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Hydroxyl- Versus Amide-directed Cyclopropanation From the Allylic Position in 1-Hydroxy-4-*N*-acyl-cyclopentenes Under Modified Simmons-Smith Conditions

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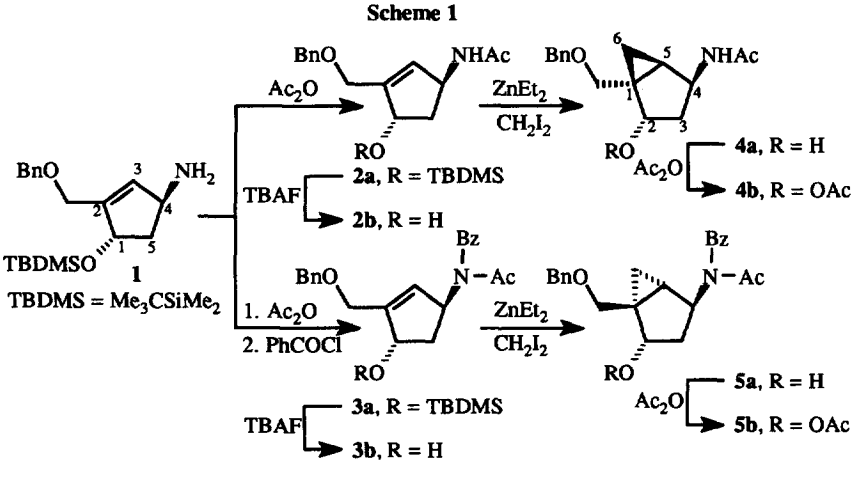
Abstract. In a functionalized cyclopentene having allylic OH and NH-acyl groups on opposite faces of the ring, the diastereoselective delivery of the incoming methylene group in the diethylzinc version of the Simmons-Smith reaction was completely directed by the NH group. The diastereoselectivity of the reaction can be reversed by complete protection of the amide.

One of the most useful features of the Simmons-Smith reaction and its modified versions is the diastereoselective delivery of the incoming methylene group by an allylic alcohol function.[1] We have successfully employed this methodology, and other hydroxyl-directed cyclopropanation reactions,[2] in the synthesis of conformationally constrained carbocyclic nucleosides built on a bicyclo[3.1.0]hexane template.[3-5] However, since many of these carbocyclic nucleoside precursors have combinations of allylic hydroxyl and amide groups simultaneously present, we investigated the differences in the stereochemical directing capacity of these two functionalities towards cyclopropanation.

The well-documented directing effect of the allylic hydroxyl group suggested that cyclopropanation of (1*S*,4*S*)-2-[(benzyloxy)methyl]-4-*N*-acetylaminocyclopent-2-enol (**2b**, Scheme 1) would provide the corresponding bicyclo[3.1.0]hexane with the cyclopropane ring below the plane of the five-member ring.

Scheme 1

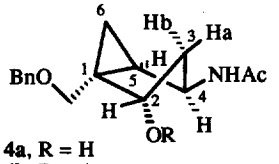


However, this was not the case, as the outcome of the cyclopropanation was absolutely controlled by the AcNH group to give **4a**. Proof that this was indeed the case was obtained by performing the reaction with the fully *N*-protected compound (**3b**), where only the allylic hydroxyl was capable of directing the delivery of the methylene group (Scheme 1). The products obtained (**4a** and **5a**) from each reaction were different, but proving their

structures was not trivial. Thanks to the fixed pseudoboat conformation characteristic of the bicyclo[3.1.0]hexane system,[6,7] and based on several X-ray structures of carbanucleosides containing this skeleton,[4,8,9] it was possible to estimate the multiplicity of key diagnostic proton signals in the ^{1}H NMR spectra of these compounds. Hence, based on the expected values of the dihedral angles shown in Chart 1, the H_2

Chart 1

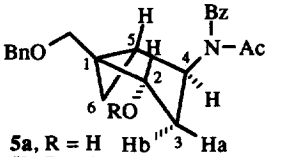
^{1}H NMR Predicted multiplicities



4a, R = H
4b, R = Ac

H_2-C_2-C_3-H_{3a} = 94
H_2-C_2-C_3-H_{3b} = -27
} H_2 (d)

H_4-C_4-C_5-H_5 = -42
H_4-C_4-C_3-H_{3a} = 27
H_4-C_4-C_3-H_{3b} = 149
} H_4 (m)



5a, R = H
5b, R = Ac

H_4-C_4-C_5-H_5 = -80
H_4-C_4-C_3-H_{3a} = 94
H_4-C_4-C_3-H_{3b} = -27
} H_4 (d)

H_2-C_2-C_3-H_{3a} = 27
H_2-C_2-C_3-H_{3b} = 149
} H_2 (dd or t)

signal for compound **4a** with the cyclopropane ring on the same side of the cyclopentane ring as the NHAc group was expected to be a doublet. On the other hand, the H_4 signal had to be a multiplet, further broadened by coupling to the NH proton. Conversely, the H_4 signal for **5a**, where delivery of the methylene occurred under the control of the OH group, should appear as a doublet, since two of the three dihedral angles approximate 90°. Finally, the H_2 signal for **5a** could appear either as a doublet of doublets, or a triplet. Analysis of the spectra for both compounds (**4a** and **5a**) was consistent with these assumptions (Table 1). However, since the two most diagnostic signals —the H_2 doublet for **4a** and the H_4 doublet for **5a**— appeared at δ 4.30 and δ 4.75, respectively, additional proof of their identity was necessary. Acetylation of the secondary alcohol in both compounds provided solid confirmation for these assignments (Table 1). In the case of **4a**, the doublet at δ 4.30 moved down-field ca. 1 ppm upon acetylation indicating that it corresponded to the H_2 proton adjacent to the OAc group in **4b**. For **5a**, the H_4 doublet at δ 4.75 remained unchanged after acetylation, whereas the H_2 triplet in **5a** revealed its identity after moving downfield 0.75 ppm following acetylation (**5b**).

In conclusion, the capacity of the allylic NH-acyl group in exerting diastereofacial control of methylene delivery under Simmons-Smith conditions prevailed over that of the hydroxyl group in this system. Such a preference makes protection of the OH function unnecessary, and reversal of the diastereoselectivity was achieved by complete protection of the amide. This methodology appears to complement nicely a published diazomethane/$Pd(OAc)_2$ protocol where cyclopropanation proceeds *anti* to the allylic NH-acyl group.[10] It must be emphasized that the definitive structural assignment of **4a,b** and **5a,b** was possible only because of the rigid nature of the bicyclo[3.1.0]hexane system. If the alternative pseudochair conformation were present, or if the

compounds were in some dynamic equilibrium between these two conformations, this analysis would not have been possible.

Table 1. ^{1}H NMR Experimental Values

Cpd.	H_2 (δ)	H_4 (δ)
4a	4.30 (d)	4.75 (m)
4b	5.32 (d)	4.73 (m)
5a	4.95 (t)	4.75 (d)
5b	5.70 (t)	4.75 (d)

Experimental

(1*S*,4*S*)-1-*O*-(*tert*-Butyldiphenylsilyl)-2-[(benzyloxy)methyl]-4-*N*-acetylaminocyclopent-2-enol (2a). A stirred ice-cold solution of **1**[11] (1.42 g, 3.10 mmol) and Et_3N (530 μL, 3.73 mmol) in dry THF (50 mL) was treated with acetic anhydride (350 μL, 3.33 mmol). The reaction was allowed to reach rt, and after 45 min it was reduced to dryness and dried overnight under vacuum. The residue was purified by silica gel flash chromatography with EtOAc (TLC, EtOAc, R_f = 0.70), and the crude solid obtained was recrystallized from benzene/hexane to give **2a** (1.27g, 82%) as a white solid, mp 122-123 °C; ^{1}H NMR ($CDCl_3$) δ 7.80-7.20 (m, 15 H, Ph), 5.62 (s, 1 H, H-3), 5.25 (br d, *J* = 8.0 Hz, 1 H, NH), 5.05 (m, 1 H, H-1), 4.95 (m, 1 H, H-4), 4.40 (s, 2 H, $PhCH_2O$), 4.05 (d, *J* = 13.4 Hz, 1 H, $PhCH_2OCHH$), 3.85 (d, *J* = 13.4 Hz, 1 H, $PhCH_2OCHH$), 2.20 (ddd, *J* = 14.1, 7.7, 3.9 Hz, 1 H, H-5a), 1.85 (s, 3 H, $NHCOCH_3$), 1.68 (ddd, *J* = 14.1, 6.8, 3.4 Hz, 1 H, H-5b), 1.05 (s, 9 H, Me_3C). Anal. Calcd for $C_{31}H_{37}NO_3Si$: C, 74.46; H, 7.52; N, 2.80. Found: C, 74.53; H, 7.48; N, 2.82.

(1*S*,4*S*)-2-[(Benzyloxy)methyl]-4-*N*-acetylaminocyclopent-2-enol (2b). A solution of **2a** (0.782 g, 1.57 mmol) in dry THF (75 mL) was treated with TBAF (1 M in THF, 6.3 mL) and stirred overnight at rt. The solution was concentrated under reduced pressure and the residue was purified by silica gel flash chromatography (TLC, EtOAc, R_f = 0.13) using a step gradient of $CHCl_3$, 2% MeOH/$CHCl_3$, and finally 5% MeOH/$CHCl_3$ to give **2b** (0.419 g, 100%) as a solid; mp 123-124 °C (benzene); ^{1}H NMR ($CDCl_3$) δ 7.40-7.20 (m, 5 H, Ph), 5.75 (s, 1 H, H-3), 5.50 (br s, 1 H, NH), 5.15 (m, 1 H, H-1), 4.92 (m, 1 H, H-4), 4.52 (s, 2 H, $PhCH_2O$), 4.15 (s, 2 H, $PhCH_2OCH_2$), 2.26 (ddd, *J* = 14.3, 7.6, 3.0 Hz, 1 H, H-5a), 2.14 (br s, 1 H, OH), 2.02-1.90 (m, 4 H, H-5b, $NHCOCH_3$). Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 69.05; H, 7.39; N, 5.36.

(1*S*,4*S*)-2-[(Benzyloxy)methyl]-4-(*N*-benzoyl,*N*-acetyl)-aminocyclopent-2-enol (3b). To a stirred solution of **2a** (0.125 g, 0.25 mmol) in dry CH_3CN (2 mL) was added Et_3N (200 μL, 1.5 mmol) and a catalytic amount of DMAP. Benzoyl chloride (90 μL, 0.75 mmol) was added and stirring was continued for 16 h. The reaction mixture was concentrated under reduced pressure and the residue was purified by silica gel flash chromatography using a step gradient of EtOAc/hexane from 0 to 10% to give 0.151 g of an orange viscous oil that was dissolved in dry CH_3CN (15 mL) and refluxed with Et_3N•3HF (98%, 0.35 mL, 2.16 mmol) for 20 min. The reaction mixture was concentrated under reduced pressure, and the residue was purified by silica gel flash chromatography [TLC, hexane/EtOAc, 2:1, R_f = 0.60 (**3a**), R_f = 0.06 (**3b**)] using a step gradient of hexanes, 25% EtOAc/hexanes, and 50% EtOAc/hexanes to give 0.077 g (84%) of **3b** as a foam; ^{1}H NMR ($CDCl_3$) δ 7.70-7.20 (m, 10 H, Ph), 5.70 (s, 1 H, H-3), 5.54 (m, 1 H, H-1), 5.05 (m, 1 H, H-4), 4.50 (AB q, *J* = 11.83 Hz, 2 H, $PhCH_2O$), 4.19 (d, *J* = 12.7 Hz, 2 H, $PhCH_2OCH_2$), 2.55 (ddd, *J* = 14.1, 7.4, 4.5 Hz, 1 H, H-5a), 2.39 (d, *J* = 3.7 Hz, 1 H, OH), 2.20 (ddd, *J* = 14.1, 8.5, 2.9 Hz, 1 H, H-5b), 2.00 (s, 3 H, $NHCOCH_3$). Anal. Calcd for $C_{22}H_{23}NO_4$•$0.5H_2O$: C, 70.56; H, 6.19; N, 3.74. Found: C, 70.16; H, 6.22; N, 3.61.

(1*S*,2*S*,4*S*,5*R*)-1-[(Benzyloxy)methyl]-2-hydroxy-4-*N*-acetylaminobicylo[3.1.0]hexane (4a). To a rt solution of **2b** (0.026 g, 0.1 mmol) in dry CH_2Cl_2 (2.5 mL) was added 1 mL of Et_2Zn (1 M in hexanes) with vigorous stirring. After 10 min the cloudy mixture was cooled over ice, and CH_2I_2 (80 µL dissolved in 1 mL of CH_2Cl_2, 1 mmol) was added dropwise. A precipitate formed, and the reaction was allowed to warm up gradually to rt overnight. After the addition of brine (4 mL), the mixture was extracted with $CHCl_3$ (10 mL), and the organic layer was washed successively with ca. 4 mL of 3N HCl, satd Na_2SO_3, and brine. The organic solution was dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was purified by silica gel flash chromatography with 5% MeOH/$CHCl_3$ (TLC, hexane/EtOAc, 1:1, R_f = 0.20) to give 0.014 g (50%) of **4a** as a foam; ^{1}H NMR ($CDCl_3$) δ 7.40-7.20 (m, 5 H, Ph), 5.50 (br d, 1 H, NH), 4.75 (m, 1 H, H-4), 4.50 (s, 2 H, $PhCH_2O$), 4.30 (d, *J* = 4.8 Hz, 1 H, H-2), 3.70 (d, *J* = 10.5 Hz, 1 H, $PhCH_2OCHH$), 3.52 (d, *J* = 10.5 Hz, 1 H, $PhCH_2OCHH$), 2.60 (br s, 1 H, OH), 2.05 (m, 1 H, H-3a), 1.92 (s, 3 H, CH_3), 1.70 (m, 1 H, H-3b), 1.10 (m, 1 H, H-5), 0.55 (m, 1 H, H-6a), 0.45 (m, 1 H, H-6b). Anal. Calcd for $C_{16}H_{21}NO_3 \cdot 0.35H_2O$: C, 68.23; H, 7.75; N, 4.97. Found: C, 68.30; H, 7.69; N, 4.83.

(1*S*,2*S*,4*S*,5*R*)-1-[(Benzyloxy)methyl]-2-*O*-acetyl-4-*N*-acetylaminobicylo[3.1.0]hexane (4b). A stirred solution of **4a** (0.012 g, 0.044 mmol) in dry THF (1 mL) was treated with acetic anhydride (11 µL, 0.1 mmol), Et_3N (15 µL) and catalytic amounts of DMAP for 1 h. The solution was concentrated under reduced pressure and the residue was purified by silica gel flash chromatography with EtOAc (TLC, hexane/EtOAc, 1:1, R_f = 0.60) to give **4b** (0.010 g, 71%) as a white solid, mp 125-128 °C (CH_2Cl_2/hexanes); NMR ($CDCl_3$) δ 7.40-7.20 (m, 5 H, Ph), 5.51 (br d, 1 H, NH), 5.32 (d, *J* = 4.9 Hz, 1 H, H-2), 4.73 (m, 1 H, H-4), 4.45 (AB q, *J* = 12.1 Hz, 2 H, $PhCH_2O$), 3.80 (d, *J* = 10.0 Hz, 1 H, $PhCH_2OCHH$), 3.05 (d, *J* = 10.0 Hz, 1 H, $PhCH_2OCHH$), 2.05 (m, 1 H, H-3a), 1.92 and 1.94 (singlets, 3 H, CH_3), 1.65 (m, 1 H, H-3b), 1.25 (m, 1 H, H-5), 0.70 (m, 2 H, H-6). Anal. Calcd for $C_{18}H_{23}NO_4 \cdot 0.1H_2O$: C, 67.73; H, 7.33; N, 4.39. Found: C, 67.49; H, 7.26; N, 4.28.

(1*R*,2*S*,4*S*,5*S*)-1-[(Benzyloxy)methyl]-2-*O*-acetyl-4-(*N*-benzoyl,*N*-acetyl)aminobicyclo-[3.1.0]hexane (5b). This reaction was performed essentially in the same manner as that for **4a** starting with **3b** (0.021 g). However, after chromatography, ^{1}H NMR analysis indicated that the desired compound (**5a**) was contaminated with ca. 25% of starting material which showed indentical mobility on TLC. Separation of these products was possible after acetylation, which was conducted in the same manner as for **4b**. After silica gel flash chromatography [TLC, hexane/EtOAc, 1:1, R_f = 0.80 (**5b**), R_f = 0.30 (**5a**)] using a step gradient of 25% EtOAc/hexanes to 50% EtOAc/hexanes, compound **5b** (0.006 g, 50%) was obtained as a foam; NMR ($CDCl_3$) δ 7.70-7.40 (m, 5 H, Ph), 7.30-7.20 (m, 5 H, Ph), 5.70 (t, *J* = 7.8 Hz, 1 H, H-2); 4.75 (d, *J* = 7.9 Hz, 1 H, H-4), 4.50 (s, 2 H, $PhCH_2O$), 3.92 (d, *J* = 9.9 Hz, 1 H, $PhCH_2OCHH$), 3.45 (d, *J* = 9.9 Hz, 1 H, $PhCH_2OCHH$), 2.50 (dd, *J* = 15.3, 8.8 Hz, 1 H, H-3a), 1.98 (singlets, 6 H, CH_3), 1.75 (m, 1 H, H-3b), 1.35 (dd, *J* = 8.5, 4.2 Hz, 1 H, H-5), 0.95 (dd, *J* = 8.5, 5.6Hz, 1 H, H-6a), 0.70 (distorted t, 1 H, H-6b). Anal. Calcd for $C_{25}H_{27}NO_5 \cdot 0.2H_2O$: C, 70.64; H, 6.50; N, 3.29. Found: C, 70.56; H, 6.49; N, 3.22.

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11. This compound was prepared in a similar manner as related carbocyclic amines (see ref. 4), and its synthesis will be reported elsewhere.

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