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A CONCISE FORMAL SYNTHESIS OF (±)-DEPLANCHEINE

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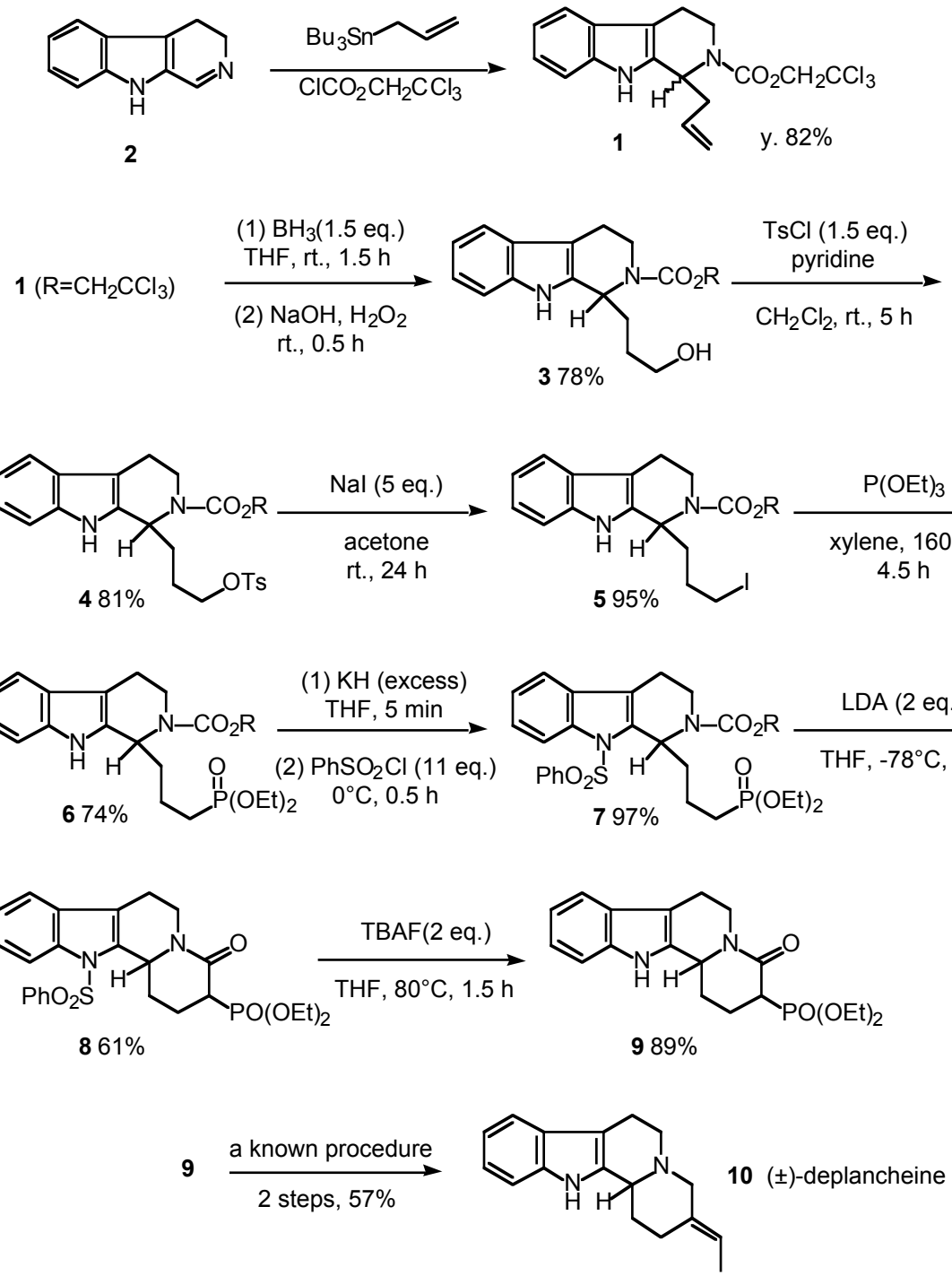
Abstract – For the purpose of verifying the utility of both enantiomers of 1-allyl-1,2,3,4-tetrahydro-β-carboline in alkaloid synthesis, the racemic one was transformed to (±)-deplancheine in 10 steps in 11% overall yield.

In the course of our research for the reaction of β-carboline with allyltributyltin in the presence of a chiral auxiliary derived from (*S*)-proline, we found that the allyl group was introduced to C-1 position in a stereoselective manner,[1] and that both enantiomers of 1-allyl-1,2,3,4-tetrahydro-β-carboline were obtained by the use of the same chiral auxiliary when allyltributyltin or tetraallyltin plus tin (IV) iodide were employed as a nucleophile.[2] We suppose that allyl group thus introduced has a potential for the transformation to many other functional groups,[3] and the allyl adduct might be a good starting material for a lot of indole alkaloids such as yohimbine, corynantheine, ajmalicine, and vincamine groups,[4] all of which have a chiral center at their C-1 position. In order to certify the usefulness of the allyl derivative as a starting material, we investigated at first the racemic version of total synthesis, and found that deplancheine, one of the corynantheine alkaloids, was readily synthesized using the allyl adduct. This paper describes these results.

Deplancheine is an alkaloid which was isolated from the New Caledonian plant *Alstonia deplanchei*,[5] and several groups reported the racemic total synthesis of the compound.[6] An asymmetric synthesis was carried out by Meyers *et al*. in 1986, and the absolute configuration of the natural product was revealed to be *R*.[7] We thought that the compound is a suitable target for verifying synthetic utility of the allyl adduct (**1**).[8] Racemic **1** was readily prepared by the addition reaction of 3,4-dihydro-β-carboline (**2**)[9] with allyltributyltin and 2,2,2-trichloroethyl chloroformate in dichloromethane.

The total synthesis was carried out by the procedure shown in Scheme. The allyl group of **1** was transformed to 3-hydroxypropyl group (compound (**3**)), and the terminal hydroxyl group was successively converted to tosyloxy, iodo, and diethylphosphoryl groups (compound (**4**), (**5**), and (**6**)). The attempt of the direct transformation of **4** to **6** resulted in the recovery of **4**, thus it was necessary to take a process to go through **5**. The compound (**7**) was initially subjected to the ring closing reaction by the use of lithium diisopropylamide (LDA) in THF expecting to obtain **9**, but the reaction did not proceed

with the recovery of the starting material. The reason for this inertness was supposed to be due to the existence of free N-H of 9-position, thus the protection of N-9 was investigated. As a result, phenylsulfonyl group was introduced by the use of potassium hydride as a base to afford **7**.



Scheme

Other protecting groups such as alkoxycarbonyl groups were found to be reluctant to react with **6**. The compound (**7**) thus obtained was treated with LDA to give the ring-closing product (**8**). The deprotection of phenylsulfonyl group was carried out using tetrabutylammonium fluoride[10] to afford

diethyl (4-oxo-1,2,3,4,6,7,12,12b-octahydro-indolo[2,3-*a*]quinolizin-3-yl)-phosphonate (**9**) in 89% yield.[11] The compound (**9**) is a known intermediate to be transformed to (±)-deplancheine in 57% in two steps. Therefore, the concise formal synthesis of the title compound was achieved in 10 steps in 10.9% overall yield from 3,4-dihydro-β-carboline (**2**).

In this paper, we described the formal total synthesis of (±)-deplancheine from 1-allyl-1,2,3,4-tetrahydro-β-carboline derivative (**1**) as a starting material. We found that the 1-allyl derivative was a versatile compound for one of the Corynantheine alkaloids. The asymmetric version of this synthesis, and the application to other alkaloids such as harmicine,[12] vincamine,[13] and dihydroantirhine[14] are now in progress in our laboratory.

EXPERIMENTAL

Melting points were measured using a Büchi 535 micro melting point apparatus and are uncorrected. The MS spectra were recorded on JMS-SX102A instrument. The NMR spectra were measured with JEOL GX400 and LA500 spectrometers using tetramethylsilane as an internal standard.

1-Allyl-1,2,3,4-tetrahydro-2-(2,2,2-trichloroethoxycarbonyl)-β-carboline (1). To the CH_2Cl_2 solution (50 mL) of 3,4-dihydro-β-carboline (5.10 g, 30 mmol) and allyltributyltin (10.9 g, 33 mmol) was added 2,2,2-trichloroethyl chloroformate (6.99 g, 33 mmol) at 0°C, and the mixture was allowed to react for 3.5 h at ambient temperature. Then 3M KF solution (30 mL) was added, and the mixture was reacted for 1 h to form a precipitate, which was filtered. The organic layer was separated, dried over $MgSO_4$, and evaporated. The residue was chromatographed on silica gel to give **1** as colorless crystals. **1-Allyl-1,2,3,4-tetrahydro-2-(2,2,2-trichloroethoxycarbonyl)-β-carboline (1)**: 9.53 g (82%); Colorless plates from hexane-AcOEt; mp 111.5-112.0°C; The NMR spectra were obtained as those of a mixture of two conformational isomers. The signals originated from the minor one are shown in parentheses. ^{1}H NMR ($CDCl_3$) δ 2.63-2.91 (4H, m), 3.23-3.36 (1H, m), 4.49-4.56 (1H, m), 4.82 (4.67) (1H, d, *J*=11.9 Hz), 4.82 (4.94) (1H, d, *J*=11.9 Hz), 5.15-5.24 (2H, m), 5.31-5.38 (1H, m), 5.90-6.06 (1H, m), 7.11 (1H, td, *J*=7.4, 2.8 Hz), 7.17 (1H, td, *J*=7.4, 1.4 Hz), 7.30-7.32 (1H, m), 7.48 (7.50) (1H, d, *J*=7.4 Hz), 7.94 (7.90) (1H, s) ; ^{13}C NMR ($CDCl_3$) δ 21.6 (21.1), 38.9 (39.26), 39.4 (39.30), 51.6 (51.5), 75.1 (75.2), 95.7 (95.5), 108.5 (109.0), 110.9 (111.0), 118.3 (118.1), 118.8 (119.2), 119.6 (119.7), 122.1 (122.0), 126.5 (126.4), 133.1 (132.8), 133.9 (134.1), 135.94 (135.92), 153.9 (153.5). Anal. Calcd for $C_{17}H_{17}N_2O_2Cl_3$: C, 52.67; H, 4.42; N, 7.23. Found: C, 52.86; H, 4.70; N, 7.16.

1,2,3,4-Tetrahtdrohydro-1-(3-hydroxypropyl)-2-(2,2,2-trichloroethoxy-carbonyl)-β-carboline.

Compound (**1**) (1.94 g, 5 mmol) was dissolved in 10 mL of THF, and the solution was cooled to 0°C under Ar. 7.5 mL (7.5 mmol) of 1M BH_3·THF solution was added to the solution, and the mixture was allowed to react for 1.5 h under Ar. Then water was added to quench excess BH_3, then 3M NaOH (2

mL, 6 mmol) and 30%H_2O_2 (2 mL, 17.6 mmol) were successively introduced. The mixture was allowed to stir for 30 min, then was diluted with water, and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, evaporated off to leave a residue, which was chromatographed on silica gel (CH_2Cl_2) to give the product **3**. **1,2,3,4-Tetrahtdrohydro-1-(3-hydroxypropyl)-2-(2,2,2-trichloroethoxycarbonyl)-β-carboline (3)** 1.58 g (78%); Colorless viscous oil; The NMR spectra were obtained as those of a mixture of two conformational isomers. The signals originated from the minor one are shown in parentheses. ^{1}H NMR ($CDCl_3$) δ 1.74-1.80 (2H, m), 1.83-2.00 (1H, m), 2.02-2.13 (1H, m), 2.25 (1H, br), 2.76 (1H, dd, *J*=15.4, 2.9 Hz), 2.90 (1H, td, *J*=15.5, 5.5 Hz), 3.23-3.36 (1H, m), 3.73-3.89 (2H, m), 4.49 (1H, dd, *J*=13.6, 4.5 Hz), 4.79 (4.63) (1H, d, *J*=12.0 Hz), 4.83 (4.92) (1H, d, *J*=12.0 Hz), 5.42-5.48 (1H, m), 7.07-7.17 (2H, m), 7.28 (7.30) (1H, d, *J*=7.7 Hz), 7.47 (7.49) (1H, d, *J*=7.3 Hz), 8.75 (8.63) (1H, s); ^{13}C NMR ($CDCl_3$) δ 21.6 (21.0), 28.2 (28.4), 31.4 (32.0), 38.8, 51.7 (51.5), 62.5 (62.7), 75.1 (75.2), 95.6, 107.7 (108.3), 111.0 (110.9), 118.0 (118.2), 119.4 (119.5), 121.8 (121.9), 126.6, 133.7 (133.4), 135.9, 154.4 (153.7). HRMS (FAB+): Calcd for $C_{17}H_{20}N_2O_3Cl_3$ $(M+H)^+$: 405.0540. Found 405.0525.

Transformation of 3 to 5. To the CH_2Cl_2 solution (4 mL) of **3** (296 mg, 1.22 mmol), pyridine (1.5 mL) and tosyl chloride (359 mg, 1.83 mmol) was added successively. The mixture was allowed to react for 5 h, then diluted with CH_2Cl_2, and washed with 1M HCl. The organic layer was dried over $MgSO_4$, and evaporated off to leave a residue, which was chromatographed on silica gel (CH_2Cl_2-AcOEt) to afford **4** as colorless viscous oil (553 mg, 81%). The structure of **4** was confirmed with ^{1}H and ^{13}C NMR, and it was used for the next step without further purification. To acetone solution (2 mL) of the compound **4** (530 mg, 0.95 mmol), NaI (719 mg, 4.75 mmol) was added, and the mixture was allowed to react for 24 h at rt. Thereafter, the mixture was diluted with water, and the mixture was extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, and evaporated to leave a residue, which was chromatographed on silica gel (CH_2Cl_2) to give **5** (463 mg, 95%) as colorless crystals. **1,2,3,4-Tetrahydro-1-(3-tosyloxypropyl)-2-(2,2,2-trichloroethoxycarbonyl)-β-carboline (4)**: The NMR spectra were obtained as those of a mixture of two conformational isomers; ^{1}H NMR ($CDCl_3$) δ 1.86-1.91 (3H, m), 2.04-2.14 (1H, m), 2.44 (3H, s), 2.73-2.77 (1H, m), 2.85-2.93 (1H, m), 3.17-3.29 (1H, m), 4.03-4.09 (1H, m), 4.34-4.43 (1H, m), 4.46 (1H, dd, *J*=13.6, 4.9 Hz), 4.76 (4.61) (1H, d, *J*=11.9 Hz), 4.80 (4.89) (1H, d, *J*=11.9 Hz), 5.35-5.42 (1H, m), 7.10 (1H, t, *J*=7.5 Hz), 7.18 (1H, t, *J*=7.5 Hz), 7.34-7.36 (1H, m), 7.35 (2H, d, *J*=8.1 Hz), 7.46 (7.48) (1H, d, *J*=7.5 Hz), 7.81 (7.79) (2H, d, *J*=8.1 Hz), 8.21 (8.23) (1H, s) ; ^{13}C NMR ($CDCl_3$) δ 20.9, 21.63 (21.58), 25.4, 29.8 (30.3), 38.85 (38.94), 50.6 (50.7), 69.7 (69.8), 75.1 (75.3), 95.6 (95.3), 108.2 (108.6), 111.1, 118.0 (118.1), 119.55 (119.63), 122.0 (122.2), 126.49 (126.53), 127.9, 130.0, 132.9 (132.8), 133.2 (132.9), 136.0, 145.0 (145.1), 154.5 (153.7). **1,2,3,4-Tetrahydro-1-(3-iodopropyl)-2-(2,2,2-trichloroethoxy-carbonyl)-β-carboline (5)**: 463 mg (95%); Colorless prisms from hexane-diisopropyl ether; mp 149-151°C; The NMR spectra were obtained as those of a mixture of two conformational isomers. The signals originated from the minor one are shown in parentheses. ^{1}H NMR ($CDCl_3$) δ 1.92-2.06 (4H, m), 2.74-2.79 (1H, m), 2.87-2.95 (1H, m), 3.21-3.34 (3H, m), 4.48-4.54 (1H, m), 4.81 (4.66) (1H, d, *J*=11.9 Hz), 4.85 (4.93) (1H, d, *J*=11.9 Hz), 5.33-5.38 (1H, m), 7.10-7.13 (1H, m), 7.18 (1H, t, *J*=7.9 Hz), 7.32 (1H, d, *J*=7.9 Hz), 7.48 (7.49) (1H, d, *J*=7.0 Hz), 7.94 (7.83) (1H, s) ; ^{13}C NMR ($CDCl_3$) δ 6.8 (6.4), 21.6 (20.9), 29.3 (29.8), 35.2 (35.8), 39.0 (39.1), 51.0 (51.2), 75.1 (75.3), 95.7

(95.4), 108.5 (109.0), 111.0 (110.9), 118.2 (118.3), 119.8 (119.9), 122.2 (122.3), 126.7, 133.1 (132.7), 136.0, 154.4 (153.7). Anal. Calcd for $C_{17}H_{18}N_2O_2Cl_3I$: C, 39.60; H, 3.52; N, 5.43. Found: C, 39.91; H, 3.28; N, 5.40.

Transformation of 5 to 6. To xylene solution (1.5 mL) of **5** (402 mg, 0.78 mmol), $P(OEt)_3$ (401 μL, 2.34 mmol)was added and the mixture was heated at 160°C for 4.5 h. Then the solvent was evaporated to leave a residue, which was chromatographed on silica gel (AcOEt) to give an oily product (**6**). It was crystallized by dispersion in hexane, and formed crystals were collected with filtration (304 mg, 74%). **1-[3-(Diethoxyphosphoryl)propyl]-1,2,3,4-tetrahydro-2-(2,2,2-trichloroethoxycarbonyl)-β-carboline (6)**: Colorless powder from AcOEt-diisopropyl ether; mp 187-188°C; The NMR spectra were obtained as those of a mixture of two conformational isomers. The signals originated from the minor one are shown in parentheses. ^{1}H NMR ($CDCl_3$) δ 1.34 (1.32) (6H, t, *J*=7.1 Hz), 1.80-2.22 (6H, m), 2.75 (1H, dd, *J*=15.4, 3.5 Hz), 2.86-2.94 (1H, m), 3.21-3.33 (1H, m), 4.04-4.19 (4H, m), 4.46-4.52 (1H, m), 4.79 (4.67) (1H, d, *J*=11.9 Hz), 4.83 (4.92) (1H, d, *J*=11.9 Hz), 5.36-5.46 (1H, m), 7.05-7.09 (1H, m), 7.12-7.16 (1H, m), 7.34 (1H, d, *J*=7.9 Hz), 7.45 (7.47) (1H, d, *J*=7.2 Hz), 9.32 (9.30) (1H, s) ; ^{13}C NMR ($CDCl_3$) δ 16.56 (16.59) (d, *J*=6 Hz), 19.03 (18.99), 21.8 (21.1), 23.9 (24.3) (d, *J*=139 Hz), 34.2 (34.8) (d, *J*=11 Hz), 39.1 (39.3), 50.6 (50.8), 61.8 (61.6) (d, *J*=7 Hz), 75.0 (75.3), 95.7 (95.4), 107.4 (108.0), 111.1, 117.7 (117.9), 119.0 (119.1), 121.5 (121.6), 126.40 (126.36), 133.8 (133.3), 135.9 (136.0), 154.1 (153.6). Anal. Calcd for $C_{21}H_{28}N_2O_5Cl_3P$: C, 47.97; H, 5.37; N, 5.33. Found: C, 48.35; H, 5.33; N, 5.30.

Transformation of 6 to 7. The excess amount of KH (35%), which was washed with pentane, was suspended in THF (5 mL), then the THF solution (5 mL) of **6** (438 mg, 0.8 mmol) was added and the mixture was allowed to stir for 5 min at 0°C. After the addition of phenylsulfonyl chloride (1.12 mL, 8.8 mmol), the mixture reacted for further 1 h. Then the reaction was stopped by the addition of water, and the mixture was extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, and evaporated off to leave a residue, which was chromatographed on silica gel (AcOEt) to give colorless crystals (519 mg, 97%). **1-[3-(Diethoxyphosphoryl)propyl]-1,2,3,4-tetrahydro-9-phenylsulfonyl-2-(2,2,2-trichloro-ethoxycarbonyl)-β-carboline (7)**: Colorless powder from hexane-diisopropyl ether; mp 92.2-94.0°C; The NMR spectra were obtained as those of a mixture of two conformational isomers. The signals originated from the minor one are shown in parentheses. ^{1}H NMR ($CDCl_3$) δ 1.32-1.35 (6H, m), 1.75-1.97 (4H, m), 2.02-2.09 (1H, m), 2.37-2.41 (1H, m), 2.66 (1H, ddd, *J*=16.2, 9.6, 4.6 Hz), 2.77-2.83 (1H, m), 3.22-3.34 (1H, m), 4.05-4.17 (4H, m), 4.41 (4.48) (1H, dd, *J*=14.0, 6.4 Hz), 4.89 (4.75) (1H, d, *J*=11.9 Hz), 4.94 (4.95) (1H, d, *J*=11.9 Hz), 5.95-6.01 (1H, m), 7.21-7.36 (5H, m), 7.42-7.49 (1H, m), 7.73 (1H, d, *J*=7.3 Hz), 7.78 (1H, d, *J*=7.6 Hz), 8.10-8.16 (1H, m) ; ^{13}C NMR ($CDCl_3$) δ 16.52 (16.49) (d, *J*=6 Hz), 19.4 (19.6) (d, *J*=5 Hz), 20.8 (21.4), 24.9 (25.2) (d, *J*=141 Hz), 34.9 (35.6) (d, *J*=18 Hz), 36.5 (36.4), 52.6 (52.5), 61.49 (61.54) (d, *J*=6 Hz), 75.0 (75.2), 95.8 (95.5), 115.6 (115.4), 118.5 (118.4), 118.6 (118.7), 124.18 (124.24), 125.1 (125.0), 126.8 (126.6), 129.1 (129.0), 130.1 (129.9), 133.7 (133.8), 135.8 (135.2), 136.7 (136.8), 136.9, 154.5 (153.7). Anal. Calcd for $C_{27}H_{32}N_2O_7Cl_3PS$: C, 48.70; H, 4.84; N, 4.21. Found: C, 48.97; H, 4.81; N, 4.25.

Transformation of 7 to 8. Compound (**7**) (336 mg, 0.5 mmol) was placed in a flask purged with Ar, and dissolved with absolute THF (5 mL). The mixture was cooled to -78°C, then the LDA solution (2M

in heptane-THF-ethylbenzene) (0.5 mL, 1 mmol) was added dropwise, and the mixture was allowed to react at -78°C for 1 h. Thereafter water (20 mL) and brine (20 mL) were added, and the mixture was acidified with 5% HCl, and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, and evaporated to leave a residue, which was chromatographed on silica gel (AcOEt:EtOH=9:3) to give the product. **Diethyl (1,2,3,4,6,7,12,12b-octahydro-4-oxo-12-phenylsulfonylindolo[2,3-*a*]quinolizin-3-yl)-phosphonate (8)**: 159 mg (61%); Pale yellow powder from ether; mp 176.2-180.1°C; The NMR spectra were obtained as those of a mixture of two diastereomeric isomers (ratio 5:2). The signals originated from the minor one are shown in parentheses. ^{1}H NMR ($CDCl_3$) δ 1.36 (1.19) (3H, t, *J*=7.0 Hz), 1.37 (1.33) (3H, t, *J*=7.0 Hz), 1.45-1.53 (1.94-2.02) (1H, m), 2.14-2.49 (2H, m), 2.52-2.70 (3H, m), 3.01-3.20 (2H, m), 4.09-4.25 (4.27-4.40) (4H, m), 5.05-5.19 (2H, m), 7.22-7.34 (5H, m), 7.43-7.47 (1H, m), 7.54-7.58 (2H, m), 8.08 (8.13) (1H, d, *J*=8.2 Hz); ^{13}C NMR ($CDCl_3$) δ 16.41 (16.28) (d, *J*=6 Hz), 16.6 (16.36) (d, *J*=6 Hz), 21.76 (21.3) (d, *J*=5 Hz), 21.8 (22.0), 32.0 (29.0) (d, *J*=12 Hz (2 Hz)), 39.4, 41.3 (42.2) (d, *J*=126 Hz (132 Hz)), 56.1 (56.4), 61.8 (62.3) (d, *J*=6 Hz), 63.4 (62.7) (d, *J*=6 Hz (7 Hz)), 116.5 (116.6), 118.7, 124.1 (124.4), 124.78 (124.80), 125.44 (125.40), 126.51 (126.49), 128.8 (128.7), 130.4 (130.5), 133.9 (133.8), 135.4 (135.7), 135.9 (135.8), 138.3 (138.4), 165.1 (165.2) (d, *J*=4 Hz (5 Hz)). Anal. Calcd for $C_{25}H_{29}N_2O_6PS$: C, 58.13; H, 5.66; N, 5.42. Found: C, 58.50; H, 5.89; N, 5.31.

Transformation of of 8 to 9. To the THF solution (1 mL) of **8** (52 mg, 0.1 mmol), tetrabutylammonium fluoride (131 mg, 0.5 mmol) was added and the mixture was refluxed for 1.5 h. The mixture was diluted with water (30 mL), and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$, and evaporated off to leave a residue, which was chromatographed on silica gel (AcOEt:EtOH=4:1) to give pale yellow crystals (**9**) (34 mg, 89%). ^{1}H NMR spectrum of the product showed it was a mixture of diastereomers (5:3), thus these diastereomers were separated by preparative TLC. The major and minor diastereomers were found to have the same NMR spectra as those of the literature. The major isomer has a mp at 236-239°C (lit.,[9] mp 236°C).

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