCD ring system of **1** as a model study.[4] We describe herein a

synthesis of the ABCD ring systems using a thioether.

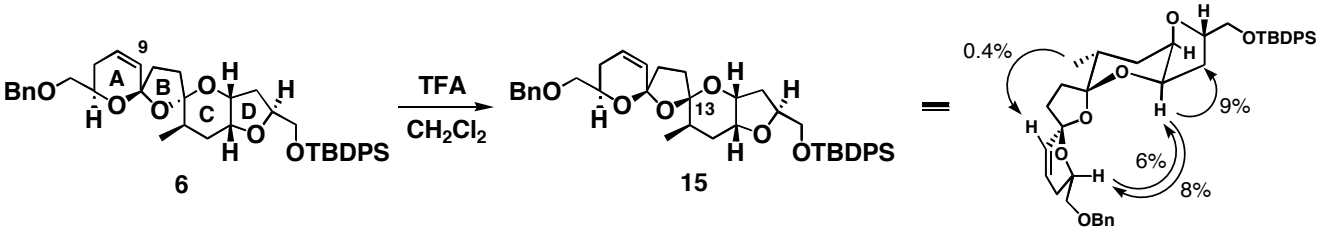
RESULTS AND DISCUSSION

To carry out the above-mentioned idea, alcohol (**9**) was employed as a starting material, which was produced by stepwise synthesis from dihydroxy ester (**10**) through construction of a tetrahydrofuran ring (**11**) and a tetrahydrothiophene ring (**12**).[4] Compound (**9**) was submitted to oxidation with SO_3•Py-DMSO to give aldehyde (**13**) in 90% yield (Scheme 2). Aldehyde (**13**) was reacted with a lithium acetylide prepared from alkyne (**14**)[4b] to give a diastereomeric mixture of an alcohol, which on Lindlar reduction and the following oxidation with SO_3•Py-DMSO furnished ketone (**8**) in 51% yield, which would be the expected precursor of acetal (**7**). The *(Z)*-α,β-unsaturated ketone structure was confirmed by a coupling constant of the sp^2 protons in the ^{1}H NMR spectrum: the H-9 proton resonated at δ 5.94 (d, *J*= 11.2 Hz) and a ddd signal observed at δ 6.17 was ascribed to H-8. According to our previous studies,[4] ketone (**8**) was treated with $Yb(OTf)_3$[5] in MeCN to give **7** as a single diastereomer in 57% yield,



Scheme 2. *Reagents and conditions*: (a) SO_3•Py, DMSO, Et_3N, CH_2Cl_2, 90%; (b) **14**, *n*-BuLi, THF, -78 ˚C; (c) H_2, Lindlar cat., benzene; (d) SO_3•Py, DMSO, *i*-Pr_2NEt, CH_2Cl_2, 51% in 3 steps; (e) $Yb(OTf)_3$, MeCN, rt, 57%; (f) Raney Ni W-4, EtOH, reflux, 72%.

the structure of which was spectroscopically determined. Configuration of the spirocenter at the C13 position was identified by the NOE correlation between the H-12 and H-17 protons. Finally, desufurization of **7** with Raney Ni W-4 afforded the desired ABCD ring system (**6**) in 72% yield, without isomerization of the C13 position. The stereostructure of **6** was also identified by the NOE correlations. In addition to the correlation between the H-12 and H-17 protons, the spirocenter at the C10 position was determined by the NOE correlation between the H-6 proton and the methyl group at the C14.



Scheme 3. Isomerization of **6** to **15**.

Further confirmation of the stereochemistry of **6** was obtained by isomerization into the corresponding unnatural **15** under acidic conditions. Thus, exposure of **6** to TFA in CH_2Cl_2, provided an isomer in 83% yield, which was spectroscopically and chromatographically assigned to be the unnatural isomer (**15**) (Scheme 3).[4b]

In conclusion, we have completed the synthesis of the ABCD ring system of azaspiracid (**1**), by controlling the stereocenter of the spiroacetal residue using a sulfur atom. The ring system assembly was confirmed by the NOE correlation experiments and chemical conversion of **6** into **12**. Further studies toward the total synthesis of azaspiracid are in progress.

EXPERIMENTAL

General. All reactions were carried out under an argon atmosphere unless otherwise noted. When necessary, solvents were dried prior to use. Tetrahydrofuran (THF) and ether (Et_2O) were purchased from Kanto Chemical Co., Inc. and stored over MS4Å. Other anhydrous solvents were also obtained through activated commercially available alumina column and stored over MS4Å an argon atmosphere. Optical rotations were measured on a JASCO DIR-360 digital polarimeter with a sodium (D line) lamp. IR spectra were recorded on a JASCO Model A-202 spectrophotometer. ^{1}H-NMR spectra and ^{13}C-NMR

spectra were obtained on JNM-EX270, JNM-α400, and JNM-GX400 spectrometers in deuteration solvent using tetramethylsilane as an internal standard. HRMS spectra were obtained on a Hitachi M-80B GC-MS spectrometer operating at the ionization energy of 70 eV. Preparative and analytical TLC were carried out on silica gel plate (Kieselgel 60 F254, E. Merck AG., Germany) using UV light and/or 5% molybdophosphoric acid in ethanol for detection. Kanto Chemical Silica 60N (spherical, neutral, 63-210 μm) was used for column chromatography.

2-[(1R,3S,4R,7R,9R,11R)-11-tert-Butyldiphenylsiloxymethyl-3-methoxy-2,10-dioxa-5-thiatricyclo[7.3.0.0^{3,7}]dodec-4-yl]ethanal ***(13)***

To a solution of **9**[4] (17.4 mg, 33 μmol) in CH_2Cl_2 (0.8 mL) were added DMSO (0.1 mL), Et_3N (0.1 mL) and SO_3•Py (46 mg, 0.29 mmol) at rt. After being stirred at the same temperature for 2 h, the reaction was quenched by the addition of H_2O. The mixture was extracted with Et_2O (3×), the combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (17% EtOAc in hexane) to afford **13** (15.7 mg, 90%) as a colorless oil: $[\alpha]^{26}_D$ +73.0° (*c* 1.00, $CHCl_3$); IR (film) ν 1724 cm^{-1}; ^{1}H-NMR (400 MHz, C_6D_6) δ 9.36 (br s, 1H), 7.86-7.82 (complex, 4H), 7.28-7.24 (complex, 6H), 4.27 (m, 1H), 3.84 (t, 1H, *J*= 7 Hz), 3.76 (dd, 1H, *J*= 10.7, 3.4 Hz), 3.70 (br d, 1H, *J*= 2.4 Hz), 3.67 (br d, 1H, *J*= 2.4 Hz), 3.57 (dd, 1H, *J*= 10.7, 4.4 Hz), 2.98 (s, 3H), 2.56 (ddd, 1H, *J*= 17.6, 7.3, 2 Hz), 2.51 (dd, 1H, *J*= 12, 9 Hz), 2.32 (dd, 1H, *J*= 9, 7 Hz), 2.21 (m, 1H), 2.13 (dd, 1H, *J*= 17.6, 7.3 Hz), 1.82-1.71 (complex, 4H), 1.18 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 198.7, 136.1, 134.0, 130.0, 128.5, 106.3, 106.3, 79.0, 75.6, 74.9, 66.7, 50.1, 48.0, 40.8, 37.8, 35.5, 31.5, 27.2, 26.5, 19.6. HREIMS calcd for $C_{29}H_{39}O_5SSi$ (M^++H): 527.2285, found: *m/z* 527.2286.

(6R)-1-[(1R,3S,4R,7R,9R,11R)-11-tert-Butyldiphenylsiloxymethyl-3-methoxy-2,10-dioxa-5-thiatricyclo[7.3.0.0^{3,7}]dodec-4-yl](3Z)-6-triethylsiloxy-7-phenylmethoxyhept-3-en-2-one ***(8)***

To a solution of **14** (97.2 mg, 0.32 mmol) in THF (3 mL) at 0 ˚C was added *n*-BuLi (1.58 M solution in hexane, 0.19 mL, 0.30 mmol). After 40 min, the reaction mixture was cooled to –78 ˚C and a solution of **13** (42.2 mg, 80 μmol) in THF (1.5 mL) was added. After being stirred at the same temperature for 20 min, sat. aq. $NaHCO_3$ was added, and the mixture was diluted with EtOAc. The organic phase was separated and the aqueous phase was extracted with EtOAc (2×). The combined organic extracts were

washed with brine, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (11→14% EtOAc in hexanes) to give an alcohol (46.4 mg) as a colorless oil.

A solution of the alcohol in the presence of catalytic amounts of Lindlar catalyst (25 mg) was stirred for 7 h at rt under a hydrogen atmosphere. After filtration through a Celite pad, the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (11→17% EtOAc in hexane) to give an olefin (36.2 mg) as a colorless oil.

To a solution of the olefin (36.2 mg, 43 μmol) in CH_2Cl_2 (1.4 mL) were added DMSO (0.3 mL), *i*-Pr_2NEt (0.3 mL) and SO_3•Py (70.3 mg, 0.44 mmol) at rt. After 15 min, the reaction was quenched by the addition of H_2O and diluted with Et_2O. The organic phase was separated, and the aqueous phase was extracted with Et_2O (2×). The combined organic extracts were washed with brine, dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The residue was purified by silica gel column chromatography (11→17% EtOAc in hexane) to give **8** (33.7 mg, 51% from **13**) as a colorless oil: $[\alpha]^{26}_D$ +58.8° (*c* 0.55, $CHCl_3$); IR (film) *ν* 1691, 1617 cm^{-1}; ^{1}H-NMR (400 MHz, C_6D_6) δ 7.85 (complex, 4H), 7.30-7.08 (complex, 10H), 6.17 (ddd, 1H, *J*= 11.2, 7, 7 Hz), 5.94 (d, 1H, *J*= 11.2 Hz), 4.35 (m, 1H), 4.32 (s, 2H), 4.26 (m, 1H), 4.06 (ddd, 1H, *J*= 10.7, 5.9, 5.4 Hz), 3.78 (dd, 1H, *J*= 11, 3.9 Hz), 3.76 (br d, 1H, *J*= 2.4 Hz), 3.69 (br d, 1H, *J*= 2.4 Hz), 3.61 (dd, 1H, *J*= 11, 4.4 Hz), 3.40 (dd, 1H, *J*= 9, 6 Hz), 3.33 (dd, 1H, *J*= 11, 4.9 Hz), 3.14 (m, 1H), 3.10 (s, 3H), 3.00 (m, 1H), 2.92 (dd, 1H, *J*= 17, 6 Hz), 2.57 (dd, 1H, *J*= 12, 8 Hz), 2.46 (dd, 1H, *J*= 17, 7 Hz), 2.40-2.28 (complex, 2H), 1.90-1.85 (complex, 2H), 1.81-1.74 (complex, 2H), 1.19 (s, 9H), 2.46 (t, 9H, *J*= 7.8 Hz), 2.46 (q, 6H, *J*= 7.8 Hz); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 198.1, 143.4, 139.0, 136.1, 134.1, 130.0, 128.6, 128.5, 106.4, 79.0, 75.7, 75.1, 74.8, 73.5, 71.6, 66.8, 50.2, 48.2, 42.2, 38.2, 35.7, 35.4, 31.4, 27.2, 26.7, 19.7, 7.4, 5.6. HREIMS calcd for $C_{40}H_{59}O_7SSi_2$ (M^+-Bn): 739.3516, found: *m/z* 739.3508.

[(1S,3S,5R,7S,9R,11R,14R,19R)-19-Phenylmethoxymethyl-2,4,8,16-tetraoxa-13-thiapentacyclo-[14.1.5.$0^{3,11}$.$0^{3,14}$.$0^{5,9}$]icos-19-en-7-yl]-tert-butyldiphenylsiloxymethane (7)

To a solution of **8** (7.3 mg, 8.8 μmol) in MeCN (1 mL) was added $Yb(OTf)_3$ (30 mg, 7.3 μmol) at 0 ˚C. After being stirred at rt for 2 h, the reaction was quenched by the addition of sat. aq. $NaHCO_3$. The resulted mixture was diluted with EtOAc, and the organic layer was separated, then the aqueous layer was extracted with EtOAc (2×). The combined organic extracts were dried over anhydrous $MgSO_4$ and

concentrated *in vacuo*. The residue was purified by preparative TLC (25% EtOAc in hexane) to afford **7** (3.4 mg, 57%) as a yellow oil: $[\alpha]^{22}_{D}$ +36.8° (*c* 0.41, $CHCl_3$); IR (film) ν 2927, 1427 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.69-7.64 (complex, 4H), 7.43-7.31 (complex, 11H), 6.00 (m, 1H), 5.67 (d, 1H, *J*= 10.4 Hz), 4.65 (d, 1H, *J*= 12.2 Hz), 4.59 (d, 1H, *J*= 12.2 Hz), 4.48 (m, 1H), 4.27 (m, 1H), 4.20 (br s, 1H), 3.96 (br s, 1H), 3.79 (d, 1H, *J*= 6.3 Hz), 3.77 (dd, 1H, *J*= 10.7, 3.9 Hz), 3.62 (dd, 1H, *J*= 10.7, 6.3 Hz), 3.61 (dd, 1H, *J*= 10.7, 3.9 Hz), 3.56 (dd, 1H, *J*= 10.3, 4.4 Hz), 3.54 (dd, 1H, *J*= 10.3, 4.9 Hz), 2.58 (dt, 1H, *J*= 11, 6 Hz), 2.44 (dd, 1H, *J*= 14, 6.3 Hz), 2.33 (d, 1H, *J*= 14 Hz), 2.24-1.95 (complex, 7H), 1.04 (s, 9H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 138.4, 135.5, 133.5, 129.5, 128.2, 127.9, 127.6, 127.5, 127.4, 119.8, 106.1, 78.4, 76.5, 75.1, 73.3, 72.8, 69.1, 66.3, 44.5, 43.7, 38.0, 35.8, 34.5, 29.7, 26.9, 26.3, 19.3. HREIMS calcd for $C_{40}H_{48}O_6SSi$ (M^+) 684.2938, found: *m/z* 684.2936.

[(2R,11S,12R,14S,15R,17R,19S)-19-tert-Butyldiphenylsiloxymethyl-15-methyl-13,18-dioxadispiro(2H-3,6-dihydropyran-6,5'-oxolane-2',3"-bicyclo[4.3.0]nonane)-2-yl]phenylmethoxymethane ***(6)***

A mixture of **7** (1.9 mg, 39 μmol) and Raney Ni W-4 (1 g) in EtOH (1 mL) was stirred at reflux temperature for 1 h. Raney Ni was removed by filtration through a Celite pad, and the filtrate was concentrated *in vacuo*. The residue was purified by preparative TLC (9% EtOAc in benzene) to afford **6** (1.3 mg, 72%) as a yellow oil: $[\alpha]^{23}_{D}$ +24.2° (*c* 0.40, $CHCl_3$); IR (film) ν 2927, 1454 cm^{-1}; ^{1}H-NMR (400 MHz, C_6D_6) δ 7.84-7.78 (complex, 4H), 7.27-7.08 (complex, 11H), 5.84 (dd, 1H, *J*= 10.3, 2 Hz), 5.70 (ddd, 1H, *J*= 10.3, 5.9, 1.5 Hz), 4.56 (m, 1H), 4.33 (complex, 3H), 3.79 (br s, 1H), 3.76 (dd, 1H, *J*= 10.7, 3.9 Hz), 3.68 (br d, 1H, *J*= 2 Hz), 3.55 (dd, 1H, *J*= 10.7, 4.4 Hz), 3.48 (dd, 1H, *J*= 10.3, 5 Hz), 3.35 (dd, 1H, *J*= 10.3, 4.9 Hz), 2.55 (m, 1H), 2.20-1.89 (complex, 7H), 1.67-1.60 (complex, 2H), 1.17 (s, 9H), 1.12 (m, 1H), 1.00 (d, 3H, *J*= 6.8 Hz); ^{13}C-NMR (100 MHz, C_6D_6) δ 139.2, 136.1, 135.3, 134.2, 130.4, 129.9, 125.6, 111.7, 104.3, 79.1, 76.5, 76.2, 73.2, 68.1, 66.7, 36.5, 34.2, 32.6, 30.2, 27.1, 23.7, 19.5, 16.1, 14.3. HREIMS calcd for $C_{40}H_{50}O_6Si$ (M^+) 654.3374, found: *m/z* 654.3381.

[(2R,11S,12R,14R,15R,17R,19S)-19-tert-Butyldiphenylsiloxy-15-methyl-13,18-dioxadispiro(2H-3,6-dihydropyran-6,5'-oxolane-2',3"-bicyclo[4.3.0]nonane)-2-yl]phenylmethoxymethane ***(15)***

To a solution of **6** (0.6 mg, 0.9 μmol) in CH_2Cl_2 (0.5 mL) was added TFA (0.2 μL, 2 μmol) at rt. After being stirred for 5 min, the solution was concentrated *in vacuo*. Purification by column chromatography (17% EtOAc in hexane) afforded **15** (0.5 mg, 83%) as a colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.68

(complex, 4H), 7.41-7.22 (complex, 11H), 5.95 (m, 1H), 5.61 (d, 1H, *J*= 10.4 Hz), 4.63 (s, 2H), 4.38 (m, 1H), 4.32 (m, 1H), 4.22 (m, 1H), 3.88 (d, 1H, *J*= 2.5 Hz), 3.62 (dd, 1H, *J*= 10.8, 4.4 Hz), 3.56 (dd, 1H, *J*= 10.8, 4.4 Hz), 3.53 (dd, 1H, *J*= 10.3, 5.4 Hz), 3.46 (dd, 1H, *J*= 10.3, 5.4 Hz), 2.19-2.14 (complex, 3H), 2.03 (t, 2H, *J*= 7.6 Hz), 1.94-1.92 (complex, 3H), 1.85-1.79 (complex, 3H), 1.76-1.70 (complex, 2H), 0.97 (s, 9H), 0.79 (d, 3H, *J*= 6.8 Hz).

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