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Asymmetric synthesis of a branched-chain analogue of azapyranoses from a 5-allylic derivative of 5-nitro-1,3-dioxane. Synthesis of (3*R*,4*S*)-6,6-bis(hydroxymethyl)-3,4-dihydroxypiperidin-2-one

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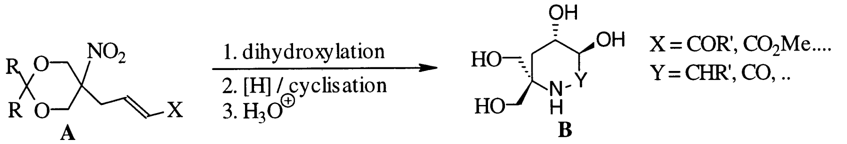
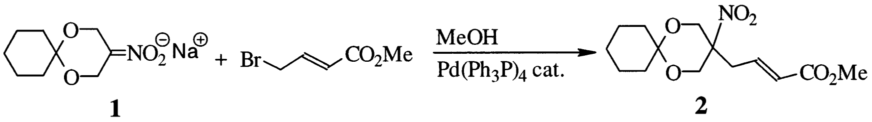
Abstract—Methyl 4-(5-nitro-1,3-dioxaspiro[5.5]undecan-5-yl)but-2-enoate **2**, obtained from the palladium(0)-catalyzed reaction of a salt of 5-nitro-1,3-dioxane **1** with methyl γ-bromocrotonate, was converted into the title piperidinone (ee 78%) in three steps.

Polyhydroxylated piperidines, frequently named as azasugars (azapyranoses), are targets of intensive synthetic studies as powerful glycosidase inhibitors and potential therapeutic agents.[1] Although numerous azasugars have been synthesized, branched-chain derivatives having a tertiary carbon at the α position to nitrogen are almost unknown.[2] A few years ago we described the synthesis of a branched-chain analogue of azafuranose, (±) 4-amino-4,4-bis(hydroxymethyl)-4-deoxythreonic-1,4-lactam, from ethyl 3-(5-nitro-1,3-dioxaspiro[5.5]-undecan-5-yl)prop-2-enoate.[3] Continuing our studies on applications of 5-nitro-1,3-dioxanes for the synthesis of polyhydroxylated heterocyclic derivatives we envisaged that branched-chain azapyranoses **B** might be readily prepared from dioxanes **A**, accessible from palladium(0)-catalyzed *C*-allylation of 5-nitro-1,3-dioxanes, via osmium-catalyzed both racemic and asymmetric dihydroxylation, reduction of the nitro group to the amine accompanied by spontaneous cyclization and deprotection of the hydroxymethyl groups (Scheme 1).

To test our concept we set up as the synthetic target 6,6-bis(hydroxymethyl)-3,4-dihydroxypiperidin-2-one (**B**, Y = CO). The starting dioxane **2** necessary for this synthesis was prepared in 52% yield from the *tetrakis*(triphenylphosphine)palladium-catalyzed reaction of the salt of nitrodioxane **1**[4] and methyl 4-bromocrotonate (Scheme 2).[5†]



Scheme 1.



Scheme 2.

Keywords: nitro compounds; palladium; asymmetric hydroxylation; δ-lactam.

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[†] All new compounds were fully characterized by HRMS, IR, ^{1}H and ^{13}C NMR spectra.

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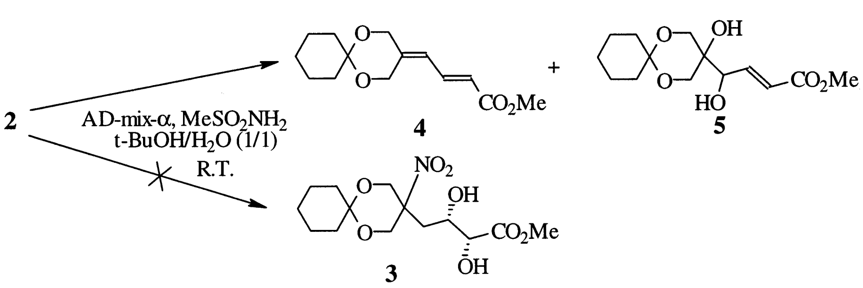
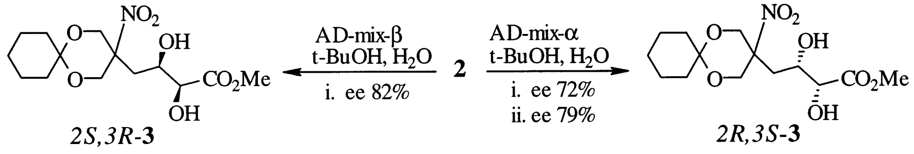
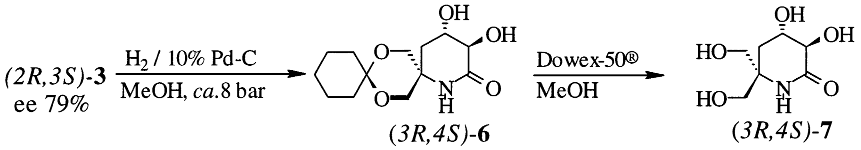


Scheme 3.



Scheme 4. Reagents and conditions: additives: i. AcOH, rt; ii. NaHCO$_3$, MeSO$_2$NH$_2$, rt.



Scheme 5.

First we prepared the target lactam as a racemate in 49% overall yield.[6,7] Encouraged with this result we submitted **2** to a Sharpless asymmetric dihydroxylation (AD).[8–10] However, the reaction of **2** with AD-mix-α (Aldrich), conducted in the presence of methanesulfonamide at room temperature failed to give the diol **3** (Scheme 3). The reaction was very sluggish and after 48 h TLC analysis disclosed the presence of substantial amounts of the substrate and two products. Chromatographic separation on silica gel gave, besides **2**, the 1,3-dienoic ester **4** in 36% yield. The second, more polar compound, isolated in tiny quantity, appeared to be the diol **5**[‡] but not the desired compound **3**.

This result is a consequence of the basic conditions (pH ca. 12.2) of the AD reaction.[11,12] Thus, under these conditions compound **2**, as a vinylog of β-nitroesters, eliminates nitrous acid to give **4**, which can then undergo dihydroxylation to yield **5**. Therefore to obtain diol **3** we had to lower the pH of the AD reaction. First this was brought down by addition of acetic acid (1 equiv. of the acid per 1 equiv. of potassium carbonate) (Scheme 4, path i). Under these conditions[§] the diol (2*R*,3*S*)-**3** was prepared in 90% yield and 72% enantiomeric excess (ee).[13]

The ee was estimated from the ^{1}H NMR spectra measured in the presence of the chiral shift reagent, Eu(hfc)$_3$, and the configuration of the major enantiomer was tentatively assigned as 2*R*,3*S* based on Sharpless' mnemonic.[8,9] The AD reaction of **2** with AD-mix-β in the presence of acetic acid gave (2*S*,3*R*)-**3** in 73% yield and 82% ee.[14] To improve the ee of (2*R*,3*S*)-**3** we conducted the AD reaction at 0°C. However, at this temperature the AD process was very slow and after 4 days (2*R*,3*S*)-**3** was obtained in only 21% yield. We did not optimize the amount of acetic acid, but we turned to the Sharpless procedure in which the pH of the AD process is lowered by the addition of sodium bicarbonate.[12,13,15] Thus, the reaction of **2** with AD-mix-α carried out at 0°C in the presence of sodium bicarbonate and methanesulfonamide afforded, after 48 h, (2*R*,3*S*)-**3** in 79% ee and 66% yield (Scheme 4, path ii).[16]

This diol (2*R*,3*S*)-**3** (ee 79%) was hydrogenated in the presence of 10% palladium-on-charcoal to afford the δ-lactam (3*R*,4*S*)-**6** in 91% yield (Scheme 5).[17] Deprotection of the hydroxymethyls was accomplished in methanol at room temperature in the presence of ion-exchange resin (Dowex-50®, H$^+$ form) to give (3*R*,4*S*)-**7** in 75% yield.

In conclusion, we have shown that the allylic derivatives of 5-nitro-1,3-dioxane are useful starting materials for the preparation of polyhydroxylated derivatives of piperidine. Further studies on improvement and extension of this approach for the synthesis of azapyranoses are underway.

[‡] This compound was identified only by ^{1}H NMR spectra. Ee was not determined.

[§] The amount of AD-mix-α and AD-mix-β were doubled compared to those reported in Ref. 9.

References

1. In *Iminosugars as Glycosidase Inhibitors, Nojirimycin and Beyond*; Stütz, A. E., Ed.; Wiley–VCH: Weinheim, 1999.
2. Wagner, J.; Vogel, P. *Tetrahedron* **1991**, *47*, 9641–9658.
3. Kuciak, R.; Sas, W. *Tetrahedron Lett.* **1994**, *35*, 8647–8648.
4. Koszytkowska-Stawińska, M.; Sas, W.; Sowińska, A. *J. Chem. Res. (S)* **1996**, 162–163.
5. Compound **2**. **1** (3.11 g, 15.5 mmol) was added under argon to a stirred solution of NaOMe, prepared from sodium (0.39 g, 17 mmol) in MeOH (35 mL) and after 0.5 h $Pd(PPh_3)_4$ (0.38 g, 0.33 mmol) was added. 4-Bromocrotonate (2 mL, 17.0 mmol) was introduced dropwise and the mixture was stirred first at ambient temperature for 2 h and then at 55–65°C for 21 h. After ca. 10 h $Pd(PPh_3)_4$ (0.12 g, 0.1 mmol) was added. Work-up afforded mixture, which was chromatographically separated (silica gel, 20–30% ethyl acetate in hexane) to afford **2** (2.41 g, 52%) as white needles, mp 55–56°C (methanol). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.39–1.76 (m, 10H, C_6H_{10}), 2.79 (dd, $J=7.7$, 1.3, 2H, C**H**$_2$CH=), 3.74 (s, 3H, Me), 3.96 (d, $J=12.8$, 2H, 2×HC**H**O), 4.43 (d, $J=12.8$, 2H, 2×**H**CHO), 5.93 (dt, $J=15.5$, 1.3, 1H, =C**H**CO_2Me), 6.72 (dd, $J=15.5$, 7.7, 1H, =C**H**–CH_2). ^{13}C NMR (50 MHz, $CDCl_3$, ATP; in all ATP spectra both CH and CH_3 give signals as minima which are marked by –) δ 22.35, 22.50, 25.35, 31.18, 32.94, 36.44, –51.74, 62.79, 85.19, 99.43, –126.71, –138.13, 165.60; IR (KBr): 1724, 1540, 1332 cm^{-1}. HRMS (EI) *m*/*z* calcd for $C_{14}H_{21}NO_6$ (M^+) 299.1369, found 299.1364.
6. The nitroester **2** was catalytically osmylated in a presence of *t*-butyl hydroperoxide[7] to afford the racemic diol in 72% yield. This was smoothly converted into the racemic title piperidone in 68% yield as is described in Ref. 17.
7. Sharpless, K. B.; Verhoeven, T. R. *Aldrichimica Acta* **1979**, *12*, 63–74.
8. Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547.
9. Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwaong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768–2771.
10. Kolb, H. C.; Andersson, P. G.; Sharpless, K. B. *J. Am. Chem. Soc.* **1994**, *116*, 1278–1291.
11. Kolb, H. C.; Bennani, Y. L.; Sharpless, K. B. *Tetrahedron*: Asymmetry **1993**, *4*, 133–141.
12. Vanhessche, K. P. M.; Wang, Z.-M.; Sharpless, K. B. *Tetrahedron Lett.* **1994**, *35*, 3469–3472.
13. The diol (2*R*,3*S*)-**3**. **2** (0.1 g, 0.33 mmol) was added to the mixture of *t*-BuOH (1.65 mL), H_2O (1.65 mL), AD-mix-α (0.925 g, Aldrich) and AcOH (0.11 mL) and this mixture was stirred for 24 h at ambient temperature. The reaction was quenched by solid Na_2SO_3. After water work up and extraction with CH_2Cl_2, crude **3** was chromatographically purified (silica gel, hexanes/ethyl acetate, 1/1, v/v) to give white crystals of (2*R*,3*S*)-**3** (0.100 g, 90%), mp 124–125°C, ee 72%, $[\alpha]_D^{20}$ –15.9 (*c* 1, CH_2Cl_2).
14. The diol (2*S*,3*R*)-**3**. The reaction of **2** with AD-mix-β[13] under conditions described above afforded after 28 h (2*S*,3*R*)-**3** in 73% yield, mp 126–127°C, ee 82%, $[\alpha]_D^{20}$ +18.2 (*c* 0.5, CH_2Cl_2). Both diols gave the same IR, ^{1}H and ^{13}C NMR spectra. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.38–1.81 (m, 10H, C_6H_{10}), 2.10, (dd, $J=15.3$, 2.0, 1H, HC**H**CHOH), 2.24 (dd, $J=15.3$, 10.4, 1H, **H**CHCHOH), 2.35 (d, $J=8.4$, 1H, OH), 3.13 (d, $J=5.2$, 1H, OH), 3.83 (s, 3H, CH_3), 4.00–4.04 (m, 2H, 2×C**H**OH), 4.05 (d, $J=12.8$, 1H, CH–O), 4.09 (d, $J=13.1$, 1H, CH–O), 4.49 (dd, $J=12.8$, 2.0, 1H, CH–O), 4.63 (dd, $J=13.1$, 2.0, 1H, CH–O). ^{13}C NMR (50 MHz, $CDCl_3$, ATP) δ 22.36, 22.49, 25.40, 29.66, 34.53, 38.03, –53.18, 63.50, 63.56, –68.15, –73.65, 85.34, 99.14, 172.67. IR (KBr): 3416, 1744, 1544, 1336, cm^{-1}. HRMS (EI) *m*/*z* calcd for $C_{14}H_{23}NO_8$ (M^+) 333.1424, found 333.1420.
15. Walsh, P. J.; Sharpless, K. B. *Synlett* **1993**, 605–606.
16. AD dihydroxylation of **2** by AD-mix-α in the presence of $NaHCO_3$. **2** (0.90 g, 0.3 mmol) was added to the mixture of *t*-BuOH (1.5 mL), H_2O (1.5 mL), AD-mix-α (0.84 g), $NaHCO_3$ (0.15g) and $MeSO_2NH_2$ (0.06 g). This mixture was stirred at 0°C for 48 h. Chromatographic purification[13] afforded 0.65 g (66%) of (2*R*,3*S*)-**3**, mp 125–126°C, ee 79%, $[\alpha]_D^{20}$ –17.5 (*c* 0.5, CH_2Cl_2).
17. Compound (3*R*,4*S*)-**7**. (2*R*,3*S*)-**3** (ee 79%, 0.18 g, 0.6 mmol) in MeOH (3 mL) was hydrogenated in the presence of 10%-Pd–C (0.06 g) at 60°C and under 8 bar pressure. The mixture was passed through a short pad of Celite®. After solvent removal, the residue was chromatographically purified (silica gel, first hexane/ethyl acetate, 1/1, v/v then methanol) to afford (3*R*,4*S*)-**6**, 0.15 g, 91%), mp 140–140.5°C, $[\alpha]_D^{20}$ –2 (*c* 1, CH_2Cl_2). (3*R*,4*S*)-**6** (0.095 g, 0.35 mmol) and ion exchange resin (0.2g, H^+, DOWEX-50®) were stirred in MeOH (5 mL) at ambient temperature until TLC (silica gel, acetone/MeOH, 2/1, v/v) showed completeness of deprotection (ca. 2 h). The resin was filtered off and washed with MeOH/H_2O (2/1, v/v). The solvent was distilled off to afford (3*R*,4*S*)-**7** (0.05 g, 75%) as colorless glass, $[\alpha]_D^{20}$ –17.5 (*c* 0.5, H_2O). ^{1}H NMR (500 MHz, D_2O) δ 1.70 (dd, $J=13.7$, 12.2, 1H, H-5a), 1.97 (dd, $J=13.7$, 4.5, 1H, H-5e), 3.33 (d, $J=11.7$, 1H, HC**H**OH), 3.41 (bs, 2H, C**H**$_2$OH), 3.42 (d, $J=11.7$, 1H, **H**CHOH), 3.80 (d, $J=9.5$, 1H, H-3), 3.92 (ddd, $J=12.2$, 9.5, 4.5, 1H, H-4). ^{13}C NMR (50 MHz, $CDCl_3$, ATP) δ 32.42, 58.73, 65.39, 65.54, –67.46, –73.53, 174.78. IR (KBr): 3384, 3280, 3188, 1660, 1076, 1044 cm^{-1}. HRMS (LSIMS) *m*/*z* calcd for $C_7H_{14}NO_5$ ($M+H^+$) 192.0872, found 192.0881.