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Deprotection of Allyl Groups with Sulfinic Acids and Palladium Catalyst

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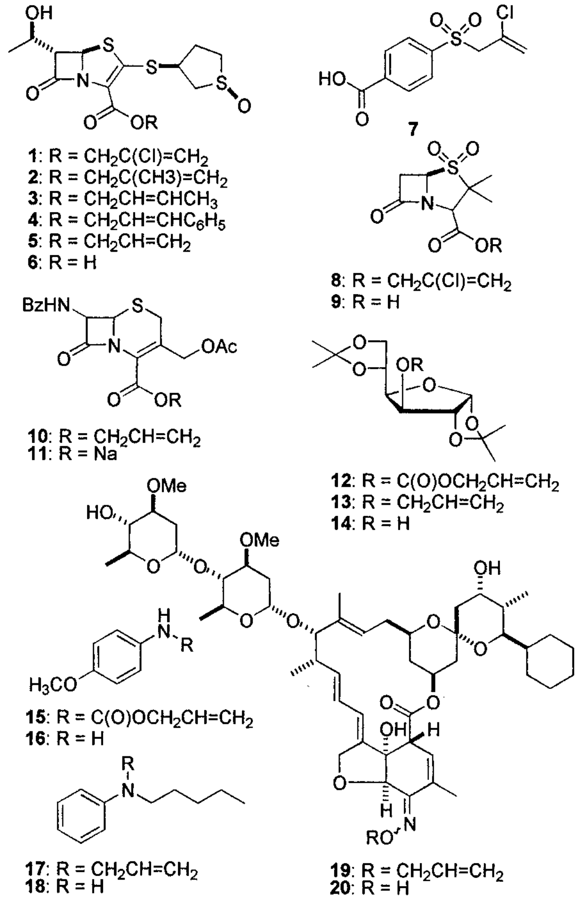
Allyl or alloxycarbonyl groups have been frequently used as suitable protecting groups for acids, alcohols, and amines in the synthesis of carbohydrates,[1] peptides,[2] nucleotides,[3] and other natural products.[4] It is known that the cleavage of the allyl groups is accomplished by palladium-catalyzed reaction with a carboxylic acid as an allyl scavenger that attacks the allyl group, forming the π allylpalladium complex.[5] Although several methods have hitherto been developed for deprotection of the allyl group,[6] in the context of our studies dealing with the mild deprotection of allyl esters of unstable penems, we have found that sulfinic acid or its salt in the presence of a catalytic amount of tetrakis(triphenylphosphine)-palladium [$Pd(PPh_3)_4$] was highly effective for facilitating the carbon−oxygen bond cleavage.[7] Furthermore, under these mild reaction conditions, cleavage of *O*-allyl ethers and *N*-allyl amines was also facilitated. Herein we describe the deprotection of a wide range of allyl derivatives, such as allyl esters, allyl carbonates, and allyl carbamates as well as *O*-allyl ethers and *N*-allyl amines to afford the corresponding carboxylic acid, alcohol, or amine in excellent yield.

Chart 1



In 1979, Tsuji and Yamakawa found that the palladium-catalyzed hydrogenolysis of allyl groups with ammonium formate was highly effective for the deprotection of a 2-propenyl ester to give the carboxylic acid and propene.[8] The more promising results for industrial synthesis were obtained by Jeffrey and McCombie, who reported that allyl esters, carbonates, and carbamates are deprotected by treatment with a carboxylic acid in the presence of $Pd(PPh_3)_4$ and additional triphenylphosphine (PPh_3).[9] According to the Jeffrey−McCombie method by using sodium 2-ethylhexanoate (SEH) and a catalytic amount of $Pd(PPh_3)_4$ with PPh_3 in dichloromethane, the deprotection of the 2-chloroallyl ester **1** proceeded to give a carboxylic acid **6** in a 76% yield (entry 3 in Table 1).[10] Although the methallyl ester **2** was subjected to the same procedures, the deprotection resulted in a 52% yield of the carboxylic acid **6** due to the slow reaction and instability of the compounds under the reaction conditions (entry 5).

We extensively investigated an alternative method for deprotection of the allyl ester **1** and found that sulfinic acids or their salts are the most effective allyl scavengers in the presence of a palladium catalyst. Use of carboxylic acids,[8] morpholine,[11] dimedone,[12] and *N,N*'-dimethylbarbituric acid[13] as allyl scavengers led to poor results. As

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Table 1. Deallylation with Sulfinic Acids in the Presence of Palladium Catalyst[a]

		catalyst							
entry	substrate	palladium	mol %	nucleophile	additive (equiv)	solvent	time (min)	product	yield (%)[b]
1	**1**	Pd(PPh3)$_4$	5.0	PhSO$_2$H	PPh3 (0.15)	CH$_2$Cl$_2$	60	**6**	96
2	**1**	Pd(PPh3)$_4$	5.9	TolSO$_2$Na	none	THF/MeOH	105	**6**	97
3	**1**	Pd(PPh$_3$)$_4$	5.4	SEH	PPh$_3$ (0.14)	CH$_2$Cl$_2$	120	**6**	76
4	**2**	Pd(PPh$_3$)$_4$	7.0	TolSO$_2$Na	none	THF/MeOH	130	**6**	94
5	**2**	Pd(PPh$_3$)$_4$	7.7	SEH	PPh$_3$ (0.15)	CH$_2$Cl$_2$	120	**6**	52
6	**1**	Pd(OAc)$_2$	21.2	TolSO$_2$Na	TEP (0.74)	THF/MeOH	80	**6**	80
7	**1**	Pd(OAc)$_2$	20.5	SEH	TEP (0.70)	THF/MeOH	360	**6**	45
8	**1**	Pd(ACN)$_2$Cl$_2$	13.7	TolSO$_2$Na	TEP (0.42)	THF/MeOH	17.5 (h)	**6**	85
9	**1**	Pd(PPh$_3$)$_4$	7.3	STS[c]	none	THF/MeOH	150	**6**	96
10	**1**	Pd(PPh$_3$)$_4$	5.9	SCNBS[d]	none	THF/MeOH	130	**6**	72
11	**1**	Pd(PPh$_3$)$_4$	6.0	*i*-BuSO$_2$Na	none	THF/MeOH	315	**6**	90
12	**1**	Pd(PPh$_3$)$_4$	6.3	Rongalit[e]	none	THF/MeOH	80	**6**	86
13	**1**	Pd(PPh$_3$)$_4$	6.0	TolSO$_2$TBA[f]	none	CH$_2$Cl$_2$	25	**6**	70
14	**3**	Pd(PPh$_3$)$_4$	4.3	TolSO$_2$Na	none	THF/MeOH	35	**6**	91
15	**4**	Pd(PPh$_3$)$_4$	5.0	TolSO$_2$Na	none	THF/MeOH	30	**6**	94
16	**5**	Pd(PPh$_3$)$_4$	4.6	TolSO$_2$Na	none	THF/MeOH	25	**6**	87
17	**8**	Pd(PPh$_3$)$_4$	5.6	TolSO$_2$Na	none	THF/MeOH	60	**9**	99
18	**10**	Pd(PPh$_3$)$_4$	6.0	TolSO$_2$Na	none	THF/MeOH	60	**11**	80
19	**12**	Pd(PPh$_3$)$_4$	7.0	TolSO$_2$H	none	CH$_2$Cl$_2$	30	**14**	98
20	**13**	Pd(PPh$_3$)$_4$	7.0	TolSO$_2$H	none	CH$_2$Cl$_2$	25	**14**	99
21	**15**	Pd(PPh$_3$)$_4$	7.0	TolSO$_2$H	none	CH$_2$Cl$_2$	40	**16**	79
22	**17**	Pd(PPh$_3$)$_4$	7.0	TolSO$_2$H	none	CH$_2$Cl$_2$	60	**18**	93
23	**19**	Pd(PPh$_3$)$_4$	10.6	TolSO$_2$H	none	CHCl$_3$	60	**20**	89

[a] All reaction were carried out at rt. [b] Isolated yield. [c] STS: sodium 2-thiophenesulfinate. [d] SCNBS: sodium 4-chloro-3-nitrobenzenesulfinate. [e] Rongalit: sodium formaldehyde sulfoxylate. [f] TBA: tetrabutylammonium.

shown in Table 1, the deallylation employing commercially available benzenesulfinic acid (PhSO$_2$H) or sodium toluenesulfinate (TolSO$_2$Na) provided the acid **6** in high yield (entries 1, 2, and 4). The reaction of **1** using TolSO$_2$Na also proceeds in the presence of other palladium catalysts such as palladium acetate or dichlorobis(acetonitrile)palladium and triethyl phosphite[14] (TEP) to give **6** in good yield (entries 6 and 8), while with SEH the yield is still low (entry 7).

Deallylation of **1** with monosodium *p*-sulfinobenzoate[15] bearing two possible nucleophilic sites proceeded smoothly to afford the acid **6** and 2-chloro-2-propenyl *p*-carboxyphenyl sulfone **7**[16] resulting from attack by sulfur. ^{1}H NMR analysis of the products suggested the absence of 2-chloro-2-propenyl sulfinobenzoate resulting from oxygen attack of the carboxylate. Other aromatic sulfinic compounds bearing either a heterocycle (entry 9) or electron-donating and -withdrawing substituents (entry 10) and aliphatic sulfinic compounds[17] (entries 11 and 12) can alternatively be used for the deallylation of allyl esters irrespective of acid salt forms such as sodium, lithium, or tetrabutylammonium (entry 13).

The same reaction conditions when applied to butenyl, cinnamyl, and propenyl esters proceeded smoothly to give the acid **6** in high yields (entries 14–16). As the present deallylation can be performed under very mild reaction conditions, the penem **8** and the cephem **10**[18] were readily deprotected to afford the corresponding acids **9**[19] and **11**, respectively, in excellent yield (entries 17 and 18). In the case of the allyl carbonate **12**[20] and the allyl carbamate **15**,[21] the palladium-catalyzed deallylation using TolSO$_2$H is comparable to those of the allyl ester (entries 19 and 21). As shown in the Table 1, sulfinic acids are highly effective allyl scavengers as compared with SEH, and the zerovalent catalyst Pd(PPh$_3$)$_4$ is clearly far superior to all the other palladium compounds in terms of the reaction speed and yield.

The excellent results described above prompted us to investigate the possibility of applying the same cleavage conditions to the oxygen–carbon bonds of an ether and the nitrogen–carbon bond of an amine. Several methods have been developed for deprotection of *O*-allyl ethers[6a,22] or *N*-allyl compounds.[6a,23] However, these deprotections are quite limited by the low chemoselectivity or the severe reaction conditions which affect the rest of the functional groups in the substrate. Our method for the deprotection of allyl groups with a sulfinic acid and Pd(PPh$_3$)$_4$ is applicable to *O*-allyl ethers or *N*-allyl compounds due to the very mild reaction conditions and high chemoselectivity. Not only did the deprotection of the allyl ether of the sugar **13**[24] proceed readily at room temperature without affecting the acid-sensitive *O*-isopropylidene group, the *N*-allyl amine **17** was deprotected easily as well (entries 20 and 22). The *O*-allyl oxime of the avermectin macrolide **19** was deprotected to **20**[25] in high yield without affecting the olefin moieties and

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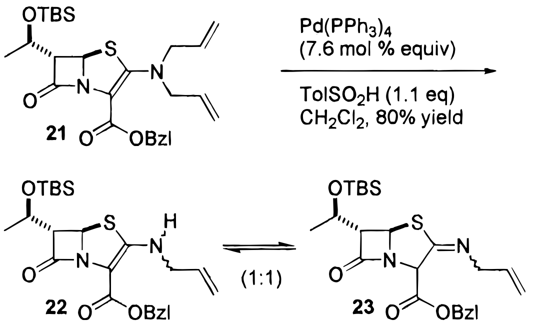
Scheme 1



glycosidic linkages (entry 23). The aminopenem **21**[26] which is unstable in basic or acidic conditions could be converted into the inseparable enamine–imine mixture (**22** and **23**) in a 1:1 ratio[27] using our reaction conditions at room temperature for 60 min (Scheme 1).

In conclusion, sulfinic acids or the corresponding salts in the presence of a catalytic amount of $Pd(PPh_3)_4$ are highly effective for facilitating the carbon–oxygen bond cleavage of allyl esters and ethers as well as the carbon–nitrogen bond of *N*-allyl amines. Considering the synthetic availability and chemostability of the allyl protecting group, our allyl deprotection method offers a new synthetic option toward complicated natural products such as polyether ionophores, macrolides, nucleotides, oligosaccharides, and alkaloids.

Experimental Section

General Procedures. Melting points are uncorrected. ^{1}H NMR spectra were recorded at 270 MHz. ^{13}C NMR spectra were recorded at 67.5 MHz. Chemical shifts are expressed in parts per million (δ) relative to tetramethylsilane for ^{1}H NMR and DMSO-d_6 (δ) for ^{13}C NMR. IR spectra of samples were recorded in KBr pressed disks for crystalline samples. Optical rotations were measured at ambient temperature at the sodium line. Column chromatography was performed on 230–400 mesh silica gel. Alkyl sulfinates were prepared from the corresponding phthalimidomethyl sulfone.[17] Other sulfinates were prepared in the usual way by the reaction of sulfonyl chloride and sodium sulfite or zinc powder. $Pd(PPh_3)_4$[28] was purchased from Kanto Chemical Co. Inc. (Tokyo, Japan).

Removal of the 2-Chloro-2-propenyl Group from 1. Method A. Benzenesulfinic acid (2.87 g, 20.2 mmol) was added at rt to a suspension of **1** (7.82 g, 18.4 mmol), PPh_3 (723 mg, 2.76 mmol), and $Pd(PPh_3)_4$ (1.06 g, 0.92 mmol) in CH_2Cl_2 (196 mL). After the reaction mixture was stirred for 1 h at rt, the resulting crystals were collected by filtration, washed three times with CH_2Cl_2 (7 mL), and then dried in vacuo to give the carboxylic acid **6** as an off-white powder (6.19 g) in 96% yield: ^{1}H NMR (270 MHz, DMSO-d_6) δ 5.74 (d, J = 1.5 Hz, 1H), 4.02–3.72 (m, 4H), 3.05–2.94 (m, 1H), 2.90–2.78 (m, 1H), 2.75–2.59 (m, 2H), 2.47–2.31 (m, 1H), 1.16 (d, J = 6.2 Hz, 3H). **Method B.** A solution of sodium *p*-toluenesulfinate tetrahydrate (155 mg, 0.615 mmol) in MeOH (2.3 mL) was added at rt to a suspension of **1** (261 mg, 0.615 mmol) and $Pd(PPh_3)_4$ (41.7 mg, 36.1 μmol) in THF (3.9 mL). The reaction mixture was stirred at rt for 105 min, and EtOAc (12 mL) was added dropwise to precipitate the sodium salt of the target compound. Celite (0.8 g) was added to the mixture. After filtration, the precipitates and Celite were washed with EtOAc (3 mL + 1.5 mL × 3), and the precipitates were dissolved in water (3 mL + 1.5 mL × 3). The aqueous solution was acidified with an ion-exchange resin (Manufactured by Mitsubishi Chem. under the trade name of DIAION PK216H), and acetone (7.5 mL) was added. The resin was filtered off and washed with acetone–water (2:1, 1.5 mL × 3). The combined filtrates were concentrated at 24 °C by an evaporator to strip acetone and freeze-dried to give light yellow powders (209 mg) in 97% yield.

Preparation of 2-Methyl-2-propenyl (5*R*,6*S*)-6-(1(*R*)-Hydroxyethyl)-2-(1(*R*)-oxo-3(*S*)-thiolanylthio)-2-penem-3-carboxylate (2). The sodium salt of the carboxylic acid **6** (0.670 g, 1.34 mmol) was dissolved in *N*,*N*-dimethylformamide (2 mL), and 1-bromo-2-methyl-2-propene (0.540 mL, 4.04 mmol) was added dropwise at 0 °C. The reaction mixture was stirred at rt for 23 h and poured into water (50 mL) and extracted with CH_2Cl_2. The extract was washed with water and concentrated in vacuo. The resulting residue was chromatographed on silica gel (EtOAc:MeOH 20:1–10:1) to give the 2-methyl-2-propenyl ester **2** as a white solid (455 mg) in 63% yield: mp 82–83 °C; $[\alpha]^{23}_{D}$ +61.6° (c 0.32, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.70 (d, J = 1.5 Hz, 1H), 5.08 (s, 1H), 4.95 (s, 1H), 4.75 (d, J = 13.2 Hz, 1H), 4.52 (d, J = 13.2 Hz, 1H), 4.24 (m, 1H), 3.94 (dd, J = 14.3, 8.4 Hz, 1H), 3.74 (dd, J = 7.0, 1.5 Hz, 1H), 3.66 (t, J = 8.4 Hz, 1H), 3.20–3.10 (m, 1H), 2.90–2.64 (m, 4H), 2.18 (s, 1H), 1.80 (s, 3H), 1.36 (d, J = 6.2 Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 171.7, 159.4, 151.3, 139.4, 118.4, 113.5, 71.4, 68.5, 65.5, 64.7, 61.2, 52.7, 46.6, 33.2, 21.9, 19.5; IR (KBr) 3264, 1779, 1673, 1492, 1323, 1213, 1125, 1017 cm^{-1}. Anal. Calcd for $C_{16}H_{21}O_5NS_3$: C, 47.62;H, 5.25; N, 3.47; S, 23.84. Found: C, 47.69; H, 5.01; N, 3.51; S, 24.09.

Removal of the 2-Methyl-2-propenyl Group from 2. The carboxylic acid **6**, a light yellow powder (198 mg, 0.567 mmol), was obtained in 94% yield from **2** (244 mg, 0.604 mmol) by the same procedure as described in method B.

Preparation of 2-Butenyl (5*R*,6*S*)-6-(1(*R*)-Hydroxyethyl)-2-(1(*R*)-oxo-3(*S*)-thiolanylthio)-2-penem-3-carboxylate (3). The sodium salt of the carboxylic acid **6** (1.75 g, 4.71 mmol) was dissolved in *N*,*N*-dimethylformamide (5.2 mL), and 1-bromo-2-butene (1.91 g, 14.1 mmol) was added. The reaction mixture was stirred at rt for 20 h and poured into water (50 mL). After stirring for 30 min, the light yellow solids were filtered off. The filtrate was extracted with CH_2Cl_2 (30 mL). The extract was dried over $MgSO_4$, concentrated, and washed with EtOAc (5 mL) and *n*-hexane (5 mL) to give light yellow solids. The solids (2.0 g) were combined, recrystallized from EtOH (20 mL), filtered off, and dried in vacuo to give the 2-butenyl ester **3** as a white solid (1.04 g) in 55% yield. The mother liquor was concentrated, washed with EtOAc (2 mL), and dried in vacuo to give the butenyl ester (0.24 g) as the second crop in 13% yield. The first and second crops were combined: mp 161–162 °C; $[\alpha]^{23}_{D}$ +96.2° (c 0.30, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 5.95–5.57 (m, 3H), 4.85–4.62 (m, 2H), 4.31–4.18 (m, 1H), 3.93 (dd, J = 14.3, 8.4 Hz, 1H), 3.72 (dd, J = 7.0, 1.5 Hz, 1H), 3.64 (t, J = 8.4 Hz, 1H), 3.21–3.10 (m, 1H), 2.90–2.62 (m, 4H), 2.27 (s, 1H), 1.72 (d, J = 6.6 Hz, 3H), 1.36 (d, J = 6.2 Hz, 3H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 171.8, 159.6, 150.9, 130.0, 123.9, 118.6, 71.4, 66.0, 65.5, 64.7, 61.2, 52.6, 46.6, 33.2, 21.9, 17.8; IR (KBr) 3280, 1778, 1768, 1675, 1496, 1328, 1126, 957 cm^{-1}. Anal. Calcd for $C_{16}H_{21}O_5NS_3$: C, 47.62; H, 5.25; N, 3.47; S, 23.84. Found: C, 47.58; H, 5.35; N, 3.49; S, 24.12.

Removal of the 2-Butenyl Group from 3. The carboxylic acid **6**, a light yellow powder (178 mg, 0.509 mmol), was obtained in 91% yield from the 2-butenyl ester **3** (227 mg, 0.562 mmol) by the same procedure as described in method B.

Preparation of Cinnamyl (5*R*,6*S*)-6-(1(*R*)-Hydroxyethyl)-2-(1(*R*)-oxo-3(*S*)-thiolanylthio)-2-penem-3-carboxylate (4). The sodium salt of the carboxylic acid **6** (6.88 g, 18.5 mmol) was dissolved in *N*,*N*-dimethylformamide (25 mL), and cinnamyl bromide (3.65 g, 18.5 mmol) was added at rt. The reaction mixture was stirred at rt for 20 h, poured into water (500 mL), and then extracted with CH_2Cl_2 (250 mL). The extract was washed with water (50 mL) and concentrated in vacuo. Isopropyl ether (200 mL) was added to the resulting residue, and the resulting precipitates were collected by filtration. The collected solids were recrystallized from 2-propanol (50 mL), filtered off, and then dried in vacuo to give the cinnamyl ester **4** as a light yellow solid (2.32 g) in 31% yield: mp 173–174 °C; $[\alpha]^{25}_{D}$ +42.2° (c 0.24, $CHCl_3$); ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.42–7.22 (m, 5H),

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[25] Bishop, B. F.; Pacey, M. S. Perry, D. M. Patent WO9415944-A1 1994.

[26] Nagakura, I.; Kadoi, H.; Yamasaki, T. *Heterocycles* **1997**, *45*, 835.

[27] For inseparable **22**–**23** (1:1) mixture: Girijavallqabhan, V. M.; Ganguly, A. K.; Liu, Y.; Pinto, P. A.; Patel, N.; Hare, R. H.; Miller, G. H. *J. Antibiot.* **1986**, *34*, 1187.

[28] The reaction rate is highly dependent on the quality of $Pd(PPh_3)_4$, and the concomitant addition of PPh_3 accelerates the reaction.[14]

6.74 (d, $J = 16.1$ Hz, 1H), 6.32 (dt, $J = 15.8$, 6.3 Hz, 1H), 5.69 (d, $J = 0.5$ Hz, 1H), 4.96−4.83 (m, 2H), 4.28−4.23 (m, 1H), 3.93 (dd, $J = 14.3$, 8.4 Hz, 1H), 3.74 (dd, $J = 7.0$, 1.5 Hz, 1H), 3.69−3.63 (m, 1H), 3.15−3.12 (m, 1H), 2.83 (ddd, $J = 14.3$, 8.4, 1.8 Hz, 1H), 2.75−2.63 (m, 2H), 1.37 (d, $J = 6.2$ Hz, 3H); ^{13}C NMR (67.5 MHz, CDCl$_3$) δ 171.7, 159.5, 151.4, 134.5, 128.5, 128.4, 128.0, 126.7, 122.7, 71.4, 65.8, 65.5, 64.7, 61.2, 52.7, 46.6, 33.2, 21.9; IR (KBr) 3488, 1750, 1680, 1475, 1344 739, 692 cm^{-1}. Anal. Calcd for $C_{21}H_{23}O_5NS_3$: C, 54.17; H, 4.98; N, 3.01; S, 20.66. Found: C, 54.09; H, 4.98; N, 2.91; S, 20.74.

Removal of the Cinnamyl Group from 4. The carboxylic acid **6**, a light yellow powder (177 mg, 0.507 mmol), was obtained in 94% yield from the cinnamyl ester **4** (251 mg, 0.540 mmol) by the same procedure as described in method B.

Removal of the 2-Propenyl Group from 5. The carboxylic acid **6**, a light yellow powder (405 mg, 1.16 mmol), was obtained from the 2-propenyl ester **5** (500 mg, 1.28 mmol) by the same procedure as described in method B. **Method C.** A solution of sodium *p*-toluenesulfinate tetrahydrate (1.06 g, 4.23 mmol) in water (7 mL) was added at rt to a suspension of the 2-propenyl ester **5** (1.54 g, 3.95 mmol) and Pd(PPh$_3$)$_4$ (209 mg, 0.180 μmol) in THF (20 mL). The reaction mixture was stirred at rt for 25 min. After partition of ether (20 mL), the ether layer was extracted with water (1 mL). The water extracts were treated with active charcoal (0.28 g) and filtered. The filter cake was rinsed with water (1.5 mL). The combined aqueous solution was cooled to 5 °C, acidified to a pH of 2.5 with HCl and stirred at 5 °C for 30 min. The precipitates were filtered off, washed with water (1 mL), and dried in vacuo to give the carboxylic acid **6** as a pale pink powder (1.20 g) in 87% yield.

Removal of the 2-Chloro-2-propenyl Group from 1 with Monosodium *p*-Sulfinobenzoate. Tetrahydrofuran (3.37 mL) and water (1.35 mL) were added at rt to a mixture of monosodium *p*-sulfinobenzoate (118 mg), the 2-chloro-2-propenyl ester **1** (200 mg, 0.471 mmol), and Pd(PPh$_3$)$_4$ (28.7 mg, 24.8 μmol). The reaction mixture was stirred at rt for 90 min. After addition of water (1 mL), the mixture was extracted three times with ether (9 mL + 4.5 mL × 2). The aqueous layer was cooled to 5 °C, acidified to a pH of 2.5 by adding concd HCl, and stirred at 5 °C for 30 min. The precipitates were filtered off, washed three times with water (1 mL × 3), and dried in vacuo to give a mixture (246 mg, an off-white powder) of the carboxylic acid **6** and 2-chloro-2-propenyl *p*-carboxyphenyl sulfone **7** in a molar ratio of 4:3.

6: ^{1}H NMR (270 MHz, DMSO-d_6) δ 5.71 (d, $J = 1.5$ Hz), 4.00−3.72 (m), 3.04−2.97 (m), 2.90−2.78 (m), 2.75−2.61 (m), 2.46−2.33 (m), 1.16 (d, $J = 6.2$ Hz).

7: ^{1}H NMR (270 MHz, DMSO-d_6) δ 8.17 (d, $J = 8.4$ Hz), 8.03 (d, $J = 8.4$ Hz), 5.54 (d, $J = 1.8$ Hz), 5.46 (s), 4.63 (s).

Preparation of 2-Chloro-2-propenyl (2*S*,5*R*)-3,3-Dimethyl-4,4,7-trioxo-4-thia(VI)-1-azabicyclo[3.2.0]heptane-2-carboxylate (8). Sodium 4,4-dioxopenicillanate[19] (3.25 g, 12.7 mmol) and 1-bromo-2-chloro-2-propene (3.96 g, 25.5 mmol) in hexamethylphosphoramide (26 mL) were stirred at 55 °C for 18 h. The mixture was diluted with ether (300 mL), washed three times with water (50 mL), dried over MgSO$_4$, and then concentrated. The resulting residue was dissolved in MeOH (10 mL) and mixed with *n*-hexane (100 mL) to effect precipitation of solid material. After 15 min of stirring, the precipitates were collected by filtration, washed three times with *n*-hexane (10 mL), and then dried in vacuo to give the 2-chloro-2-propenyl ester **8** as a white solid (3.36 g) in 86% yield: mp 79.5−80.5 °C; $[\alpha]^{24}_{D}$ +192.9° (*c* 0.31, CHCl$_3$); ^{1}H NMR (270 MHz, CDCl$_3$) δ 5.58 (m, 1H), 5.52 (d, $J = 1.8$ Hz, 1H), 4.90 (dd, $J = 13.0$, 0.9 Hz, 1H), 4.68 (dd, $J = 12.8$, 0.7 Hz, 1H), 4.64−4.62 (m, 1H), 4.44 (s, 1H), 3.48 (m, 2H), 1.66 (s, 3H), 1.46 (s, 3H); ^{13}C NMR (67.5 MHz, CDCl$_3$) δ 170.7, 166.3, 134.6, 118.0, 68.0, 63.1, 62.8, 61.0, 38.3, 20.2, 18.3; IR (KBr) 1793, 1763, 1644, 1318 cm^{-1}. Anal. Calcd for $C_{11}H_{14}O_5NSCl$: C, 42.93; H, 4.59; N, 4.55; S, 10.42. Found: C, 43.03; H, 4.54; N, 4.54; S, 10.69.

Removal of the 2-Chloro-2-propenyl Group from 8. The carboxylic acid **9**, a white powder (242 mg, 1.04 mmol), was obtained in 99% yield from the 2-chloro-2-propenyl ester **8** (323 mg, 1.05 mmol) by the same procedure as described in method B.

Preparation of 2-Propenyl 7-Benzamido-3-(acetoxymethyl)-3-cepham-4-carboxylate (10). Tetrabutylammonium hydrogen sulfate (1.08 g, 3.19 mmol) was dissolved in water (4.6 mL), and the solution was adjusted to pH 6 with aqueous 5 N sodium hydroxide solution. This was mixed with sodium 7-benzamido-3-(acetoxymethyl)-3-cepham-4-carboxylate (1.00 g, 2.51 mmol), stirred at rt for 2 h while keeping the pH value at 6.6 by addition of an aqueous 1 N NaOH solution, and then extracted three times with CHCl$_3$ (4.6 mL + 2.3 mL × 2). The CHCl$_3$ extracts were mixed with allyl bromide (912 mg, 7.53 mmol) and stirred at 50 °C for 2 h. The reaction solution was poured into EtOAc (200 mL), washed three times with water (20 mL), dried over MgSO$_4$, and then concentrated. The resulting residue was purified by a silica gel column chromatography (CHCl$_3$:acetone 97:3−95:5) to give the 2-propenyl ester **10** as a light yellow viscous liquid (905 mg) in 87% yield; $[\alpha]^{24}_{D}$ +58.7° (*c* 0.15, CHCl$_3$); ^{1}H NMR (270 MHz, CDCl$_3$) δ 7.84 (dd, $J = 8.2$, 1.3 Hz, 2H), 7.58−7.42 (m, 3H), 7.30 (d, $J = 8.8$ Hz, 1H), 6.06−5.89 (m, 2H), 5.42−5.15 (m, 3H), 5.08 (d, $J = 4.8$ Hz, 1H), 4.85 (d, $J = 13.6$ Hz, 1H), 4.75 (dd, $J = 6.0$, 0.9 Hz, 2H), 3.61 (d, $J = 18.3$ Hz, 1H), 3.42 (d, $J = 18.3$ Hz, 1H), 2.09 (s, 3H); ^{13}C NMR (67.5 MHz, CDCl$_3$) δ 170.5, 167.3, 164.8, 161.0, 132.7, 131.8, 128.7, 127.3, 125.9, 125.6, 119.5, 76.5, 66.9, 63.0, 59.8, 57.6, 26.5, 20.7; IR (KBr) 3280, 1776, 1748, 1720, 1646, 1522, 1390, 1038 cm^{-1}. Anal. Calcd for $C_{20}H_{20}O_6N_2S$: C, 57.68, H, 4.84, N, 6.73. Found: C, 57.62, H, 4.81, N, 6.70.

Removal of the 2-Propenyl Group from 10. Methanol solution (3.0 mL) of sodium *p*-toluenesulfinate tetrahydrate (218 mg, 0.871 mmol) was added at rt to a solution of the 2-propenyl ester **10** (330 mg, 0.792 mmol) and Pd(PPh$_3$)$_4$ (54.9 mg, 47.5 μmol) in THF (5.0 mL). The reaction mixture was stirred for 60 min at rt. After addition of EtOAc (16 mL), the mixture was stirred for 30 min. The resulting precipitate was collected by filtration, washed three times with EtOAc (2 mL), and dried in vacuo at rt to give the sodium salt of the carboxylic acid **11** as a white powder (253 mg) in 80% yield.

Removal of the Allyloxycarbonyl Group from 12. *p*-Toluenesulfinic acid (59.3 mg, 0.380 mmol) was added to a CH$_2$Cl$_2$ solution (3.3 mL) of 3-*O*-(allyloxycarbonyl)-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**12**) (115 mg, 0.334 mmol) and Pd(PPh$_3$)$_4$ (27.0 mg, 23.4 μmol). The reaction mixture was stirred for 30 min at rt, mixed with triethylamine (6.8 mg, 67 μmol), and then subjected to a silica gel chromatography (hexanes:EtOAc 1:1) to give di-*O*-isopropylidene-α-D-glucofuranose (**14**) as a white solid (85.6 mg) in 98% yield.

Removal of the Allyl Group from 13. *p*-Toluenesulfinic acid (78.5 mg, 0.503 mmol) was added at rt to a solution of 3-*O*-allyl-1,2:5,6-di-*O*-isopropylidene-α-D-glucofuranose (**13**) (136 mg, 0.452 mmol) and Pd(PPh$_3$)$_4$ (36.6 mg, 31.7 μmol) in CH$_2$Cl$_2$ (4.5 mL). The reaction mixture was stirred at rt for 25 min, and triethylamine (9.1 mg, 90 μmol) was added. The mixture was subjected to a silica gel chromatography (hexanes:EtOAc 1:1) to give di-*O*-isopropylidene-α-D-glucofuranose (**14**) as a white solid (117 mg) in 99% yield.

Removal of the Allyloxycarbonyl Group from 15. Pd(PPh$_3$)$_4$ (30.3 mg, 26.2 μmol) was added to a CH$_2$Cl$_2$ solution (3.7 mL) of *p*-toluenesulfinic acid (64.3 mg, 0.411 mmol) and allyl *N*-(*p*-methoxyphenyl)carbamate (**15**) (77.6 mg, 0.374 mmol). The reaction mixture was stirred for 40 min at rt. The reaction solution was subjected to a silica gel chromatography (hexanes: EtOAc 65:35 to 6:4) to give *p*-anisidine **16** (36.3 mg) in 79% yield.

Preparation of *N*-Allyl-*N*-pentylaniline (17). *N*-Allylaniline (1.95 g, 14.7 mmol) and bromopentane (2.22 g, 14.7 mmol) were stirred at 80 °C for 16 h. After being cooled to rt, the mixture was treated with a solution of sodium hydroxide (714 mg, 17.9 mmol) in water (1.5 mL), stirred for 30 min, and extracted with ether (80 mL). The extract was dried over potassium carbonate and concentrated in vacuo. The residue was chromatographed on silica gel (CHCl$_3$:acetone:water 95:5: 0.1−90:10:0.2) to give *N*-allyl-*N*-pentylaniline **17** as a colorless oil (1.68 g) in 56% yield; ^{1}H NMR (270 MHz, CDCl$_3$) δ 7.21 (dd, $J = 8.5$, 0.8 Hz, 1H), 7.18 (dd, $J = 8.5$, 0.8 Hz, 1H), 6.71−6.61 (m, 3H), 5.91−5.77 (m, 1H), 5.21−5.11 (m, 2H), 3.91−3.89 (m, 2H), 3.27 (t, $J = 7.7$ Hz, 2H), 1.63−1.54 (m, 2H), 1.37−1.28 (m, 4H), 0.91 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (67.5 MHz, CDCl$_3$) δ 148.4, 134.3, 129.1, 115.7, 115.6, 111.9, 53.1, 50.8, 29.3, 27.0, 22.6, 14.1; IR (neat) 3072, 2944, 2880, 1600, 1507, 745, 690 cm^{-1}. HRMS (EI) Calcd for $C_{14}H_{21}N$ 203.1674, found 203.1673.

Removal of the Allyl Group from 17. *p*-Toluenesulfinic acid (188 mg, 1.20 mmol) was added at rt to a solution of *N*-allyl-*N*-pentylaniline **17** (221 mg, 1.08 mmol) and Pd(PPh$_3$)$_4$ (87.8 mg, 75.9 μmol) in CH_2Cl_2 (11 mL). The reaction mixture was stirred at rt for 60 min, and saturated aqueous sodium hydrogen carbonate (6.8 mL) was added. After stirred for 5 min, the mixture was extracted with ether (80 mL). The extract was dried over $MgSO_4$ and concentrated in vacuo. Silica gel chromatography (hexanes:EtOAc 9:1) of the residue afforded *N*-pentylaniline **18** as a colorless oil (164 mg) in 93% yield.

Preparation of (2a*E*,4*E*,8*E*)-(4′*R*,5′*S*,6*S*,6′*R*,7*S*,11*R*,13*S*,15*S*,17a*R*,20a*R*,20b*S*)-6′-Cyclohexyl-4′,20b-dihydroxy-20-(2-propenyloxyimino)-5′,6,8,19-tetramethyl-3′,5′,6,6′,7,10,11,14,15,17a,20,20a,20b-tridecahydro-17-oxospiro[11,15-methano-2*H*,13*H*,17*H*-furo[4,3,2-*pq*][2,6]benzodioxacyclooctadecin-13,2′-[2*H*]pyran]-7-yl 2,6-Dideoxy-4-*O*-(2,6-dideoxy-3-*O*-methyl-α-L-*arabino*-hexopyranosyl)-3-*O*-methyl-α-L-*arabino*-hexopyranoside (19). 25-Cyclohexylavermectin B2 (5.00 g, 5.47 mmol) was dissolved in CH_2Cl_2 (70 mL), and activated MnO_2 (17.5 g, 0.201 mol) was added. After stirring for 15 h, an additional activated MnO_2 (4.0 g, 46 mmol) was added in two portions. After 23 h, the reaction mixture was filtered, and MnO_2 was washed with CH_2Cl_2 (100 mL). The filtrate and the washing liquid were combined and concentrated in vacuo to give the 20-oxo form (4.14 g) as a light white yellow solid in 83% yield. The 20-oxo form given above (800 mg, 878 mmol) was dissolved in a mixture of MeOH (6 mL) and dioxane (6 mL). *O*-Allylhydroxyamine hydrochloride (580 mg, 5.25 mmol) in water (6 mL) was added dropwise to the mixture at rt. After being stirred for 16 h, the reaction solution was poured into water (30 mL). The resulting white solids were filtered and washed with water (15 mL). The solids were chromatographed on silica gel (hexanes:EtOAc 5:3−5:4) to give the *O*-allyloxime **19** as a white solid (520 mg) in 61% yield: mp 169−171 °C; $[\alpha]^{25}_{D}$ +28.0° (*c* 0.55, $CHCl_3$); ^1H NMR (270 MHz, $CDCl_3$) δ 6.10−5.70 (m, 5H), 5.45−5.20 (m, 4H), 5.04−4.95 (m, 1H), 4.80−4.65 (m, 4H), 4.60 (s, 1H), 3.95 (s, 1H), 3.90−3.37 (m, 17H), 3.25 (t, J = 9.1 Hz, 1H), 3.15 (t, J = 9.1 Hz, 1H), 2.60−2.20 (m, 6H), 2.03−1.40 (m, 22H), 1.34−1.15 (m, 12H), 0.96−0.80 (m, 4H); ^{13}C NMR (67.5 MHz, $CDCl_3$) δ 173.1, 150.1, 138.3, 138.2, 135.6, 133.9, 132.4, 124.8, 124.3, 121.2, 117.7, 117.5, 99.6, 98.4, 94.8, 81.7, 80.3, 79.3, 78.6, 78.1, 76.0, 75.9, 73.2, 72.5, 69.9, 68.6, 68.2, 68.1, 67.6, 67.2, 56.4, 56.3, 46.3, 41.1, 40.6, 39.8, 38.1, 35.1, 34.1, 31.1, 26.9, 26.4, 24.4, 20.1, 18.4, 17.6, 17.4, 15.1, 13.7; IR (KBr) 3528, 2944, 1734, 1720, 1452, 1381, 1342, 986 cm^{-1}. Anal. Calcd for $C_{53}H_{79}O_{15}N$: C, 65.61, H, 8.21, N, 1.44. Found: C, 65.27, H, 8.08, N, 1.53.

Removal of the Allyl Group from 19. The *O*-allyloxime **19** (53.0 mg, 54.0 μmol) and *p*-toluenesulfinic acid (14.9 mg, 95.4 μmol) were dissolved in $CHCl_3$ (550 μL). $Pd(PPh_3)_4$ (6.6 mg, 5.7 μmol) was added. The reaction mixture was stirred for 1 h at rt. Silica gel chromatography (hexanes:EtOAc 2:3 to 1:4) of the mixture afforded the oxime **20**[25] as a light brown powder (44.7 mg) in 89% yield: mp 197−199 °C; ^1H NMR (270 MHz, $CDCl_3$) δ 7.94 (s, 1H), 5.92−5.74 (m, 4H), 5.50−5.30 (m, 2H), 5.03−4.92 (m, 1H), 4.80−4.70 (m, 2 H), 4.67 (s, 1H), 3.95 (s, 1H), 3.85 (s, 1H), 3.82−3.35 (m, 16H), 3.25 (t, J = 9.1 Hz, 1H), 3.16 (t, J = 9.1 Hz, 1H), 2.60−2.20 (m. 6H), 2.06−1.40 (m, 22H), 1.35−1.12 (m, 12H), 0.92−0.84 (m, 4H).

Removal of the Allyl Group from 21. $Pd(PPh_3)_4$ (45.9 mg, 39.7 μmol) was added at rt to a solution of **21** (269 mg, 0.521 mmol) and *p*-toluenesulfinic acid (90.9 mg, 0.582 mmol) in CH_2Cl_2 (5.2 mL). The reaction mixture was stirred at rt for 20 min. After addition of saturated aqueous sodium hydrogen carbonate (3 mL), the mixture was extracted with ether (50 mL). The extract was washed with brine, dried over $MgSO_4$ and concentrated in vacuo. Silica gel chromatography (hexanes:EtOAc 85:15) of the residue afforded a mixture of **22** and **23** (198 mg) as a slightly yellow oil in 80% yield; IR (neat) 3296, 2960, 2936, 2864, 1788, 1744, 1656, 1571, 1421, 1253, 837, 779 cm^{-1}; HRMS (FAB) Calcd for $C_{24}H_{35}O_4N_2SSi$ + H 475.2008, found 475.2075.

Removal of the 2-Chloro-2-propenyl Group from 1 Using Palladium Diacetate. The carboxylic acid **6**, a light yellow powder (121 mg, 0.346 mmol), was obtained in 80% yield from the 2-chloro-2-propenyl ester **1** (182 mg, 0.430 mmol) by the same procedure as described in method B except that palladium diacetate (20.5 mg, 91.3 μmol) and triethyl phosphite (52.6 mg, 0.317 mmol) were used.

Removal of the 2-Chloro-2-propenyl Group from 1 Using Dichlorobis(acetonitrile)palladium. The carboxylic acid **6**, a light yellow powder (166 mg, 0.475 mmol), was obtained in 85% yield from the 2-chloro-2-propenyl ester **1** (237 mg, 0.558 mmol) by the same procedure as described in method B except that dichlorobis(acetonitrile)palladium (19.9 mg, 13.7 μmol) and triethyl phosphite (38.3 mg, 0.230 mmol) were used.

Removal of the 2-Chloro-2-propenyl Group from 1 Using Sodium Hydroxymethanesulfinate. The carboxylic acid **6**, a light yellow powder (94.5 mg, 0.270 mmol), was obtained in 86% yield from the 2-chloro-2-propenyl ester **1** (142 mg, 0.335 mmol) by the same procedure as described in method B except that sodium hydroxymethanesulfinate (61.9 mg, 0.402 mmol) was used.

Removal of the 2-Chloro-2-propenyl Group from 1 Using Tetrabutylammonium Benzenesulfinate. CH_2Cl_2 (7.0 mL) was added at rt to a mixture of tetrabutylammonium benzenesulfinate (300 mg, 0.81 mmol), **1** (300 mg, 0.707 mmol) and $Pd(PPh_3)_4$ (49 mg, 42.4 μmol). The reaction mixture was stirred for 25 min at rt and extracted with water (1.5 mL and 1 mL × 2). The water layers were combined, cooled to 5 °C, acidified to pH 2.5 by adding aqueous 1 N HCl, and then stirred at 5 °C for 30 min. The precipitate thus formed was collected by filtration, washed with cold water (2 mL), and dried in vacuo to give acid **6** as a white powder (173 mg) in 70% yield.

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