JOC The Journal of Organic Chemistry

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pubs.acs.org/joc

Asymmetric Synthesis of *cis*-Aminocyclopentenols, Building Blocks for Medicinal Chemistry

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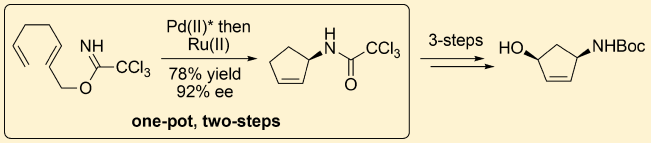
Supporting Information

ABSTRACT: A highly efficient one-pot multistep process involving an asymmetric Pd(II)-catalyzed Overman rearrangement and a Ru(II)-catalyzed ring-closing metathesis reaction has been developed for the preparation of (*R*)- or (*S*)-aminocyclopenta-2-enes. The rapid strategy employed and the relatively mild conditions of the one-pot process allowed the multigram synthesis of the carbocycles in high enantiomeric excess (92% ee). The synthetic utility of these compounds was demonstrated by the stereoselective incorporation of hydroxyl groups, generating *cis*-4- and *cis*-5-aminocyclopenta-2-en-1-ols, important building blocks for medicinal chemistry.



cis-Aminocyclopentenols are valuable chiral building blocks found in a range of natural products and pharmaceuticals. For example, (1*S*,4*R*)-4-aminocyclopenta-2-en-1-ol **1** and its derivatives have been used as building blocks for the preparation of a wide range of antiviral and anticancer carbocyclic nucleosides, such as aristeromycin **2** and noraristeromycin **3** (Figure 1).[1,2] They have also been used as key

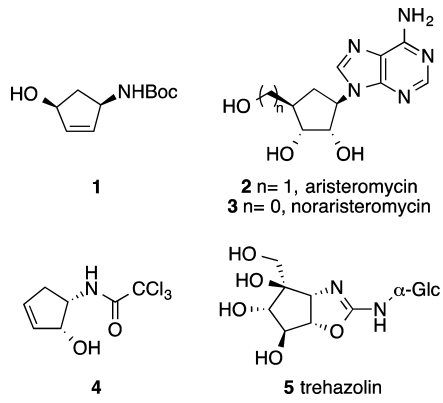


Figure 1. *cis*-Aminocyclopentenol building blocks (**1**, **4**) and examples of biological targets.

intermediates for the preparation of hydroxylated cyclic α-amino acids,[3] the total synthesis of the oroidin alkaloid, (−)-agelastatin A,[4] and for the generation of phosphodiesterase inhibitors.[5] In a similar fashion, (1*R*,5*S*)-5-aminocyclopenta-2-en-1-ols (e.g., **4**) are important building blocks for the synthesis of highly functionalized cyclopentanes, such as the core of the natural product, trehazolin **5**, a potent glycosidase inhibitor.[6,7]

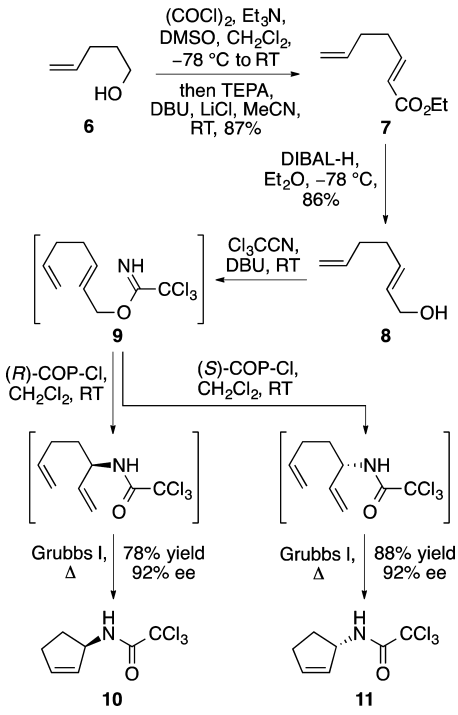
Because of the importance of *cis*-4- and 5-aminocyclopenta-2-en-1-ols in medicinal chemistry, many general methods for their asymmetric synthesis have been reported. A range of chiral auxiliary derived nitrogen-containing compounds have been used in hetero-Diels−Alder reactions,[8] electron transfer reductions,[9] and in conjugate addition reactions[10] en route toward the synthesis of these compounds. The research groups of O'Brien[11] and Asami[12] have used chiral lithium amide mediated rearrangements of functionalized cyclopentene epoxides, while enzymatic hydrolytic kinetic resolutions[13] and hydroxynitrile lyase-type reactions[14] have also allowed access to these compounds. A rare example of a catalytic asymmetric method was described by Trost and co-workers, who used the desymmetrization of *meso*-cyclopentene-1,4-diol derivatives with palladium(0) and a chiral 2-(diphenylphosphino)-based ligand.[15] Although many of these approaches generate *cis*-4- or *cis*-5-aminocyclopenta-2-en-1-ols with high levels of asymmetric induction, they are restrictive for one enantiomer and one type of substitution pattern. We now report the scalable preparation of *cis*-4- and *cis*-5-aminocyclopenta-2-en-1-ol building blocks based on a one-pot multistep catalytic asymmetric synthesis of amino-substituted carbocycles. This general approach allows the late-stage synthesis of either enantiomer and 1,4- or 1,5-substitution patterns.

Our strategy for the asymmetric synthesis of *cis*-4- and *cis*-5-aminocyclopenta-2-en-1-ols focused on the use of a one-pot Overman rearrangement[16] and a ring-closing metathesis (RCM) reaction with a suitably derived allylic alcohol to give an amino-substituted cyclopentene, followed by an oxidation process to incorporate the hydroxyl functionality. The substrate for the one-pot process, (2*E*)-hepta-2,6-dien-1-ol (**8**) was prepared from 4-penten-1-ol (**6**) using a one-pot Swern oxidation and a Horner−Wadsworth−Emmons (HWE) reaction with triethyl phosphonoacetate (TEPA) under Masumune−Roush conditions (Scheme 1).[17,18a] This gave the corresponding *E*-α,β-unsaturated ester **7** in 87% yield. Chemoselective reduction of the ester with DIBAL-H then gave **8** in 86% yield. Allylic trichloroacetimidate **9** was formed using

Received: December 6, 2013
Published: January 6, 2014

   dx.doi.org/10.1021/jo402712r | *J. Org. Chem.* 2014, 79, 1511−1515

Scheme 1. Asymmetric Synthesis of (*R*)- and (*S*)-Aminocyclopenta-2-enes 10 and 11



trichloroacetonitrile and DBU under standard conditions and without purification; **9** was subjected to the one-pot two-step process.[18] Asymmetric Overman rearrangement[19] was performed using the commercially available, chiral palladium(II)-catalyst, (*R*)-COP-Cl (2.5 mol %) (**12**, Figure 2), and this was followed by the addition of Grubbs first-generation catalyst (5 mol %), which gave (1*R*)-1-(2′,2′,2′-trichloromethylcarbonyl-amino)cyclopenta-2-ene (**10**) in 78% yield from allylic alcohol **8** and in 92% enantiomeric excess. Repeating the process using (*S*)-COP-Cl (**13**) gave the (*S*)-enantiomer **11** in 88% yield over the three steps and in 92% enantiomeric excess. The enantiopurity of **10** and **11** could be improved (>99% ee) by recrystallization from ethyl acetate and petroleum ether. Because of the ease and efficiency of this approach (58% and 66% overall yield of **10** and **11**, respectively), multigram quantities of these building blocks were rapidly accessed.

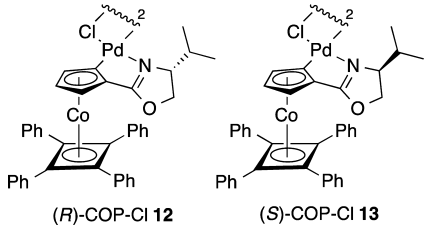
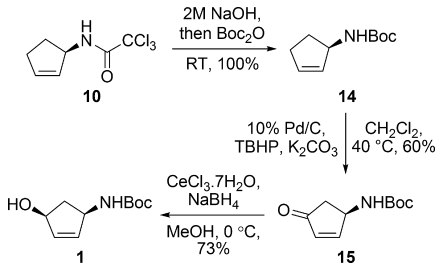


Figure 2. Structures of (*R*)-COP-Cl **12** and (*S*)-COP-Cl **13** catalysts.

The next stage of the synthesis of the *cis*-aminocyclopentenols required the stereoselective introduction of the hydroxyl groups. Our proposed strategy to access (1*S*,4*R*)-4-aminocyclopenta-2-en-1-ol **1** involved allylic oxidation of **10**, followed by a stereoselective reduction. Our initial attempts at allylic oxidation of **10** returned none of the desired ketone, with NMR analysis of the crude reaction mixture showing decomposition of the trichloroacetamide moiety. Therefore, the Boc-protected analogue **14** was prepared in quantitative yield using a one-pot procedure involving trichloroacetamide hydrolysis, followed by reprotection of the resulting amine with Boc_2O (Scheme 2).

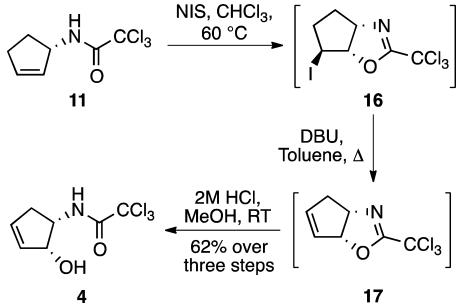
Scheme 2. Stereoselective Synthesis of *cis*-4-Aminocyclopenta-2-en-1-ol 1



Attempted allylic oxidation of **14** using SeO_2/*tert*-butyl hydroperoxide (TBHP)[20] or PCC[21] returned only starting material, while the diacetoxyiodobenzene-TBHP protocol, which generates the *tert*-butylperoxy radical in a σ-donor solvent, gave 4-aminocyclopenta-2-en-1-one **15** in only 15% yield.[22] Efficient allylic oxidation of **14** was achieved on optimization of a procedure described by Yu and Corey that utilizes 10% Pd/C and TBHP (Scheme 2).[23] At 40 °C, this gave **15** in 60% yield. Unlike other attempted methods of allylic oxidation of **14**, this procedure was found to be particularly clean with starting material **14** (20−25%), the only other isolated compound from this reaction. With 4-aminocyclopenta-2-en-1-one **15** in hand, regio- and stereoselective reduction was performed under Luche conditions[9b,10] and gave (1*S*,4*R*)-4-aminocyclopenta-2-en-1-ol **1** in 73% yield.[24]

To access (1*R*,5*S*)-5-aminocyclopenta-2-en-1-ol **4**, a three-step strategy involving stereoselective incorporation of the hydroxyl group and consecutive migration of the alkene was implemented (Scheme 3). Initially, (*S*)-cyclopenta-2-ene **11**

Scheme 3. Stereoselective Synthesis of *cis*-5-Aminocyclopenta-2-en-1-ol 4



was treated with *N*-iodosuccinimide, effecting formation of the *anti*-iodonium intermediate and subsequent cyclization of the trichloroacetamide to give 4,5-dihydro-1,3-oxazole **16**.[25] Without purification, **16** was heated in the presence of DBU, forming **17** via elimination of HI. Hydrolysis of the 4,5-dihydro-1,3-oxazole ring under mild acid-mediated conditions gave (1*R*,5*S*)-5-aminocyclopenta-2-en-1-ol **4** in 62% yield over the three steps. Difference NOE experiments showed correlation between the C-1 and C-5 hydrogen atoms, confirming the relative stereochemistry of the (1*R*,5*S*)-isomer **4**.[26]

In summary, a one-pot multistep process involving two different transition-metal catalysts has allowed the high yielding

dx.doi.org/10.1021/jo402712r | J. Org. Chem. 2014, 79, 1511−1515

asymmetric, multigram synthesis of (*R*)- and (*S*)-aminocyclopenta-2-enes. The synthetic utility of these compounds was demonstrated by the development of strategies for the stereoselective incorporation of hydroxyl groups, resulting in the formation of *cis*-4- or *cis*-5-aminocyclopenta-2-en-1-ols, important building blocks for synthetic and medicinal chemistry. We believe that the generation of functionalized carbocycles using this approach has significant potential and are currently developing applications of this process for the asymmetric synthesis of natural products and novel, medicinally active compounds.

EXPERIMENTAL SECTION

All reagents and starting materials were obtained from commercial sources and used as received. All dry solvents were purified using a solvent purification system. ^{1}H NMR spectra were recorded on a NMR spectrometer at either 400 or 500 MHz (chemical shift in ppm relative to tetramethylsilane as the internal standard). ^{13}C NMR spectra were recorded on an NMR spectrometer at either 101 or 126 MHz (chemical shift in ppm relative to tetramethylsilane or $CDCl_3$ as internal standard, δ 77.0 ppm). Infrared spectra were recorded on an FTIR spectrometer; wavenumbers are indicated in cm^{-1}. HRMS spectra were recorded using a dual-focusing magnetic analyzer mass spectrometer. Melting points are uncorrected. Optical rotations were determined as solutions irradiating with the sodium D line (λ = 589 nm) using a polarimeter. $[\alpha]_D$ values are given in units 10^{-1} deg cm^2 g^{-1}. The chiral HPLC method was calibrated with the corresponding racemic mixture.

Ethyl (2*E*)-2,6-heptadienoate (7).[18a] Dimethyl sulfoxide (6.20 mL, 88.0 mmol) was added to a stirred solution of oxalyl chloride (4.28 mL, 50.5 mmol) in dichloromethane (200 mL) at −78 °C. The reaction mixture was stirred for 0.3 h before 4-penten-1-ol (**6**) (3.02 g, 35.1 mmol) in dichloromethane (100 mL) was slowly added. The reaction mixture was stirred for a further 0.3 h before triethylamine (24.4 mL, 175.1 mmol) was added. This reaction mixture was stirred for 0.5 h at −78 °C and then allowed to warm to room temperature and stirred for a further 2 h. A solution of lithium chloride (2.68 g, 63.1 mmol), triethyl phosphonoacetate (12.5 mL, 63.1 mmol), and 1,8-diazabicyclo[5,4,0]undec-7-ene (9.44 mL, 63.1 mmol) in acetonitrile (150 mL) was prepared and stirred for 1 h. The Swern solution was concentrated in vacuo; then the HWE solution was added and the reaction mixture was stirred at room temperature overnight. The reaction was quenched by the addition of a saturated solution of ammonium chloride (100 mL) and concentrated to give an orange residue, which was then extracted with diethyl ether (4 × 100 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated to give an orange oil. Flash column chromatography (petroleum ether/diethyl ether, 20:1) yielded ethyl (2*E*)-2,6-heptadienoate (**7**) (4.70 g, 87% yield) as a colorless oil (the spectroscopic data were as reported in the literature[18a]): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.29 (t, 3H, *J* 7.2 Hz), 2.18−2.35 (m, 4H), 4.19 (q, 2H, *J* 7.2 Hz), 4.99−5.09 (m, 2H), 5.75−5.88 (m, 2H), 6.96 (dt, 1H, *J* 15.6, 6.8 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 14.3 (CH_3), 31.5 (CH_2), 32.1 (CH_2), 60.2 (CH_2), 115.6 (CH_2), 121.7 (CH), 137.1 (CH), 148.3 (CH), 166.7 (C); MS (CI) *m*/*z* 155 (MH^+, 100), 129 (6), 109 (17), 85 (10); HRMS (CI) calcd for $C_9H_{15}O_2$ (MH^+), 155.1072; found, 155.1075.

(2*E*)-Hepta-2,6-dien-1-ol (8).[18a] Ethyl (2*E*)-2,6-heptadienoate (**7**) (5.00 g, 32.5 mmol) was dissolved in diethyl ether (200 mL) and cooled to −78 °C. DIBAL-H (71.5 mL, 71.5 mmol, 1 M in hexane) was added dropwise, and the reaction mixture was stirred at −78 °C for 3 h, before warming to room temperature. The solution was cooled to 0 °C and quenched by the addition of a saturated solution of ammonium chloride (100 mL) and warmed to room temperature with vigorous stirring over 1 h, producing a white precipitate. The precipitate was filtered through a pad of Celite and washed with diethyl ether (400 mL). The organic solution was then dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash column chromatography (petroleum ether/diethyl ether, 7:3) yielded (2*E*)-hepta-2,6-dien-1-ol (**8**) (3.12 g, 86% yield) as a colorless oil (the spectroscopic data were as reported in the literature[18a]): ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (br s, 1H), 2.10−2.15 (m, 4H), 4.09 (d, 2H, *J* 4.8 Hz), 4.97 (d, 1H, *J* 10.0 Hz), 5.03 (d, 1H, *J* 17.2 Hz), 5.62−5.84 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 31.5 (CH_2), 33.3 (CH_2), 63.8 (CH_2), 114.9 (CH_2), 129.4 (CH), 132.4 (CH), 138.1 (CH); MS (CI) *m*/*z* 113 (MH^+, 41), 97 (100), 83 (36), 71 (52); HRMS (CI) calcd for $C_7H_{13}O$ (MH^+), 113.0966; found 113.0964.

(1*R*)-1-(2′,2′,2′-Trichloromethylcarbonylamino)cyclopenta-2-ene (10). (2*E*)-Hepta-2,6-dien-1-ol (**8**) (3.50 g, 31.0 mmol) was dissolved in dichloromethane (50 mL) and cooled to 0 °C. 1,8-Diazabicyclo[5.4.0]undec-7-ene (1.04 mL, 6.95 mmol) was then added to the solution, followed by trichloroacetonitrile (4.61 mL, 46.0 mmol). The reaction mixture was warmed to room temperature and stirred for 2 h. The reaction mixture was then filtered through a short pad of silica gel and washed with diethyl ether (100 mL). The resulting filtrate was then concentrated to give allylic trichloroacetimidate **9**, which was used without further purification. Allylic trichloroacetimidate **9** was dissolved in dichloromethane (150 mL). (*R*)-COP-Cl **12** (1.14 g, 0.78 mmol) was then added to the solution, and the reaction mixture was stirred at room temperature for 24 h. Grubbs first-generation catalyst (1.28 g, 1.55 mmol) was then added, and the reaction mixture was heated under reflux overnight. The mixture was cooled to room temperature and then filtered through a short pad of Celite, which was washed with diethyl ether (400 mL). Concentration of the filtrate, followed by flash column chromatography (petroleum ether/diethyl ether, 7:3), gave (1*R*)-1-(2′,2′,2′-trichloromethylcarbonylamino)cyclopenta-2-ene (**10**) (5.53 g, 78%) as a white solid: mp 82−83 °C; Chiral HPLC analysis using 0.5% isopropanol in hexane as the elution solvent (0.75 mL/min) indicated 92% ee. Retention time: t_S = 12.7 min, and t_R = 14.5 min; IR (NaCl) 3291, 1684, 1528, 823 cm^{-1}; $[\alpha]_D^{23}$ +87.4 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.65−1.73 (m, 1H), 2.34−2.56 (m, 3H), 4.93−5.01 (m, 1H), 5.72−5.77 (m, 1H), 6.05−6.10 (m, 1H), 6.57 (br s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 30.8 (CH_2), 31.3 (CH_2), 57.9 (CH), 92.7 (C), 129.4 (CH), 136.5 (CH), 161.2 (C); MS (CI) *m*/*z* 230 (MH^+, 18), 228 (20), 194 (32), 160 (10), 113 (24), 89 (100); HRMS (CI) calcd for $C_7H_9NO^{35}Cl_2{}^{37}Cl$ (MH^+), 229.9721; found 229.9718.

(1*S*)-1-(2′,2′,2′-Trichloromethylcarbonylamino)cyclopenta-2-ene (11). The reactions were performed as described above for (*R*)-cyclopentene **10**, except using (*S*)-COP-Cl **13** and on a smaller scale, (2*E*)-hepta-2,6-dien-1-ol (1.50 g, 13.4 mmol). Flash column chromatography (petroleum ether/diethyl ether, 7:3) gave (1*S*)-1-(2′,2′,2′-trichloromethylcarbonylamino)cyclopenta-2-ene (**11**) (2.70 g, 88%) as a white solid. $[\alpha]_D^{23}$ −86.6 (*c* 1.0, $CHCl_3$). All other data for **11** were in accordance with that obtained for **10**, as described above.

(1*R*)-1-(*tert*-Butoxycarbonylamino)cyclopenta-2-ene (14).[27] (1*R*)-1-(2′,2′,2′-Trichloromethylcarbonylamino)cyclopenta-2-ene (**10**) (3.00 g, 12.0 mmol) was dissolved in 2 M sodium hydroxide (100 mL) and stirred vigorously for 12 h at room temperature. Di-*tert*-butyl dicarbonate (6.55 g, 30.0 mmol) was added, and the solution was stirred for 6 h before a further portion of di-*tert*-butyl dicarbonate (3.28 g, 15.0 mmol) was added and the reaction mixture was stirred for a further 12 h. The reaction mixture was extracted with ethyl acetate (4 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated in vacuo. Flash column chromatography (petroleum ether/ethyl acetate, 9:1) gave (1*R*)-1-(*tert*-butoxycarbonylamino)cyclopenta-2-ene (**14**) (2.40 g, 100%) as a white solid: mp 85−86 °C; (lit.[27] mp 87.5 °C); $[\alpha]_D^{23}$ +65.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.51 (s, 9H), 1.55−1.58 (m, 1H), 2.21−2.49 (m, 3H), 4.50 (br s, 1H), 4.66−4.76 (m, 1H), 5.66−5.71 (m, 1H), 5.87−5.93 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 28.4 (3 × CH_3), 31.0 (CH_2), 31.7 (CH_2), 56.8 (CH), 79.1 (C), 131.6 (CH), 134.1 (CH), 155.3 (C); MS (CI) *m*/*z* 184 (MH^+, 45), 128 (100), 119 (27), 113 (11), 84 (7).

(4*R*)-4-(*tert*-Butoxycarbonylamino)cyclopenta-2-en-1-one (15).[10] To a solution of (1*R*)-1-(*tert*-butoxycarbonylamino)-cyclopenta-2-ene (**14**) (1.00 g, 5.46 mmol) in dichloromethane (70

dx.doi.org/10.1021/jo402712r | J. Org. Chem. 2014, 79, 1511−1515

mL) were added 10% palladium on carbon (0.09 g), *tert*-butyl hydroperoxide (3.64 mL, 20.0 mmol, 5.0−6.0 M in decane), and anhydrous potassium carbonate (0.13 g, 0.94 mmol). The reaction mixture was heated at 40 °C for 24 h. A further quantity of *tert*-butyl hydroperoxide (3.64 mL, 20.0 mmol, 5.0−6.0 M in decane) and 10% palladium on carbon (0.09 g) were added, and the reaction mixture was heated at 40 °C for a further 24 h. The reaction mixture was filtered through a pad of silica, which was subsequently washed with dichloromethane (150 mL). After removal of solvent under reduced pressure, the crude material was purified by flash column chromatography (petroleum ether/diethyl ether, 9:1) and gave (4*R*)-4-(*tert*-butoxycarbonylamino)cyclopenta-2-en-1-one (**15**) (0.65 g, 60%) as white solid: mp 122−124 °C; (lit.[10] mp 124−125 °C); $[\alpha]_D^{23}$ +66.8 (*c* 1.0, $CHCl_3$), lit.[10] $[\alpha]_D^{20}$ +69.6 (*c* 2.6, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.46 (s, 9H), 2.16 (d, 1H, *J* 18.6 Hz), 2.88 (dd, 1H, *J* 18.6, 6.4 Hz), 4.60−4.72 (br m, 1H), 4.90−5.02 (br m, 1H), 6.25 (dd, 1H, *J* 6.4, 1.4 Hz), 7.50−7.56 (br m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 28.3 (3 × CH_3), 42.5 (CH_2), 51.0 (CH), 80.3 (C), 135.3 (CH), 155.0 (C), 162.2 (CH), 206.5 (C); MS (CI) *m*/*z* 198 (MH^+, 8), 155 (12), 142 (100), 126 (4), 85 (14), 69 (12).

(1*S*,4*R*)-4-(*tert*-Butoxycarbonylamino)cyclopenta-2-en-1-ol (1).[10] To a stirred solution of (4*R*)-4-(*tert*-butoxycarbonylamino)-cyclopenta-2-en-1-one (**15**) (0.06 g, 0.31 mmol) in methanol (10 mL) was added cerium(III) chloride heptahydrate (0.46 g, 1.22 mmol). The solution was stirred at room temperature for 0.5 h and then cooled to 0 °C. Sodium borohydride (0.05 g, 1.22 mmol) was added, and the reaction mixture was stirred at 0 °C for 3 h. The mixture was quenched with water (5 mL) and concentrated under vacuum. The resulting aqueous solution was extracted with diethyl ether (2 × 50 mL) and ethyl acetate (2 × 50 mL). The combined organic layers were washed with brine (25 mL), dried ($MgSO_4$), filtered, and concentrated. Flash column chromatography (petroleum ether/ethyl acetate, 1:1) afforded (1*S*,4*R*)-4-(*tert*-butoxycarbonylamino)-cyclopenta-2-en-1-ol (**1**) (0.04 g, 73%) as a white solid: mp 62−64 °C; $[\alpha]_D^{22}$ +63.9 (*c* 1.0, $CHCl_3$), lit.[10] $[\alpha]_D^{20}$ +65.3 (*c* 0.6, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.44 (s, 9H), 1.50−1.56 (m, 1H), 2.73 (dt, 1H, *J* 14.0, 7.5 Hz), 2.86 (br s, 1H), 4.38−4.44 (m, 1H), 4.65−4.71 (m, 1H), 4.84 (br s, 1H), 5.84 (dd, 1H, *J* 5.5, 1.0 Hz), 5.97 (br d, 1H, *J* 5.5 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 28.4 (3 × CH_3), 41.5 (CH_2), 54.9 (CH), 75.2 (CH), 79.6 (C), 134.2 (CH), 136.1 (CH), 155.2 (C); MS (CI) *m*/*z* 200 (MH^+, 9), 182 (5), 144 (20), 126 (100), 100 (6); HRMS (CI) calcd for $C_{10}H_{18}NO_3$ (MH^+), 200.1287; found, 200.1288.

(1*R*,5*S*)-5-(2′,2′,2′-Trichloromethylcarbonylamino)-cyclopenta-2-en-1-ol (4). To a solution of (1*S*)-1-(2′,2′,2′-trichloromethylcarbonylamino)cyclopenta-2-ene (**11**) (0.80 g, 3.50 mmol) in chloroform (30 mL) was added *N*-iodosuccinimide (1.18 g, 5.25 mmol), and the mixture was heated at 60 °C for 15 h. The solvent was removed in vacuo. The resulting residue was dissolved in ethyl acetate (40 mL), and the organic phase was washed with water (3 × 20 mL), dried ($MgSO_4$), and filtered. The solvent was removed in vacuo. The residue obtained, **16**, was dissolved in toluene (30 mL), and 1,8-diazabicyclo[5,4,0]undec-7-ene (0.52 mL, 3.50 mmol) was added. The reaction mixture was heated under reflux for 12 h. The reaction mixture was then cooled, and the solvent was removed in vacuo. The resulting solid **17** was dissolved in methanol (40 mL). Hydrochloric acid (2.0 M, 10 mL) was added, and reaction mixture was stirred at room temperature for 1 h. The reaction mixture was then diluted with a saturated solution of sodium hydrogen carbonate (20 mL) and extracted with ethyl acetate (3 × 40 mL). The organic layers were combined, dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by flash column chromatography (petroleum ether/diethyl ether, 1:1) gave (1*R*,5*S*)-5-(2′,2′,2′-trichloromethylcarbonylamino)-cyclopenta-2-en-1-ol (**4**) (0.53 g, 62%) as white solid: mp 111−113 °C; IR (NaCl) 3380, 2946, 1693, 1505, 1042, 822 cm^{-1}; $[\alpha]_D^{23}$ +53.7 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.05 (d, 1H *J* 6.4 Hz), 2.36 (dddd, 1H, *J* 17.2, 6.4, 4.4, 2.0 Hz), 2.90 (dddd, 1H, *J* 17.2, 6.4, 2.4, 2.0 Hz), 4.33 (pent, 1H, *J* 6.4 Hz), 4.72−4.79 (m, 1H), 5.93 (ddd, 1H, *J* 6.4, 4.4, 2.4 Hz), 6.08 (dt, 1H, *J* 6.4, 2.0 Hz), 7.66 (br s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 37.2 (CH_2), 52.4 (CH), 74.3 (CH), 92.6 (C), 131.2 (CH), 135.3 (CH), 162.0 (C); MS (CI) *m*/*z* 244 (MH^+, 20), 226 (100), 192 (31), 126 (21), 85 (21); HRMS (CI) calcd for $C_7H_9{}^{35}Cl_3NO_2$ (MH^+), 243.9699; found, 243.9695.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

NOE data for compound **4** and ^{1}H and ^{13}C NMR spectra for all key compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors are grateful to the Libyan People's Bureau, London, HEC Pakistan, and the University of Glasgow for funding.

■ REFERENCES

(1) For general reviews of the synthesis of carbocyclic nucleosides, see: (a) Crimmins, M. T. *Tetrahedron* **1998**, *54*, 9229. (b) Mathé, C.; Périgaud, C. *Eur. J. Org. Chem.* **2008**, 1489. (c) Boutureira, O.; Matheu, M. I.; Díaz, Y.; Castillón, S. *Chem. Soc. Rev.* **2013**, *42*, 5056.

(2) (a) Ghosh, A.; Ritter, A. R.; Miller, M. J. *J. Org. Chem.* **1995**, *60*, 5808. (b) Jiang, M. X.-W.; Jin, B.; Gage, J. L.; Priour, A.; Savela, G.; Miller, M. J. *J. Org. Chem.* **2006**, *71*, 4164. (c) Tardibono, L. P., Jr.; Miller, M. J.; Balzarini, J. *Tetrahedron* **2011**, *67*, 825.

(3) Huang, W.; Miller, M. J. *Tetrahedron: Asymmetry* **2008**, *19*, 2835.

(4) Yoshimitsu, T.; Ino, T.; Tanaka, T. *Org. Lett.* **2008**, *10*, 5457.

(5) Jiang, M. X.-W.; Warshakoon, N. C.; Miller, M. J. *J. Org. Chem.* **2005**, *70*, 2824.

(6) Hansel, J.-G.; O'Hogan, S.; Lensky, S.; Ritter, A. R.; Miller, M. J. *Tetrahedron Lett.* **1995**, *36*, 2913.

(7) Li, J.; Lang, F.; Ganem, B. *J. Org. Chem.* **1998**, *63*, 3403.

(8) (a) Muxworthy, J. P.; Wilkinson, J. A.; Procter, G. *Tetrahedron Lett.* **1995**, *36*, 7535. (b) Vogt, P. F.; Hansel, J.-G.; Miller, M. J. *Tetrahedron Lett.* **1997**, *38*, 2803.

(9) (a) Ramesh, N. G.; Klunder, A. J. H.; Zwanenburg, B. *Tetrahedron Lett.* **1998**, *39*, 1429. (b) Ramesh, N. G.; Klunder, A. J. H.; Zwanenburg, B. *J. Org. Chem.* **1999**, *64*, 3635.

(10) Davis, F. A.; Wu, Y. *Org. Lett.* **2004**, *6*, 1269.

(11) (a) O'Brien, P.; Towers, T. D.; Voith, M. *Tetrahedron Lett.* **1998**, *39*, 8175. (b) Oxenford, S. J.; O'Brien, P.; Shipton, M. R. *Tetrahedron Lett.* **2004**, *45*, 9053.

(12) Asami, M.; Ogawa, M.; Inoue, S. *Tetrahedron Lett.* **1999**, *40*, 1563.

(13) Dauvergne, J.; Happe, A. M.; Jadhav, V.; Justice, D.; Matos, M.-C.; McCormack, P. J.; Pitts, M. R.; Roberts, S. M.; Singh, S. K.; Snape, T. J.; Whittall, J. *Tetrahedron* **2004**, *60*, 2559.

(14) van den Nieuwendijk, A. M. C. H.; Ghisaidoobe, A. B. T.; Overkleeft, H. S.; Brussee, J.; van der Gen, A. *Tetrahedron* **2004**, *60*, 10385.

(15) Trost, B. M.; Stenkamp, D.; Pulley, S. R. *Chem.—Eur. J.* **1995**, *1*, 568.

(16) Overman, L. E.; Carpenter, N. E. In *Organic Reactions*; Overman, L. E., Ed.; Wiley: Hoboken, NJ, 2005; Vol. *66*, pp 1−107 and references therein.

(17) Blanchette, M. A.; Choy, W.; Davis, J. T.; Essenfeld, A. P.; Masumune, S.; Roush, W. R.; Sakai, T. *Tetrahedron Lett.* **1984**, *25*, 2183.

(18) (a) Swift, M. D.; Sutherland, A. *Org. Lett.* **2007**, *9*, 5239. (b) Swift, M. D.; Donaldson, A.; Sutherland, A. *Tetrahedron Lett.* **2009**, *50*, 3241. (c) Zaed, A. M.; Swift, M. D.; Sutherland, A. *Org. Biomol. Chem.* **2009**, *7*, 2678. (d) Ahmad, S.; Thomas, L. H.; Sutherland, A.

Org. Biomol. Chem. **2011**, *9*, 2801. (e) Ahmad, S.; Swift, M. D.; Farrugia, L. J.; Senn, H. M.; Sutherland, A. *Org. Biomol. Chem.* **2012**, *10*, 3937.
(19) Overman, L. E.; Owen, C. E.; Pavan, M. M.; Richards, C. J. *Org. Lett.* **2003**, *5*, 1809.
(20) Warpehoski, M. A.; Chabaud, B.; Sharpless, K. B. *J. Org. Chem.* **1982**, *47*, 2897.
(21) Rathore, R.; Saxena, N.; Chandrasekaran, S. *Synth. Commun.* **1986**, *16*, 1493.
(22) Zhao, Y.; Yeung, Y.-Y. *Org. Lett.* **2010**, *12*, 2128.
(23) Yu, J.-Q.; Corey, E. J. *Org. Lett.* **2002**, *4*, 2727.
(24) For the reduction of 4-aminocyclopenta-2-en-1-ones such as **15**, Luche conditions are required for a highly efficient and stereoselective reduction. The use of only sodium borohydride results in lower stereoselectivity and the formation of other products. See ref 9b for further details.
(25) Cardillo, G.; Orena, M.; Sandri, S. *J. Chem. Soc., Chem. Commun.* **1983**, 1489.
(26) See the Supporting Information for NOE data for compound **4**.
(27) da Zhang, Z.; Scheffold, R. *Helv. Chim. Acta* **1993**, *76*, 2602.