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Synthesis of (2R,5R)-2-Amino-5-Hydroxyhexanoic Acid by Intramolecular Cycloaddition*

Tuvia Sheradsky and Elliad R. Silcoff**

Department of Organic Chemistry, the Hebrew University, Jerusalem 91904, Israel.
Tel.+972 2 658 5284, Fax +972 2 658 5345, Email stuvia@vms.huji.ac.il

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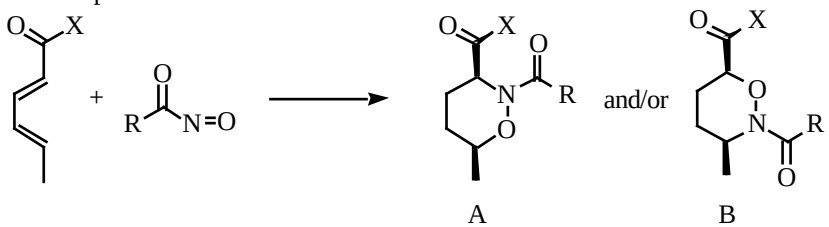
Abstract: The title compound was synthesized from sorbic acid by an eight step sequence. The key step was the stereospecific intramolecular Diels-Alder reaction of the acylnitroso derivative of N-sorbyl-L-proline (5). L-Proline served as a temporary tether which directed both the stereochemistry and the regiochemistry of the cycloaddition.

Keywords: Intramolecular cycloaddition, enantiospecifity, proline, acylnitroso.

Introduction

The induction of asymmetry in cycloaddition reactions presents an interesting but difficult problem as all participating atoms are either sp^2 carbons or heteroatoms and thus cannot be chiral. Most cycloadditions are also non-catalytic. These limitations impel the synthetic chemist to use the auxiliary approach. The chiral auxiliary, however, is usually remote in relation to the reactive centers and therefore, in order to completely obstruct the approach from one side it needs to be very bulky [1, 2] and often even this is not good enough to impart high enantioselectivity. It is however well known that intramolecular cycloadditions proceed under a much higher stereocontrol and that even small chiral substituents on the chain connecting the two components can induce complete asymmetry [3-5].

Previously we have reported the double use of proline as a removable chiral tether and a chiral auxiliary in hetero Diels-Alder reactions [6]. We now describe an extension of this methodology, which involves the Diels-Alder reaction of a sorbic acid derivative with an acylnitroso dienophile [7]. The proline bridge in this case not only induced asymmetry, but also reversed the regiochemistry as it led to product A whereas the corresponding intermolecular reaction gives exclusively the undesired product B (figure 1) [8].



A B

Figure 1: Two possible regiomers in the addition of an acylnitroso group to a diene.

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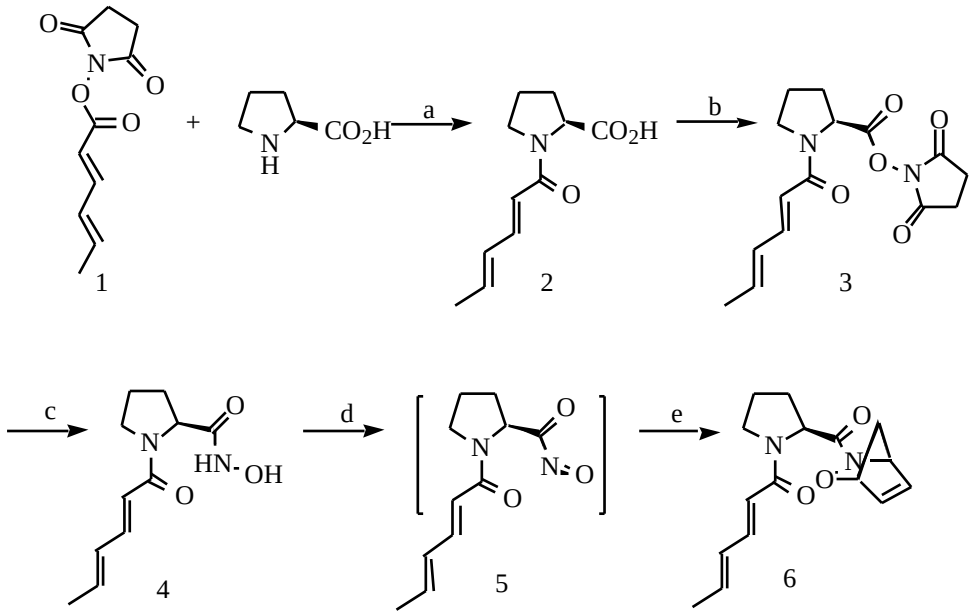
** To whom correspondence should be addressed.

Product A is a cyclic α-amino acid which can undergo a selective cleavage at the N-O bond, leading to the target molecule named in the title.

Results and Discussions

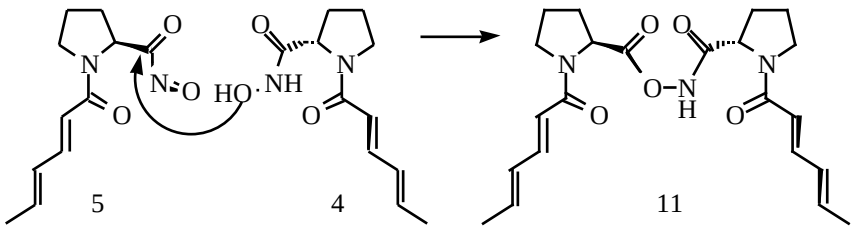
An appropriate substrate which contains the structural elements necessary for this synthesis is the intermediate **5**. Its preparation involved the conversion of N-sorbyl-L-proline, **2**, to its N-hydroxy-succinimide ester **3**. Reaction of this active ester with hydroxylamine under basic Schotten-Baumann like conditions gave the hydroxamic acid **4**. This was followed by oxidation, using tetraethylammonium periodate to give **5** as an active intermediate *in situ* [9].

Due to the low dienic reactivity of the sorbic moiety in **5**, the acylnitroso function did not undergo intramolecular cycloaddition, but rather acted as an acylating agent on unoxidized **4** still present in the system to produce only the diacylhydroxylamine **11**. This result indicated that **5** had to be generated in a medium free of **4** and of other nucleophiles. This was achieved by trapping compound **5** as its cyclopentadiene adduct [9-10]. Oxidation of **4** in the presence of the highly reactive diene cyclopentadiene yielded solely the cycloadduct **6** which was purified by column chromatography.

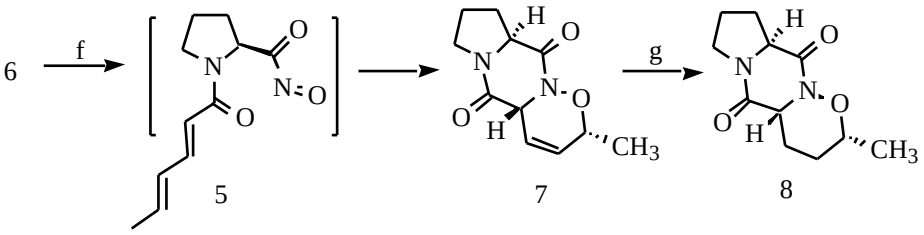


a: $NaHCO_3$, H_2O/glyme, reflux 4h, 90%. b: N-Hydroxysuccinimide, D.C.C., EtOAc, 0°C, 84%.
c: $NH_2OH{\cdot}HCl$, CH_3OH/CH_3ONa, r.t., 92%. d: $N(Et)_4IO_4$, CH_2Cl_2. e: Cyclopentadiene, CH_2Cl_2, 0°C, 1h, 61%.

Scheme 1. Synthesis of the intermediate **6**.



Scheme 2. The reaction to give the diacylhydroxylamine **11**.



f: Toluene, reflux, 5h, 40%. g: H_2 (60 p.s.i.), Pd/C, CH_3OH, 5h, 90%.

Scheme 3. The Synthesis of the chiral diketopiperazine **8**.

Table 1. Dimensional parameters for **8**:

Intramolecular distances involving non hydrogen atoms. Distances are in angstroms (Å). Estimated standard deviation in the least significant figure are given in parentheses.

atom	atom	distance
O(1)	N(1)	1.407(4)
O(1)	C(1)	1.474(5)
O(2)	C(10)	1.222(5)
O(3)	C(5)	1.239(5)
N(1)	C(4)	1.436(5)
N(1)	C(10)	1.333(5)
N(2)	C(5)	1.318(6)
N(2)	C(6)	1.465(6)
N(2)	C(9)	1.476(5)
C(1)	C(2)	1.529(7)
C(1)	C(11)	1.485(7)
C(2)	C(3)	1.518(7)
C(3)	C(4)	1.510(6)
C(4)	C(5)	1.511(6)
C(6)	C(7)	1.487(7)
C(7)	C(9)	1.535(7)
C(8)	C(9)	1.531(6)
C(9)	C(10)	1.501(5)

Intramolecular bond angles involving non hydrogen atoms. Angles are in degrees. Estimated standard deviations in the least significant figure in parentheses.

atom	atom	atom	angle
N(1)	O(1)	C(1)	108.8(3)
O(1)	N(1)	C(4)	113.3(3)
O(1)	N(1)	C(10)	117.2(3)
C(4)	N(1)	C(10)	129.4(4)
C(5)	N(1)	C(6)	124.5(4)
C(5)	N(2)	C(9)	125.6(4)
C(6)	N(2)	C(9)	109.8(3)
O(1)	C(1)	C(2)	107.5(3)
O(1)	C(1)	C(11)	111.5(3)
C(2)	C(1)	C(11)	115.7(4)
C(1)	C(2)	C(3)	112.3(3)
C(2)	C(3)	C(4)	110.2(4)
N(1)	C(4)	C(3)	110.0(4)
N(1)	C(4)	C(5)	113.4(3)
C(3)	C(4)	C(5)	113.4(4)
O(3)	C(5)	N(2)	122.8(5)
O(3)	C(5)	C(4)	119.0(4)
N(2)	C(5)	C(4)	118.0(4)
N(2)	C(6)	C(7)	106.0(4)
C(6)	C(7)	C(8)	106.1(4)
C(7)	C(8)	C(9)	102.8(4)
N(2)	C(9)	C(8)	101.9(3)
N(2)	C(9)	C(10)	114.4(3)
C(8)	C(9)	C(10)	115.3(3)
O(2)	C(10)	N(1)	123.5(4)
O(2)	C(10)	C(9)	121.2(4)
N(1)	C(10)	C(9)	115.2(3)

The remaining steps involved reductive cleavage of the N-O bond and hydrolytic removal of the auxiliary, L-proline. The harsh conditions needed for the hydrolysis of diketopiperazines caused the complete decomposition of **8**. Thus by reductive cleavage with a Na/Hg amalgam [13], the N-O bond was severed, resulting in **9**, a cyclic diamide of proline and a new chiral unnatural amino acid, in a 79% yield. This substance was then hydrolyzed into its components.

The hydrolysis of diketopiperazines usually requires harsh acidic conditions (6N HCl, 20 hrs reflux) which, however, do not cause racemization. Indeed such hydrolysis of **9** afforded a mixture which clearly exhibited two ninhydrin spots on a TLC plate, a yellow one for proline and a violet one for the new amino acid **10**. Separation of the two components was attempted both directly (as hydrochlorides or free bases) or through derivitizations. Although we were able to recover proline in most cases, we have not yet acquired a pure sample of 10 and it appears that a large portion of it was decomposed during the hydrolysis.

Table 2. Positional parameters and B(eq) for non hydrogen atoms for **8**. Estimated standard deviations in the least significant figure in parentheses**.**

atom	x	y	z	B(eq)
O(1)	0.2999(3)	0.1010(1)	0.5877(5)	3.4(1)
O(2)	0.0560(3)	0.0643(1)	0.7896(6)	4.2(1)
O(3)	0.2797(4)	0.2422(1)	1.191(1)	7.1(2)
O(4)	0.6924(3)	-0.0034(2)	0.3352(7)	6.0(2)
N(1)	0.2349(3)	0.1242(1)	0.8077(7)	2.9(1)
N(2)	0.1141(4)	0.1777(1)	1.2110(7)	3.4(1)
C(1)	0.4349(4)	0.0755(2)	0.6691(8)	3.6(2)
C(2)	0.5329(5)	0.1189(2)	0.778(1)	4.6(2)
C(3)	0.4619(5)	0.1503(2)	0.995(1)	4.2(2)
C(4)	0.3142(4)	0.1683(2)	0.9114(9)	3.5(2)
C(5)	0.2343(5)	0.1983(2)	1.121(1)	4.0(2)
C(6)	0.0131(5)	0.2056(2)	1.382(1)	4.5(2)
C(7)	-0.1222(6)	0.1743(2)	1.375(1)	5.3(2)
C(8)	-0.1050(5)	0.1344(2)	1.151(1)	4.5(2)
C(9)	0.0572(4)	0.1247(1)	1.1457(8)	3.0(2)
C(10)	0.1147(4)	0.1019(2)	0.8962(8)	2.9(2)
C(11)	0.4079(5)	0.0299(2)	0.846(1)	4.6(2)

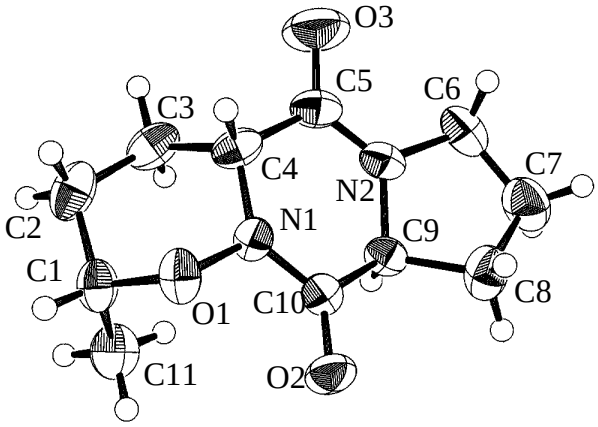
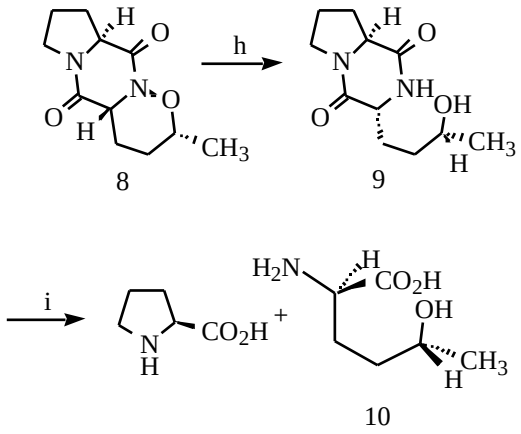


Figure 2. The x-ray crystal structure of **8**.



h: Na(Hg), Na_2HPO_4, EtOH, 79%. i: HCl/H_2O, reflux, 12h.

Scheme 4. The separation of **10** from the chiral tether.

As we have encountered the same problem previously in the synthesis of 1,5-diaminohexanoic acid by the same methodology, work is now in progress on the replacement of the proline by other cyclic amino acids which allow milder hydrolysis conditions and easier separation.

Conclusion

In summary, we have demonstrated the synthetic use of an amino acid as a temporary tether which controls both the *stereo* and *regio*chemistry of a cycloaddition reaction and is then removed. Further applications of this approach are now under study.

Experimental Section

General

NMR spectra (^{1}H, ^{13}C and 2D experiments) were performed on Bruker AMX-400, AMX-300 or WP-200-SY FT-NMR spectrometers. The chemical shifts are reported in ppm on the δ scale relative to TMS (tetramethylsilane). IR spectra were recorder on either a Nicolet Impact 400 FT-IR spectrometer, on a Perkin-Elmer 1600 series FT-IR, or a Perkin-Elmer 157G grating IR spectrometer. The mass spectra were carried out on a Finnigan TSQ 70 mass spectrometer at the Hebrew University of Jerusalem. High resolution mass spectrometry (HRMS) was carried out on a Varian MAT model 711 at the mass spectrometry center at the Technion, Haifa. Melting points were determined on a Mel-Temp II apparatus and are uncorrected. Elemental analyses were performed by the Microanalysis Laboratory, the Hebrew University of Jerusalem. Column chromatography was conducted with silica gel, 200-400 mesh. TLC analysis was conducted on silica gel 60 plates with F_{254} indicator.

Materials

All reagents were purchased from either Aldrich, Sigma or Fluka. Solvents and solutions were purchased from Frutarom, Aldrich, BDH or Baker. Chromatography products were purchased from Merck.

Synthesis of the compounds

Sorbyl N-hydroxysuccinimide ester (**1**)

To a stirred solution of sorbic acid (1.15g, 10 mmoles) in 20 ml of ethyl acetate was added N-hydroxysuccinimide (1.12g, 10 mmoles). The mixture was cooled to 0°C. A solution of 1,3-dicyclohexyl carbodiimide (D.C.C.) (2.06g, 10 mmoles) in 15 ml of ethyl acetate was added slowly over 30 minutes. The mixture was stirred at room temperature for **4** hours and then left in the freezer overnight. The solution was repeatedly cooled and filtered until no dicyclohexyl urea precipitated. The solution can be evaporated and the crude product used without purification for the next step. The substance was recrystallized from ethyl acetate and petroleum ether, to give the pure compound **1** (1.85g, 8.9 mmol, 89%). M.P. 98°C.

^{1}H NMR (200MHz, $CDCl_3$, r.t.) ppm 1.8 (d, 3H, J=4.7 Hz), 2.8 (s, 4H), 5.9 (d, 1H, J=10.6), 6.2 (m, 2H), 7.4 (dd, 1H, J=10.6 Hz, J=4.4 Hz).

Anal. calcd for $C_{10}H_{11}NO_4$ C:57.41, H:5.30, N:6.70. Found C:57.17, 5.42, N:6.69.

N-Sorbyl-L-proline (**2**)

To a stirred solution of L-Proline (5.7g, 50 mmoles) in 55 ml of water was added sodium bicarbonate (4.2g, 50 mmoles). A solution of **1** (7.3g, 35 mmoles) in 65 ml of dimethoxyethane was added over the course of an hour. The mixture was stirred for an additional 90 minutes. It was then diluted with 33 ml of water, and acidified with concentrated hydrochloric acid. Some precipitate formed on acidification. The mixture was extracted several times with chloroform and dried over magnesium sulfate. Evaporation of the solvent gave a viscous yellow oil, which solidified upon standing. This product proved pure enough for the next step. Alkali extraction gave the pure product as an oil, **2** (6.59g, 31.5 mmol, 90%) which solidifies at approximately 5°C.

^{1}H NMR (200MHz, $CDCl_3$, r.t.) ppm 1.85 (d, 3H, J=4.7 Hz), 1.9-2.3 (m, 4H), 3.5 (m, 2H), 3.75 (dd, 1H, J=9.2 Hz, J=5.4 Hz), 6.1 (d, 1H, J=10.4), 6.25 (m, 2H), 7.35 (dd, 1H, J=9.6 Hz, J=4.1 Hz).

^{13}C NMR (100.62 MHz, $CDCl_3$, r.t.) ppm 18.7, 24.6, 30.9, 77.2, 117.2, 140.6, 143.4, 145.5, 150.3, 169.4, 172.2.

Anal. calcd for $C_{11}H_{15}NO_3$ C:63.14, H:7.23, N:6.69. Found C:63.51, 7.06, N:6.67.

$[\alpha]^{D}_{20}$=-212.5 (c=0.5, $CHCl_3$).

N-Sorbyl L-proline N-hydroxysuccinimide ester (**3**)

To a stirred solution of **2** (3.66g, 17 mmoles) in 40 ml of ethyl acetate was added N-hydroxysuccinimide (1.95g, 17 mmoles). The mixture was cooled in an ice bath. An equimolar solution of dicyclohexyl carbodiimide in 20 ml of ethyl acetate was added slowly. The mixture was stirred at room temperature for 8 hours and left in the freezer overnight. The solution was repeatedly cooled and filtered until the majority of the dicyclohexyl urea was accounted for. The solvent was then evaporated to give the crude product as an oil (4.37g, 14.3 mmol, 84%).

^{1}H NMR (200MHz, $CDCl_3$, r.t.) ppm 1.65 (d, 3H, J=4.6 Hz), 1.8-2.35 (m, 4H), 2.7 (s, 4H), 3.55 (m, 2H), 4.7 (dd, 1H, J=8.3 Hz, J=5.1 Hz), 5.9-6.2 (m, 3H), 7.15 (dd, 1H, J=10.4 Hz, J=4.4 Hz).

$[\alpha]^{D}_{20}$=-198.0 (c=0.5, $CHCl_3$).

N-Sorbyl L-proline hydroxamic acid (**4**)

Sodium (1.61g, 70 mmoles) was reacted with 50 ml of ethanol. To this basic solution was added hydroxylamine hydrochloride (5.1g, 70 mmoles) and the mixture was stirred until all the reagent was dissolved. This solution of hydroxylamine was filtered and added drop-wise to a solution of **3** (21.4g, 70 mmoles) in 50 ml of methanol. The mixture was stirred for 48 hours at room temperature. Evaporation of the solvent gave a brown oil. This oil was chromatographed using first 3:1 chloroform:ethyl acetate to elute the impurities, and then methanol to remove the desired product. Evaporation of the proper fraction gave a yellow oil. This can be chromatographed again using 1:1 methanol:chloroform to give the product as a light yellow solid (15.7g, 64 mmol, 92%). M.P. 97°C.

^{1}H NMR (200MHz, $CDCl_3$, r.t.) ppm 1.75 (d, 3H, J=4.8 Hz), 1.8-2.1 (m, 4H), 3.55 (m, 2H), 4.4 (dd, 1H, J=7.2 Hz, J=2.1 Hz), 6.0-6.2 (m, 3H), 7.15 (dd, 1H, J=10.5 Hz, J=3.6 Hz).

M.S. m/e-=224.26.

H.R.M.S.: calcd: 224.11608, found: 224.1188.

$[\alpha]^{D}_{20}$= -217.5 (c=1, CH_3OH).

Tetraethylammonium periodate

Paraperiodic acid (2.28g, 10 mmoles) was dissolved in 50 ml of water. This was cooled in an ice bath, as tetraethylammonium hydroxide (5.65 ml, 1 equivalent from a 35% solution) was added in portions of half a milliliter. The mixture was stirred for 2 hours and then evaporated *in vacuo*, to leave a crude product. This product was purified by dissolving it in hot *tert*-butanol and precipitating in with isopropyl ether, giving the product (2.67g, 8.3 mmol, 83%). M.P. 177°C. The substance decomposes both in thermal and photochemical conditions and therefore, it is recommended to store it in a dark freezer.

2-N-Sorbyl-L-prolinyl-1-oxa-2-azatricyclo[2,2,1]hepta-4-ene (**6**)

A stirred solution of tetraethylammonium periodate (3.9g, 10.5 mmoles) and cyclopentadiene (1.74g, 21 mmoles, 2 equivalents) in 80 ml of dichloromethane was cooled in an ice bath. A solution of **4** (2.36g, 10.5 mmoles) in 80 ml of dichloromethane was added slowly over 15 minutes in a darkened hood. The mixture was stirred at 0°C for an additional 15 minutes and then for 45 minutes at room temperature. Ethyl acetate (230 ml) was added and the brown turbid solution was rinsed consecutively with a 1M solution of sodium carbonate containing 5% sodium thiosulfate or sodium sulfite, and then several times with brine. Evaporation of the solvent gave a brown oil. This oil was purified by column chromatography with an eluent of 1:1 ethyl acetate:chloroform. The second lowest peak according to thin layer chromatography was collected. Evaporation of the eluent gave the product as a yellow oil **6** (1.84g, 6.4 mmol, 61%).

^{1}H NMR (400 MHz, $CDCl_3$, r.t.) ppm 1.8 (d, 3H, J=5.8), 1.9-2.2 (m, 6H), 3.65 (m, 2H), 4.75 (dd, 1H, J=12.7 Hz, J=3.4 Hz), 5.35 (two m, 2H), 6.0-6.3 (m, 3H), 6.40

(dd, 1H, J=6.8 Hz, J=2.1 Hz), 6.60 (dd, 1H, J=6.8 Hz, J=2.1 Hz), 7.2 (dd, 1H, J=9.7 Hz, J=3.4 Hz).

^{13}C NMR (100.62 MHz, $CDCl_3$, r.t.) ppm 18.5, 33.85, 47.0, 47.1, 48.8, 58.6, 62.2, 84.3, 119.0, 130.1, 132.5, 136.3, 139.05, 142.15, 165.1, 165.5.

3,10-Diaza-5-methyl-4-oxatricyclo[8,4,0^{3,7},0]deca-6-ene-2,9-dione (**7**)

A solution of 6 (2.5g, 8.7 mmoles) in 200 ml of toluene was refluxed for 5 hours. The solution was filtered hot from the small amount of precipitate formed and evaporated to give a brown solid. This was purified by column chromatography using a 2:1 ethyl acetate:chloroform solution. This gave a solid which was further purified by recrystallization from chloroform and petroleum ether to give the pure product (0.77g, 3.5 mmol, 40%). M.P. 76°C.

^{1}H NMR (200MHz, $CDCl_3$, r.t.) ppm 1.40 (d, 3H, J= 6.6 Hz), 1.8-2.1 (m, 4H), 3.6 (m, 2H), 4.25 (dq, 1H, J=6.6 Hz, J=2.4 Hz), 4.7 (dd, 1H, J=11.2 Hz, J=2.3 Hz), 5.1 (m, 1H), 5.8 (dd, 1H, J=5.8 Hz, J=2.4 Hz), 6.3 (d, 1H, J= 5.8 Hz).

IR: ν (Nujol) 1630, 1670, 1730 cm^{-1}.

M.S. m/e-=222.24

Anal. calcd for $C_{11}H_{14}N_2O_3$ C:59.45, H:6.35, N:12.60. Found C:59.04, 6.10, N:12.16.

$[\alpha]^{D}_{20}$= -114.3 (c=0.25, $CHCl_3$).

3,10-Diaza-5-methyl-4-oxatricyclo[8,4,0^{3,7},0]deca-2,9-dione (**8**)

A solution of **7** (1g, 4.5 mmoles) was dissolved in 50 ml of methanol. It was hydrogenated in the presence of 0.5g 5% Pd/C at 60 p.s.i. for 5 hours. Filtration and evaporation of the solvent afforded of the saturated substance 8 (0.98g, 4.4 mmol, 98%). This product recrystallized as needles from dichloromethane-hexane. M.P. 143°. A higher overall yield (68%) can be obtained by hydrogenation of the crude **7**.

^{1}H NMR (400 MHz, $CDCl_3$, r.t.) ppm 1.4 (d, 3H, J= 6.6 Hz), 1.7 (m, 1H), 1.85-2.0 (m, 3H), 2.05 (m, 1H), 2.2 (m, 2H), 2.3 (m, 1H), 3.45 (ddq, J=9.1 Hz, J=6.6 Hz, J=3.4 Hz), 3.8 (m, 1H), 4.15 (dd, 1H, J=12.0 Hz, J=1.8 Hz),4.28 (dd, 1H, J=12.0 Hz, J=6.0 Hz), 4.5 (m, 1H).

^{13}C NMR (100.62 MHz, $CDCl_3$, r.t.) ppm 16.0, 19.3, 21.6, 22.8, 28.3, 29.4, 45.0, 58.0, 61.3, 76.2, 160.5, 163.1.

IR: ν (Nujol) 1630, 1670 cm^{-1}.

M.S. m/e-=224.26.

Anal. calcd for $C_{11}H_{16}N_2O_3$ C:58.91, H:7.19, N:12.49. Found C:58.91, 7.03, N:12.21.

$[\alpha]^{D}_{20}$= -87.5 (c=0.5, $CHCl_3$).

3-(3-hydroxy-1-butyl)-pyrrolo[1,2-e]pyrazine-2,5-dione (**9**)

Compound **8** (0.3g, 1.3 mmoles) was dissolved in 20 ml of dry ethanol and cooled to 0°C. Under a static atmosphere of nitrogen, disodium hydrogen phosphate (0.89g, 4.7 equivalents) was added followed by 4.5g (x15 w/w) of a freshly prepared powdered 6% Na(Hg) amalgam. The mixture was stirred at 0° for 10 hours. The solution yellowed slightly with time. After diluting with 40 ml of THF the mixture was filtered, and the solids carefully disposed of. Evaporation of the solvent, gave the product as a yellow oil (0.24g, 1.1 mmol, 79%). Recrystallization in ethyl acetate/hexane gave the pure product as a colourless solid. M.P. 147°C.

^{1}H NMR (200MHz, $CDCl_3$, r.t.) ppm 1.15 (d, 3H, J=6.6 Hz), 1.5-2.3 (m, 8H), 3.4 (t, 1H, J=8.4), 3.6 (m, 2H), 3.85 (m, 1H), 4.1 (dd, 1H, J=10.5 Hz, J~1 Hz)

^{13}C NMR (100.62 MHz, $CDCl_3$, r.t.) ppm 16.0, 19.3, 21.6, 22.8, 28.3, 29.4, 47.2, 59.3, 60.4, 76.4, 160.5, 167.0.

IR.: ν (Nujol) 1625, 1640, 3260, 3560 cm^{-1}

Anal. calcd for $C_{11}H_{18}N_2O_3$ C:58.34, H:8.02, N:12.38. Found C:58.89, 7.61, N:12.28.

$[\alpha]^{D}_{20}$= -100.5 (c=0.25, $CHCl_3$).

(2R,5R)-2-Amino-5-hydroxyhexanoic acid (**10**)

Compound **9** (0.3g, 1.33 mmoles) in 50 ml of a 6M hydrochloric acid solution containing 5% acetic acid was refluxed overnight. The solvent was rinsed with dichloromethane and then evaporated under reduced pressure to give a yellow oil. This oil gave an NMR spectrum consistent with the presence of proline and **10**.

References and Notes

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11. X-ray diffraction data was measured with either an ENRAF-NONIUS CAD-4 automatic diffractometer or a Phillips four circle computer controlled diffractometer. The crystallographic computing was done on a VAX 900 computer using TAXAN analysis software.
12. Formula $C_{11}H_{16}N_2O_3$; M 224.26; space group $P2_12_12_1$; a (Å) 9.317(2); b (Å) 25.216(5); c (Å) 5.122(2); V (Å^3) 1203.4(7); z 4; ρ (g cm^{-3}) 1.34; m MoKα (cm^{-1}) 9.6; no. of unique reflections 1271; no. of reflections with $I \geq 3\sigma_I$ 1046; R 0.050; R_W 0.067.
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Sample Availability: available from the authors.