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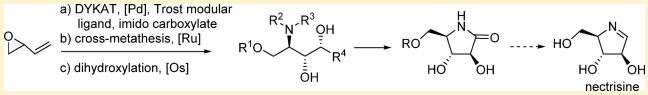
Enantioselective Formal Synthesis of Nectrisine Using a Palladium-Catalyzed Asymmetric Allylic Amination and Cross-Metathesis as Key Steps

Sébastien Soriano, Mariam Azzouz, Josep Llaveria, Patricia Marcé, M. Isabel Matheu, Yolanda Díaz,* and Sergio Castillón*

Departament de Química Analítica i Química Orgànica, Facultat de Química, Universitat Rovira i Virgili, C/Marcel·lí Domingo no. 1,43007 Taragona, Spain

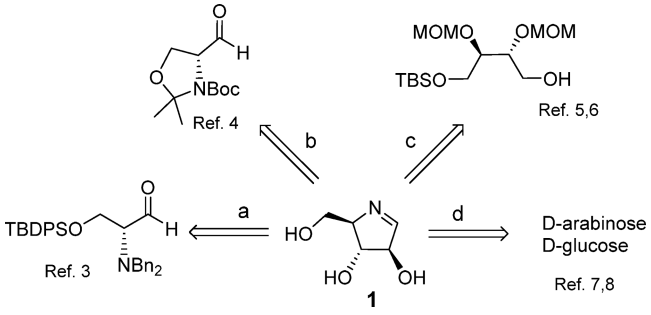
Supporting Information

ABSTRACT: A formal enantioselective synthesis of nectrisine, a potent α-glucosidase inhibitor, was carried out starting from butadiene monoepoxide through a synthetic sequence involving enantioselective allylic substitution, cross-metathesis, dihydroxylation, and cyclization.



Nectrisine (**1**) is an azasugar isolated in 1988 by Shibata et al. from a strain of the fungus *Nectria lucida* F-4490 as immunomodulator FR-900483,[1] and found to exhibit inhibitory activity on α-glucosidases.[2] Moreover, nectrisine has been found to restore to a normal level the capacity of immunosuppressed mice to produce antibodies against sheep red blood cells,[1a] and to prevent different diseases such as Newcastle disease virus.[1b] Due to this important biological activity, there is a great interest in developing new methods to synthesize nectrisine and related compounds. Several stereoselective synthesis of nectrisine have been reported starting from compounds of the chiral pool like amino acids (Scheme 1, path a),[3] Garner's aldehyde (path b),[4] diethyl tartrate (path c),[5,6] and carbohydrates (path d).[7,8]

Scheme 1. Reported Procedures for Nectrisine Synthesis Starting from the Chiral Pool



Recently, we have described that Trost's dynamic kinetic asymmetric transformation (DYKAT) process, in combination with cross-metathesis and dihydroxylation reactions, is an efficient strategy for accessing important natural products such as sphingosine[9] and jaspine.[10] A similar protocol has also been described for the synthesis of phytosphingosine.[9,11] We considered that a related procedure could be applied to the synthesis of iminosugars such as nectrisine. Here, we report the first enantioselective formal synthesis of nectrisine based on Trost's DYKAT, cross-metathesis, and dihydroxylation reaction as key steps.

Scheme 2 shows the nectrisine retrosynthetic scheme where the final step is the formation of the imine bond by two different approaches: (a) via intramolecular nucleophilic addition from amino aldehyde **2**, or (b) from lactam **3** which can be obtained from amino ester **4**. Nectrisine had been already prepared from compound **3**, and consequently, its synthesis would involve a formal synthesis of nectrisine.[3] In our approach, compound **2** can be obtained from the allyl amine **5**, which is accessible in high enantiomeric purity from butadiene monoepoxide by using Pd/*trans*-1,2-diaminocyclohexane (DACH)-derived Trost modular ligand as catalytic system.[12] Cross-metathesis from **5** will allow increasing the chain length. Configuration of the resulting double bond from this process must be *E* in order to provide the correct configuration of hydroxyl groups in **2** or **3** after the dihydroxylation reaction.[8]

The DYKAT process allows obtaining differently protected 2-amino-4-buten-1-ols in a practically enantiomerically pure form. Thus, 2-amino-3-buten-1-ol derivative **7** was prepared from compound **6** in excellent yield (99%) and ee (99%) using $[(\eta^3\text{-}C_3H_5)PdCl]_2$/(*R*,*R*)-DACH-naphthyl ligand as a catalytic system under the conditions optimized by Trost[12c] (Scheme 3). Protection of compound **7** using $(Boc)_2O$ and DMAP in Et_3N as solvent for 20 h afforded the fully protected compound **8** in a quantitative yield (Scheme 3). This substrate was selected because structurally related diprotected substrates had already been shown to give better yields and stereoselectivies in cross-metathesis/dihydroxylation sequences related to their monoprotected counterparts.[11]

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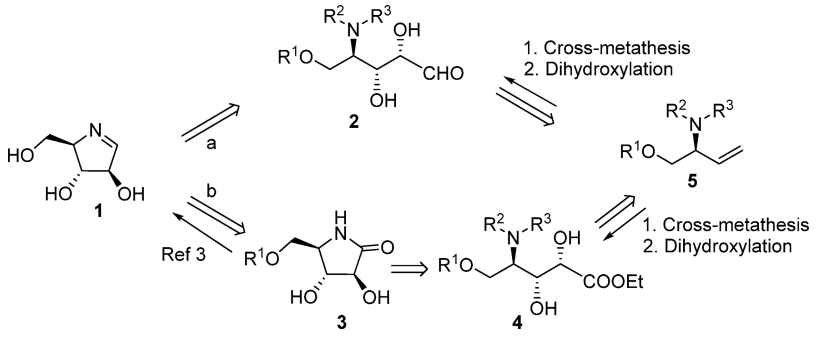
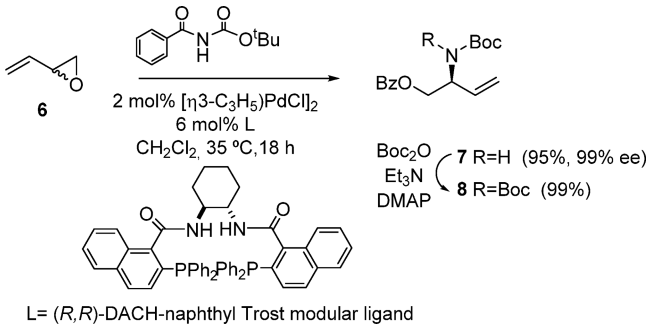
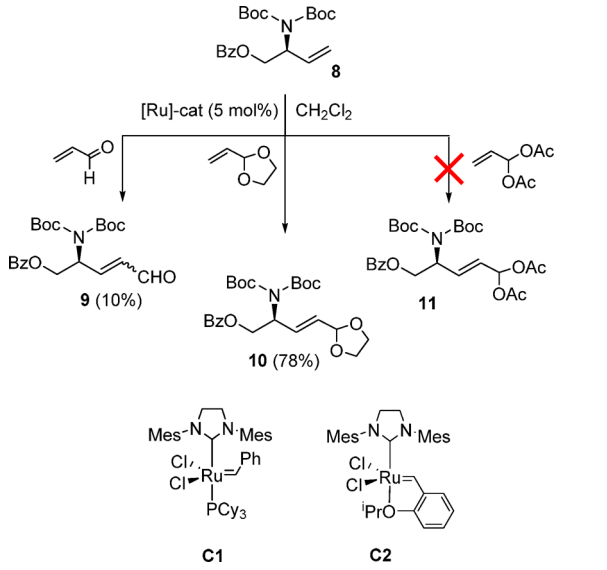
Scheme 2. Retrosynthesis of Nectrisine (1)



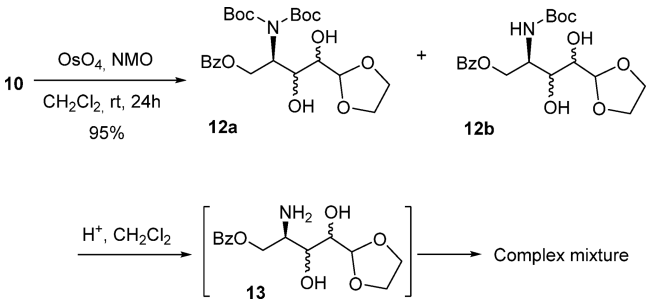
Scheme 3



Scheme 4



Scheme 5



Cross-metathesis is a powerful tool for synthesizing functionalized olefins.[13,14] In this regard, we initially decided to explore cross-metathesis of compound **8** with acrolein, since, after dihydroxylation, it would provide a direct access to nectrisine. Acrolein, however, has been rarely used in cross-metathesis reactions probably due to its lower reactivity as compared to other acrylic derivatives.[13] Actually, when compound **8** was treated with acrolein in dichloromethane at rt, or in toluene at 80 °C, in the presence of second generation Grubb's catalyst (**C1**), the reaction did not proceed at all. Using the same catalyst and driving the reaction in refluxing dichloromethane rendered compound **9** in 10% yield (Scheme 4) as a diastereomeric mixture. The use of the Hoveyda–Grubb's catalysts (**C2**) in refluxing dichloromethame or the use of an excess of acrolein did not improve the yield either.

In view of these results, we decided to test the cross-metathesis using acrolein surrogates such as 2-vinyldixolane and prop-2-ene-1,1-diyl diacetate. Cross-metathesis of 2-vinyldioxolane with **8** (4:1 ratio) afforded product **10** in 55% yield, with both catalysts **C1** and **C2** (5 mol %). The yield was increased to 78% when an 8-fold excess of 2-vinyldioxolane related to **8** was used.

The cross-metathesis reaction of **8** with prop-2-ene-1,1-diyl diacetate in the presence of **C1** or **C2** catalysts did not provide the desired product **11**. The high steric bulkiness of the two alkene reactants might be responsible for the failure of this reaction.

Dihydroxylation of **10** with OsO_4/NMO proceeded with excellent yield to afford products **12** as an inseparable mixture of **12a**,**12b**[15] (Scheme 5). Diastereoselective dihydroxylation of compound **10** using chiral ligands such as AD-mix β, which in other cases had allowed us to improve the selectivity,[9,10] provided in this case low yields (33%) and also poor selectivities.

Compounds **12a**,**b** incorporate all the functionalities required for nectrisine synthesis, and in principle, it would be possible to readily access it by cleavage of the protecting amino and aldehyde groups in acid medium. Deprotection of **12a**,**b** in HCl, however, led to degradation products. Treatment of **12a**,**b** with trifluoroacetic acid in dichoromethane allowed us to remove the Boc group, but the dioxolane ring still remained intact. Any attempt to remove the dioxolane ring from **12a**,**b** by treatment with HCl or *p*-TsOH[16] in THF, either at room temperature or 50 °C, led to degradation products.

Considering the problems accounted in the cross-metathesis reaction possibly due to the steric hindrance of the reactants, we prepared the mono-boc derivative **14** from **7** by hydrolysis of the ester group. Cross-metathesis of **14** with prop-2-ene-1,1-

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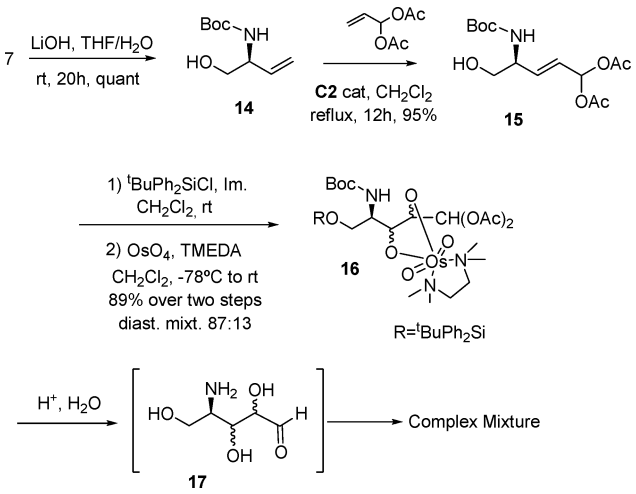
diyl diacetate in the presence of catalyst **C2** rendered compound **15** in 95% yield (Scheme 6). Protection of the

Scheme 6



primary hydroxyl group and subsequent catalytic dihydroxylation using OsO_4/MNO in dichloromethane either at room temperature or at 0 °C gave complex mixtures, probably due to acetate hydrolysis. Stoichiometric dihydroxylation using 1 equiv OsO_4 in the presence of bidentate amine such as TMEDA[17] has been reported to proceed efficiently even at very low temperatures, giving in some examples increased stereoselectivities compared to those observed for the catalytic process.[15] When the reaction was performed under these conditions, osmate **16** was obtained in very good yield (89% for two steps), as an inseparable (87:13) mixture of diastereoisomers. The osmate functionality proved more robust than foreseen, as it was not hydrolyzed in the workup process with sodium bisulphite.

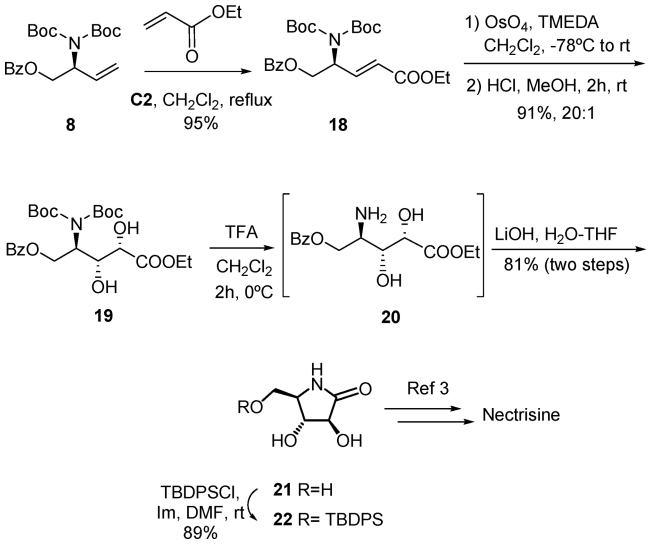
Nevertheless, access to nectrisine appeared feasible through the amino-aldehyde intermediate **17** by complete removal of the Boc protecting group and hydrolysis of the osmate and 1,1-diacetate in compound **16**. However, any attempt to do so (e.g., HCl/THF/basic resin; TBAF; TFA/CH_2Cl_2; MeONa/MeOH) afforded degradation products or complex mixtures. Cyclization of opened intermediates has been reported to be problematic.[18]

Formal Synthesis of Nectrisine. The synthetic approaches discussed above allowed the preparation of a molecular open-chain framework that incorporates all the functionalities for nectrisine synthesis but failed in the step of removal of protecting groups/cyclization, providing mixture of compounds where nectrisine was detected by mass spectrometry.

In view of the unsuccessful cyclization using aldehyde equivalents, we turned our attention to the synthesis of lactam **3** (R^1 = $SiPh_2{}^tBu$), which had been already transformed into nectrisine (Scheme 2). Related lactams had been prepared using the chiral-pool approach, and by anchoring allylamines in the amino function of **4** following by ring-closing metathesis.[19] We envisaged that lactam **3** could be prepared modifying our synthesis by first replacing acrolein surrogates by acrylates.

Thus, cross-metathesis reaction of **8** with ethyl acrylate in the presence of 5 mol % of catalyst **C2** afforded product **18** with excellent yield (95%) (Scheme 7). The reaction of compound **18** with stoichiometric OsO_4 and TMEDA afforded the osmate

Scheme 7



ester in excellent stereoselectivity (20:1), which again resulted inert to hydrolysis under the reductive workup procedure. Nevertheless, controlled hydrolysis in the presence of HCl in MeOH (c = 0.24 M) rendered the desired diol **19** product in 91% overall yield.

With compound **19** in hand, the removal of di-Boc protecting-group was attempted by treatment with hydrochloric acid[3] in THF and with TFA in dichloromethane at 0 °C.[4] However, the in situ spontaneous formation of the lactam ring was not observed. In previous reported formal and total syntheses of nectrisine, cyclization is always produced in a fully deprotected product.[3−8] Moreover, in parallel studies with other substrates, we had observed that benzoate group in **19** prevented cyclization. Hence, after hydrolysis of Boc groups in **19** with TFA, the resultant crude **20** was treated with LiOH to afford lactam **21** in 81% yield for the two steps, whose data well matched with those reported in the literature.[5,8b,20] Further protection of primary hydroxyl group by reaction with TBDPSCl provided compound **22** in 89% yield. The synthesis of nectrisine from this compound has been previously reported.[3]

In summary, the first enantioselective formal synthesis of the glucosidase inhibitor nectrisine has been carried out in 7 steps and 48% overall yield starting from the commercially available racemic butadiene monoepoxide. Key steps of the process are the Pd-catalyzed DYKAT process, cross-metathesis with ethyl acrylate, and dihydroxylation.

EXPERIMENTAL SECTION

General Methods. All chemicals used were reagent grade and used as supplied unless otherwise specified. HPLC grade dichloromethane (CH_2Cl_2), tetrahydrofuran (THF), and dimethylformamide (DMF) were dried using a solvent purification system (Pure SOLV system-4). Toluene was purified using standard procedure.

^{1}H and ^{13}C NMR spectra were recorded on a 400 and 100.6 MHz instrument, respectively, in $CDCl_3$ as solvent, with chemical shifts (δ) referenced to internal standards $CDCl_3$ (7.26 ppm 1H, 77.16 ppm ^{13}C) or Me_4Si as an internal reference (0.00 ppm). 2D correlation spectra (gCOSY, NOESY, gHSQC, gHMBC) were visualized using VNMR program. ESI MS were run on an LC/MSD instrument. Optical rotations were measured at room temperature in 10 cm cells. IR spectra were recorded on a Fourier Transform Infrared Spectrometer. Reactions were monitored by TLC carried out on

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0.25 mm E. Merck silica gel 60 F254 glass or aluminum plates. Developed TLC plates were visualized under a short-wave UV lamp (250 nm) and by heating plates that were dipped in ethanol/H_2SO_4 (15:1) and basic solution of potassium permanganate. Flash column chromatography was carried out using forced flow of the indicated solvent on silica gel 60 (230−400 mesh). Flash column chromatography (FCC) was performed using flash silica gel (32−63 μm) and using a solvent polarity correlated with TLC mobility.

Compounds (−)-(*S*)-*tert*-butyl-1-benzoyloxybut-3-ene-2-yl-carbamate **7**,[12c] (−)-(*S*)-*tert*-butyl-1-hydroxybut-3-en-2-ylcarbamate **16**,[21] and prop-2-ene-1,1-diyl diacetate,[22] were synthesized according to reported procedures. ^{1}H NMR and ^{13}C NMR were identical to the reported ones.

*(2S)-2-((Bis-tert-butoxycarbonyl)amino)but-3-en-1-yl Benzoate (**8**).* Compound **7** (1.24 g, 3.17 mmol) was dissolved in freshly destilled triethylamine (11 mL), and then DMAP (1.04 g, 8.51 mmol) was added. The mixture was cooled at 0 °C and di-*tert*-butyl dicarbonate (4.9 mL, 16.48 mmol) was added. After 10 min, the mixture was warmed at room temperature and it was stirred for 10 h. The crude was dissolved in NH_4Cl aqueous, and the aqueous phase was extracted with ethyl acetate. The combined organic layers were washed with water and brine, and they were dried over $MgSO_4$. The solvent was removed under vacuum, and the crude was purified by silica gel chromatography using 97:3 hexanes/ethyl acetate as a solvent to afford 1.23 g of product **8** as a colorless oil (99%). $[\alpha]_D^{25} = -30.5$ (*c* 1, $CHCl_3$). FTIR-ATR (cm^{-1}): 3094, 2979, 2933, 1723, 1700, 1452, 1367, 1347, 1267, 1112, 855, 710 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.06−7.99 (m, 2H), 7.59−7.49 (m, 1H), 7.47−7.36 (m, 2H), 6.01 (ddd, *J* = 17.2, 10.5, 6.1 Hz, 1H), 5.33 (dd, *J* = 17.2, 1.2 Hz, 1H), 5.27 (dd, *J* = 10.5, 1.2 Hz, 1H), 5.22−5.16 (m, 1H), 4.66 (dd, *J* = 11.0, 8.9 Hz, 1H), 4.60 (dd, *J* = 11.0, 6.0 Hz, 1H), 1.46 (s, 18H). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 166.2, 152.8, 133.7, 133.1, 130.1, 129.8, 128.4, 118.4, 82.8, 64.8, 57.2, 28.1. HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{21}H_{29}NaNO_6$: 414.1893. Found: 414.1892.

*(2S,3E)-2-(Bis(tert-butoxycarbonyl)amino)-4-(1,3-dioxolan-2-yl)-but-3-en-1-yl Benzoate (**10**).* To a solution of product **8** (100 mg, 0.26 mmol) and of II generation Grubbs catalyst (11 mg, 0.013 mmol) in dichlorometane (6 mL) was added 2-vinyldioxolane (0.13 mL, 1.3 mmol) at 55 °C. Reaction stirred at reflux for 12 h, and then evaporation of solvent and purification by silica gel chromatography (hexanes/AcOEt, 10:3) provided the desired product **10** as a colorless oil in 78% yield (94 mg). FTIR-ATR (cm^{-1}): 2979, 2933, 2888, 1721, 1701, 1367, 1348, 1267, 1147, 1113, 968, 712 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.02 (d, *J* = 8.4 Hz, 2H), 7.54 (t, *J* = 7.6 Hz, 1H), 7.41 (dd, *J* = 8.4, 7.6 Hz, 2H), 6.11 (dd, *J* = 16.0, 6.4 Hz, 1H), 5.74 (dd, *J* = 16.0, 6.0 Hz, 1H), 5.28 (d, *J* = 6.0 Hz, 1H), 5.29−5.23 (m, 1H), 4.69 (dd, *J* = 11.2, 10.8 Hz, 1H), 4.58 (dd, 1H, *J* = 11.2, 6.0 Hz), 3.97−3.91 (m, 4H), 1.45 (s, 18H). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 166.3, 152.6, 133.3, 131.5, 130.1, 130.0, 128.5, 103.2, 83.1, 65.2, 64.7, 55.9, 28.2. HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{24}H_{33}NaNO_8$: 486.2104. Found: 486.2109.

*(+)-(2S,3E)-4-(tert-Butoxycarbonylamino)-5-hydroxypent-2-ene-1,1-diyl Diacetate (**15**).* Compound **14** (50 mg, 0.267 mmol) and prop-2-ene-1,1-diyl diacetate (157 μL, 1.068 mmol) were dissolved in CH_2Cl_2 (2 mL) at room temperature. Second generation Grubbs catalyst (0.011 g, 5 mol %) was added to the solution, and the reaction mixture was then refluxed under argon for 12 h. After the reaction mixture cooled, it was concentrated and purified by column chromatography with hexanes/ethyl acetate (6:4) to afford compound **15** (80 mg, 95%) as a brown oil. $[\alpha]_D^{25} = +175.0$ (*c* 7.5, $CHCl_3$). FTIR-ATR (cm^{-1}): 3370, 2977, 2931, 1761, 1695, 1521, 1168, 960. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.10 (d, *J* = 6.0 Hz, 1H), 5.99 (dd, *J* = 15.7, 4.8 Hz, 1H), 5.73 (dd, *J* = 15.7, 6.0 Hz, 1H), 5.05 (bs, 1H), 4.82−4.77 (m, 1H), 3.67−3.62 (m, 2H), 2.70 (bs, 1H), 2.06 (s, 6H), 1.42 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz,): δ 168.8, 155.8, 134.7, 125.1, 89.0, 80.0, 64.8, 53.3, 28.4 (3C), 21.0 (2C). HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{14}H_{23}NNaO_7$: 340.1367. found: 340.1340.

*(2R/S,3R/S,4R)-4-(tert-Butoxycarbonylamino)-5-(tert-butyldiphenylsilyloxy)-2,3-dihydroxypentane-1,1-diyl Diacetate Tetramethylenediamine Osmate Derivative (**16**).* Compound **15** (260 mg, 0.82 mmol) was dissolved in dry DMF (1 mL) and treated under argon with *tert*-butylchlorodiphenylsilane (256 μL, 0.98 mmol) and imidazole (112 mg, 1.64 mmol). The mixture was then stirred for 16 h at room temperature. Workup (extraction with Et_2O) and a short column chromatography on silica gel with hexanes/ethyl acetate (9:1) provided the silyl derivative as a colorless oil which was directly used in the next reaction. The silyl derivative obtained (418 mg, 0.75 mmol) was dissolved in CH_2Cl_2 (1 mL) at −78 °C under dry argon. TMEDA (0.012 mL, 0.82 mmol) was added, and the reaction was stirred for 5 min before the rapid addition of osmium tetraoxide (191 mg, 0.75 mmol). The dark colored solution was stirred for 2 h at −78 °C before being warmed to room temperature. The solvent was removed in vacuo to obtain a black residue. Purification by silica gel chromatography using 8:2 EtOAc/MeOH as eluent afforded **16** as an inseparable mixture of two diastereoisomers (87:13 ratio) (676 mg, 89%, for the two steps) as a dark oil. **Compound 16 (major)**. FTIR-ATR (cm^{-1}): 3436, 2930, 2857, 1763, 1707, 1474, 1367, 1242, 1112, 1011, 838, 704 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.70 (m, 5H), 7.42−7.29 (m, 5H), 7.17 (d, *J* = 5.4 Hz, 1H), 5.56 (d, *J* = 9.2 Hz, 1H), 4.77 (dd, *J* = 5.4, 2.4 Hz, 1H), 4.53−4.44 (m, 1H), 4.27 (t, *J* = 5.4 Hz, 1H), 3.90 (t, *J* = 9.0 Hz, 1H), 3.73 (dd, *J* = 9.0, 5.5 Hz, 1H), 3.10 (d, *J* = 10.5 Hz, 2H), 2.96 (d, *J* = 10.5 Hz, 2H), 2.85−2.70 (m, 12H), 2.10 (s, 3H), 2.03 (s, 3H), 1.37 (s, 9H), 1.04 (s, 9H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.1, 168.7, 156.1, 135.8, 135.7, 134.0, 129.5, 129.4, 127.6, 127.6, 88.4, 88.2, 85.5, 78.5, 64.3, 63.5, 56.1, 52.4, 51.5, 51.2, 28.5, 26.9, 21.1, 21.1. HRMS (ESI-TOF) *m*/*z*: $[M + Na]^+$ calcd for $C_{36}H_{57}N_3NaO_{11}OsSi$: 950.3275. Found: 950.3252.

*Ethyl (2E,4S)-5-Benzoyloxy-4-(bis(tert-butoxycarbonyl)amino)-pent-2-enoate (**18**).* To a solution of product **8** (0.3 g, 0.77 mmol) and Hoveyda-Grubbs catalyst (0.024 g, 0.0385 mmol) in dichlorometane (2 mL) was added ethyl acrylate (0.41 mL, 3.85 mmol) at 55 °C. Reaction mixture was further stirred at reflux for 12 h. Evaporation of solvent and purification of the crude by silica chromatography using hexanes/ethyl acetate (90:6) provided the desired product **18** as yellow liquid in 95% yield (339 mg). $[\alpha]_D^{25} = +13.8$ (*c* 1.1, $CHCl_3$). IR (neat): 2979, 1720, 1452, 1367, 1350, 1265, 1231, 1149, 1112, 975, 854, 710 cm^{-1}. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.97 (d, *J* = 8.4, 2H), 7.55−7.47 (m, 1H), 7.41−7.33 (t, *J* = 8.4, 2H), 7.00 (dd, *J* = 16.0, 5.0 Hz, 1H), 5.97 (d *J* = 16.0, 1H), 5.41−5.30 (m, 1H), 4.69−4.58 (m, 2H), 4.15 (q, *J* = 7.1 Hz, 2H), 1.41 (s, 18H), 1.23 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100.6 MHz): δ 165.9, 165.7, 152.1, 143.5, 133.2, 129.7, 128.3, 122.8, 83.3, 64.1, 60.6, 55.3, 27.9, 14.2. HRMS (ESI-TOF) $[M + Na]^+$ calcld for $C_{24}H_{33}NNaO_8$: 486.2104. Found: 486.2123.

*Ethyl (2S,3R,4R)-5-(Benzoyloxy)-4-((bis-tert-butoxycarbonyl)-amino)-2,3-dihydroxypentanoate (**19**).* Compound **18** (890 mg, 1.92 mmol) was dissolved in CH_2Cl_2 (20 mL) under dry argon. TMEDA (320 μL, 2.11 mmol) was added at −78 °C, and the reaction stirred for 5 min at that temperature before rapid addition of osmium tetraoxide (488 mg, 1.92 mmol). The dark colored solution stirred for 2 h at −78 °C before being warmed to room temperature and stirred for 5 h. The solvent was removed in vacuo, and the black solid was resolved in methanol (5 mL). Concentrated hydrochloric acid (10 drops) was added and the reaction stirred for 2 h. The solvent was removed in vacuo to afford product **19** as a syrup in 91% yield (870 mg) as one diastereoisomer. $[\alpha]_D^{25} = -6.2$ (*c* 10, $CHCl_3$). IR (neat): 3484, 2979, 2931, 1723, 1452, 1367, 1348, 1268, 1227, 1149, 1114, 711. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 8.05 (d, *J* = 7.5 Hz, 2H), 7.53 (t, *J* = 7.5 Hz, 1H), 7.40 (t, *J* = 7.5 Hz, 2H), 4.86−4.71 (m, 2H), 4.71−4.63 (m, 1H), 4.48 (t, *J* = 8.1 Hz, 1H), 4.33−4.23 (m, 3H), 3.30 (d, *J* = 5.0 Hz 1H), 2.82 (d, *J* = 9.1 Hz, 1H), 1.43 (s, 18H), 1.28 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz): δ 172.9, 166.3, 133.1, 130.1, 129.8, 128.3, 83.4, 71.9, 70.9, 63.1, 62.2, 57.8, 27.9, 14.2. HRMS (ESI-TOF) $[M + Na]^+$ calcd for $C_{24}H_{35}NNaO_{10}$: 520.2159. Found: 520.2156.

*(3S,4R,5R)-3,4-Dihydroxy-5-(hydroxymethyl)pyrrolidin-2-one (**21**).*[5] An ice-cooled solution of dihydroxy ester **19** (117 mg, 0.2354 mmol) in CH_2Cl_2 (1 mL) was treated with trifluoroacetic acid (1 mL). The mixture was then stirred for 2 h at 0 °C. Removal of all volatiles under reduced pressure gave crude **20** which was dissolved in THF.

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An aqueous solution of LiOH (0.4 mL, 0.6 mmol, 1 M) was added to that solution, and the mixture was stirred at room temperature for 20 h. The crude was diluted with water, and it was extracted with dichloromethane. The combined organic layers were washed with brine, dried over ahydrous $MgSO_4$, and filtered, and the solvent was removed under vacuum. The crude was purified by silica gel chromatography using $CHC1_3$/MeOH/28% aq. NH_4OH, 5:3:1 as a solvent to afford compound **21** (28 mg) in 81% yield as a white solid. Mp 136−137 °C (mp 135−137 °C described). $[\alpha]_D^{25}$ +15.4 (*c* 0.12, H_2O), ($[\alpha]_D^{20}$ +15.6 (*c* 0.5, H_2O) described). ^{1}H NMR (D_2O, 400 MHz): δ 4.32 (d, *J* = 8.0 Hz, 1H), 4.02 (t, *J* = 8.0 Hz, 1H), 3.80 (dd, *J* = 12.3, 3.1 Hz, 1H), 3.63 (dd, *J* = 12.3, 4.9 Hz, 1H), 3.47 (ddd, *J* = 8.0, 4.9, 3.1 Hz, 1H). ^{13}C NMR (D_2O, 100 MHz): δ 175.4, 75.4, 74.4, 59.8, 57.8. HRMS (ESI-TOF) *m*/*z*: $[M - H]^-$ calcd for $C_5H_8NO_4$: 146.0453. Found: 146.0434.

(3S,4R,5R)-5-(tert-Butyldiphenylsilyloxymethyl)-3,4-dihydroxypyrrolidin-2-one (22).[3] Compound **21** (14 mg, 0.0951 mmol) was dissolved in dry DMF (1 mL) and treated under argon with *tert*-butyldiphenyl chloride (29 μL, 0.11 mmol) and imidazole (15 mg, 0.11 mmol). The mixture was then stirred for 16 h at room temperature. Workup (extraction with Et_2O) and column chromatography on silica gel (EtOAc) provided **22** in 89% yield (32 mg) as a foam. ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.66−7.57 (m, 4H), 7.47−7.33 (m, 6H), 6.07 (bs, 1H), 4.28 (d, *J* = 7.5 Hz, 1H), 4.00 (t, *J* = 7.5 Hz, 1H), 3.89 (dd, *J* = 10.5, 3.2 Hz, 1H), 3.63 (dd, *J* = 10.5, 7.4 Hz, 1H), 3.53 (td, *J* = 7.4, 3.2 Hz, 1H), 1.04 (s, 9H).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b00494.

^{1}H and ^{13}C NMR spectra for compounds **8**, **10**, **15**, **16**, **18**, **19**, **21** and **22** (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

*E-mail: yolanda.diaz@urv.cat

*E-mail: sergio.castillon@urv.cat

Notes

The authors declare no competing financial interest.

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(15) Treatment of the mixture **12a,12b** with Boc_2O afforded an inseparable diastereomeric mixture of di-Boc-derivatives **12a**. ESI-HRMS of the mixture: major isomer [M + 23] calcd for $C_{24}H_{35}NNaO_{10}$: 520.2159. Found: 520.2128; minor isomer [M + 23] calcd $C_{19}H_{27}NNaO_8$: 420.1634. Found: 420.1592.

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