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Ring-Closing Metathesis of Chiral Allylamines. Enantioselective Synthesis of (2*S*,3*R*,4*S*)-3,4-Dihydroxyproline

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The ring-closing metathesis (RCM) of two types of unsaturated chiral allylamines **III,** easily available from enantiomerically enriched epoxy alcohols, has been studied. Fully protected allylamines **IIIa** [^{1}R = CH_2−$(CH_2)_n$−CH=CH_2; ^{2}R = Boc; ^{3}R = PMB] have been prepared from unsaturated epoxy alcohols, whereas bis-allylamines **IIIb** (^{1}R = Ph, ^{2}R = allyl,^{3}R = Boc or PMB) have been prepared from 2,3-epoxy-3-phenylpropanol. Both types have been subjected to RCM to provide either cyclic allylamine **I** or **II**. The synthetic potential of these intermediates has been demonstrated by the enantioselective synthesis of (2*S*,3*R*,4*S*)-3,4-dihydroxyproline.

Introduction

Polyhydroxylated cyclic amines are widespread in nature and exhibit multiple biological activities. Many of them such as polyhydroxypyrrolidines,[1] polyhydroxypiperidines,[2,3] or aminocyclitols[4] are potent glycosidase inhibitors[5,6] with potential therapeutic importance. Although the most usual access to these compounds is by functional group manipulation from carbohydrates, the development of practical asymmetric synthesis leading to them is a subject of great interest.

Dihydroxylation of unsaturated cyclic amines is a convenient entry to many polyhydroxylated alkaloids. Since ring-closing metathesis (RCM)[7,8] has emerged as one of the most powerful reactions for the preparation of cycloalkenes, we envisaged that cyclic amines[9,10] of generic structures **I** and **II** could be prepared from allylamines **III** bearing an appropriate unsaturated chain in ^{1}R (**IIIa**) or ^{2}R (**IIIb**) (Figure 1). These allylamines, in turn, would be readily accessible in enantiopure form by deoxygenation of 3-amino-1,2-diols **IV**,[11,12] arising from the regioselective ring-opening of Sharpless[13] epoxy alcohols **V** with appropriate nitrogen nucleophiles. We describe herein the successful application of this strategy to the stereoselective preparation of several cyclic amines of structures **I** and **II** from enantiomerically enriched epoxy alcohols. Moreover, the synthetic potential of those intermediates is illustrated by the development of an

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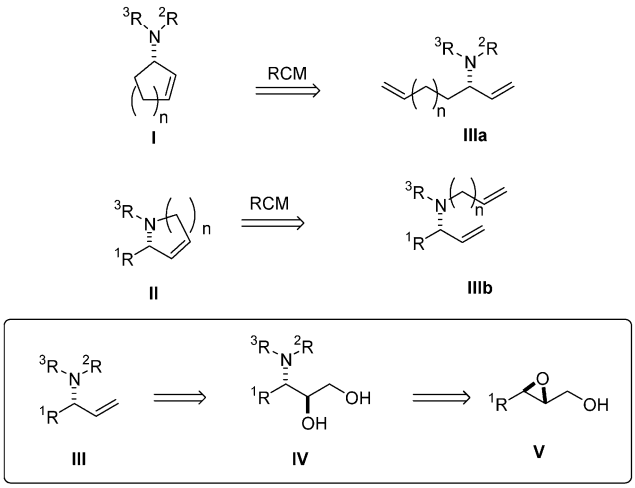

FIGURE 1. Retrosynthetic analysis of cyclic allylamines.

enantioselective synthesis of protected (2*S*,3*R*,4*S*)-3,4-dihydroxyproline from (2S)-*N*-Boc-2-phenyl-2,5-dihydropyrrole

Results and Discussion

Our approach to enantiopure dialkylaminocycloalkenes (**I**) is based on the preparation of chiral allylamines **IIIa** derived from unsaturated allyl alcohols. To this end, epoxy alcohols **1a**−**c** of high enantiomeric excess (91−94% ee) were prepared by Sharpless catalytic epoxidation of the corresponding alkadienols and converted in high yield to the known *N*-Boc-*N*-(4′-methoxybenzyl)-3-amino-1,2-diols **2a**−**c** by our previously described procedure, involving regioselective ring-opening with 4-methoxybenzylamine and subsequent protection with Boc_2O.[14] In this event, by blocking both NH of the amino group we intended to avoid the potential deleterious effect of the secondary amine in the RCM, since it is known that a basic amine can inactivate the catalyst.[15] Aminodiols **2a**−**c** bearing a fully protected amino group were deoxygenated with the Corey−Hopkins protocol.[12] Thus, thionocarbonates **3a**−**c** were prepared in high yield by treatment with thiophosgene in the presence of 4-(dimethylamino)pyridine and subsequently heated at 60 °C in 1,3-dimethyl-2-phenylphosphazolidine. In this way the pyrolysis took place smoothly affording bis-allylamines **4a**−**c**. With the bis-olefinic amines in hand, the RCM was performed with 2% mol of benzylidene (bis(tricyclohexyl)-phosphine)ruthenium(II) dichloride (Grubbs's catalyst).[7] The cyclopentene and cyclohexene amines **5b** and **5c** were obtained in excellent yield in what represents a straightforward synthesis of these intermediates of high enantiomeric purity. Not surprisingly, the attempted cyclization of **4a** completely failed. In this case, most probably due to the strain of the cyclobutane ring, the starting material was completely recovered. Our projected preparation of enantiopure heterocyclic amines **II** involved chiral allylamines **IIIb** bearing an allyl fragment directly bonded to the amino group. We envisaged that these compounds could be easily prepared by using allylamine as a nucleophile in the epoxide ring-opening. We selected 2,3-epoxy-3-phenylpropanol (**6**) as starting material for two reasons: it is readily available in enantiopure form and the phenyl group is a known precursor of a carboxylic group. Thus, epoxyalcohol **6** of >99% ee was prepared from cinnamyl alcohol by Sharpless epoxidation.[13a] Two well-established protecting groups for the amino function, *p*-methoxybenzyl (PMB) and *tert*-butoxycarbonyl (Boc), were selected. The PMB group was tried first because the corresponding allylamines bearing it (i.e. *N*-allyl-*p*-methoxybenzylamine) are still very nucleophilic and consequently offered the advantage that they could be directly used as nucleophiles in the epoxide ring-opening. According to our expectations, the treatment of epoxy alcohol **6** with *N*-allyl-*p*-methoxybenzylamine under Sharpless conditions afforded aminodiol **7a** in excellent yield (Scheme 2). However, due to the difficulties encountered in the dihydroxylation and in the deprotection of the PMB (vide infra), the Boc-protected aminodiol **7b** was also prepared. The poor reactivity of *N*-Boc-allylamine prevented its introduction by nucleophilic ring opening so epoxide **6** was treated with allyl-

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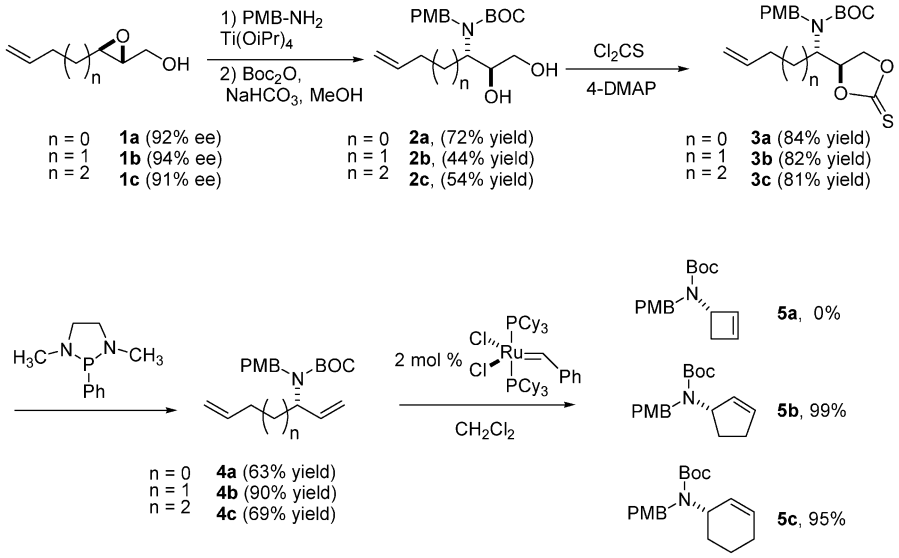
SCHEME 1



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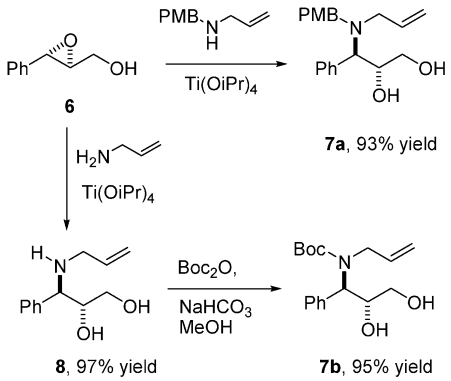

amine in the presence of titanium tetraisopropoxide and the resulting aminodiol **8** was protected with Boc_2O to afford **7b** in good yield.

Both aminodiols **7a** and **7b** were submitted to the Corey−Hopkins protocol[12] with the same reaction conditions as in the preparation of **4a**−**c**, but the intermediate thionocarbonates were not characterized but used directly in the pyrolysis step. In both cases the deoxygenation took place in good yields affording bis-allylamines **10a**,**b**. These amines were treated with Grubbs's catalyst in CH_2Cl_2 at room temperature. In both cases pyrrolidines **11a**,**b** were obtained in excellent yields. The enantiomeric purity of **11a**,**b** was checked by DSC and, as expected, was in both cases >99%. These compounds, like other related dehydropyrrolidines, are useful intermediates in the synthesis of heterocyclic compounds and some of them such as **11b** have already been prepared.[10] To further demonstrate their potential, we have used them as precursors in the synthesis of an important biologically active amino acid: 3,4-dihydroxyproline.[16,17] The key steps for this synthesis would be the dihydroxylation of the double bond and the oxidation of the phenyl ring. After much experimentation we could neither dihydroxylate[18] the *p*-methoxybenzyl derivative **11a** nor deprotect the PMB group in acceptable yield. Gratifyingly, however, the dihydroxylation of **11b**[10e] with $K_3Fe(CN)_6$ and a catalytic amount of OsO_4 took place in excellent yield and with complete facial selectivity, anti to the phenyl group. After protection of the diol as an acetonide, the phenyl group was oxidized with $NaIO_4$ and a catalytic amount of ruthenium trichloride[19] to afford the protected 3,4-dihydroxyproline **14b**. This compound showed the same rotatory power as the product prepared from Zanardi and co-workers and their spectra were completely coincident.[16c] In summary, chiral allylamines **III** prepared by deoxygenation of 3-amino-1,2-diols have been tested in RCM reactions. Doubly olefinic compounds **IIIa** have been readily prepared from unsaturated epoxy alcohols, and their RCM has provided cyclic allylamines **I** in excellent yields and high enantiomeric purity. On the other hand, starting from 2,3-epoxycinnamyl alcohol, a nucleophilic ring opening by allylamines followed by a deoxygenation protocol afforded bis-allylamines **IIIb**, which upon RCM provided unsaturated pyrrolidines **II** also in excellent yields. One of these pyrrolidines has been used in the preparation of enantiomerically pure fully protected (2*S*,3*R*,4*S*)-3,4-dihydroxyproline.

Experimental Section

General Methods. Optical rotations were measured at room temperature (23 °C) (concentration in g/100 mL). Infrared spectra were recorded with NaCl film. ^1H NMR were obtained at 200 or 300 MHz with tetramethylsilane as internal standard. ^{13}C NMR were obtained at 50.3 or 75.4 MHz in $DCCl_3$,

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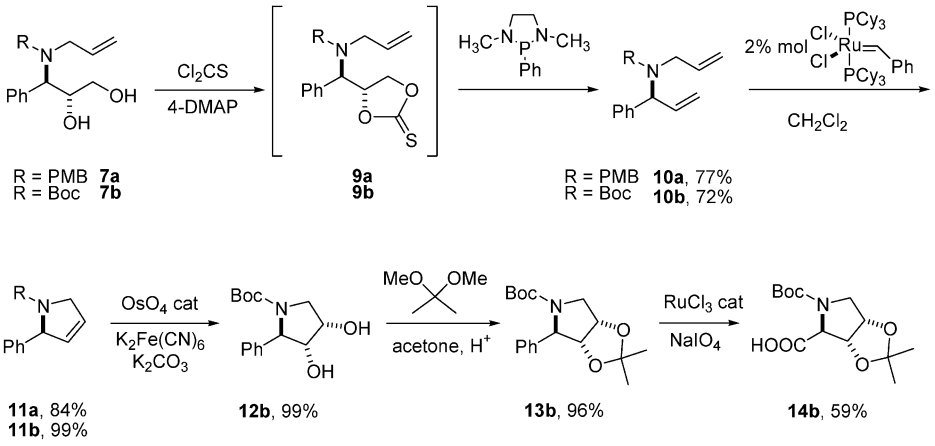
SCHEME 3



and referenced to the solvent signal. Chemical shifts are recorded in ppm. Signal multiplicities have been assigned by DEPT experiments. Chromatographic separations were carried out with NEt_3 pretreated (2.5% v/v) SiO_2 (70−230 mesh). Compounds **2a**−**c**[14] and **6**[13a] were prepared according to known procedures. All other compounds are novel except **11b**[10e] and **14b.**[16c]

(4*S*,1′*S*)-*N*-(*tert*-Butoxycarbonyl)-*N*-(4-methoxybenzyl)-4-(1′-aminobut-3′-enyl)[1,3]dioxolane-2-thione (3a). To a stirred solution of **2a** (1.25 g, 3.57 mmol) and 4-DMAP (1.05 g, 8.57 mmol) in dichloromethane (14.3 mL) at 0 °C under nitrogen was added thiophosgene (95%, 350 μL, 4.28 mmol). After 1 h of stirring at 0 °C, silica gel (7.14 g) was added and the mixture was allowed to warm to 25 °C. Solvent was removed in vacuo, and the remaining solid was loaded onto a column of silica gel (21.4 g) and eluted with 20% ethyl acetate in hexane to afford 1.17 g of thionocarbonate **3a** (84% yield) as an oil. $[\alpha]_D$ +43.7 (*c* 2.0, $CHCl_3$). IR (film) ν 3100, 2977, 1750, 1692, 1613, 1586, 1515, 1459, 1395, 1291 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 7.17 (d broad, 2H), 6.87 (d, J = 8.4 Hz, 2H), 5.7 (m, 1H), 5.25−5.1 (m, 2H), 5.1 (m, 1H), 4.5−3.8 (m, 5H), 3.8 (s, 3H), 2.61 (m, 2H), 1.5 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 159.3 (C), 155 (C), 133.1 (CH), 129.2 (CH), 118.6 (CH2), 114.3 (CH), 82.8 (CH), 81.0 (C), 71.8 (CH_2), 58.9 (CH), 55.2 (CH_3), 50.3 (CH_2), 33.8 (CH_2), 28.3 (CH_3). MS (CI−NH_3) *m/e* 295 (83%), 394 (M + 1, 2%), 395 (M + 2, 12%), 411 (M + 18, 100%).

(3*S*)-*N*-(*tert*-Butoxycarbonyl)-*N*-(4-methoxybenzyl)-(1-vinylbut-3-enyl)amine (4a). A suspension of thionocarbonate **3a** (1.68 g, 4.27 mmol) in 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine (2.3 mL, 12.8 mmol) was stirred under nitrogen for 20 h at 45 °C. After cooling to 25 °C, the contents were directly chromatographed on silica gel (elution with 2% ethyl acetate in hexane) to afford 850 mg of olefin **4a** (63% yield) as an oil. $[\alpha]_D$ −20.2 (*c* 1.4, $CHCl_3$). IR (film) ν 3080, 2977, 1690, 1613 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 7.17 (d, J = 8.5 Hz, 2H), 6.82 (d, J = 8.5 Hz, 2H), 5.95−5.55 (m, 2H), 5.15−4.95 (m, 4H), 4.3 (m, 3H), 3.79 (s, 3H), 2.4 (m, 2H), 1.43 (s, 9H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 158.4 (C), 156 (C), 137.3 (CH), 135.1 (CH), 131.7 (C), 128.6 (CH), 116.9 (CH_2), 116.2 (CH_2), 113.5 (CH), 79.7 (C), 58.6 (CH), 55.2 (CH_3), 47.9 (CH_2), 36.8 (CH_2), 28.4 (CH_3). MS (CI−NH_3) *m/e* 235 (M + 18, 100%), 318 (M + 1, 74%), HRMS calcd for $C_{19}H_{27}NO_3$ 317.2003, found 317.1991.

(1*S*)-*N*-(*tert*-Butoxycarbonyl)-*N*-(*p*-methoxybenzyl)cyclopent-2-enylamine (5b). To a Schlenk flask containing a solution of **4b** (82 mg, 0.25 mmol) in anhydrous dichloromethane (1.54 mL) was added benzylidene (bis(tricyclohexyl)-phosphine)ruthenium(II) dichloride (8 mg, 0.03 mmol) under argon. After 1 h of stirring at room temperature, air was bubbled for 3 h. The solvent was removed in vacuo and the crude product was purified by column chromatography eluting with hexanes/ethyl acetate mixtures to afford 75 mg of **5b** (99% yield). $[\alpha]_D$ −91.7 (*c* 1.0, $CHCl_3$). IR (film) ν 3000, 2950, 1700, 1620, 1520, 1460, 1410 cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$) δ 7.13 (d, J = 8.5 Hz, 2H), 6.82 (d, J = 8.5 Hz, 2H), 5.87 (m, 1H), 5.5 (m, 1H), 5.3 (broad, 1H), 4.21 (s broad, 2H), 3.78 (s, 3H), 2.25 (m, 2H), 1.55 (m, 2H), 1.41 (s broad, 9H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 158.1 (C), 155.8 (C), 134.2 (CH), 132.4 (C), 130.8 (2CH), 127.8 (CH), 113.4 (2CH), 79.5 (C), 62.4 (CH), 55.2 (CH_3), 46.0 (CH_2), 31.3 ($2CH_2$), 28.4 ($3CH_3$). HRMS calcd for $C_{18}H_{26}NO_3$ (M + 1) 304.1913, found 304.1921.

(2*R*,3*R*)-3-[Allyl(4-methoxybenzyl)amino]-3-phenylpropane-1,2-diol (7a). To a solution of (2*R*,3*S*)-2,3-epoxy-3-phenylpropanol (**6**; 2.2 g, 14.65 mmol) in anhydrous dichloromethane (55 mL) at room temperature was added titanium tetraisopropoxide (13.3 mL, 44 mmol) dropwise under nitrogen. The mixture was briefly stirred at room temperature for 30 min, allyl(4-methoxybenzyl)amine (5.2 g, 29.3 mmol) was added, and the mixture was heated for 15 h at 65 °C. Then the reaction mixture was allowed to reach room temperature and quenched with 23.5 mL of a 10% aqueous solution of sodium hydroxide saturated with sodium chloride. Stirring was maintained for an additional 4 h at room temperature and the mixture was filtered through a pad of Celite and washed with dichloromethane. The aqueous layer was extracted with dichloromethane and the combined organic phases were washed with brine. The organic layer was dried and evaporated. The resulting residue was purified by column chromatography eluting with hexanes/ethyl acetate mixtures to afford **7a** (4.46 g, 93% yield) as a colorless oil. $[\alpha]^{23}_D$ −123.14 (*c* 1.1, $CHCl_3$). IR (NaCl) ν 3407, 3064, 1613, 1514, 1454 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.41−7.19 (m, 7H), 6.88 (d, J = 8,8 Hz, 2H), 5.82 (m, 1H), 5.21 (m, 2H), 4.38 (m, 1H), 3.81 (m, 9H), 3.39 (m, 1H), 2.92 (d, J = 16.3 Hz, 1H), 2.59 (dd, J = 16.3, 8.1 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.8 (C), 135.7 (CH), 133.9 (C), 131.4 (C), 130.1 (CH), 129.9 (CH), 128.5 (CH), 128.0 (CH), 118.4 (CH_2), 114.0 (CH), 68.8 (CH), 66.7 (CH), 66.5 (CH_2), 55.2 (CH_3), 53.9 (CH_2), 53.2 (CH_2). MS (CI−NH_3) *m/z* (%) 328(100) $[M + 1]^+$, 345 (41) $[M + 18]^+$. HRMS calcd for $C_{20}H_{25}NO_3$ 327.1834, found 327.1819.

(2*R*,3*R*)-3-Allylamino-3-phenylpropane-1,2-diol (8). To a solution of (2*R*,3*S*)-2,3-epoxy-3-phenylpropanol (**6**) (1.00 g, 6.66 mmol) in anhydrous dichloromethane (24 mL) at room temperature was added titanium tetraisopropoxide (6 mL, 20 mmol) dropwise under nitrogen. The mixture was stirred for 15 min and allylamine (1.5 mL, 20 mmol) was added dropwise. Then, the mixture was stirred for 8 h at 65 °C. The reaction was allowed to cool to room temperature and quenched with 23.5 mL of a 10% aqueous solution of sodium hydroxide saturated with sodium chloride. Stirring was maintained for an additional 6 h at room temperature and the mixture was filtered through a pad of Celite, washing with dichloromethane. The aqueous layer was extracted with dichlo-

romethane and the combined organic phases were washed with brine, dried (sodium sulfate), and evaporated. The residue was purified by column chromatography eluting with hexanes/ethyl acetate mixtures yielding **8** as a yellow solid (1.32 g, 97% yield). $[\alpha]^{23}_D$ −67.04 (*c* 1.1, $CHCl_3$). Mp 63−65 °C. IR (NaCl) ν 3315, 1641, 1603, 1496, 1463 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.37−7.26 (m, 5H), 5.91−5.77 (m, 1H), 5.17−5.07 (m, 2H), 3.88−3.81 (m, 2H), 3.58 (d, J = 5 Hz, 2H), 3.21 (dd, J = 13.6, 5.6 Hz, 1H), 3.03 (dd, J = 13.2, 7.5 Hz, 1H), 2.71 (br s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.2 (C), 136.0 (CH), 128.5 (CH), 127.7 (CH), 127.6 (CH), 116.4 (CH_2), 73.5 (CH), 65.3 (CH), 64.4 (CH_2), 49.7 (CH_2). MS (CI−NH_3) *m*/*z* (%) 208 (100) $[M + 1]^+$, 225 (25) $[M + 18]^+$. Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.33; H, 8.15; N, 6.72.

(2*R*,3*R*)-3-*tert*-Butoxycarbonylamino-3-phenylpropane-1,2-diol (7b). To a solution of **8** (1.1 g, 6.28 mmol) in MeOH (25 mL) at room temperature were added Boc_2O (1.4 g, 7.54 mmol) and $NaHCO_3$(18.84 mmol). The reaction mixture was placed for 12 h in a ultrasonic bath being monitored by TLC. The mixture was filtered through a pad of Celite and washed with Et_2O. The organic phase was dried and evaporated and the crude product was purified by column chromatography eluting with hexanes/ethyl acetate mixtures to yield **7b** as a white solid (1.55 g, 95% yield). $[\alpha]^{23}_D$ −57,4 (*c* 1.1, $CHCl_3$). Mp 44−45 °C. IR (NaCl) ν 3387, 2997, 1689, 1614, 1461, 1411 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.41−7.25 (m, 5H), 5.58−5.39 (m, 1H), 5.16 (d, J = 9.1 Hz, 1H), 4.96−4.83 (m, 2H), 4.16 (br s, 1H), 3.72−3.26 (m, 5H), 2.63 (br s, 1H), 1.49 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.6 (CO), 136.8 (C), 134.4 (CH), 129.6 (CH), 128.5 (CH), 127.9 (CH), 117.0 (CH_2), 81.2 (CH), 69.9 (CH), 62.9 (CH_2), 59.8 (C), 47.0 (CH_2), 28.4 (CH_3). MS (CI−NH_3) *m*/*z* (%) 308 (100) [M + 1], 325 (34) $[M + 18]^+$. Anal. Calcd for $C_{17}H_{25}NO_4$: C, 66.43; H, 8.2; N, 4.56. Found: C, 66.47; H, 8.06; N, 4.39.

(1*S*)-*N*-Allyl-*N*-(*tert*-butoxycarbonyl)-1-phenylallylamine (10b). To a solution of **7b** (1.4 g, 4.55 mmol) and 4-(dimethylamino)pyridine (1.33 g, 10.94 mmol) in anhydrous dichloromethane (25 mL) at 0 °C was added thiophosgene (0.47 mL, 5.46 mmol) slowly under nitrogen. The reaction mixture was stirred for 2 h, at which time TLC showed the reaction to be complete. Evaporation of the solvent (using a KOH trap) afforded a crude product (**9b**) that was used without further purification in the next step.

In a 50-mL round-bottomed flask, the crude thiocarbonate (1.44 g, 4.12 mmol) and freshly distilled 1,3-dimethyl-2-phenyl-[1,3,2]diazaphospholidine (2.4 mL, 12.41 mmol) were placed under nitrogen. The reaction mixture was warmed to 65 °C for 24 h. The residual crude was directly purified by column chromatography eluting with hexanes/ethyl acetate mixtures to yield **10b** (0.86 g, 72% overall yield from **7b**) as a colorless oil. $[\alpha]^{23}_D$ −43.59 (*c* 1.3, $CHCl_3$). IR (NaCl) ν 2982, 1691, 1461, 1402, 1373, 1264 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.39−7.29 (m, 5H), 6.23−6.11 (m, 1H), 5.62 (br s, 1H), 5.39−5.22 (m, 2H), 5.01 (d, J = 11.2 Hz, 2H), 3.86−3.69 (m, 3H), 1.46 (s, 9H).^{13}C NMR (75 MHz, $CDCl_3$) δ 155.55 (CO), 140.09 (C), 135.71 (CH), 135.3 (CH), 128.25 (CH), 127.71 (CH), 127.2 (CH), 117.83 (CH_2), 115.9 (CH_2), 79.92 (CH), 61.88 (C), 47.72 (CH_2), 28.37 (CH_3). MS (CI−NH_3) *m*/*z* (%) 274 (100) $[M + 1]^+$, 291 (41) $[M + 18]^+$. HRMS (CI) calcd for $C_{17}H_{23}NO_2$ (M^+) 273.1729, found 273.1746.

(2*S*)-*N*-*tert*-Butoxycarbonyl-2-phenyl-2,5-dihydropyrrole (11b). To a solution of **10b** (0.72 g, 2.64 mmol) in anhydrous dichloromethane was added Grubbs's catalyst (0.11 g, 5% mol) dropwise under nitrogen. The resulting mixture was stirred at room temperature. When the reaction was complete by TLC (ca. 1 h), the reaction mixture was concentrated and chromatographed eluting with hexanes/ethyl acetate mixtures to afford **11b** (0.63 g, 99% yield) as a white solid. $[\alpha]^{23}_D$ −280.5 (*c* 1.0, $CHCl_3$). IR (NaCl) ν 3021, 1705, 1645 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 55 °C) δ 7.32−7.19 (m, 5H), 5.87 (s, 1H), 5.73 (s, 1H), 5.37 (s, 1H), 4.33 (s, 2H), 1.21 (s, 9H).^{13}C NMR (75 MHz, $CDCl_3$, 55 °C) δ 154.67 (CO), 140.14 (C), 131.34 (CH), 128.24 (CH), 127.21 (CH), 126.67 (CH), 124.61 (CH), 79.54 (CH), 64.93 (C), 48.13 (CH_2), 28.28 (CH_3). MS (CI−NH_3) *m*/*z* (%) 246 (90) $[M + 1]^+$, 263 (100) $[M + 18]^+$. Purity by DSC: 99.5% (mp 81.01 °C). Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.45; H, 7.72; N, 5.65.

(2*R*,3*R*,4*S*)-*N*-*tert*-Butoxycarbonyl-3,4-dihydroxy-2-phenylpyrrolidine (12b). To a solution of **11b** (0.1 g, 0.41 mmol) in ^{t}BuOH (3 mL) and H_2O (3 mL) were added potassium hexacyanoferrate (0.403 g) and K_2CO_3 (0.167 g). The mixture was stirred for 15 min at room temperature and a solution of OsO_4 (0.1 mL, 0.051 mM in ^{t}BuOH) was added slowly. After 24 h of stirring the reaction was complete by TLC. Et_2O (2 mL) was added and the aqueous layer was extracted with ethyl ether. The combined organic layers were washed with brine and dried ($MgSO_4$). The solvent was removed in vacuo to give **12b** (0.113 g, 99% yield) as a colorless oil. $[\alpha]^{23}_D$ −16.2 (*c* 1.6, $CHCl_3$). IR (NaCl) ν 3434, 2979, 1700, 1399 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 55 °C) δ 7.33−7.15 (m, 5H), 4.61 (br s, 1H), 4.22 (dd, J = 7.3, 3.3 Hz, 1H), 3.99 (m, 1H), 3.73 (dd, J = 11.7, 5.7 Hz, 1H), 3.64 (br s, 1H), 3.21 (br s, 2H), 1.24 (s, 9H).^{13}C NMR (75 MHz, $CDCl_3$, 55 °C) δ 154.8 (CO), 140.2 (C), 128.5 (CH), 127.1 (CH), 125.7 (CH), 80.0 (CH), 69.6 (CH), 66.9 (CH), 61.4 (C), 51.4 (CH_2), 28.2 (CH_3). MS (CI−NH_3) *m*/*z* (%) 280 (86) $[M + 1]^+$, 297 (100) $[M + 18]^+$. Anal. Calcd for $C_{15}H_{21}NO_4$: C, 64.50; H, 7.58; N, 5.01. Found: C, 64.67; H, 7.61; N, 5.05.

(2*R*,3*R*,4*S*)-*N*-*tert*-Butoxycarbonyl-3,4-dihydroxy-2-phenylpyrrolidine Isopropylidene Acetal (13b). To a solution of **12b** (0.1 g, 0.36 mmol) in acetone (5 mL)were added 2,2-dimethoxypropane (0.11 mL, 0.54 mmol) and a *p*-TsOH·H_2O (ca. 6 mg). When the reaction was complete by TLC (ca. 3 h) the mixture was concentrated and purified by column chromatography eluting with hexanes/ethyl acetate mixtures to afford **13b** (0.11 g, 96% yield) as a white solid. $[\alpha]^{23}_D$ −48.14 (*c* 1.4, $CHCl_3$). Mp 98−100 °C. IR (NaCl) ν 2981, 1700, 1603 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$, 55 °C) δ 7.39−7.19 (m, 5H), 5.11 (br, 1H), 4.78 (t, J = 5.2 Hz, 1H), 4.69 (d, J = 6 Hz, 1H), 4.01 (d, J = 12.3 Hz, 1H), 3.65 (br s, 1H), 1.54 (s, 6H), 1.29 (s, 9H).^{13}C NMR (75 MHz, $CDCl_3$, 55 °C) δ 154.53 (CO), 140.35 (C), 128.67 (CH), 127.24 (CH), 125.79 (CH), 112.05 (CH), 87.45 (CH), 79.86 (CH), 78.94 (C), 67, 37 (C), 52.76 (CH_2), 28.27 (CH_3), 27.13 (CH_3), 25.21 (CH_3). MS (CI−NH_3) *m*/*z* (%) 320 (23) $[M + 1]^+$, 327 (100) $[M + 18]^+$. Anal. Calcd for $C_{18}H_{25}NO_4$: C, 67.69; H, 7.89; N, 4.39. Found: C, 67.89; H, 7.94; N, 4.46.

(2*S*,3*R*,4*S*)-*N*-*tert*-Butoxycarbonyl-3,4-dihydroxyproline Isopropylidene Acetal (14b). A 50-mL, three-necked, round-bottomed flask equipped with a wide-bore gas outlet (because the generation of carbon dioxide) was charged with **13b** (100 mg, 0.32 mmol), carbon tetrachloride (2.2 mL), acetonitrile (2.2 mL), water (4.5 mL), and sodium bicarbonate (0.45 g, 5.35 mmol). The mixture was briefly stirred until both phases were clear. Sodium periodate (1.22 g, 6.28 mmol) was added and the mixture stirred for 15 min. Ruthenium trichloride hydrate (8 mg, 10% mol) was added and the mixture vigorously stirred for 55 h. Then, diethyl ether (3 mL) was added (a deep black color appeared at this point) at 0 °C with vigorous stirring. After 10 min the organic phase was separated and the aqueous layer extracted with ether. The combined organic layers were washed with brine, dried, filtered, and concentrated. The crude product was purified by column chromatography eluting with methanol/dichloromethane mixtures to afford pure **14b** (53 mg, 59% yield) as a colorless oil. $[\alpha]^{23}_D$ −44.1. (*c* 0.07, $CHCl_3$). IR (NaCl) ν 3433, 1745, 1581 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$) δ 7.19 (bs, 1H), 4.78 (m, 2H), 4.43 (m,1H), 3.77 (m, 2H), 1.48 (s, 9H), 1.42 (s, 3H), 1.29 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3 (CO), 154.1 (CO), 111.8 (CH), 82.3 (CH), 81.4 (CH), 80.3(C), 66.9 (C), 52.1 (CH_2), 28.5 (CH_3), 26.8 (CH_3), 25.1 (CH_3). MS (CI−NH_3) *m*/*z* (%) 288 (47) $[M + 1]^+$, 305 (100) $[M + 18]^+$. Anal. Calcd for $C_{13}H_{21}NO_6$: C, 54.35; H, 7.37; N, 4.88. Found: C, 54.27; H, 7.41; N, 4.81.

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Supporting Information Available: Experimental details for the preparation of compounds **3b**, **4b**, **3c**, **4c**, **5c**, **10a**, and **11a** and; ^{1}H NMR and ^{13}C NMR spectra of compounds **4a**, **4b**, **4c**, **5b**, **5c**, **7a**, **10a**, **11a**, **8**, **10b**, **11b**, **12b**, and **13b**. This material is available free of charge via the Internet at http://pubs.acs.org.

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