Unexpected One-Pot Epoxy Sulfone−Enaminone Transformation. Synthesis of 5a-Carba-β-mannopyranosylamine

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The nucleophilic ring opening of 1,2-epoxy sulfones is a well-established protocol for the preparation of α-substituted ketones via nucleophilic addition with a concomitant desulfonation process (Scheme 1).[1]

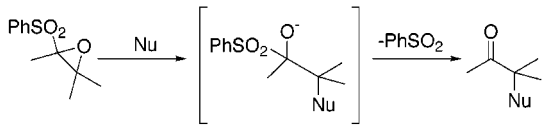
In a previous paper concerning the total synthesis of (±)-validamine and its C_1 and C_2 stereoisomers[2] we speculated that the ring opening of both epoxy sulfones **A** and **B** by an azide ion[3] would give azido ketones **C** and **D**, respectively, direct precursors of the target compounds (Scheme 2).

In our hands the reaction of sulfones **A** and **B** (P = Bn) with sodium azide (DMF, 100 °C) resulted in the recovering of starting material. However, when sulfones **1a** and **1b** were treated under the same conditions, the enaminone **2a** was obtained in 95% and 85% isolated yields, respectively, as the only product, as established by its spectral properties, especially from the distinctive IR and ^{13}C NMR data (see experimental and complementary material) (Scheme 3). The exceptional ease with which the persilyl epoxides **1** react with azide is possibly due to anchimeric assistance[4] provided by the silyl group at C-3.

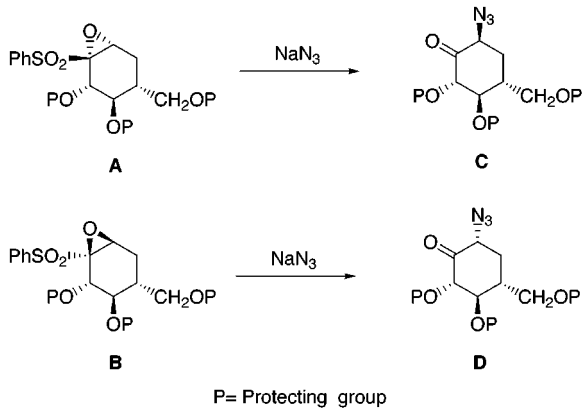
In addition to the well-known synthetic utility of the enaminone moiety in the field of heterocyclic synthesis,[5] we envisaged the possibility of using this unexpected process for the synthesis of aminocarbasugars with well-established stereochemistry.[6] As an example, we have developed a short synthesis of 5a-carba-β-mannopyranosylamine, a C_1 and C_2 diastereomer of validamine[7] (Scheme 4).

Thus, reaction of **2a** with Ac_2O/pyridine followed by catalytic hydrogenation of the resulting *N*-acetylenaminone **2b** afforded amido ketone **3** (46% isolated yield, together with 22% of recovered starting material). Reduction of **3** ($NaBH_4$, 100%) gave rise to the protected aminocarbasugar **4**. Treatment of **4** with tetrabutylammonium fluoride yielded the *N*-acetyl-5a-carba-β-mannopyranosylamine, which was fully characterized as the pentaacetate[2] (70% two-step yield).

Scheme 1



Scheme 2



The transformation of the *N*-acetylenaminone **2b** into compound **3** with concomitant TBS group migration should be produced through the related enolic form to give the most stable stereoisomer with all substituents in equatorial position[8] (Scheme 5).

Regarding the reaction path for the one-pot transformation of the epoxy sulfones **1** into compound **2a**, we propose as a reasonable hypothesis the sequence indicated in the Scheme 6. The attack of the nucleophilic agent on the epoxy sulfones should occur in the normal fashion to give the first intermediate **6**, which would undergo desulfonation affording **7**. Evolution of nitrogen in **7** should give nitrene **8**, which, after a 1,2 hydrogen shift,[9] would afford intermediate **9**. This intermediate

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(8) For some studies concerning the migration of silyl protecting groups, see the following. (a) Ogilvie, K. K.; Beaucage, S. L.; Schifman, A. L.; Theriault, N. Y.; Sadana, K. L. *Can. J. Chem.* **1978**, *56*, 2768−2780. (b) Jones, S. S.; Reese, C. B. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2762−2764.

(9) For a discussion of the generation of nitrenes from azides and 1,2 hydrogen shifts in these systems, see the following. Moody, Ch. J.; Whitham, G. H. In *Reactive Intermediates*; Oxford Science Publications: Oxford, U.K., 1995; Chapter 4, pp 52−53, 61−62.

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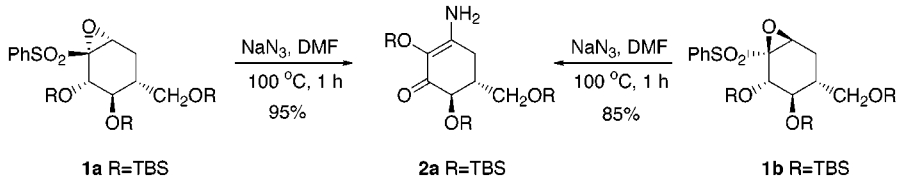
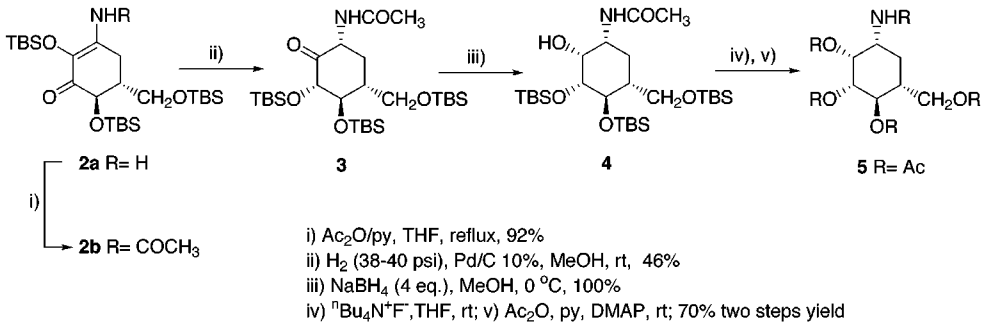
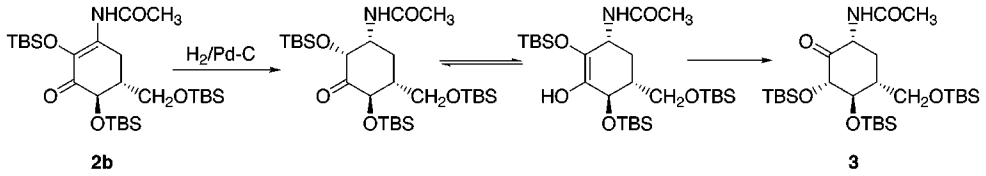
Scheme 3



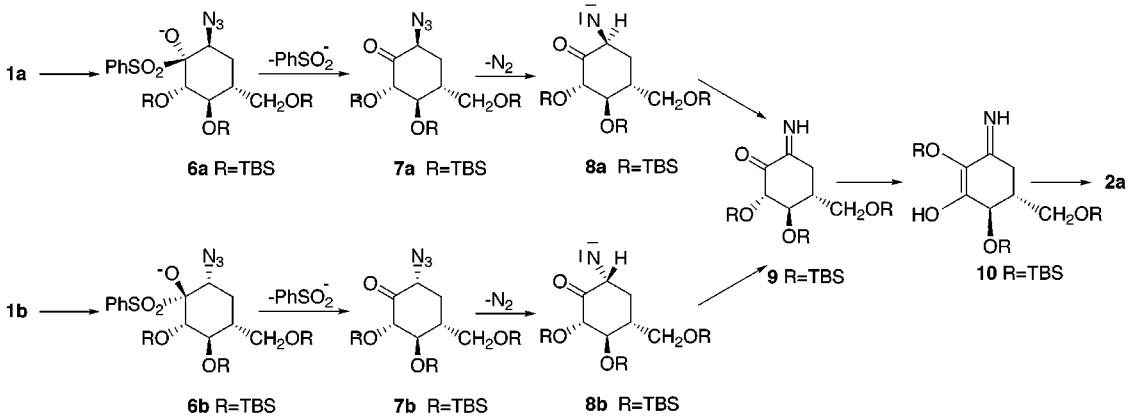
Scheme 4



Scheme 5



Scheme 6



would evolve to **10** via 1,2-silyl migration of its enolic form. After the workup of the reaction crude, two sequences of keto−enol and imine−enamine tautomerism should give rise to the final observed product **2a**. This proposed mechanism is supported by the observation that both stereoisomeric epoxides **1a** and **1b** were transformed into **2a** under the same reaction conditions and in almost the same isolated yields.[10]

In summary a new transformation epoxy, sulfone−enaminone, via treatment with NaN_3 and restricted to the use of silyl protecting groups has been described. This transformation allowed us to develop a short synthesis of 5a-carba-β-mannopyranosylamine.

Experimental Section

General. Reagents and solvents were handled by using standard syringe techniques. Tetrahydrofuran was distilled from sodium and benzophenone, 2,6-lutidine, and *N*,*N*-dimethylformamide from CaH_2. The remaining solvents and chemicals were commercial and used as received. ^{1}H NMR and ^{13}C NMR were recorded at 200 or 300 MHz. Chemical shifts (δ) are reported in ppm from internal $(CH_3)_4Si$. Flash chromatography was performed using 230−400 mesh silica gel. Analytical TLC was carried out on silica gel plates. Melting points are uncorrected. Elemental analyses were performed at the Universidad Complutense de Madrid.

Preparation of (1*S,2*S**,3*R**,4*R**,6*S**)-2,3-Bis((*tert*-butyldimethylsilyl)oxy)-4-(((*tert*-butyldimethylsilyl)oxy)methyl)-1-(phenylsulfonyl)-7-oxabicyclo[4.1.0]heptane (1b).** To a solution of (1*S**,2*S**,3*R**,4*R**,6*S**)-3-((*tert*-butyldimethylsilyl)oxy)-4-(((*tert*-butyldimethylsilyl)oxy)methyl)-1-(phenylsulfonyl)-7-oxabicyclo[4.1.0]heptan-2-ol[2] (65 mg, 0.12 mmol) in anhydrous CH_2Cl_2 (0.12 mL) were added dropwise dry 2,6-lutidine (0.09 mL, 0.74 mmol) and *tert*-butyldimethylsilyl triflate (0.11 mL, 0.49 mmol). After the solution was stirred for 3 days at room temperature, the aqueous layer was separated and extracted with CH_2Cl_2 and the combined organics were washed with cold sodium bicarbonate and dried over Na_2SO_4. The solvent was removed in vacuo, and the crude was purified by column chromatography (silica gel, hexane/EtOAc 20:1) to afford **1b** as

(10) We thank one of the reviewers for suggesting the experiment starting from **1b** in order to clarify the proposed mechanism.

a yellow oil (79 mg, 100%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ −0.10 (s, 3 H), −0.03 (s, 3 H), 0.04 (s, 3 H), 0.05 (s, 3 H), 0.16 (s, 3 H), 0.32 (s, 3 H), 0.67 (s, 9 H), 0.89 (s, 9 H), 0.96 (s, 9 H), 1.84−1.90 (m, 1 H), 2.01 (ddd, 1 H, J = 14.7, 9.8, 1.5 Hz), 2.23 (ddd, 1 H, J = 14.7, 6.4, 2.9 Hz), 3.45−3.59 (m, 3 H), 3.77 (bs, 1 H), 4.25 (d, 1 H, J = 2.0 Hz), 7.54 (t, 2 H, J = 6.8 Hz), 7.65 (t, 1 H, J = 7.3 Hz), 7.92 (d, 2 H, J = 7.3 Hz). ^{13}C NMR ($CDCl_3$, 50 MHz): δ −5.4, −5.3, −5.1, −4.7, −4.6, −3.4, 17.6, 18.1, 18.4, 25.5, 26.0, 29.7, 41.4, 56.1, 65.6, 71.5, 72.1, 72.5, 128.8, 129.6, 133.9, 136.1. IR (KBr): ν 2957, 2930, 1472, 1325, 1103, 1084 cm^{-1}. Anal. Calcd for $C_{31}H_{58}O_6SSi_3$: C, 57.94; H, 9.03. Found: C, 58.04; H, 9.13.

Preparation of (5*R,6*R**)-3-Amino-2,6-bis((*tert*-butyldimethylsilyl)oxy)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-cyclohex-2-en-1-one (2a).** To a suspension of NaN_3 (58 mg, 0.90 mmol) in DMF (0.9 mL) was slowly added a solution of **1a**[2] (115 mg, 0.18 mmol) in DMF (0.9 mL). The mixture was stirred at 100 °C for an hour and quenched with water. The whole was extracted with Et_2O/CH_2Cl_2 (7:3), the organic extracts were dried ($MgSO_4$), and the solvent was eliminated under reduced pressure. The crude was purified by column chromatography on silica gel using a 10:1 mixture of hexanes−EtOAc as eluant, yielding 88 mg (95%) of **2a** as a white solid.

From **1b**, **2a** was also obtained under the same reaction conditions (78 mg, 85%): mp 134−135 °C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.06 (s, 6 H), 0.08 (s, 3 H), 0.19 (s, 3 H), 0.21 (s, 3 H), 0.23 (s, 3 H), 0.90 (s, 18 H), 0.96 (s, 9 H), 2.11−2.19 (m, 1 H), 2.45 (d, 2 H, J = 7.3 Hz), 3.69 (dd, 1 H, J = 9.8, 6.4 Hz), 3.78 (dd, 1 H, J = 9.8, 3.9 Hz), 3.99 (d, 1 H, J = 10.3 Hz), 4.33 (bs, 2 H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ −5.6, −5.5, −5.4, −4.2, −3.8, −3.6, 18.3, 18.6, 18.8, 25.9, 26.1, 26.3, 28.2, 43.8, 63.3, 73.8, 126.3, 146.0, 188.1. IR (KBr): ν 3500, 3390, 1660, 1610 cm^{-1}. Anal. Calcd for $C_{25}H_{53}NO_4Si_3$: C, 58.25; H, 10.29; N, 2.72. Found: C, 58.14; H, 10.15; N, 2.52.

Preparation of (5*R,6*R**)-3-Acetamido-2,6-bis((*tert*-butyldimethylsilyl)oxy)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)cyclohex-2-en-1-one (2b).** To a solution of **2a** (102 mg, 0.20 mmol) in 0.2 mL of THF was added 0.43 mL of acetic anhydride and 0.004 mL of pyridine. This mixture was heated slowly until starting material dissolved, and then it was refluxed for 4 h. The solvent was removed in vacuo, and the residue was purified by column chromatography on silica gel using a 20:1 mixture of hexanes−EtOAc as eluant to yield **2b** (102 mg, 92%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.06 (s, 3 H), 0.08 (s, 6 H), 0.20 (s, 3 H), 0.21 (s, 3 H), 0.24 (s, 3 H), 0.91 (s, 9 H), 0.92 (s, 9 H), 0.97 (s, 9 H), 2.05−2.19 (m, 1 H), 2.12 (s, 3 H), 2.95 (dd, 1 H, J = 19.3, 10.5 Hz), 3.38 (dd, 1 H, J = 19.3, 5.1 Hz), 3.70 (dd, 1 H, J = 10.0, 3.2 Hz), 3.82 (dd, 1 H, J = 10.2, 5.1 Hz), 4.12 (d, 1 H, J = 11.3), 7.71 (bs, 1 H). ^{13}C NMR ($CDCl_3$, 50 MHz): δ −5.5, −5.5, −5.3, −4.1, −3.9, −3.9, 18.3, 18.6, 18.7, 25.0, 26.0, 26.1, 26.3, 29.7, 44.3, 62.6, 73.7, 130.9, 137.9, 168.1, 192.1. IR (KBr): ν 3402, 1713, 1682, 1624 cm^{-1}. Anal. Calcd for $C_{27}H_{55}NO_5Si_3$: C, 58.14; H, 9.87; N, 2.51. Found: C, 58.57; H, 9.67; N, 2.31.

Preparation of (2*S,3*R**,4*R**,6*R**)-6-Acetamido-2,3-bis((*tert*-butyldimethylsilyl)oxy)-4-(((*tert*-butyldimethylsilyl)-oxy)methyl)cyclohexanone (3).** A solution of **2b** (41 mg, 0.07 mmol) and 10% Pd/C (87 mg, 0.08 mmol) in MeOH (3.8 mL) was hydrogenated (38−40 psi) for 4 h at room temperature. The reaction mixture was filtered through a short path of SiO_2 with MeOH. This crude was purified by column chromatography (silica gel, hexane/EtOAc 10:1) to afford **3** as a yellow oil (18 mg, 46%) together with 22% of the recovered starting material: ^{1}H NMR ($CDCl_3$, 300 MHz): δ −0.04 (s, 3 H), 0.03 (s, 6 H), 0.07 (s, 3 H), 0.09 (s, 3 H), 0.13 (s, 3 H), 0.87 (s, 9 H), 0.92 (s, 9 H), 0.97 (s, 9 H), 1.14 (c, 1 H, J = 12.7 Hz), 1.94−1.99 (m, 1 H), 2.04 (s, 3 H), 2.49 (ddd, 1 H, J = 10.3, 5.9, 3.4 Hz), 3.56 (t, 1 H, J = 8.8 Hz), 3.66 (dd, 1 H, J = 9.8, 4.9 Hz), 3.73 (dd, 1 H, J = 9.8, 3.4 Hz), 4.21 (d, 1 H, J = 8.8 Hz), 4.57 (dt, 1 H, J = 12.2, 5.9), 6.38 (d, 1 H, J = 6.4). ^{13}C NMR ($CDCl_3$, 50 MHz): δ −5.5, −5.3, −4.6, −4.5, −3.5, −2.5, 18.1, 18.3, 18.6, 23.3, 26.0, 26.2, 26.3, 29.7, 43.2, 55.4, 62.4, 76.2, 82.1, 169.7, 204.5. IR (KBr): ν 3416, 1711, 1670 cm^{-1}. Anal. Calcd for $C_{27}H_{57}NO_5Si_3$: C, 57.96; H, 10.20; N, 2.50. Found: C, 58.16; H, 10.35; N, 2.60.

Preparation of (1*R,2*R**,3*R**,4*R**,6*R**)-6-Acetamido-2,3-bis((*tert*-butyldimethylsilyl)oxy)-4-(((*tert*-butyldimethyl-silyl)oxy)methyl)cyclohexanol (4).** A stirred solution of **3** (20 mg, 0.04 mmol) in MeOH (0.4 mL) was cooled to 0 °C in an ice bath. To the cooled mixture was added sodium borohydride (6 mg, 0.16 mmol). The mixture was stirred for 30 min at 0 °C before water was added. The solvent was eliminated under reduced pressure, yielding 20 mg (100%) of **4** as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.03 (s, 3 H), 0.04 (s, 3 H), 0.12 (s, 3 H), 0.14 (s, 3 H), 0.16 (s, 3 H), 0.17 (s, 3 H), 0.89 (s, 9 H), 0.91 (s, 9 H), 0.95 (s, 9 H), 1.59−1.66 (m, 1 H), 1.93 (s, 3 H), 1.95−1.98 (m, 1 H), 2.13−2.27 (m, 1 H), 3.55 (dd, 1 H, J = 9.8, 5.9 Hz), 3.62−3.65 (m, 1 H), 3.92 (t, 2 H, J = 9.8 Hz), 3.96−4.06 (m, 1 H), 4.08 (bs, 1 H), 4.11−4.18 (m, 1 H), 6.48 (d, 1 H, J = 8.3). ^{13}C NMR ($CDCl_3$, 50 MHz): δ −5.4, −5.3, −5.0, −4.8, −4.7, 22.5, 22.7, 23.5, 25.7, 25.9, 25.9, 29.4, 31.9, 43.0, 49.2, 64.9, 71.1, 72.5, 73.7, 169.1. IR (KBr): ν 3369, 1655 cm^{-1}. Anal. Calcd for $C_{27}H_{59}NO_5Si_3$: C, 57.75; H, 10.52; N, 2.50. Found: C, 57.95; H, 10.68; N, 2.41.

Preparation of Penta-*N*,*O*-acetyl-5a-carba-β-mannopyranosylamine (5). To a solution of **4** (50 mg, 0.09 mmol) in THF (0.6 mL) was added tetrabutylammonium fluoride (0.54 mL, 0.54 mmol). The mixture was stirred for 1 h at room temperature. After that time, the reaction mixture was quenched with distilled water and concentrated under reduced pressure. The residue was acetylated with acetic anhydride (0.4 mL), pyridine (0.4 mL), and DMAP (ca. 2 mg) for 3 days. The solvent was removed in vacuo, and the crude was purified by column chromatography on silica gel using EtOAc as eluant to give **5** as a white solid (24 mg, 70% overall yield). Its spectral features were identical to those reported in the literature.[2]

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Supporting Information Available: ^{1}H NMR and ^{13}C NMR spectra for compounds **1b**, **2a**,**b**, **3**, and **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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