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A CONCISE ACCESS TO 6-AZABICYCLO[3.1.0]HEXANES *VIA* HIGH-PRESSURE PROMOTED CYCLOADDITION REACTION OF AZIDES TO ABH

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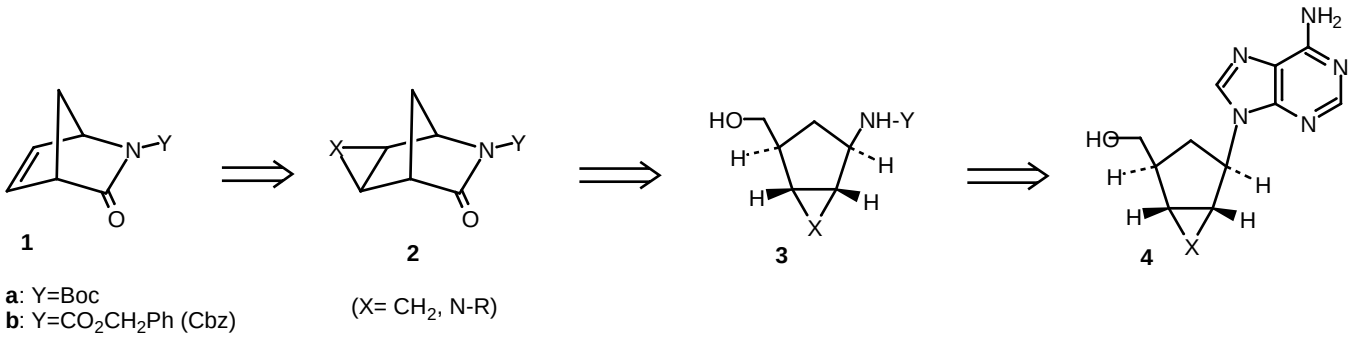
Abstract - Cycloaddition reaction of electron-deficient azides (**5a, b**) to 2-aza-bicyclo[2.2.1]hept-5-en-3-one (ABH) (**1**) was accelerated by high-pressure, leading to a mixture of regioisomeric triazolines (**6**) in good yields. Then, **6** were in turn, through photolysis and ring opening sequences, converted to 6-azabicyclo[3.1.0]-hexanes (**8**).

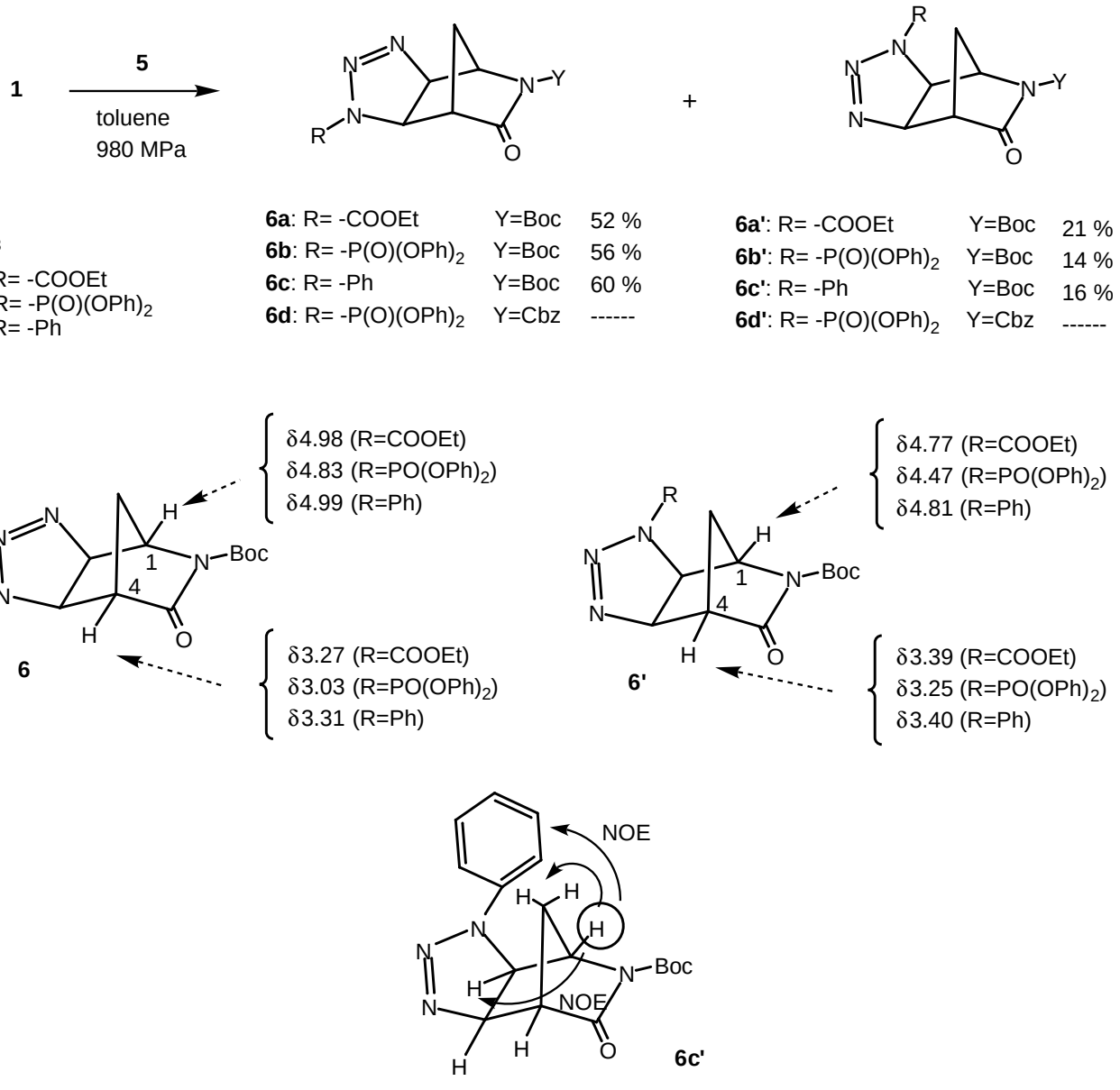
Prompted by the recent reports of the intriguing biological activities of methano-nucleosides,[1] we have previously reported the preparation of methano-cabocyclic nucleoside (**4**; X=CH_2) whose cyclopentane ring is conformationally restricted due to the methylene group fused between the 2' and 3' positions (Scheme 1).[2] In due course, we have also interested in azamethano-carbocyclic nucleosides (**4**; X=N-R), and we disclose in this paper a concise construction of 6-azabicyclo[3.1.0]hexane (**3**; X=N-R) that may serve as a versatile intermediate for further transformation to azamethano-carbocyclic nucleosides (**4**; X=N-R), where a key method utilizes an intermolecular [2+3] cycloaddition reaction of azides to *N*-substituted 2-azabicyclo[2.2.1]hept-5-en-3-ones (ABH) (**1**) at high-pressure.



Scheme 1

In general, cycloaddition reactions of acyl azides to olefins take place through 1,3-dipolar reaction path to give triazolines as primary products, and the subsequent decomposition of the resulted triazolines affords

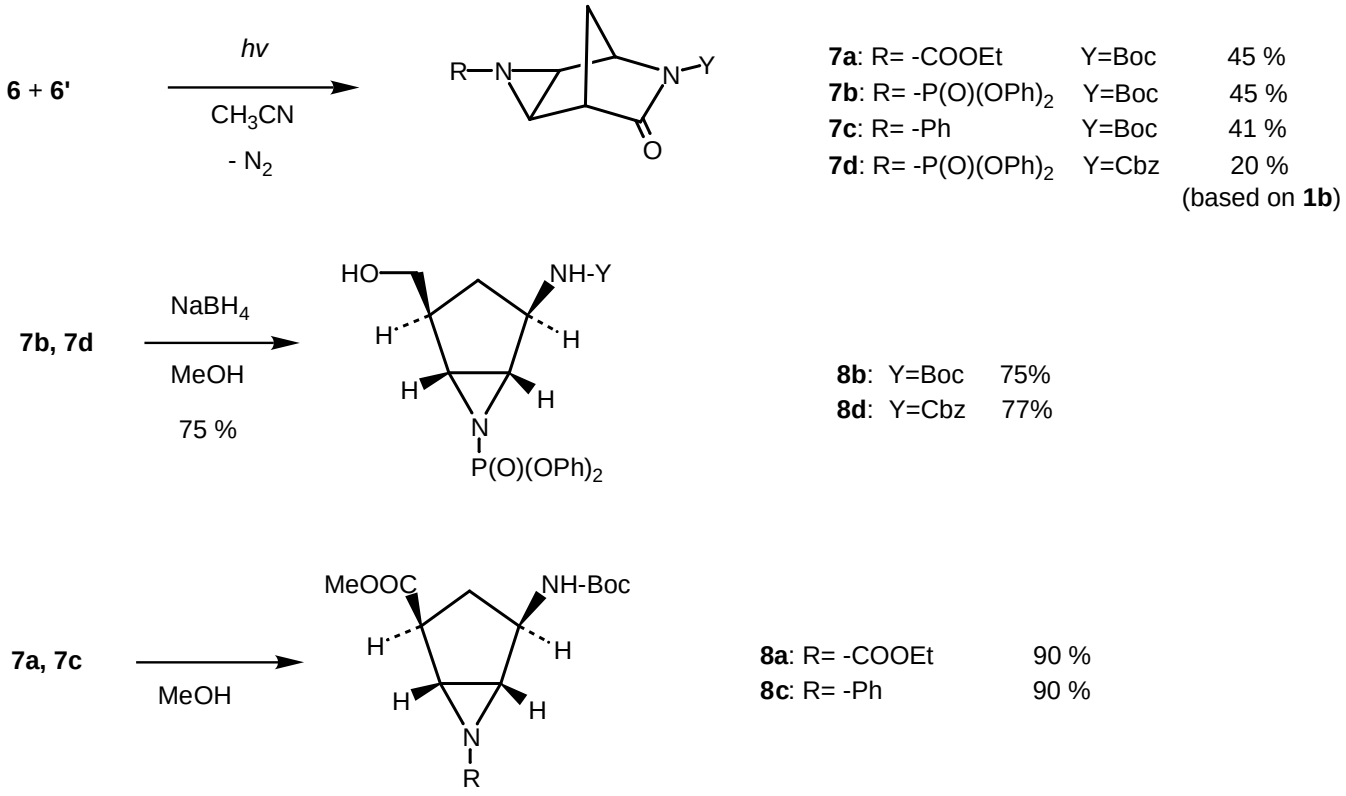
aziridines.[3] Our initial attempts to react ABH (**1**) with ethyl azidoformate (**5a**) under various conditions (in toluene reflux; sealed tube in toluene at 100°C) failed to result in complex mixtures, whereas benzoyl azide is known to add to norbornene rapidly at low temperature.[4] It has been demonstrated in a few literatures that the cycloaddition reaction of arylsulfonyl azide to electron-rich olefins, and alkyl and aryl azides to electron-poor olefins could be effectively accelerated by high-pressure.[5] It was therefore envisioned that the present cycloaddition reaction of electron-poor azides (**5a**) to ABH (**1**) should be affected by high-pressure, as well. Therefore, the cycloaddition of **5a** to ABH (**1a**) was undertaken in toluene at 980 MPa for 70 hours at room temperature to give a mixture of two regioisomeric triazolines (**6a** and **6a'**) in 73 % yield, liberating major isomer (**6a**) as precipitates, and minor isomer (**6a'**) was also isolated by the repeated recrystallization of the filtrate (Scheme 2). Similar treatments of azides (**5b**, **c**) with ABH (**1a**) under high-pressure afforded crystalline regioisomers (**6b** and **6b'**, **6c** and **6c'**) with the selectivity in favor of **6b** and **6c**, and these isomers could be also isolated as well. The structure of **6c'** was assigned on the basis of NOE experiments. In the ^{1}H-NMR spectrum, the major isomers (**6**) were



Scheme 2

distinguished from the minor isomers (**6'**) by both downfield shift of the H-1 proton and upfield shift of the H-4 proton relative to those of **6'**. Unfortunately, neither isomer arising from the reaction of **1b** with **5b** separated out in crystallized form, and due to their instability to both silica gel and alumina, **6d** and **6d'** could not be separated by chromatography. Therefore, crude mixture of **6d** and **6d'** was subjected to the further step.

Next, a mixture of regioisomeric triazolines (**6**) was irradiated in CH_3CN with high-pressure mercuric lamp to afford aziridines (**7**) (Scheme 3). When **6a** was subjected to thermal decomposition in toluene at 100°C, **7a** was obtained but in low yield. In line with our previous studies,[6] **7** were treated with $NaBH_4$ in MeOH in the hope that the reductive ring opening would occur. In the cases of **7b** and **7d**, the reduction effectively took place to provide 6-azabicyclo[3.1.0]hexanes (**8b** and **8d)** in 75 % and 77% yields, respectively. The ring opening of **7a** and **7c** was attained simply by stirring in MeOH at room temperature for 20 hours, quantitatively giving **8a** and **8c**.



Scheme 3

In summary, we have shown a concise approach to 6-azabicyclo[3.1.0]hexanes (**8**) through the cyclo-addition of azides (**5**) to ABH (**1**) leading to triazolines (**6**) as a key step, which demonstrates the potential utility of high-pressure method to promote the cycloaddition reaction.

ACKNOWLEDGEMENTS

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EXPERIMENTAL

The high-pressure promoted cycloaddition reaction of 5b to 1a: Typical procedure

High-pressure reaction was carried out by using a piston-cylinder apparatus equipped with a K.P.15.B pump (Hikari Koatsu KiKi Ltd., Co., Japan). A solution of **5b** (2.75 g, 10 mmol) and **1a** (2.09 g, 10 mmol) in toluene (5 mL) was placed in a Teflon tube with Teflon stopper. The tube was placed in a high-pressure reactor and pressurized to 980 MPa at rt for 7 days. After the pressure was released, the precipitates of **6b** (1.69 g, 35%) were collected by vacuum filtration and washed with ether. The filtrate and washing were concentrated under reduced pressure and the residue was recrystallized from ether to give **6b** (1.01 g, 21%). Furthermore, recrystallization of the filtrate from ether provided 677 mg (14 %) of **6b'**.

6a: mp 135-137°C (recryst. from AcOEt-hexane). IR ($CHCl_3$): 1790, 1752, 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.29 (d, 1H, *J*=11 Hz), 1.40 (t, 3H, *J*=7.2 Hz), 1.55 (s, 9H), 2.02 (d, 1H, *J*=11 Hz), 3.27 (s, 1H), 4.34 (d, 1H, *J*=8.3 Hz), 4.41(q, 2H, *J*=7.2 Hz), 4.98 (s, 1H), 5.24 (d, 1H, *J*=8.3 Hz). ^{13}C-NMR ($CDCl_3$) δ: 14.3, 27.9, 31.5, 51.6, 54.6, 61.0, 63.6, 84.1, 88.1, 148.4, 150.4, 170.6. *Anal*. Calcd for $C_{14}H_{20}N_4O_5$: C, 51.84; H, 6.22; N, 17.27. Found: C, 51.72; H, 6.24; N, 16.94. **6a'**: mp 137-139°C (recryst. from AcOEt-hexane). IR ($CHCl_3$): 1792, 1758, 1728 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.26 (d, 1H, *J*=11 Hz), 1.42 (t, 3H, *J*=7.1 Hz), 1.54 (s, 9H), 2.01 (d, 1H, *J*=11 Hz), 3.39 (s, 1H), 4.31 (d, 1H, *J*=8.3 Hz), 4.36-4.50 (m, 2H), 4.77 (s, 1H), 5.23 (d, 1H, *J*=8.3 Hz). ^{13}C-NMR ($CDCl_3$) δ: 14.4, 27.9, 31.2, 51.1, 57.3, 60.9, 63.6, 84.0, 84.3, 148.2, 150.5, 170.9. *Anal*. Calcd for $C_{14}H_{20}N_4O_5$: C, 51.84; H, 6.22; N, 17.27. Found: C, 51.93; H, 6.19; N, 17.09. **6b**: mp 106-107°C (recryst. from ether). IR ($CHCl_3$): 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.74 (d, 1H, *J*=11 Hz), 1.51 (s, 9H), 1.67 (d, 1H, *J*=11 Hz), 3.03 (s, 1H), 4.18 (d, 1H, *J*=8 Hz), 4.83 (s, 1H), 5.18 (d, 1H, *J*=8 Hz), 7.15-7.45 (m, 10H). ^{13}C-NMR ($CDCl_3$) δ: 27.9, 30.9, 52.8, 56.5, 60.7, 84.1, 89.1, 120.3, 120.4, 120.6, 120.7, 126.0, 126.1, 130.0, 148.6, 149.5, 149.6, 149.7, 149.8, 170.3. *Anal*. Calcd for $C_{23}H_{25}N_4O_6P$: C, 57.02; H, 5.20; N, 11.57. Found: C, 56.94; H, 5.23; N, 11.69. **6b'**: mp 108-109°C (recryst. from ether). IR ($CHCl_3$): 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 0.75(d, 1H, *J*=11 Hz), 1.50 (s, 9H), 1.68 (d, 1H, *J*=11 Hz), 3.25 (s, 1H), 4.12 (d, 1H, *J*=8 Hz), 4.47 (s, 1H), 5.16 (d, 1H, *J*=8 Hz), 7.22-7.42 (m, 10H). ^{13}C-NMR ($CDCl_3$) δ: 27.9, 30.6, 50.9, 59.1, 61.9, 85.4, 85.1, 120.4, 120.5, 120.6, 120.7, 126.0, 126.1, 130.0, 148.2, 149.6, 149.7, 170.8. *Anal*. Calcd for $C_{23}H_{25}N_4O_6P$: C, 57.02; H, 5.20; N, 11.57. Found: C, 56.97; H, 5.02; N, 11.74. **6c**: mp 181-183°C (recryst. from AcOEt-hexane). IR ($CHCl_3$): 1790, 1764, 1712 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.38 (d, 1H, *J*=11 Hz), 1.57 (s, 9H), 1.98 (d, 1H, *J*=11 Hz), 3.30 (s, 1H), 4.44 (d, 1H, *J*=8.8 Hz), 4.98 (s, 1H), 5.25 (d, 1H, *J*=8.8 Hz), 7.10 (t, 1H, *J*=7.2 Hz), 7.30-7.42 (m, 4H). ^{13}C-NMR ($CDCl_3$) δ: 28.0, 31.6, 51.3, 57.0, 61.8, 84.0, 86.0, 114.3, 123.3, 129.6, 138.8, 148.4, 171.4. *Anal*. Calcd for $C_{17}H_{20}N_4O_3$: C, 62.18; H, 6.14; N, 17.06. Found: C, 61.95; H, 6.14; N, 16.87. **6c'**: mp 172-174°C (recryst. from AcOEt-hexane). IR ($CHCl_3$): 1792, 1712 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.36 (d, 1H, *J*=11 Hz), 1.60 (s, 9H), 1.97 (d, 1H, *J*=11 Hz), 3.40 (s, 1H), 4.38 (d, 1H, *J*=8.8 Hz), 4.80 (s, 1H), 5.23 (d, 1H, *J*=8.8 Hz), 7.07-7.14 (m, 1H), 7.34-7.44 (m, 4H). ^{13}C-NMR ($CDCl_3$) δ: 28.0, 31.1, 51.7, 59.9, 60.5, 82.1, 84.0, 113.7, 123.1, 129.6, 139.2, 148.8, 171.2. *Anal*. Calcd for $C_{17}H_{20}N_4O_3$: C, 62.18; H, 6.14; N, 17.06. Found: C, 62.23; H, 6.30; N, 16.90.

Photolysis of triazoles (6a and 6a'): Typical procedure

A mixture of **6a** and **6a'** (500 mg) was dissolved in acetnitrile (300 mL), and irradiated with a 100 W high-pressure mercury lamp through a Pyrex filter under a nitrogen atmosphere at 0°C for 3 h. The solvent was removed, and the residue was separated by medium pressure liquid chromatography (SiO_2 with hexane:AcOEt=1:1) to give 205 mg (45 %) of **7a**.

7a: mp 104-106°C (recryst. from AcOEt-hexane). IR ($CHCl_3$): 1788, 1760, 1716 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.29 (t, 3H, *J*=7.3 Hz), 1.53 (s, 9H), 1.61 (d, 1H, *J*=11 Hz), 1.89 (d, 1H, *J*=11 Hz), 3.10-3.12 (m, 1H), 3.14 (d, 1H, *J*=5.3 Hz), 3.37 (d, 1H, *J*=5.3 Hz), 4.17 (q, 2H, *J*=7.3 Hz), 4.65 (s, 1H). ^{13}C-NMR ($CDCl_3$) δ: 14.2, 28.0, 36.2, 40.2, 47.3, 58.0, 63.0, 83.4, 149.5, 160.2, 172.9. *Anal.* Calcd for $C_{14}H_{20}N_2O_5$: C, 56.74; H, 6.80; N, 9.45. Found: C, 56.68; H, 6.92; N, 9.37. **7b**: mp 130-132°C (recryst. from ether). IR ($CHCl_3$): 1700 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.52 (s, 9H), 1.60 (d, 1H, *J*=9 Hz), 1.89 (d, 1H, *J*=9 Hz), 3.00 (s, 1H), 3.30 (d, 1H, *J*=16.6 Hz) 3.50 (d, 1H, *J*=16.6 Hz) 4.59 (s, 1H), 7.18-7.38 (m, 10H). ^{13}C-NMR ($CDCl_3$) δ: 28.0, 36.3, 39.9, 47.2, 58.2, 120.1, 125.6, 129.9, 172.7. *Anal.* Calcd for $C_{23}H_{25}N_2O_3P$: C, 60.52; H, 5.52; N, 6.14. Found: C, 60.61; H, 5.65; N, 6.02. **7c**: mp 133°C (recryst. from AcOEt-hexane). IR ($CHCl_3$): 1784, 1758, 1708 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.55 (s, 9H), 1.65 (d, 1H, *J*=11 Hz), 2.11 (d, 1H, *J*=11 Hz), 2.84 (d, 1H, *J*=5.4 Hz), 3.10 (d, 1H, *J*=5.4 Hz), 3.18 (s, 1H), 4.73 (s, 1H), 6.94-7.02 (m, 3H), 7.22-7.29 (m, 2H). ^{13}C-NMR ($CDCl_3$) δ: 28.0, 28.7, 37.9, 42.6, 47.8, 58.5, 83.1, 120.4, 122.7, 129.1, 150.5, 173.8. *Anal.* Calcd for $C_{17}H_{20}N_2O_3$: C, 67.98; H, 6.71; N, 9.33. Found: C, 68.12; H, 6.86; N, 9.33. **7d**: IR ($CHCl_3$): 1720 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.57 (d, 1H, *J*=12 Hz), 1.88 (d, 1H, *J*=12 Hz), 3.02 (s, 1H), 3.28 (dd, 1H, *J*=16 Hz), 3.51 (d, 1H, *J*=17 Hz), 4.65 (s, 1H), 5.23 (s, 2H), 7.17-7.43 (m, 15H). ^{13}C-NMR ($CDCl_3$) δ: 28.0, 36.0, 39.7, 47.1, 58.3, 77.5, 120.1, 125.6, 128.6, 128.7, 129.9, 172.3. High-resolution MS m/z: Calcd for $C_{26}H_{27}N_2O_6P$: 494.1607. Found: 494.1608.

The reduction of 7b with $NaBH_4$.: Typical procedure

To a solution of **7b** (200 mg, 0.49 mmol) in MeOH (30 mL) under ice-cooling, $NaBH_4$ (29 mg, 0.66 mmol) was added portionwise, and the mixture was stirred at rt for 30 min. The mixture was concentrated on rotary evaporator and the residue was extracted with AcOEt, washed with brine and dried over $MgSO_4$. The solvent was removed and the residue was separated by separated by medium pressure liquid chromatography (SiO_2 with hexane:AcOEt=2:1) to give 170 mg (75 %) of **8b**.

8b: IR ($CHCl_3$): 3600, 3380, 1690 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.35-1.50 (m, 1H), 1.43 (s, 9H), 2.00-2.18 (m, 1H), 2.20-2.27 (m, 1H), 3.15-3.30 (m, 2H), 3.40 (br s, 1H), 3.50 (d, 1H, *J*=10 Hz), 3.73 (d, 1H, *J*=10 Hz), 4.25 (br s, 1H), 6.13 (br s, 1H), 7.10-7.20 (m, 6H), 7.22-7.30 (m, 4H). ^{13}C-NMR ($CDCl_3$) δ: 28.4, 33.6, 40.8, 47.0, 47.1, 50.3, 63.4, 79.1, 120.3, 125.3, 129.7, 150.3, 150.7, 155.4. High-resolution MS m/z: Calcd for $C_{23}H_{29}N_2O_6P$: 460.1763. Found: 460.1759. **8d**: IR ($CHCl_3$): 3624, 3372, 1710 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.40 (s, 1H), 2.09-2.24 (m, 1H), 2.24-2.27 (m, 1H), 3.18-3.27 (m, 2H), 3.50 (s, 1H), 3.74 (s, 1H), 4.28 (s, 1H), 5.09 (s, 2H), 7.15-7.34 (m, 15H). ^{13}C-NMR ($CDCl_3$) δ: 33.7, 40.7, 46.4, 46.9, 50.7, 63.5, 76.7, 120.3, 125.3, 128.5, 129.7, 129.8, 155.8. High-resolution MS m/z: Calcd for $C_{26}H_{23}N_2O_6P$: 490.1294. Found: 490.1293.

The ring opening of 7a: Typical procedure

A solution of **7a** (200 mg) in MeOH (30 mL) was stirred at rt for 20 h, and the mixture was concentrated under reduced pressure. The residue was separated by medium pressure liquid chromatography (SiO_2 with hexane:AcOEt=3:1) to give 197 mg (90 %) of **8a**.

8a: IR ($CHCl_3$): 3400, 2968, 1730, 1708 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.21 (t, 3H, *J*=7 Hz), 1.39 (s, 9H), 1.74-1.90 (m, 2H), 3.07 (s, 1H), 3.16 (d, 1H, *J*=7 Hz), 3.21 (s, 1H), 3.71 (s, 3H), 4.08 (q, 2H, *J*=7 Hz), 4.25-4.35 (m, 1H), 5.49 (d, 1H, *J*=9 Hz). ^{13}C-NMR ($CDCl_3$) δ: 14.2, 28.3, 31.8, 43.6, 44.2, 45.9, 50.5, 52.4, 62.7, 79.4, 155.0, 161.1, 175.0. High-resolution MS m/z: Calcd for $C_{15}H_{24}N_2O_6$: 328.1634. Found: 328.1628 **8c**: IR ($CHCl_3$): 3408, 2972, 1728, 1712 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.42 (s, 9H), 1.83 (d, 1H, *J*=14 Hz), 1.98 -2.10 (m, 1H), 2.87 (d, 1H, *J*=4 Hz), 2.99 (d, 1H, *J*=4 Hz), 3.21 (d, 1H, *J*=8 Hz), 3.73 (s, 3H), 4.35-4.45 (m, 1H), 5.58 (d, 1H, *J*=9 Hz), 6.85-6.95 (m, 3H), 7.10-7.20 (m, 2H). ^{13}C-NMR ($CDCl_3$) δ: 28.3, 32.8, 44.6, 47.0, 48.1, 51.3, 52.3, 79.2, 120.4, 122.5, 128.9, 151.5, 155.2, 175.4. High-resolution MS m/z: Calcd for $C_{18}H_{24}N_2O_4$: 332.1736. Found: 332.1716.

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