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Synthesis of a 2-Deoxy-Ribose Type 1-*N*-Iminosugar†

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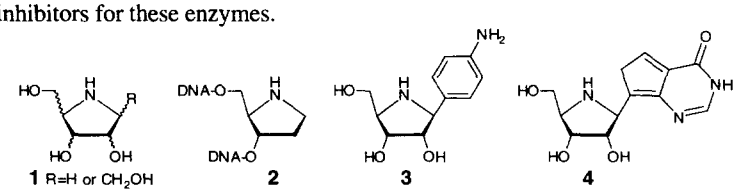
Abstract: A 2-deoxy-ribose-type 1-*N*-iminosugar **5** was synthesized, in multi-gram scale, from fumaric acid monoethyl ester employing Sharpless asymmetric epoxidation followed by a Lewis acid-catalyzed (Yamamoto's aluminum reagent) cyanide epoxy ring-opening reactions.

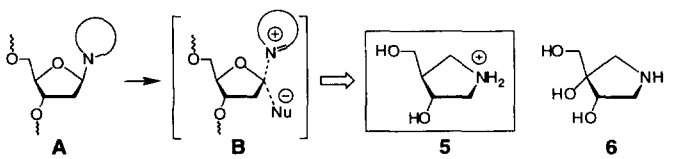
Keyword: iminosugar, 2-deoxyribose, enzyme inhibitor, cyanide

Five-membered azasugar (pyrrolidine) derivatives **1** are known potent inhibitors of glycosidases.[1] They have also been incorporated into nucleoside analogs by further chemical functionalization and used as effective molecular probes.[2] The Verdine group prepared **2**[3] for *N*-glycosylases which catalyze cleavage of *N*-glycosidic bonds of damaged bases of DNA chain which is the first step of the DNA base-excision repair pathway.[4] Other pyrrolidine analogs **3**[5] and **4**[6] were also applied by the Schramm group to *N*-glycosylase (trypanosomal nucleoside hydrolase) and PNP (purine nucleoside pyrophosphorylase), respectively, and were shown to be extremely potent inhibitors for these enzymes.



1 R=H or CH_2OH **2** **3** **4**

In the course of our research program on designing new inhibitors of glycosidase, 1-*N*-iminosugars,[7–9] we designed a 2-deoxyribose-type 1-*N*-iminosugar **5** based on a possible reaction mechanism of *N*-glycosidic bond-cleavage (**A**→**B**). The Bols group has already reported a synthesis of a 2-deoxy-ribose type 1-*N*-iminosugar **6**, from D-mannose, with an additional OH group at the C-4 position (its possible disadvantageous role was mentioned in this article) and its inhibitory potency against PNP (from human).[10] A racemic synthesis of such pyrrolidinediol was reported by Jaeger and Biel,[11] and its conjugates with nucleoside bases via N-N bond were prepared by Youn et al.[12] and others.[13,14] We describe herein efficient synthesis of a 2-deoxyribose-type 1-*N*-iminosugar **5** employing the Sharpless asymmetric epoxidation[15] and an epoxide ring-opening by cyanide anion using Yamamoto's aluminum reagent.[16]



A **B** **5** **6**

†A preliminary account of this work has been reported at the ACS meeting in Dallas, March 29–April 2, 1998.

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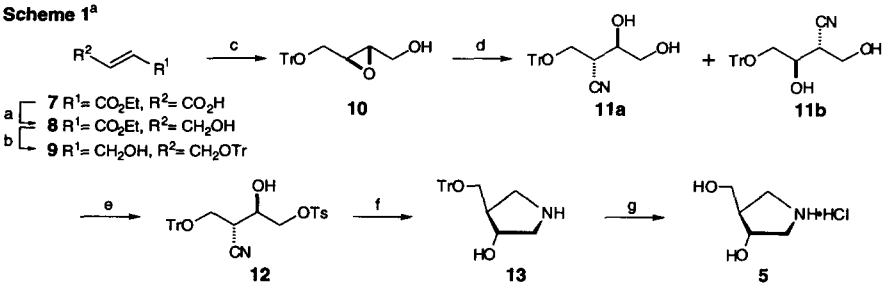
Scheme 1[a]



[a]Reagents and conditions: (a) BH_3/THF/0°C to rt./17h (50%); (b) i) TrCl/Et_3N/DMAP/CH_2Cl_2/rt/15h, ii) DIBAL-H/CH_2Cl_2/–78°C/1h (72% from **8**); (c) (+)-diethyl tartrate/$Ti(OiPr)_4$/tBuOOH/MS4A/CH_2Cl_2/–20 to –10°C/12h (74%; 96% d.e.); (d) 2,6-*tert*-butyl-4-methylphenol/Et_2AlCN/toluene/0°C to rt/72h (63%; **11a**:**11b**=3~4:1); (e) *p*TsCl/Et_3N/DMAP/CH_2Cl_2/0°C to rt/17h (71%); (f) H_2/Raney® Ni /EtOH/rt/72h (73%); (g) 1N HCl/MeOH/rt/8h (89%).

Fumaric acid monoethyl ester **7** was reduced with BH_3 to give an alcohol **8**,[17] which was subsequently tritylated, to differentiate the two primary hydroxyl groups, and reduced with DIBAL-H to yield the alcohol **9**[18] in 72% yield in two steps. Sharpless asymmetric epoxidation[15,19] of the *E*-allylic alcohol **9** proceeded smoothly to give the (2*S*,3*R*)-epoxide **10**[18] in 74% yield with 96% d.e. determined with its MTPA ester.[20]

The key step of the synthesis was a conversion of the epoxide **10** to a nitrile alcohol **11a**. While a cyanide (nitrile) group is a chemically versatile functional group, there are not many examples of regioselective epoxy ring-opening reaction with a cyanide anion. When Sharpless conditions[21] were applied (entries 1–3, Table 1) with KCN and titanium alkoxide as Lewis acids, the observed selectivity was in favor of the formation of the regioisomer **11b**.[22] Employing DIBAL as a Lewis acid sacrificed both chemical yield and selectivity (entry 4). When the epoxide **10** was treated with LiCN[23] prepared from LiH and acetone cyanohydrin,[24] the regioisomer **11b** was obtained in excellent selectivity (entry 5). Attempts to use other Lewis acids such as ZnBr-KCN, $ZnBr_2$-TMSCN, $Al(OiPr)_3$-KCN, $Al(OiPr)_3$-TMSCN, $SnCl_2$-KCN, $SnCl_2$-TMSCN resulted in no reaction or trimethylsilylation of the OH group of **10**.

Nagata's reagent,[25] Et_2AlCN, gave a good selectivity of 4:1 in 77% yield; however, this method was found not to be applicable for large scale synthesis (>10 g) because the trityl group came off during the reaction and thereby lowered the chemical yield as well as selectivity (entry 6). We then applied Yamamoto's method of using

Table 1.
Epoxy ring-opening reactions of **10** with cyanide and a Lewis acid.

entry	conditions	yield	product ratio (**11a**:**11b**)
1	$Ti(O^iPr)_4$, KCN, Bu_4NI, DMSO, rt, 72h	85%	1:2
2	$Ti(OMe)_4$, KCN, Bu_4NI, DMSO, rt, 72h	90%	1:2
3	$Ti(O^iPr)_4$, KCN, 18-crown-6, benzene, rt, 72h	70%	1:1
4	DIBAL-H, TMSCN, hexane, rt, 72h	28%	1:1.5
5	LiH, acetone cyanohydrin, THF, reflux, 8.5h	52%	1:>15
6	Et_2AlCN, tolune, 0°C to rt, 72h	77%	3~4:1[a]
7	Et_2AlCN, 2,6-di-tert-butyl-4-methylphenol toluene, 0°C to rt, 48h	63%	3:1

[a]Yields varied due to *O*-detritylation during the reaction.

a bulky organoaluminum compound (entry 7).[16] When 2,6-di-tert-butyl-4-methylphenol and Et_2AlCN were mixed in a molar ratio of 2:1 in toluene, a clear solution was obtained with vigorous evolution of gas. The epoxy alcohol **10** was added to this solution to give the products **11a**[18] and **11b** (3:1) in 63% yield. This procedure was found to be reproducible even in a large scale preparation (>10 g).

Tosylation of **11a** gave a primary tosylate **12** which was then reductively cyclized with Raney® Ni to afford a five-membered iminocycitol **13**[18] in high yield. Acidic treatment of **13** gave the 2-deoxyribose type 1-*N*-iminosugar **5**.[18] We evaluated inhibitory activity of **5** against PNP (from human) as described in the literature,[26] and obtained an IC_{50} of 160 μM while Bols et al. reported the Ki value of 180 μM for **6**.[10]

In summary, we have developed an efficient synthesis of 2-deoxyribose type 1-*N*-iminosugars employing Sharpless asymmetric epoxidation and epoxy ring-opening reaction of cyanide with Yamamoto's bulky aluminum reagent. Additionally this procedure was proven to be applicable to a large scale synthesis (>10 g). Further modification of this 2-deoxyribose type 1-*N*-iminosugar into nucleoside analogs and their biological activities will be published elsewhere.

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Addition: Very recently Godskesen and Lundt reported a synthesis of a cis-isomer of **5** (2-deoxy-xylose type). See: Godskesen, M.; Lundt, I. *Tetrahedron Lett.* **1998**, *39*, 5841–5844.

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18. Compound **9**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 (br s, 1H, OH), 3.64 (dd, 2H, J= 1.0, 5.0 Hz), 4.17 (m, 2H), 5.83 (dt, 1H), 5.99 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 63.0, 64.0, 86.8, 126.9, 127.7, 128.3, 128.5, 130.0, 144.0. FAB HRMS calcd for $C_{25}H_{25}O_3$ $(M+H)^+$ 373.1802, found 373.1804.

    Compound **10**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.68 (t, 1H, J= 6.5 Hz), 3.11–3.40 (dd, 2H, J= 1.0, 5.0 Hz), 3.63 (dq, 1H, J= 4.0, 12.5 Hz), 3.95 (dq, 1H, 3.0, 12.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 54.4, 55.9, 61.2, 63.3, 86.7, 127.0, 127.8, 128.6, 143.7. FAB HRMS $C_{23}H_{22}O_3$ $(M)^+$ 346.1569, found 346.1568.

    Compound **11a**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.89 (m, 1H), 2.47 (d, 1H, J= 5.0 Hz), 2.91 (dt, 1H, J= 5.0, 8.5 Hz), 3.38 (dd, 1H, J= 5.0, 9.5 Hz), 3.58 (dd, 1H, J= 5.0, 9.5 Hz), 3.71 (dt, 1H, J= 6.0, 11.0 Hz), 3.82 (ddd, 1H, J= 3.0, 5.0, 11.0 Hz), 4.01 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.2, 60.2, 63.9, 69.6, 87.5, 118.6, 127.4, 128.1, 128.5. FAB HRMS $C_{24}H_{23}NO_3$ $(M)^+$ 373.1678, found 373.1677.

    Compound **13**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.32 (m, 1H), 2.59 (m, 1H), 2.91 (m, 1H), 3.07 (t, 1H, J= 9.0 Hz), 3.12 (t, 1H, J= 9.0 Hz), 3.26 (m, 1H), 3.59 (m, 1H), 4.12 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 48.6, 48.7, 54.4, 64.0, 74.5, 86.4, 126.8, 127.6, 128.4, 143.7.

    Compound **5** (HCl salt): ^{1}H NMR (300 MHz, D_2O) δ 1.20 (m, 1H), 3.11 (dd, 1H, J= 6.0, 12.0 Hz), 3.21 (dd, 1H, J= 2.0, 12.0 Hz), 3.38 (dd, 1H, J= 5.0, 12.0 Hz), 3.51–3.61 (m, 3H), 4.36 (dt, 1H, J= 3.0, 5.0Hz); ^{13}C NMR (75 MHz, D_2O) δ 47.5, 48.4, 53.4, 62.4, 72.3. EI HRMS $C_5H_{11}NO_2$ (free base form) $(M)^+$ 117.0790, found 117.0790.
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