A Selective Access to Amino Hydroxy Oxetanes

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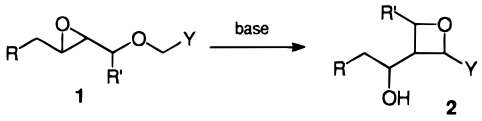
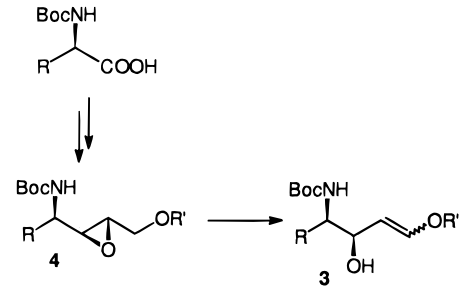
Oxetanes constitute an interesting class of compounds,[1] being found in a large variety of natural products such as taxane alkaloids and the antiviral and antibiotic nucleoside oxetanocin[2−8] just to mention a few of them.

We have recently discovered an easy and selective access to di- (**2**, R′ = H) and trisubstituted (**2**, R′ = CH_3) oxetanes via isomerization of suitably substituted oxiranyl ethers **1**.[9]

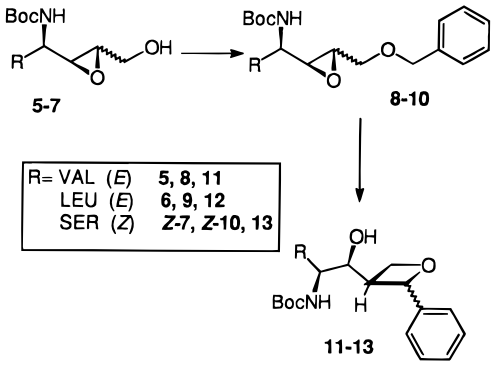


Our method allowed us to get access to hydroxy-substituted oxetanes which may represent the starting point for the synthesis of more complex, oxetane-containing, molecules. Moreover, our interest in the base-promoted isomerization of heterosubstituted oxiranes [10−12] led us to report an access to *syn*-amino alcohols **3**[13] from amino acids via amino alkoxy oxiranes **4**. When the alkoxy group R′O is methoxymethoxy,[14] treatment with the equimolar mixture butyllithium/diisopropylamine/potassium *tert*-butoxide (LIDAKOR[10,15]) led to the corresponding amino alcohol **3** as the unique product.[13]

On the basis of our previous findings,[14] we assumed that the replacement of the methoxymethoxy group with a benzyloxy substituent could allow us to access amino alcohols bearing an oxetane moiety which we envisaged as useful building blocks for the synthesis of peptide isosteres.[16−18] We then prepared the required substrates



following known procedures[13,19,20] starting with the amino acids valine, leucine, and serine. The (*E*)-oxiranes derived from valine and leucine and the (*Z*)-oxirane derived from serine were obtained via reduction to the corresponding *N*-Boc-amino aldehyde,[21−23] selective olefination to the (*E*)-[24] or (*Z*)-α,β-unsaturated[25] ester, respectively, reduction to the allylic alcohol,[19] and epoxidation with *m*-chloroperbenzoic acid.[26,27] The oxidation step is highly *syn*-selective for these three substrates whereas the (*E*)-allylic alcohol derived from serine gives a 1:1 mixture of *syn*- and *anti*-epoxy amines.[20] The epoxy alcohols **5**−**7** were converted into the benzyl oxiranyl ethers **8**−**10** and then submitted to treatment with LIDAKOR in tetrahydrofuran at −50 °C. Oxetanes **11**−**13** were obtained in good yields and with a selectivity which is related to the configuration of the starting benzyl oxiranyl ethers. *E*-**8** and *E*-**9** derived from valine and leucine, respectively, afforded the *anti*-oxetanes **11** and **12** as the unique detectable products.



This result agrees well with our previous findings on the isomerization of *trans*-oxiranyl ethers[14] where a remarkable *anti*-selectivity was found. When the (*Z*)-isomer derived from serine (***Z*-10**) was submitted to base-promoted isomerization, we found a lower selectivity with a 30:70 (*syn*:*anti*) mixture of oxetane **13** being isolated. We postulate this to be due to the steric interaction in the transition state geometry required for the 4-*exo* ring closure.

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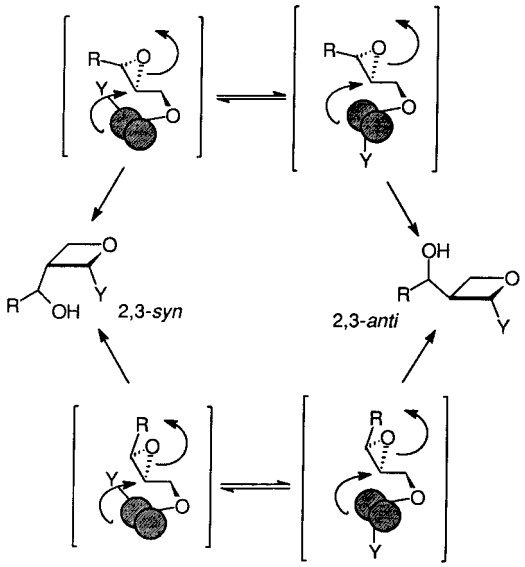
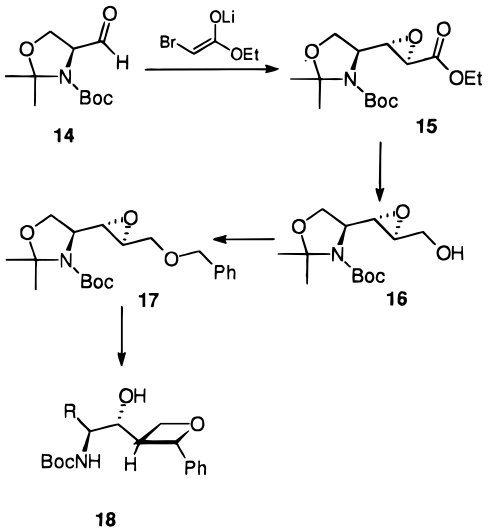
The *anti*-selectivity associated with the (*E*)-oxiranes is due to the steric repulsions between the R and Y groups. On the other hand, (*Z*)-oxiranes do not experience a similar crowding. In fact, the R group being far from substituent Y results in a mixture of *syn*- and *anti*-oxetanes.



This was confirmed by the isomerization of the (*E*)-benzyl oxiranyl ether **17** derived from serine which was prepared using a different approach. The amino aldehyde **14** was treated with the lithium enolate of ethyl bromoacetate,[28] and the (*E*)-epoxy ester **15** thus obtained was selectively reduced with sodium borohydride in tetrahydrofuran/water and benzylated.

When **17** was submitted to treatment with LIDAKOR, the expected oxetane **18** was again obtained as pure *anti*-isomer.



It is worth noting that the choice of the base is of great importance for the stereo- and regiochemical outcome of the reaction. When we submitted a benzyloxy oxirane to treatment with a series of lithium amides and activated organolithium reagents, we found very different results. Only LIDAKOR gives the oxetane, while all the other lithium derivatives lead to mixtures of oxetanes and the regioisomeric enethers. LDA without potassium *tert*-butoxide does not react at all. This simple and highly selective access to amino hydroxy oxetanes seems promising in view of a subsequent application to the synthesis of oxetane-containing molecules.

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Experimental Section

General. Air and moisture sensitive compounds were stored in Schlenk tubes. They were protected by and handled under an atmosphere of 99.99% pure nitrogen. Ethereal extracts were dried with sodium sulfate. The temperature of dry ice−ethanol baths is consistently indicated as −78 °C, that of ice bath as 0 °C, and "room temperature" as 25 °C. If no reduced pressure is specified, boiling ranges were determined under ordinary atmospheric conditions (720 ± 35 mmHg). Purifications by flash column chromatography[29] were performed using glass columns (10−50 mm wide); silica gel 230−400 mesh was chosen as the stationary phase (15 cm high), with an elution rate of 5 cm/min. Nuclear magnetic resonance spectra of hydrogen nuclei were recorded at 200 or 500 MHz. Chemical shifts were determined relative to the residual solvent peak ($CHCl_3$: 7.26 ppm). Nuclear magnetic resonance spectra of carbon-13 nuclei were recorded at 50.3 or 75.5 MHz. Chemical shifts were determined relative to the residual solvent peak ($CHCl_3$: 77.0 ppm).

Materials. Starting materials were commercially available unless otherwise stated. All commercial reagents were used without further purification except diisopropylamine, which was distilled over calcium hydride. Anhydrous tetrahydrofuran was distilled from sodium diphenylketyl. Petroleum ether, unless specified, was the 40−70 °C boiling fraction.

Compounds ***E*-5**, ***E*-6**, and ***Z*-7** have been prepared according to our already reported procedures.[13]

Preparation of (2′*S*,3′*S*,4*S*)-(−)-(*E*)-2,2-Dimethyl-3-*N*-(*tert*-butoxycarbonyl)-4-[3′-(1′-hydroxy-2′,3′-epoxypropyl)]oxazolidine (16). (1′*R*,2′*S*,4*S*)-(*E*)-2,2-Dimethyl-3-*N*-(*tert*-butoxycarbonyl)-4-[3′-(1′-carbethoxy-1′,2′-epoxyethyl)]oxazolidine (15). A solution of butyllithium in hexane (4.8 mmol, 3.4 mL of a 1.6 M solution) was evaporated under reduced pressure and the residue dissolved at −78 °C in precooled THF (7 mL). Then diisopropylamine (4.8 mmol, 0.48 g) was added and the mixture stirred for 30 min before being slowly added to a solution of (*S*)-(−)-2,2-dimethyl-3-*N*-(*tert*-butoxycarbonyl)-4-formyloxazolidine **14** (Garner's aldehyde,[30] 3.0 mmol, 0.68 g) and ethyl bromoacetate (4.8 mmol, 0.80 g) in THF (7 mL) at −78 °C. The mixture was then slowly warmed to 25 °C and, after 3 h, treated with H_2O (20 mL) and extracted with Et_2O (3 × 20 mL). The organic layer was washed with saturated NaCl and dried. After evaporation of the solvent, the residue (1.28 g) was purified by flash column chromatography (petroleum ether:ethyl acetate 6:1 + 4% triethylamine) affording pure **15** (0.58 g, 61%). ^{1}H NMR ($CDCl_3$, 200 MHz): 4.34−3.94 (5H, m); 3.60 (1H, d, J = 4.0); 3.20 (1H, dd, J = 4.0, 8.8); 1.65 (3H, s); 1.58 (3H, s); 1.44 (9H, s); 1.33 (3H, t, J = 7.4). ^{13}C NMR ($CDCl_3$, 50.3 MHz): 167.89; 152.03; 93.85; 80.84; 80.40; 66.19; 61.55; 58.15; 53.65; 28.32; 27.72; 24.21; 14.02. MS (*m*/*z* %): 300 (1, $M^+ - CH_3$); 242 (2); 200 (47); 86 (12); 84 (38); 57 (100).

(2′*S*,3′*S*,4*S*)-(−)-(*E*)-2,2-Dimethyl-3-*N*-(*tert*-butoxycarbonyl)-4-[3′-(1′-hydroxy-2′,3′-epoxypropyl)]oxazolidine (16). Epoxy ester **15** (1.84 mmol, 0.58 g) was dissolved in THF (10 mL) and H_2O (10 mL) and cooled to 0 °C. $NaBH_4$ (2.76 mmol, 0.11 g) was then added and the mixture stirred 12 h at 25 °C before it was treated with H_2O (20 mL) and extracted with Et_2O (2 × 20 mL) and dried. After evaporation of the solvent under vacuum, the residue (0.42 g) was purified by flash column chromatography (petroleum ether:ethyl acetate 4:1 + 4% triethylamine), affording 0.28 g (54%) of pure **16**. $[\alpha]^{22}_D = -22.3°$ (c = 0.7, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz): 4.56 (1H, dd, J = 11.2, 3.0); 4.16−3.94 (3H, m); 3.79 (1H, ddd, J = 9.6, 5.4, 1.7); 3.50 (1H, ddd, J = 12.0, 9.6, 2.7); 3.29 (1H, dt, J = 3.9, 10.0); 3.03 (1H, dd, J = 9.6, 3.9); 1.61 (3H, s); 1.51 (3H, s); 1.49 (9H, s). ^{13}C NMR ($CDCl_3$, 50.3 MHz): 153.00; 94.38; 81.87; 66.28; 59.47; 56.89; 56.38; 53.98; 28.33; 27.49; 24.27. MS (*m*/*z* %): 258 (2, $M^+ - CH_3$); 202 (8); 186 (6); 158 (28); 116 (17); 100 (14); 98

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(12); 84 (14); 69 (13); 59 (29); 57 (100); 56 (25). Anal. Calcd for $C_{13}H_{23}NO_5$: C, 57.13; H, 8.49; N, 5.13. Found: C, 57.23; H, 8.52; N, 5.11.

Protection of the Hydroxyl Group as Benzyl Ether. General Procedure. NaH (4.0 mmol, 60% in oil) was washed with pentane (3 × 5 mL) and vacuum-dried. Freshly distilled THF (2 mL) was added and the resulting suspension cooled to 0 °C before the oxiranyl alcohol (2.0 mmol in 8 mL THF) was added and the mixture stirred for 1 h at 25 °C. Benzyl bromide (2.4 mmol) was then added at 0 °C, and the reaction mixture was stirred for 12−15 h at 25 °C. The reaction was then quenched with ice/H_2O (8 mL) and extracted with ether (3 × 8 mL), and the organic layer was washed with saturated NaCl and dried. After evaporation of the solvent, the residue was purified by flash column chromatography.

(2*R*,3*R*,4*S*)-(*E*)-4-[*N*-(*tert*-Butoxycarbonyl)amino]-5-methyl-1-(benzyloxy)-2,3-epoxyhexane (8). According to the general procedure, 0.35 g (52%) of the benzyl ether was obtained upon purification (petroleum ether:ethyl acetate 3:1). ^{1}H NMR ($CDCl_3$, 200 MHz): 7.40−7.23 (5H, m); 4.56 (2H, m, AB system); 4.50 (1H, m); 3.80 (1H, dd, J = 11.8, 2.2 Hz); 3.68 (1H, dd, J = 11.8, 3.0 Hz); 3.48−3.39 (1H, m); 3.03−2.99 (2H, m); 1.98−1.81 (1H, m); 1.43 (9H, s); 1.00 (3H, d, J = 4.6 Hz); 0.97 (3H, d, J = 4.6 Hz). ^{13}C NMR ($CDCl_3$, 50.3 MHz): 155.72; 137.00; 128.38; 127.87; 127.51; 79.18; 73.19; 69.55; 58.63; 55.20; 53.36; 31.19; 28.20; 19.02; 18.22. MS (*m*/*z* %): 292 (2, $M^+ - C_3H_7$); 266 (3); 236 (5); 192 (7); 91 (100); 57 (100).

(2*R*,3*R*,4*S*)-(*E*)-4-[*N*-(*tert*-Butoxycarbonyl)amino]-6-methyl-1-(benzyloxy)-2,3-epoxyheptane (9). According to the general procedure, 0.43 g (62%) of the benzyl ether was obtained upon purification (petroleum ether:ethyl acetate 3:1). ^{1}H NMR ($CDCl_3$, 200 MHz): 7.38−7.28 (5H, m); 4.56 (2H, m, AB system); 4.40 (1H, m); 3.98 (1H, m); 3.80 (1H, app d, J = 12.0); 3.46 (1H, m); 3.06 (1H, m); 2.91 (1H, m); 1.71 (1H, hept, J = 6.6); 1.42 (9H, s); 1.4 (2H, m); 0.94 (6H, d, J = 6.6). ^{13}C NMR ($CDCl_3$, 50.3 MHz): 155.32; 137.58; 128.12; 127.42; 127.39; 78.95; 72.94; 69.41; 57.09; 54.20; 46.72; 41.93; 28.07; 24.36; 22.79; 21.84. MS (*m*/*z* %): 318 (6); 300 (5); 232 (6); 218 (10); 192 (11); 176 (14); 130 (26); 129 (42); 106 (14); 91 (100); 86 (35); 85 (50); 68 (16); 57 (100).

(2′*S*,3′*R*,4*S*)-(*Z*)-2,2-Dimethyl-3-[*N*-(*tert*-butoxycarbonyl)]-4-[3′-(1′-(benzyloxy)-2′,3′-epoxypropyl)]oxazolidine (*Z*-10). According to the general procedure, 0.45 g (60%) of the benzyl ether was obtained upon purification (petroleum ether:ethyl acetate 3:1). ^{1}H NMR ($CDCl_3$, 200 MHz): 7.40−7.26 (5H, m); 4.46 (2H, s); 4.00−3.90 (2H, m); 3.76−3.54 (3H, m); 3.19−3.05 (2H, m); 1.62 (3H, s); 1.49 (12H, bs). ^{13}C NMR (50.3 MHz): 152.09; 137.52; 128.75; 128.09; 127.47; 93.96; 79.98; 73.10; 67.84; 65.70; 58.31; 56.58; 51.46; 28.10; 26.70; 24.23. MS: (*m*/*z* %): 348 (2; $M^+ - CH_3$); 248 (27);186 (10); 91 (100); 57 (100).

(2′*S*,3′*S*,4*S*)-(*E*)-2,2-Dimethyl-3-*N*-(*tert*-butoxycarbonyl)-4-[3′-(1′-(benzyloxy)-2′,3′-epoxypropyl)]oxazolidine (17). According to the general procedure, 0.51 g (70%) of the benzyl ether was obtained upon purification (petroleum ether:ethyl acetate 7:1 + 4% triethyl amine). ^{1}H NMR ($CDCl_3$, 200 MHz): 7.39−7.24 (5H, m); 4.70−4.53 (2H, m); 4.23 (1H, d, J = 11.6); 4.12 (1H, dd, J = 9.2, 2.2); 4.00−3.93 (1H, m); 3.70−3.63 (1H, m); 3.57−3.47 (1H, m); 3.36−3.32 (1H, m); 3.05 (1H, dd, J = 8.8, 4.4); 1.59 (3H, s); 1.47 (12H, s). ^{13}C NMR ($CDCl_3$, 50.3 MHz): 152.23; 138.20; 128.32; 127.72; 127.55; 94.07; 80.51; 73.16; 69.30; 66.19; 57.77; 56.35; 55.07; 28.38; 27.65; 24.50. MS (*m*/*z* %): 308 (16); 250 (12); 248 (19); 186 (18); 142 (15); 128 (21); 112 (11); 107 (17); 105 (12); 100 (43); 98 (21); 91 (100); 89 (14); 85 (12); 84 (26); 79 (13); 77 (9); 65 (30); 57 (98); 56 (24); 55 (11).

LIDAKOR-Induced Isomerization of the Oxiranyl Ethers. General Procedure. A solution of butyllithium in hexane (2.0 mmol) was evaporated under reduced pressure and the residue dissolved at −78 °C in precooled THF (2.0 mL). Then diisopropylamine (2.0 mmol) and potassium *tert*-butoxide (2.0 mmol) was added and the mixture stirred for 30 min. After the addition of the substrate (1.0 mmol) the reaction mixture was kept for 15 h at −50 °C before it was treated with H_2O (2.0 mL) and allowed to reach 25 °C. The aqueous phase was extracted with Et_2O (3 × 5 mL), and the organic layer was washed with saturated NaCl and dried over Na_2SO_4: after evaporation of the solvent, the residue was purified by flash column chromatography.

(1′*S*,2′*S*,2*S*,3*R*)-2-Phenyl-3-[[1′-(3′-methyl-2′-[*N*-(*tert*-butoxycarbonyl)amino]-1′-hydroxybutyl]oxetane (11). According to the general procedure, 0.31 g (46%) of the oxetane was obtained upon purification (petroleum ether:ethyl acetate 1:1); mp 105−107 °C. $[\alpha]^{21}_D = +13.6°$ (c = 1.1, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 500 MHz): 7.45−7.36 (5H, m); 5.54 (1H, d, J = 6.5); 4.80 (1H, app t, J = 7.0); 4.73 (1H, d, J = 9.0); 4.65 (1H, app t, J = 8.5); 4.07 (1H, bs); 3.22−3.17 (1H, m); 3.03 (1H, dd, J = 7.0, 8.0); 1.94−1.90 (1H, m); 1.38 (9H, s); 0.97 (3H, d, J = 6.5); 0.92 (3H, d, J = 6.5). ^{13}C NMR ($CDCl_3$, 50.3 MHz): 156.35; 142.10; 128.51; 128.03; 125.67; 84.71; 79.59; 70.49; 69.13; 59.75; 48.38; 29.43; 28.27; 19.09; 19.28. MS (*m*/*z* %): 292 (0.2, $M^+ - C_3H_7$); 236 (2); 192 (7); 172 (12); 116 (88); 77 (14); 72 (82); 57 (100). Anal. Calcd for $C_{19}H_{29}NO_4$: C, 68.06; H, 8.72; N, 4.18. Found: C, 68.28; H, 8.69; N, 4.21.

(1′*S*,2′*S*,2*S*,3*R*)-2-Phenyl-3-[[1′-(4′-methyl-2′-*N*-(*tert*-butoxycarbonyl)amino]-1′-hydroxypentyl]oxetane (12). According to the general procedure, 0.53 g (76%) of the oxetane was obtained upon purification (petroleum ether:ethyl acetate 1:1). $[\alpha]^{21}_D = +4.2°$ (c = 1.2, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz): 7.50−7.26 (5H, m); 5.60 (1H, d, J = 7.0); 4.83 (1H, app t, J = 6.6); 4.66 (1H, dd, J = 8.4, 6.2); 4.53 (1H, d, J = 8.8); 3.86 (1H, m); 3.51 (1H, m); 3.10 (1H, m); 1.66 (3H, m); 1.40 (9H, s); 1.38 (1H, m); 0.91 (3H, d, J = 6.6); 0.89 (3H, d, J = 6.6). ^{13}C NMR ($CDCl_3$, 50.3 MHz): 156.60; 142.64; 129.05; 128.58; 126.21; 85.32; 80.11; 73.60; 69.40; 52.73; 48.49; 41.49; 28.78; 25.18; 23.62; 22.54. MS (*m*/*z* %): 292 (2, $M^+ - C_4H_9$); 236 (2); 186 (10); 174 (4); 133 (13); 130 (89); 117 (24); 107 (22); 105 (22); 91 (17); 86 (100); 84 (15); 77 (15); 57 (95). Anal. Calcd for $C_{20}H_{31}NO_4$: C, 68.74; H, 8.94; N, 4.01. Found: C, 68.64; H, 8.79; N, 4.07.

(2*R*,3*S*,4′*S*,5*S*)- and (2*S*,3*S*,4′*S*,5*S*)-2-Phenyl-3-[[4′-(2′,2′-dimethyl-3′-*N*-(*tert*-butoxycarbonyl)oxazolidinyl)]hydroxymethyl]oxetane (13). According to the general procedure, 0.47 g (65%) of the oxetane was obtained (petroleum ether: ethyl acetate 1:1) as a mixture of 2,3-*syn*/2,3-*anti* diastereoisomers (30:70). An additional purification (dichloromethane: ethyl acetate 8:1) led to pure isomers.

2,3-*Syn* isomer: $[\alpha]^{21}_D = +30.7°$ (c = 0.7, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz): 7.54−7.28 (5H, m); 5.95 (1H, d, J = 8.0); 4.88 (1H, dd, J = 8.0, 6.5); 4.48 (1H, app t, J = 6.4); 4.12−4.01 (1H, m); 3.99−3.78 (3H, m); 3.54−3.36 (1H, m); 1.53 (3H, s); 1.49 (9H, s); 1.42 (3H, s). MS (*m*/*z* %): 348 (0.1, $M^+ - CH_3$); 250 (7); 200 (23); 144 (53); 133 (11); 117 (18); 107 (42); 105 (44); 100 (98); 91 (22); 84 (15); 83 (25); 79 (18); 77 (31); 57 (100); 55 (24). Anal. Calcd for $C_{20}H_{29}NO_5$: C, 66.09; H, 8.04; N, 3.85. Found: C, 66.04; H, 8.07; N, 3.81.

2,3-*Anti* isomer: $[\alpha]^{21}_D = -32.6°$ (c = 1.3, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz): 7.51−7.28 (5H, m); 5.81 (1H, d, J = 6.2); 4.72−4.67 (2H, m); 4.48−4.38 (1H, m); 4.17−4.07 (1H, m); 3.94−3.85 (1H, m); 3.76−3.67 (1H, m); 3.60−3.49 (1H, m); 3.04−2.90 (1H, m); 1.56 (3H, s); 1.51 (9H, s); 1.46 (3H, s). ^{13}C NMR ($CDCl_3$, 50.3 MHz): 154.67; 142.82; 128.48; 127.75; 125.50; 94.20; 84.17; 81.68; 74.83; 69.78; 64.33; 60.93; 47.41; 29.67; 28.34. MS (*m*/*z* %): 200 (3, $M^+ - C_{10}H_{11}O_2$); 133 (4); 106 (5); 105 (35); 100 (7); 77 (17); 57 (100); 56 (44); 55 (13); 43 (24); 42 (13); 41 (54). Anal. Calcd for $C_{20}H_{29}NO_5$: C, 66.09; H, 8.04; N, 3.85. Found: C, 66.12; H, 8.09; N, 3.79.

(2*S*,3*S*,4′*S*,5*R*)-2-Phenyl-3-[[4′-(2′,2′-dimethyl-3′-*N*-(*tert*-butoxycarbonyl)oxazolidinyl)]hydroxymethyl]oxetane (18). According to the general procedure, 0.43 g (60%) of the oxetane was obtained upon purification (dichloromethane: ethyl acetate 8:1). $[\alpha]^{21}_D = +17.4°$ (c = 0.9, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 200 MHz): 7.51−7.27 (5H, m); 5.74 (1H, d, J = 6.6); 4.69−4.54 (2H, m); 4.38−4.22 (1H, m); 4.07−3.84 (3H, m); 3.58−3.44 (1H, m); 3.38−2.86 (1H, m); 1.61 (3H, s); 1.48 (9H, bs); 1.45 (3H, s). ^{13}C NMR ($CDCl_3$, 50.3 MHz): 153.92; 142.56; 128.37; 127.62; 125.29; 94.34; 86.08; 83.64; 75.13; 70.05; 64.43; 61.10; 46.72; 29.69; 28.36; 26.54. MS (*m*/*z* %): 200 (6, $M^+ - C_{10}H_{11}O_2$); 144 (7); 133 (3); 105 (10); 100 (21); 77 (11); 57 (100); 55 (8).

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