SYNTHETIC APPROACHES TO PHORBOLS VIA THE INTRAMOLECULAR NITRILE OXIDE CYCLOADDITION: STEREOCONTROL OF THE B-C RING JUNCTION†

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Abstract--- The intramolecular cycloaddition of the nitrile oxide, synthesized from (+)-3-carene *via* **9**, provided the tetracyclic isoxazoline (**10**) stereospecifically. The isoxazoline (**10**) was converted to the carbotetracycle (**17**) *via* **15** utilizing the intramolecular McMurry coupling as a key step.

Protein kinase C (PKC), a serine and threonine phosphorylating enzyme, plays crucial roles in signal transduction.[1] The enzyme is proposed to be activated by 1,2-diacylglycerol compounds and by structurally diverse tumor promoters such as phorbol 12-myristate 13-acetate (PMA) (**1**), ingenol, aplysiatoxin, bryostatin and teleocidin. Computer modeling of these tumor promoters has shown a marked similarity in the relative positions of certain heteroatoms and hydrophobic groups.[2]

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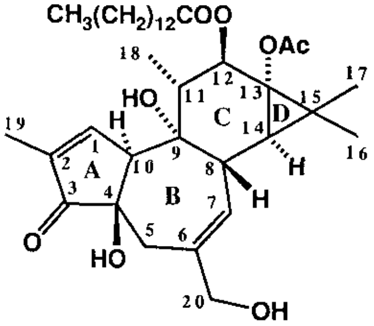
† Dedicated to Professor Emeritus Masatomo Hamana of Kyushu University on the occation of his 75th birthday.

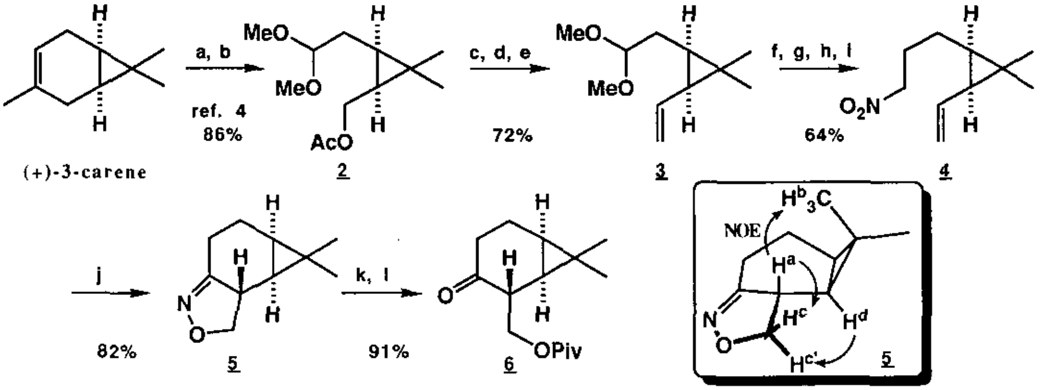
For phorbol, this mapping appears to consist of the carbonyl group at C-3 and/or hydroxyl groups at C-4, C-9 and C-20 as well as hydrophobic region filled by a long-chain acyl functionality attached to the C-12 position. In order to find out either agonists with more selective biological activities or antagonists as well as to confirm the above-mentioned hypothesis, we have undertaken synthetic studies on phorbol and related compounds. In this communication, we report an efficient synthesis of the optically active carbotricycle (**11**) having synthetic potential for phorbol construction and its transformation to the carbotetracycle (**17**) with the *cis* A-B ring junction.[3] The synthesis involves the two intramolecular nitrile oxide cycloadditions to construct the tricyclic isoxazoline (**5**) and the tetracyclic isoxazoline (**10**) as key steps.



PMA : 1

Figure 1

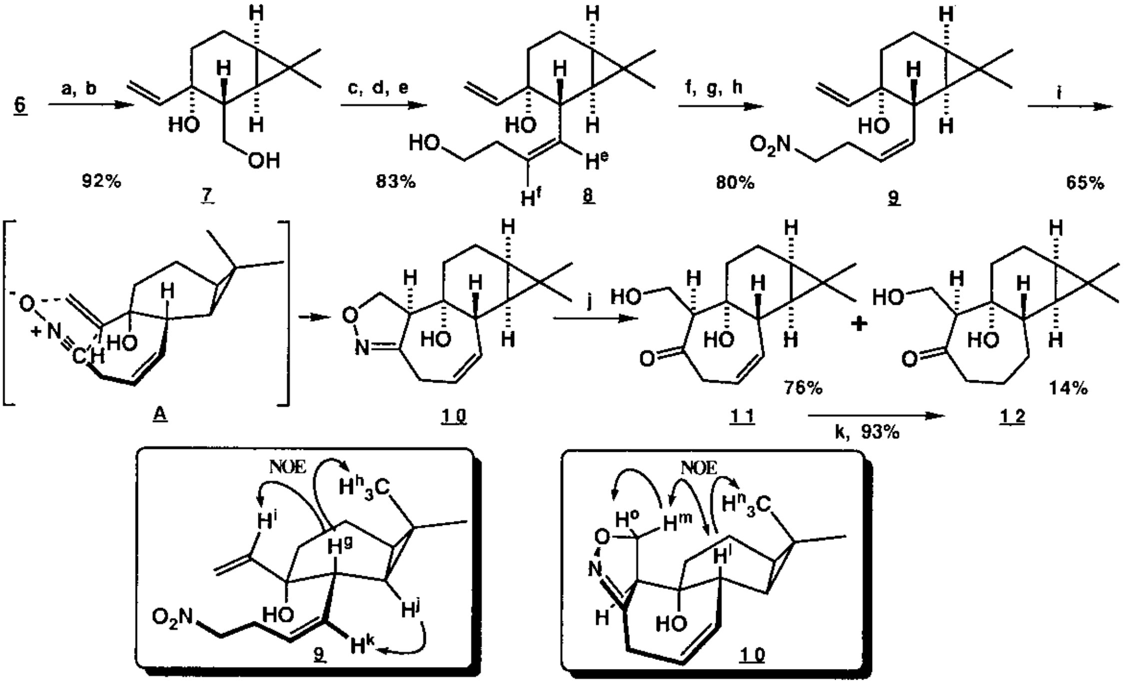
Following the reported procedure,[4] (+)-3-carene was first converted to **2**, which underwent hydrolysis, Swern oxidation and Wittig olefination to give **3** in 72% overall yield. Hydrolysis of an acetal functionality, followed by treatment with nitromethane in the presence of potassium fluoride, afforded the nitro aldol, which was subjected to acetylation and reduction to furnish **4** in 64% overall yield. With the compound (**4**) available, the stage was set for the first intramolecular nitrile oxide cycloaddition. Treatment of **4** with methyl isocyanate in the presence of triethylamine[5] at room temperature gave the isoxazoline (**5**) in 82% yield stereospecifically. The stereochemistry of **5** was unequivocally determined by the NOE experiments. That is, irradiation of H^a showed an enhancement of H^b and H^c, and irradiation of H^d showed an enhancement of $H^{c'}$. The isoxazoline (**5**) was converted to **6**, a versatile intermediate, in 91% yield by treatment with aqueous $TiCl_3$[5,6] followed by reaction with pivaloyl chloride.



a) O_3, MeOH, -78 °C, then Me_2S, room temperature; b) mCPBA, $CHCl_3$, room temperature; c) 10% NaOH, MeOH, 0 °C; d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78 °C~room temperature; e) $Ph_3P^+MeBr^-$, BuLi, THF, -78 °C~room temperature; f) 30% $HClO_4$, THF, 0 °C; g) $MeNO_2$, KF, Bu_4NCl, toluene, room temperature; h) Ac_2O, pyridine, DMAP, CH_2Cl_2, room temperature; i) $NaBH_4$, EtOH, 0 °C; j) MeNCO, Et_3N, benzene, room temperature; k) aq. $TiCl_3$, MeOH, room temperature; l) PivCl, pyridine, CH_2Cl_2, room temperature.

Scheme 1

In order to investigate the possibility of **6** as a key intermediate for the construction of phorbols, direct transformation of **6** to the phorbol skeleton was first attempted.[7] Treatment of **6** with vinylmagnesium bromide in THF at -55 °C, followed by reduction with lithium aluminum hydride, gave **7** in 92% yield as a sole product. The stereochemistry of **7** was determined at the later stage. Oxidation of the diol (**7**) with SO_3•pyridine complex afforded the aldehyde, which underwent Wittig olefination by $Ph_3P=CH(CH_2)_2OC(OMe)Me_2$,[8] followed by hydrolysis, furnishing **8** in 83% overall yield. The stereochemical assignment for the olefinic double bond followed from the ^1H nmr, which showed $J_{ef}=10.6$ Hz. The diol (**8**) was further converted to the nitro alcohol (**9**) in a three-step sequence of reactions (80% overall yield). At this stage, in NOE experiments, irradiation of H^g showed an enhancement of H^h and H^i, and irradiation of H^j showed an enhancement of H^k, thus proving the stereochemistry of the above-mentioned Grignard reaction.[9] With the compound (**9**) available, the stage was set for the most crucial intramolecular nitrile oxide cycloaddition to construct a seven-membered ring. After several attempts, it was found that exposure of **9** to *p*-chlorophenyl isocyanate and triethylamine in benzene at 55 °C[5,10] gave the desired isoxazoline (**10**) stereospecifically in 65% yield *via* the transition state **A**. The stereochemical assignment for **10** with correct phorbol stereochemistry at the B-C ring junction followed from the NOE experiments. That is, irradiation of H^l showed an enhancement of H^m and H^n, and irradiation of H^m showed an enhancement of H^l and H^o. Transformation of the isoxazoline (**10**) to the tricyclic compound (**11**) was best carried out by treatment with Raney Ni (W-2) and a large excess of boric acid under an atmosphere of hydrogen,[5,10,11] giving **11** in 76% yield together with **12** (14%).[12] Catalytic hydrogenation of **11** led to the formation of **12** in 93% yield.

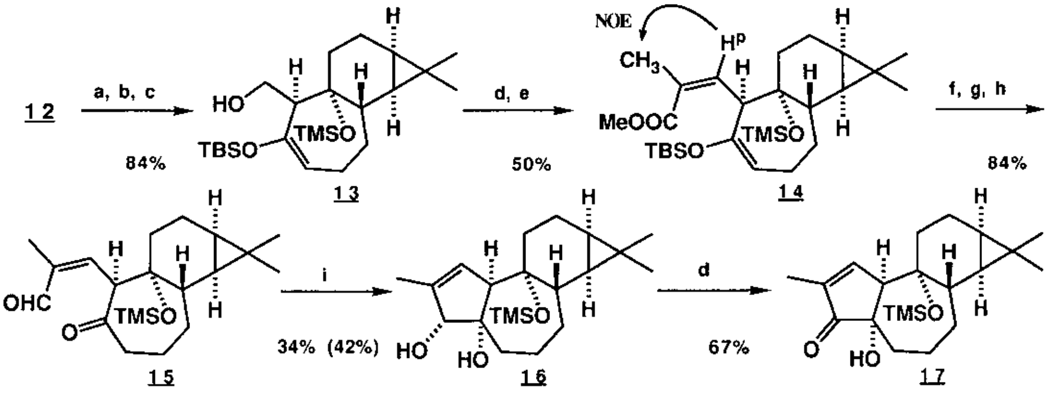


a) CH_2=CHMgBr, THF, -78 °C~-55 °C; b) $LiAlH_4$, Et_2O, 0 °C; c) SO_3•pyridine, Et_3N, DMSO, room temperature; d) $Ph_3P^+(CH_2)_3OC(OMe)Me_2Br^-$, $KN(TMS)_2$, THF, HMPA, -78 °C~room temperature; e) 50% AcOH, THF, room temperature; f) *p*-TsCl, pyridine, DMAP, CH_2Cl_2, room temperature; g) NaI, 2-butanone, room temperature; h) $AgNO_2$, Et_2O, room temperature; i) *p*-ClC_6H_4NCO, Et_3N, benzene, 55 °C; j) H_2, Raney Ni (W-2), $B(OH)_3$, MeOH, H_2O, room temperature; k) H_2, 10% Pd-C, AcOEt, room temperature.

Scheme 2

Having established an efficient synthesis of the optically active carbotricycles (**11**) and (**12**), we further attempted the transformation of **12** into the phorbol skeleton.

Reaction of **12** with trimethylsilyl chloride and imidazole gave the disilyl ether, which was converted to the silyl enol ether on exposure to *tert*-butyldimethylsilyl triflate and triethylamine.[13] The silyl enol ether underwent selective deprotection of the trimethylsilyl ether at the C-1 position (PMA numbering) by K_2CO_3 in MeOH to give **13** in 84% overall yield. Oxidation of **13** with SO_3•pyridine complex provided the aldehyde, which was transformed into the α,β-unsaturated ester (**14**) stereospecifically in 50% overall yield.[14] The stereochemical assignment for the olefinic double bond followed from the NOE experiments, which showed an enhancement of the methyl proton when H^p was irradiated. Diisobutylaluminum hydride reduction, deprotection of a silyl enol ether with tetrabutylammonium fluoride and MnO_2 oxidation provided the dicarbonyl compound (**15**) in 84% overall yield. With the compound (**15**) available, we thought that the intramolecular McMurry coupling of **15** would produce the desired phorbol skeleton stereoselectively, because the phorbol skeleton appeared to be more stable than the corresponding *cis*-stereoisomer. However, treatment of **15** with the low-valent titanium reagent generated from $CpTiCl_3$ and $LiAlH_4$[15] provided the undesired *cis*-stereoisomer (**16**) stereospecifically in 34% yield (42% yield based on the recovery of the starting material). The stereochemistry of **16** was supported by the experimental and the spectroscopic data as follows. First, MnO_2 oxidation of **16** led to



a) TMSCl, imidazole, DMF, room temperature; b) TBSOTf, Et_3N, CH_2Cl_2, 0 °C; c) K_2CO_3, MeOH, 0 °C; d) SO_3•pyridine, Et_3N, DMSO, room temperature; e) $(CF_3CH_2O)_2P(O)CH(Me)COOMe$, DBU, LiCl, MeCN, room temperature; f) DIBAH, toluene, -78 °C; g) TBAF, THF, -45 °C; h) MnO_2, pentane, room temperature; i) $CpTiCl_3$, $LiAlH_4$, THF, 50 °C.

Scheme 3

the formation of the dicarbonyl compound (**15**), thus showing that the relative stereochemistry of the resulting two alcohols was *cis*.[16] Second, the ^{1}H nmr spectrum of the allylic epoxide (**18**), derived from **16** by treatment with *m*-chloroperbenzoic acid (83% yield), showed J_{qr}=~0 Hz, indicating that the relative stereochemistry of H^q and H^r was *trans*, and the results shown in Figure 2 were also obtained by NOE experiments. Furthermore, the structure of **16** was unequivocally determined by X-ray crystallographic analysis as shown in Figure 3.[17] Oxidation of **16** with SO_3•pyridine complex gave the keto alcohol (**17**) in 67% yield.

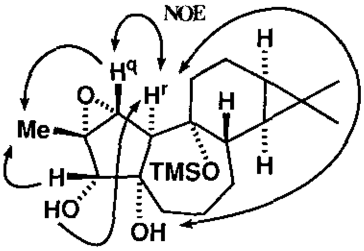


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Figure 2

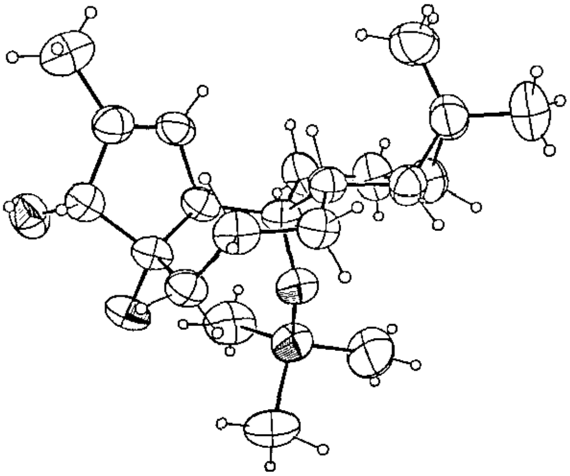

Figure 3. ORTEP drawing of 16

In conclusion, we have succeeded in achieving a stereocontrolled synthesis of the B-C-D ring system of phorbols starting with (+)-3-carene, in which the two intramolecular nitrile oxide cycloadditions are involved as key steps. Furthermore, the carbotetracycle (**17**) with the *cis* A-B ring junction has been constructed using the intramolecular McMurry coupling as a key step. We believe that the compounds (**6**) and (**11**) should be valuable synthetic intermediates for the synthesis of phorbol and related compounds. Further studies along this line are under investigation.

ACKNOWLEDGEMENTS

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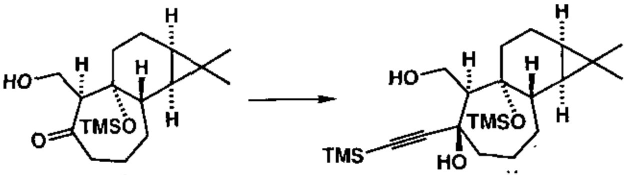
3. Treatment of **i** with TMS-C≡C-Li and $CeCl_3$ at -50 °C gave **ii** in 92% yield stereospecifically. Transformation of **ii** to phorbol skeleton is under investigation.



i ii

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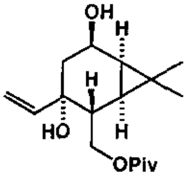
7. The compound (**6**) has been already converted to **iii**. The details will be published elsewhere.



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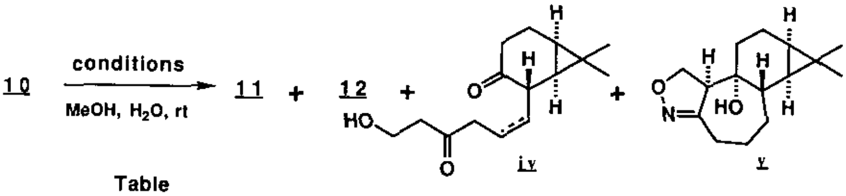
12. The results obtained under the different reaction conditions are as follows.



Table

run	conditions	yield (%) 11	12	iv	v
1	aq. $TiCl_3$	27	—	—	—
2	H_2, Pd-$BaSO_4$, quinoline	—	—	28	59
3	H_2, Pd-C	—	—	59	—
4	H_2, Pd-C, AcOH	—	19	20	43
5	H_2, Raney Ni (W-2), $B(OH)_3$ (6 eq.)	46	8	17	—
6	H_2, Raney Ni (W-2), $B(OH)_3$ (15 eq.)	76	14	—	—

13. Attempts at protecting the carbonyl function of **12** as a ketal or TMS cyanohydrin turned out to be unsuccessful.
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17. Crystal data for **16**: $C_{21}H_{36}O_3Si$; monoclinic, space group $P21$ (No. 4), a=16.5274 (83) Å, b=7.4276 (54) Å, c=8.9852 (32) Å, α=90°, β=102.8278 (340)°, γ=90°, V=1075.4882 $Å^3$, Z=2, D_{calcd}=1.126 g/cm^3, The final R value was 0.046.

18. Satisfactory analytical data were obtained for all new compounds. Selected data are as follows:
Compound **5**; $[\alpha]_D^{20}$ +212.02° (*c* 1.03, CHCl$_3$); ir ν_{max} (neat): 1620 cm^{-1}; ms m/z : 165 (M$^+$), 148, 120; high resolution ms calcd for C$_{10}$H$_{15}$NO 165.1153, found 165.1140; ^{1}H nmr (CDCl$_3$) δ 0.60 (dd, J=9.0, 4.0 Hz, 1H), 0.77 (ddd, J=9.0, 7.3, 5.5 Hz, 1H), 1.06 (s, 3H), 1.07 (s, 3H), 1.56 (dddd, J=14.6, 7.7, 6.8, 5.5 Hz, 1H), 2.10 (dddd, J=14.6, 7.3, 7.3, 6.6 Hz, 1H), 2.32 (dddd, J=16.5, 6.8, 6.6, 1.5 Hz, 1H), 2.45 (dddd, J=16.5, 7.7, 7.3, 1.5 Hz, 1H), 2.93 (ddddd, J=12.5, 10.6, 4.0, 1.5, 1.5 Hz, 1H), 3.87 (dd, J=12.5, 7.7 Hz, 1H), 4.67 (dd, J=10.6, 7.7 Hz, 1H).
Compound **7**; $[\alpha]_D^{22}$ -4.51° (*c* 0.63, CHCl$_3$); mp 97.0~97.1 °C (n-hexane); ir ν_{max} (nujol): 3370, 3270, 1635 cm^{-1}; ms m/z : 178 (M$^+$-H$_2$O), 163, 105; Anal. Calcd for C$_{12}$H$_{20}$O$_2$: C, 73.43; H, 10.27. Found: C, 73.43; H, 10.25; ^{1}H nmr (CDCl$_3$) δ 0.64~0.86 (m, 2H), 0.96 (s, 3H), 1.08 (s, 3H), 1.12~2.24 (m, 5H), 2.59 (br s, 2H), 3.72 (dd, J=10.7, 3.7 Hz, 1H), 4.08 (dd, J=10.7, 3.2 Hz, 1H), 5.14 (dd, J=10.5, 2.0 Hz, 1H), 5.38 (dd, J=17.2, 2.0 Hz, 1H), 5.87 (dd, J=17.2, 10.5 Hz, 1H).
Compound **8**; $[\alpha]_D^{23}$ -73.54° (*c* 1.04, CHCl$_3$); ir ν_{max} (neat): 3370, 1640 cm^{-1}; ms m/z : 236 (M$^+$), 218 (M$^+$-H$_2$O), 203, 166; Anal. Calcd for C$_{15}$H$_{24}$O$_2$: C, 76.23; H, 10.24. Found: C, 76.26; H, 10.37; ^{1}H nmr (CDCl$_3$) δ 0.41 (dd, J=8.8, 4.4 Hz, 1H), 0.71 (ddd, J=8.8, 8.4, 1.1 Hz, 1H), 1.05 (s, 3H), 1.06 (s, 3H), 1.19 (ddd, J=14.3, 11.7, 7.7 Hz, 1H), 1.53 (ddd, J=14.3, 8.4, 1.1 Hz, 1H), 1.70 (dddd, J=15.0, 7.7, 1.1, 1.1 Hz, 1H), 2.00 (dddd, J=15.0, 11.7, 8.4, 8.4 Hz, 1H), 2.08 (ddd, J=9.2, 4.4, 0.8 Hz, 1H), 2.30 (ddt, J=7.4, 1.4, 6.6 Hz, 2H), 3.65 (t, J=6.6 Hz, 2H), 5.04 (dd, J=11.0, 1.5 Hz, 1H), 5.21 (dd, J=17.6, 1.5 Hz, 1H), 5.42 (ddt, J=10.6, 0.8, 7.4 Hz, 1H), 5.75 (dd, J=17.6, 11.0 Hz, 1H), 5.83 (ddt, J=10.6, 9.2, 1.4 Hz, 1H); ^{13}C nmr (CDCl$_3$) δ 14.8, 15.1, 17.8, 18.4, 24.2, 29.0, 31.3, 34.2, 38.1, 62.1, 72.0, 112.4, 125.1, 134.8, 144.3.
Compound **9**; $[\alpha]_D^{22}$ -58.92° (*c* 0.94, CHCl$_3$); ir ν_{max} (neat): 3480, 1635, 1550, 1375 cm^{-1}; ms m/z : 265 (M$^+$), 248 (M$^+$-OH), 148; Anal. Calcd for C$_{15}$H$_{23}$NO$_3$: C, 67.90; H, 8.74; N, 5.28. Found: C, 67.84; H, 8.82; N, 5.19; ^{1}H nmr (C$_6$D$_6$) δ 0.24 (dd, J=9.2, 4.4 Hz, 1H), 0.37 (ddd, J=9.2, 8.1, 1.2 Hz, 1H), 0.95 (s, 3H), 1.00 (s, 3H), 0.99 (ddd, J=14.3, 11.7, 8.0 Hz, 1H), 1.34 (br s, 1H), 1.41 (ddd, J=14.3, 8.1, 1.2 Hz, 1H), 1.48 (dddd, J=15.0, 8.0, 1.2, 1.2 Hz, 1H), 1.80 (dddd, J=15.0, 11.7, 8.1, 8.1 Hz, 1H), 1.89 (ddd, J=9.2, 4.4, 1.1 Hz, 1H), 2.19~2.41 (m, 2H), 3.64 (t, J=7.3 Hz, 2H), 5.02 (ddt, J=10.6, 1.1, 7.3 Hz, 1H), 5.05 (dd, J=10.6, 1.8 Hz, 1H), 5.31 (dd, J=17.2, 1.8 Hz, 1H), 5.64 (dd, J=17.2, 10.6 Hz, 1H), 5.92 (ddt, J=10.6, 9.2, 1.5 Hz, 1H).
Compound **10**; $[\alpha]_D^{21}$ +126.17° (*c* 1.07, CHCl$_3$); mp 145.8~146.1 °C (n-hexane); ir ν_{max} (nujol): 3420, 1611 cm^{-1}; ms m/z : 247 (M$^+$), 230 (M$^+$-OH), 202; Anal. Calcd for C$_{15}$H$_{21}$NO$_2$: C, 72.84; H, 8.56; N, 5.66. Found: C, 72.74; H, 8.58; N, 5.66; ^{1}H nmr (C$_6$D$_6$) δ 0.15 (dd, J=9.2, 4.8 Hz, 1H), 0.36 (ddd, J=9.2, 7.7, 1.8 Hz, 1H), 0.65 (s, 3H), 0.91 (s, 3H), 0.68 (ddd, J=14.3, 11.0, 7.0 Hz, 1H), 1.20 (ddd, J=14.3, 7.4, 2.6 Hz,

1H), 1.24 (dddd, J=14.8, 7.0, 2.6, 1.8 Hz, 1H), 1.73 (dddd, J=14.8, 11.0, 7.7, 7.4 Hz, 1H), 2.04 (ddddd, J=4.8, 2.9, 1.6, 1.6, 1.6 Hz, 1H), 2.91 (ddddd, J=18.0, 3.3, 3.3, 1.6, 1.0 Hz, 1H), 3.26 (dddd, J=18.0, 6.2, 1.6, 1.6 Hz, 2H), 3.28 (ddd, J=12.1, 10.3, 1.0 Hz, 1H), 3.73 (dd, J=12.1, 8.4 Hz, 1H), 4.01 (dd, J=10.3, 8.4 Hz, 1H), 5.22 (dddd, J=11.4, 3.3, 1.6, 1.6 Hz, 1H), 5.46 (dddd, J=11.4, 6.2, 3.3, 2.9 Hz, 1H); ^{13}C nmr (C_6D_6) δ 14.8, 15.0, 17.6, 19.4, 25.8, 27.0, 29.4, 33.1, 36.1, 61.5, 70.6, 71.6, 125.7, 134.8, 158.3.

Compound **11**; $[\alpha]_D^{23}$ +4.28° (*c* 1.53, $CHCl_3$); mp 94.5~95.2 °C (n-hexane); ir ν_{max} (nujol): 3474, 3308, 1696, 1663 cm^{-1}; ms m/z : 250 (M$^+$), 232 (M$^+$-H_2O), 215 (M$^+$-H_2O-OH), 159; Anal. Calcd for $C_{15}H_{22}O_3 \cdot (H_2O)_{1/3}$: C, 70.28; H, 8.91. Found: C, 70.41; H, 8.98; ^{1}H nmr (C_6D_6) δ 0.39~0.50 (m, 2H), 0.70 (s, 3H), 0.92 (s, 3H), 1.03 (ddd, J=13.9, 10.6, 8.1, Hz, 1H), 1.33~1.57 (m, 2H), 1.53~1.65 (br s, 1H), 1.71~1.88 (m, 2H), 2.08~2.18 (br s, 1H), 2.55 (dd, J=20.5, 7.7 Hz, 1H), 2.97 (ddddd, J=20.5, 2.9, 2.6, 1.1, 1.1 Hz, 1H), 3.55 (dt, J=1.1, 7.3 Hz, 1H), 3.95 (br d, J=7.3 Hz, 1H), 5.50 (dddd, J=10.3, 7.7, 2.6, 1.8 Hz, 1H), 5.76 (ddd, J=10.3, 6.2, 2.9 Hz, 1H); ^{13}C nmr ($CDCl_3$) δ 14.5, 14.8, 17.7, 17.9, 23.9, 28.6, 28.7, 39.9, 45.6, 59.4, 60.0, 77.4, 124.4, 136.7, 210.1.

Compound **12**; $[\alpha]_D^{21}$ +61.93° (*c* 1.02, $CHCl_3$); mp 124.2~124.4 °C (n-hexane); ir ν_{max} (nujol): 3380, 1698, 1682 cm^{-1}; ms m/z : 252 (M$^+$), 234 (M$^+$-H_2O), 217 (M$^+$-H_2O-OH), 150; Anal. Calcd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.25; H, 9.81; ^{1}H nmr (C_6D_6) δ 0.12 (dd, J=9.2, 5.5 Hz, 1H), 0.36 (ddd, J=9.2, 8.4, 1.5 Hz, 1H), 0.76 (s, 3H), 0.94 (s, 3H), 0.89 (ddd, J=11.4, 5.5, 2.6 Hz, 1H), 1.07 (ddd, J=13.9, 10.6, 8.1, Hz, 1H), 1.29~1.53 (m, 4H), 1.56~1.70 (m, 1H), 1.74 (dddd, J=14.7, 10.6, 8.4, 8.4 Hz, 1H), 1.82 (t, J=4.9 Hz, 1H), 1.93~2.11 (m, 1H), 2.05 (s, 1H), 2.25 (ddd, J=15.8, 8.4, 5.9 Hz, 1H), 2.35 (ddd, J=15.8, 7.0, 5.5 Hz, 1H), 3.32 (t, J=7.0 Hz, 1H), 3.93 (dd, J=7.0, 4.9 Hz, 2H); ^{13}C nmr ($CDCl_3$) δ 14.8, 15.1, 17.9, 18.6, 22.7, 25.5, 28.9, 30.0, 30.7, 39.4, 43.3, 59.9, 61.6, 72.5, 212.6.

Compound **13**; $[\alpha]_D^{22}$ +3.52° (*c* 0.78, $CHCl_3$); mp 82.8~83.1 °C (n-hexane); ir ν_{max} (KBr): 3530, 1665 cm^{-1}; ms m/z : 438 (M$^+$), 420 (M$^+$-H_2O), 381 (M$^+$-^{t}Bu), 236; Anal. Calcd for $C_{24}H_{48}O_3Si_2$: C, 65.69; H, 10.57. Found: C, 65.62; H, 10.62; ^{1}H nmr ($CDCl_3$) δ 0.08~0.20 (m, 1H), 0.15 (s, 9H), 0.16 (s, 3H), 0.19 (s, 3H), 0.52 (ddd, J=9.2, 6.6, 2.6 Hz, 1H), 0.91 (s, 9H), 0.92 (s, 3H), 0.99 (s, 3H), 1.17 (ddd, J=11.0, 5.5, 3.3 Hz, 1H), 1.24~1.56 (m, 5H), 1.74~1.96 (m, 2H), 1.98~2.20 (m, 2H), 2.52 (ddd, J=9.2, 4.8, 1.2 Hz, 1H), 3.66 (ddd, J=10.6, 7.7, 4.8 Hz, 1H), 3.88 (ddd, J=10.6, 9.2, 5.1 Hz, 1H), 4.93 (ddd, J=7.7, 5.5, 1.2 Hz, 1H); ^{13}C nmr ($CDCl_3$) δ -3.8, 2.8, 15.5, 17.3, 17.3, 18.1, 20.5, 24.0, 26.0, 27.9, 29.6, 32.2, 36.8, 39.5, 61.7, 62.7, 74.6, 105.6, 154.2.

Compound **14**; $[\alpha]_D^{20}$ -151.25° (*c* 1.01, $CHCl_3$); ir ν_{max} (neat): 1723, 1663, 1638 cm^{-1}; ms m/z : 506 (M$^+$), 491 (M$^+$-Me), 475 (M$^+$-MeO), 449 (M$^+$-^{t}Bu), 283; high resolution ms calcd for $C_{28}H_{50}O_4Si_2$ 506.3247, found 506.3272; ^{1}H nmr ($CDCl_3$) δ -0.02 (s, 3H), 0.11 (s, 3H), 0.08~0.20 (m, 1H), 0.17 (s, 9H), 0.50 (ddd, J=9.2, 8.1, 1.2 Hz, 1H), 0.86 (s, 9H), 0.88 (s, 3H), 0.98 (s, 3H), 1.10 (ddd, J=14.6, 11.7, 7.3 Hz, 1H), 1.30 (ddd, J=11.0, 4.4, 3.3 Hz, 1H), 1.44 (dd, J=14.6, 7.3 Hz, 1H), 1.46~1.58 (m, 1H), 1.63 (ddd, J=14.3, 7.7, 1.5 Hz, 1H), 1.77~2.25 (m, 3H), 1.90 (d, J=1.5 Hz, 3H), 3.67 (s, 3H), 4.09 (dd, J=12.1, 1.5 Hz, 1H), 4.93 (ddd, J=8.8, 4.4, 1.5 Hz, 1H), 4.93 (dq, J=12.1, 1.5 Hz, 1H); ^{13}C nmr ($CDCl_3$) δ -5.5, -3.7, 2.4, 15.4, 16.5, 16.9, 17.9, 19.4, 21.5, 24.0, 25.7, 27.6, 29.5, 32.4, 34.8, 39.0, 51.2, 58.5, 75.0, 106.5, 127.4, 137.6, 153.2, 168.1.

Compound **15**; $[\alpha]_D^{21}$ -140.60° (*c* 0.91, $CHCl_3$); ir ν_{max} (KBr): 1689 cm^{-1}; ms m/z : 362 (M^+), 347 (M^+-Me), 272 (M^+-TMSO-1), 236; high resolution ms calcd for $C_{21}H_{34}O_3Si$ 362.2277, found 362.2305, ^{1}H nmr ($CDCl_3$) δ 0.15 (s, 9H), 0.26 (dd, J=9.3, 4.9 Hz, 1H), 0.59 (ddd, J=9.3, 7.7, 2.8 Hz, 1H), 0.93 (s, 3H), 1.04 (s, 3H), 1.15~1.31 (m, 2H), 1.34~1.57 (m, 3H), 1.81 (d, J=1.7 Hz, 3H), 1.75~1.97 (m, 4H), 2.47 (ddd, J=18.2, 10.2, 5.4 Hz, 1H), 2.59 (ddd, J=18.2, 5.3, 4.0 Hz, 1H), 4.36 (d, J=11.0 Hz, 1H), 6.61 (dq, J=11.0, 1.7 Hz, 1H), 10.15 (s, 1H); ^{13}C nmr ($CDCl_3$) δ 2.4, 15.4, 16.0, 17.3, 17.6, 19.7, 21.8, 26.7, 29.1, 33.9, 35.9, 38.3, 42.7, 66.2, 77.7, 139.1, 139.7, 191.1, 209.4.

Compound **16**; $[\alpha]_D^{19}$ -67.42° (*c* 0.68, $CHCl_3$); mp 176.1~176.8 °C (MeOH); ir ν_{max} (KBr): 3401, 3279, 1657 cm^{-1}; ms m/z : 364 (M^+), 346 (M^+-H_2O), 331 (M^+-H_2O-Me), 274 (M^+-TMSO-1), 256; ^{1}H nmr ($CDCl_3$) δ 0.16 (dd, J=9.3, 6.8 Hz, 1H), 0.20 (s, 9H), 0.59 (ddd, J=9.3, 7.8, 6.4 Hz, 1H), 0.88 (ddd, J=11.0, 6.8, 3.4 Hz, 1H), 0.91 (s, 3H), 1.00 (s, 3H), 0.95~1.07 (m, 1H), 1.19~1.32 (m, 2H), 1.54~1.87 (m, 9H), 2.13~2.22 (m, 1H), 2.37 (br s, 1H), 2.70 (d, J=5.7 Hz, 1H), 2.92~2.97 (m, 1H), 4.02 (br d, J=5.7, 1H), 5.27 (dq, J=1.5, 1.5 Hz, 1H); ^{13}C nmr ($CDCl_3$) δ 2.8, 14.7, 15.2, 17.7, 18.0, 22.2, 22.2, 27.2, 29.1, 35.0, 36.4, 38.8, 40.6, 69.6, 78.8, 81.0, 84.0, 128.9, 140.4.

Compound **17**; $[\alpha]_D^{21}$ -429.11° (c, 0.04, $CHCl_3$); ir ν_{max} (neat): 3455, 1711, 1638 cm^{-1}; ms m/z : 362 (M^+), 347 (M^+-Me), 344 (M^+-H_2O), 329 (M^+-H_2O-Me), 272 (M^+-TMSO-1), 254; ^{1}H nmr (C_6D_6) δ 0.25 (dd, J=9.2, 5.9 Hz, 1H), 0.40 (s, 9H), 0.63 (ddd, J=9.2, 7.7, 4.8 Hz, 1H), 0.79~0.92 (m, 1H), 0.88 (s, 3H), 1.02 (s, 3H), 1.07~1.21 (m, 1H), 1.64 (dd, J=2.6, 1.1 Hz, 3H), 1.30~1.98 (m, 7H), 2.02 (dd, J=12.8, 7.7 Hz, 1H), 2.13 (br s, 1H), 2.36 (ddd, J=12.8, 11.7, 1.1 Hz, 1H), 3.03 (dq, J=2.6, 2.6 Hz, 1H), 6.60 (dq, J=2.6, 1.1 Hz, 1H).

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