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# A New Synthesis of (2*S*)-4-Oxopipecolic Acid by Thermal Rearrangement of Enantiopure Spirocyclopropaneisoxazolidine[1]

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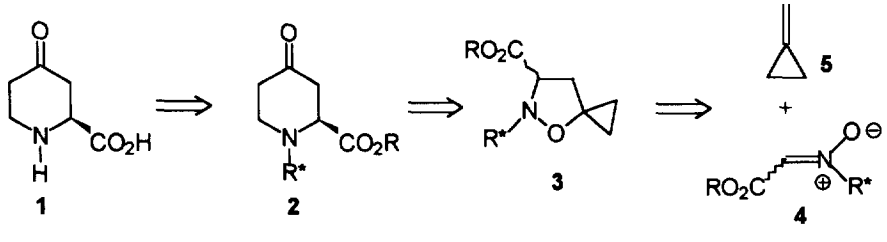
***Abstract**: A novel synthesis of (2S)-4-oxo-pipecolic acid is reported. The synthetic route employs as a key step the diastereoselective cycloaddition of the N-glycosylnitrone 7 to methylenecyclopropane followed by thermal rearrangement of the spirocyclopropaneisoxazolidine **8a**. Stereoselective reduction of the N-BOC methyl ester of 4-oxopipecolic acid by L-selectride® gives the protected cis-4-hydroxy-pipecolic acid **14**.* Copyright © 1996 Elsevier Science Ltd

(2*S*)-4-Oxopipecolic acid (**1**), a rare amino-acid constituent of the *virginiamycin* family of cyclic peptides,[2] has been the object of several studies in the last years, that have also shown its biosynthetic origin from lysine.[3] The interest in this amino-acid and its use as precursor of other important natural products such as 4-hydroxy,[2d] 4-sulfate,[3c] and 4-aminopipecolic acids,[4] has prompted us to propose a new total synthesis of **1**. Our synthetic plan relies on a new application of our methylenecyclopropane-nitrone cycloaddition-rearrangement methodology,[5] that has already shown its efficacy for the synthesis of tetrahydropyrid-4-one derivatives.

**Scheme 1**

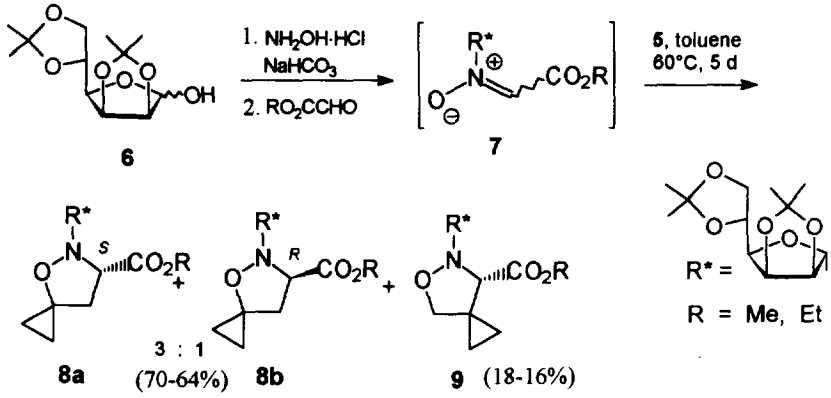



The ketoester **2** can be obtained by thermal rearrangement of the isoxazolidine **3** which can be prepared by cycloaddition of nitrone **4** and methylenecyclopropane **5** (Scheme 1). The control of absolute configuration of the stereocenter in **1** can be achieved in the cycloaddition step by using an optically active nitrone, as thermal rearrangement of the isoxazolidine cycloadduct does not affect the stereochemistry of the C-3 (isoxazolidine numbering).

Asymmetric nitrone cycloadditions have been widely studied as a means to synthesize optically pure 1,3-aminoalcohols.[6] Chiral nitrones can be prepared by introducing a stereogenic center either in the substituent at

carbon or in the substituent at nitrogen. The second option generally allows the recovery of the chiral auxiliary used for asymmetric induction and appears more versatile for synthetic purposes. Among the latter compounds, those sugar-derived developed by Vasella,[7] appeared the most appropriate for our methodology. In fact, a glycosidic protecting group of the nitrogen does not interfere with the amino radical intermediate of the rearrangement[8], and can be easily removed by acid hydrolysis.

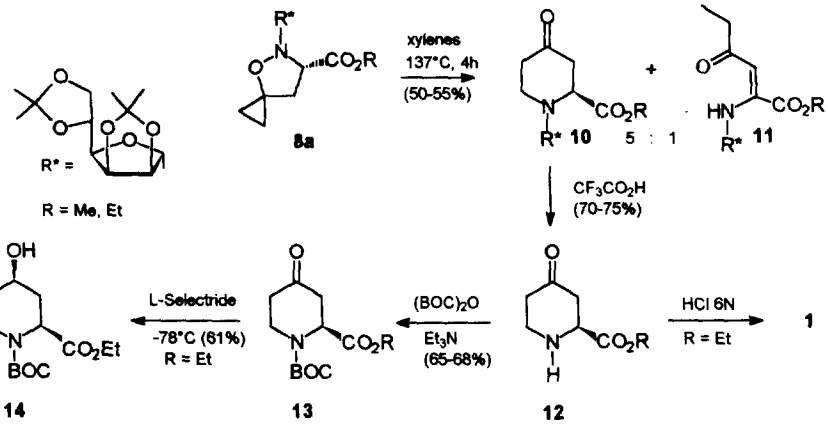
**Scheme 2**




The nitrone 7 (R = Et), obtained *in situ* from 2,3:5,6-diisopropylidene-mannofuranose (**6**), hydroxylamine and ethyl glyoxylate according to Vasella,[7] was reacted in a sealed tube with methylenecyclopropane (**5**) at 60°C for 5 days. Regioisomeric isoxazolidines **8** and **9** were obtained in good yields (88%) and a 4:1 ratio.[9] The major regioisomer **8** was present as a mixture of two diastereoisomers in 3:1 ratio, easily detectable by the two NMR signals for the C3 (isoxazolidine numbering) protons (δ 2.78 and 2.69 ppm for **8a** and **8b**, respectively), but only partially separable by flash chromatography. The pure major diastereoisomer **8a** could be obtained by crystallization from diisopropyl ether, and completely analysed,[10] albeit the assignment of the configuration at C3 (isoxazolidine numbering) was impossible by NMR spectroscopy. The low diastereoselectivity observed in the cycloaddition (50% d.e.), in analogy to previous observations,[7a,7d,11] can be ascribed to the nature of alkoxycarbonyl substituted nitrones fast equilibrating between the *E* and *Z* configurations.[12] According to the preferred *anti* attack of the dipolarophile to the most stable O-*endo* conformation of the nitrone,[7a,13] the major isomer **8a** originated from the *Z*-nitrone. This configuration should be favored by the bulkiness of the *N*-glycosyl substituent.[12b] A higher diastereoselectivity was apparently achieved in the process leading to the regioisomer **9**, as only one of the two possible isomers was isolated.

The thermal rearrangement of isoxazolidine **8a**, carried out by heating a 0.1 M solution in xylenes at reflux temperature, gave, besides minor amounts of the expected open chain side product **11**, the tetrahydropyridone **10** which was purified by flash chromatography. Acid hydrolysis (EtOH, $CF_3CO_2H$) gave 4-oxopipecolic acid ethyl (or methyl) ester **12**[9] with concomitant recovery of the sugar chiral auxiliary after column chromatography. Acid hydrolysis (HCl 6N) of ester **12** followed by neutralization gave (2*S*)-4-oxopipecolic acid (**1**) with $[\alpha]_D^{23}$ −19.2 (c 0.5, $H_2O$), identical to that of natural compound ($[\alpha]_D^{25}$ −17 (c 1, $H_2O$)).[3d] This correlation is an indirect assignment of the 2*S* and 2*R* configuration of C(3) stereocenters of isoxazolidines **8a** and **8b**, respectively. Treatment of **12** with $(BOC)_2O$ and triethylamine afforded the BOC protected 4-oxopipecolic acid ethyl (or methyl) ester **13**[9,14] suitably protected for peptide syntheses.

**Scheme 3**




L-selectride® reduction of ketone **13** (R = Et) in THF at -78°C afforded the *cis* 4-hydroxy-*N*-BOC-pipecolic acid ethyl ester **14**[9,15] in 60% yield whereas $NaBH_4$ reduction gave a mixture of diastereoisomeric alcohols (*cis*, *trans* 1.5:1).[2c] The assignment of a *cis* relationship between hydroxyl and carbethoxy groups relies on comparison with a racemic sample of *cis*-4-hydroxypipecolic acid obtained as reported in the literature.[3d] The preference for an axial orientation of the methoxycarbonyl group in **13** to reduce allylic 1,3-strain,[16] as proven also by us by computational studies (MacroModel V 4.5),[17] dictates the attack of the bulky reducing agent to give the observed *cis* relationship of **14**.

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8. *N*-Benzyl substituted 5-spirocyclopropane isoxazolidines give poor results in the rearrangement because of the instability of the *N*-benzyl radical: Brandi, A. Cordero, F.M. unpublished results.
9. All the new compounds were fully characterized by spectroscopical and analytical means.
10. **8a** (R = Et): M.p. 81-82 °C (diisopropyl ether). $[\alpha]_D^{23}$ +7.5 (c 0.975, $CHCl_3$). $^1$H-NMR (200 MHz, $CDCl_3$): δ 4.92-4.8 (m, 2H), 4.70 (s, 1H), 4.42-3.94 (m, 8H), 2.78 (dd, *J* = 12, 5.8 Hz, 1H), 2.38 (dd, *J* = 12, 8.8 Hz, 1H), 1.48 (s, 3H), 1.42 (s, 3H), 1.37 (s, 3H), 1.33 (s, 3H), 1.31 (t, *J* = 7.1 Hz, 3H), 1.12-0.90 (m, 2H), 0.82-0.60 (m, 2H).$^{13}$C-NMR (200 MHz, $CDCl_3$): δ 171.4 (s), 112.4 (s), 109.3 (s), 97.73 (d), 83. 95 (d), 82.13 (d), 80.23 (d), 73.02 (d), 66.79 (t), 64.19 (d), 63.73 (s), 61.55 (t), 37.13 (t), 26.89 (q), 25.98 (q), 25.21 (q), 24.56 (q), 14.15 (q), 13.09 (t), 7.58 (t).
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14. **13** (R = Et): $[\alpha]_D^{23}$ – 9.2 (c 0.91, $CHCl_3$). $^1$ H-NMR (200 MHz, $CDCl_3$): δ 5.05 and 4.80 (m, 1H, two conformers), 4.16 (q, *J* = 7.4 Hz, 1H), 4.02 (dt, *J* = 14, 5.8 Hz, 1H), 3.64 (m, 1H), 2.80 (m, 2H), 2.54 (m, 2H), 1.48 (s, 9H), 1.26 (t, *J* = 7.4 Hz, 3H). $^{13}$C-NMR (200 MHz, $CDCl_3$): δ 205.9 (s), 171.1 (s), 146.7 (s), 81.1 (s), 61.7 (t), 54.8 and 54.1 (d, two conformers), 41.1 (t), 40.46 and 39.33 (t, two conformers), 39.7 (t), 28.2 (q, 3C), 14.1 (q).
15. **14** (R = Et): $[\alpha]_D^{23}$ –30.6 (c 0.83, $CHCl_3$).$^1$ H-NMR (200 MHz, $CDCl_3$): δ 4.78 and 4.63 (m, two conformers, 1H), 4.90 and 4.20 (q, *J* = 7.3 Hz, two conformers, 2H), 4.14 (m, 1H), 4.00-3.69 (m,1H), 3.48-3.19 (m, 1H), 2.43 (dm, *J* = 14.7 Hz, 1H), 1.90 (ddd, *J* = 14.4, 7.0, 2.4 Hz, 1H), 1.79-1.45 (m, 2H+OH), 1.45 (s, 9H), 0.91 (t, *J* = 7.3 Hz, 3H). $^{13}$C-NMR (200 MHz, $CDCl_3$): δ 172.6 (s), 156.1 (s), 79.9 (s), 73.3 (t), 63.2 (d), 51.6 and 50.5 (d, two conformers), 36.1 and 34.9 (t, two conformers), 33.3 (t), 31.0 (t), 28.3 (q, 3C), 19.1 (q).
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