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Ti-Mediated Synthesis of Aminocyclopropyl-Substituted Carbohydrates

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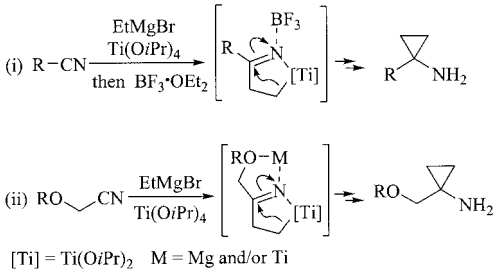
Carbohydrates bearing aminocyclopropyl moieties were conveniently prepared from the corresponding nitriles by titanium-mediated addition of Grignard reagents. A wide range of protective groups are tolerated.

Introduction

Incorporation of cyclopropane units onto carbohydrates has recently been shown to be of great interest, due to the combination of the reactivity of cyclopropanes with the optical purity and functional density associated with sugars.[1,2] The classical methods used in the formation of cyclopropanated carbohydrates are the Simmons–Smith reaction,[3] dihalocarbene cycloaddition[3c,4] and diazoester cyclopropanation[5] of unsaturated carbohydrates, with most of these works having been devoted to the cyclopropanation of glycal derivatives.

Whereas cyclopropylamines are crucial moieties in a variety of biologically active compounds,[6,7] there are only a few examples of carbohydrates bearing aminocyclopropyl units.[8] Recently, synthetic approaches towards monosaccharide-containing cyclopropylamines[9] and spirocyclic cyclopropylamines[10] have been described. These multi-step approaches typically involve diazoester cyclopropanation, followed by the Curtius rearrangement.

We have recently reported a convenient synthesis of cyclopropylamines from nitriles and Grignard reagents in the presence of titanium isopropoxide (Scheme 1).[11,12] The contraction of the intermediate metallacycle thus formed is usually achieved by the addition of $BF_3{\cdot}OEt_2$ [Scheme 1 (i)].[11a] In a particular case, that of α-alkoxynitriles, however, the spontaneous ring contraction of the metallacycle occurred without addition of a Lewis acid [Scheme 1 (ii)].[11b] The chelation of the nitrogen atom by a metal salt is believed to be responsible for the ring contraction.



Scheme 1. Synthesis of cyclopropylamines from nitriles.

Since nitriles can be incorporated into a carbohydrate skeleton in various ways,[13] the latter procedure should be convenient for the preparation of new carbohydrate derivatives incorporating aminocyclopropyl groups. In this context, we attempted to evaluate the scope and the limitations of this method by targeting several Grignard reagents and sugar-derived nitriles as substrates and by focusing on the tolerance of protecting groups.

Results and Discussion

Open-chain or cyclic nitriles **1**–**4** feature a range of representative carbohydrate protecting groups such as acetals, ethers and esters (Figure 1).

Compounds **1**–**3** were prepared from the known oximes **5**–**7** (Table 1).[14] Initial attempts to convert the oxime **5** into the nitrile **1** under the conditions described by Vasella et al. (PPh_3, CBr_4)[15] failed. Under these conditions, the removal of the labile 4,5-*O*-isopropylidene protecting group occurred, due to the effect of HBr formed in situ. We have found that the dehydration can be achieved in higher yield by use of methanesulfonyl chloride in pyridine (Entry 2).[16] Accordingly, treatment of D-*arabino*-aldoxime **6** with pivaloyl chloride as the dehydrating agent gave nitrile **2** in quantitative yield (Entry 3). The nitrile **3** has been prepared by

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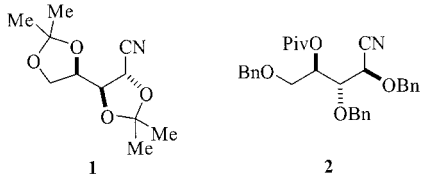

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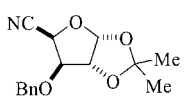

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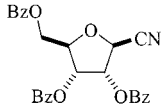

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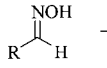
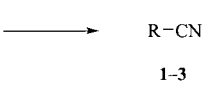
Figure 1. Nitriles **1**–**4**.

dehydration of the corresponding aldoxime **7** with ruthenium salts.[17] We performed the same transformation in high yield by employing the conditions used for the preparation of **1** (Entry 4). Finally, the known nitrile **4** was prepared in one step from commercial 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-D-ribofuranose by the described procedure.[18]

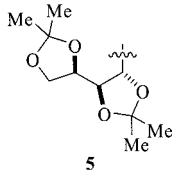
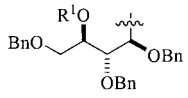
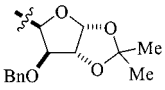
Table 1. Synthesis of nitriles **1**–**3** from the corresponding oximes.



5–**7**

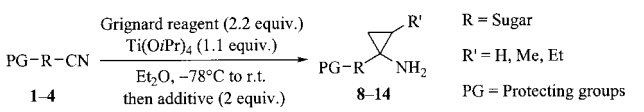


1–**3**

Entry	R	Conditions	Nitrile	Yield [%]
1	 **5**	PPh_3, CBr_4	**1**	22
2		MsCl pyridine		53
3	 **6** (R^1 = H)	PivCl pyridine	**2** (R^1 = Piv)	99
4	 **7**	MsCl pyridine	**3**	91

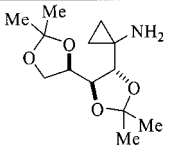
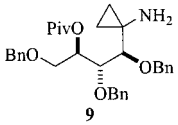
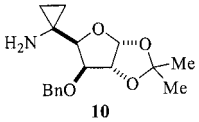
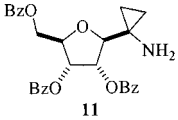
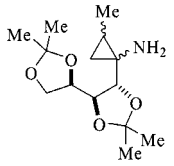
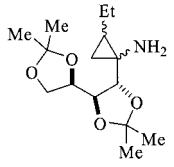
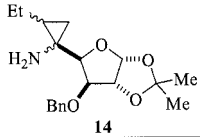
Nitrile **1** was used as a model substrate to check the optimal conditions for the cyclopropanation reaction (Table 2). Ethylmagnesium bromide was added at room temperature to a solution of **1** and Ti(O*i*Pr)$_4$ in Et_2O. As there is an oxygen atom in the α-position relative to the nitrile group, the subsequent addition of BF_3·OEt_2 was avoided. Unfortunately, cyclopropylamine **8** was obtained only in low yield (32%) among other unidentified products. Further assays clearly demonstrated that the amount of cyclopropylamine was increased by adding the Grignard reagent at a lower temperature, after which the reaction mixture was warmed to room temperature. The addition of EtMgBr at 0 °C or –78 °C gave 50% or 57% yields, respectively, of the desired product (Table 2, Entry 1). The addition of BF_3·OEt_2 did not improve the yield, as had been expected. When the pivaloyl-protected nitrile **2** was treated under the above conditions, the cyclopropylamine **9** was obtained in good yield (Entry 2). Remarkably, neither the benzyl protective groups, nor the pivaloate ester group were affected during the process.

Table 2. Preparation of cyclopropylamines **8**–**14** from nitriles **1**–**4**.



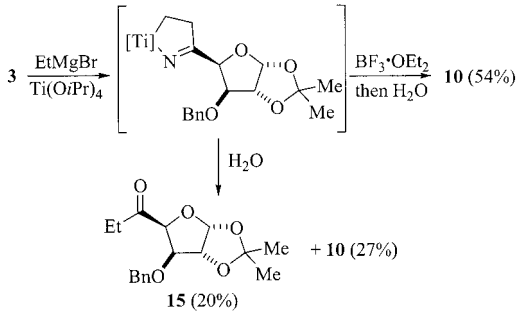
1–**4** — Grignard reagent (2.2 equiv.), Ti(O*i*Pr)$_4$ (1.1 equiv.), Et_2O, –78°C to r.t., then additive (2 equiv.) — **8**–**14**

R = Sugar; R' = H, Me, Et; PG = Protecting groups

Entry	Nitrile	Grignard reagent	Additive	Product	Yield[a] [%]
1	**1**	EtMgBr	–	 **8**	57
2	**2**	EtMgBr	–	 **9**	62
3	**3**	EtMgBr	–	 **10**	27
4	**3**	EtMgBr	BF_3·OEt_2		54
5	**4**	EtMgBr	BF_3·OEt_2	 **11**	55
6	**1**	*i*PrMgBr	–	 **12**	59 (51:21:17:11)
7	**1**	*n*BuMgBr	–	 **13**	63 (45:22:22:11)
8	**3**	*n*BuMgBr	BF_3·OEt_2	 **14**	50 (40:26:22:12)

[a] Isolated yields; the diastereoisomeric ratios are indicated in parentheses.

Preliminary assays conducted on nitriles **3** afforded a low yield (27%) of the corresponding cyclopropylamine **10** (Entry 3), under the conditions used for **1** and **2**. The major side-product was the ketone **15**, arising from the hydrolysis of the five-membered titanacycle intermediate (Scheme 2). In this case, the rigid cyclic system might prevent the neighbouring assistance of the α-alkoxy group and thus preclude an efficient spontaneous ring contraction occurring with acyclic compounds. Fortunately, addition of BF_3·OEt_2 increased the yield of **10** to 54% without noticeable degradation (Entry 4). Similarly, nitrile **4** was converted into **11** in 55% yield (Entry 5).



Scheme 2. Formation of the side-product **15**.

Other substituted cyclopropanes can also be obtained by employing higher Grignard reagents (Entries 6–8). Thus, treatment of the nitrile **1** with *i*PrMgBr or *n*BuMgBr in place of ethylmagnesium bromide gave the corresponding cyclopropylamines **12** and **13**, respectively, in good yields (Entries 6 and 7). In each case a mixture of the four possible diastereomers was obtained. Low diastereoselectivity was already observed when achiral nitriles were treated with *n*BuMgBr.[11b] Here, the sugar moiety was not able to induce a significant diastereoselection. The use of the more rigid nitrile **3** did not increase the diastereoselectivity of the reaction (Entry 8). The four stereoisomers of **12**–**14** were separated only as mixtures of two pairs of diastereomers (see Exp. Sect.), and so the stereochemistry on the cyclopropane moiety has not been elucidated.

Conclusions

We have shown that the titanium-mediated synthesis of cyclopropylamines from nitriles can be applied to polyfunctional compounds such as carbohydrate analogues. A wide range of protecting groups is tolerated, including acetals, esters or ethers. Work to study the properties of these cyclopropane-substituted carbohydrates and to synthesize new carbohydrate-derived cyclopropylamines is in progress in our laboratory.

Experimental Section

General Remarks: All reactions were performed under argon. Diethyl ether was distilled from sodium/benzophenone ketyl before use. Ti(O*i*Pr)$_4$ was used as received. Grignard reagents were titrated in THF with menthol in the presence of orthophenanthroline. Merck silica gel (F254, 0.2 mm) was used for TLC plates, with detection being carried out by spraying with an alcoholic solution of phosphomolybdic acid, followed by heating. Flash column chromatography was performed on silica gel (Merck 9385, 40–63 μm, Kieselgel 60). IR spectra were recorded with an IR™ plus MIDAC spectrophotometer. NMR spectra were recorded with a Bruker AC 250 spectrometer (250 MHz for ^{1}H, 62.5 MHz for ^{13}C) or a Bruker AC 500 (500 MHz for ^{1}H) instrument when indicated. Chemical shifts are expressed in ppm from TMS (δ = 0 ppm) for ^{1}H and from $CDCl_3$ (δ = 77.00 ppm) for ^{13}C as internal standards. Coupling constants are in Hz and splitting pattern abbreviations are: br, broad; s, singlet; d, doublet; t, triplet; q, quadruplet; m, multiplet. Optical rotations were determined with a Perkin–Elmer Model 241 polarimeter in the specified solvents. Mass spectra were recorded with a ThermoFinnigan Trace MS spectrometer. High-resolution mass spectra (HRMS) were performed with a Q-TOF Micro micromass positive ESI (CV = 30 V).

2,3:4,5-Di-*O*-isopropylidene-D-xylononitrile (1): A solution of the aldoxime **5**[14a] (0.964 g, 3.9 mmol) in pyridine (5 mL) was added at 0 °C to a solution of MsCl (1.93 mL, 25 mmol) in pyridine (5 mL). After the mixture had been stirred at room temp. for 3 h, cold water was added and the solution was extracted twice with ethyl acetate. The combined organic layers were dried ($MgSO_4$) and concentrated to give a yellow oil, which was purified by flash chromatography on silica gel with petroleum ether/ethyl acetate (7:3). The nitrile **1** was obtained as a white solid (0.473 g, 53%). $[\alpha]_D^{20}$ = –22.6 (*c* = 2.2, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.32 (s, 3 H), 1.45 (s, 3 H), 1.48 (s, 3 H), 1.50 (s, 3 H), 3.89 (dd, *J* = 5.5, 8.9 Hz, 1 H), 4.11 (dd, *J* = 6.9, 8.9 Hz, 1 H), 4.36 (m, 1 H), 4.50 (dd, *J* = 3.9, 6.5 Hz, 1 H), 4.65 (d, *J* = 6.5 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 25.1, 25.2, 26.5, 26.7, 64.7, 65.3, 74.1, 80.2, 110.8, 113.8, 118.3 ppm. IR (neat): $\tilde{\nu}$ = 2992, 2244, 1456, 1384, 1371 cm^{-1}. HRMS (ESI): calcd. for $C_{11}H_{17}NO_4Na$ [*M* + Na]$^+$: *m*/*z* = 250.1055; found 250.1049.

2,3,5-Tri-*O*-benzyl-4-*O*-pivaloyl-D-arabinononitrile (2): The oxime **6**[14b] (1.5 g, 3.44 mmol) afforded the nitrile **2** as a colourless oil (1.70 g, 98%) by a procedure analogous to that employed for the synthesis of **1**, but with use of PivCl (2.46 mL, 20 mmol) instead of MsCl. $[\alpha]_D^{20}$ = –58.5 (*c* = 0.43, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.10 (s, 9 H), 3.65 (d, *J* = 3.7 Hz, 2 H), 4.06 (dd, *J* = 7.3, 3.2 Hz, 1 H), 4.24 (d, *J* = 3.7 Hz, 1 H), 4.40 (s, 2 H), 4.44 (d, *J* = 10.8 Hz, 1 H), 4.62 (d, *J* = 10.8 Hz, 1 H), 4.80 (d, *J* = 10.8 Hz, 2 H), 5.14 (td, *J* = 7.3, 3.7 Hz, 1 H), 7.25–7.35 (m, 15 H) ppm. ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 27.3, 40.2, 67.8, 67.9, 71.0, 73.0, 73.8, 75.6, 77.9, 116.8, 127.7–128.7 (15 C), 135.3, 137.1, 137.7, 173.9 ppm. IR (neat): $\tilde{\nu}$ = 3032, 2970, 1732, 1455 cm^{-1}. HRMS (ESI): calcd. for $C_{31}H_{35}NO_5Na$ [*M* + Na]$^+$: *m*/*z* = 524.2413; found 524.2418.

3-*O*-Benzyl-1,2-*O*-isopropylidene-α-D-xylofuranurononitrile (3): The procedure described for the synthesis of **1** was used with the oxime **7**[14c] (0.545 g, 1.86 mmol), to afford the nitrile **3** as a colourless oil (0.462 g, 91%). $[\alpha]_D^{20}$ = –14.2 (*c* = 1.07, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 1.32 (s, 3 H), 1.48 (s, 3 H), 4.15 (d, *J* = 3.4 Hz, 1 H), 4.62 (d, *J* = 3.4 Hz, 1 H), 4.77 (s, 2 H), 4.88 (d, *J* = 3.4 Hz, 1 H), 6.00 (d, *J* = 3.4 Hz, 1 H), 7.30–7.42 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 26.6, 27.4, 69.8, 73.3, 81.9, 82.5, 106.1, 113.5, 115.2, 128.5, 128.8, 129.1, 136.7 ppm. IR (neat): $\tilde{\nu}$ = 2990, 2258, 1455, 1377 cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{17}NO_4Na$ [*M* + Na]$^+$: *m*/*z* = 298.1055; found 298.1046.

General Experimental Procedure for the Synthesis of Cyclopropylamines 8–14: The Grignard reagent (1.1 mL, 2.2 mmol, 2 M in Et_2O) was added under argon at –78 °C to a solution of the nitrile **1**–**4** (1 mmol) and Ti(O*i*Pr)$_4$ (0.33 mL, 1.1 mmol) in Et_2O (10 mL). The solution was slowly warmed to room temperature during 1 h and was then stirred at room temp. for 30 min. At this stage, BF_3·OEt_2 (0.25 mL, 2 mmol) could be added (see Table 2), and stirring was continued for 30 min. Water (1 mL) was added, followed by 10% aq. HCl (10 mL) and Et_2O (20 mL). A 10% aq. NaOH solution was added to the resulting clear mixture until the pH became basic. The product was extracted with Et_2O (2 × 20 mL). The combined organic extracts were dried with $MgSO_4$. After evaporation of the solvent, the product was purified by flash chromatography on silica gel (Et_2O/Et_3N, 98:2).

(1*S*)-1-*C*-(1-Aminocyclopropyl)-1,2:3,4-di-*O*-isopropylidene-D-threitol (8): Yellow oil (0.146 g, 57%). R_f = 0.26 (diethyl ether/NEt_3, 98:2). $[\alpha]_D^{20}$ = –7.3 (*c* = 0.99, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz): δ = 0.53 (ddd, *J* = 9.8, 6.0, 4.3 Hz, 1 H), 0.63 (ddd, *J* = 9.8, 6.0, 3.7 Hz, 1 H), 0.69 (ddd, *J* = 9.2, 5.7, 4.3 Hz, 1 H), 0.75 (ddd, *J* = 9.2, 5.7, 3.7 Hz, 1 H), 1.39 (s, 3 H), 1.43 (s, 3 H), 1.45 (s, 3 H), 1.49 (s, 3 H), 1.60 (brs, 2 H, NH_2), 3.41 (d, *J* = 8.1 Hz, 1 H), 3.93 (t, *J* = 8.1 Hz, 1 H), 4.03 (dd, *J* = 8.2, 3.8 Hz, 1 H), 4.08 (dd, *J* = 8.2, 6.6 Hz, 1 H), 4.14 (ddd, *J* = 8.1, 6.6, 3.8 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 11.4, 14.6, 26.1, 26.6, 27.3, 27.8, 32.7, 66.5, 75.7, 77.1, 84.0, 109.1, 110.0 ppm. IR (neat): $\tilde{\nu}$ = 3368, 2986, 2927, 1597, 1456, 1375, 1158, 1071 cm^{-1}. HRMS (ESI): calcd. for $C_{13}H_{24}NO_4$ $[M + H]^+$: *m*/*z* = 258.1705; found 258.1711.

(1*R*)-1-*C*-(1-Aminocyclopropyl)-1,2,4-tri-*O*-benzyl-3-*O*-pivaloyl-D-erythritol (9): Colourless oil (0.329 g, 62%). R_f = 0.14 (diethyl ether/NEt_3, 98:2). $[\alpha]_D^{20}$ = –0.7 (*c* = 2.03, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz): δ = 0.42 (m, 1 H), 0.50 (m, 1 H), 0.74 (m, 2 H), 1.21 (s, 9 H), 1.80 (brs, 2 H, NH_2), 2.85 (d, *J* = 6.2 Hz, 1 H), 3.83 (d, *J* = 5.0 Hz, 2 H), 3.98 (dd, *J* = 6.2, 3.1 Hz, 1 H), 4.45 (d, *J* = 10.7 Hz, 1 H), 4.47 (d, *J* = 10.7 Hz, 1 H), 4.67 (d, *J* = 11.1 Hz, 1 H), 4.70 (d, *J* = 11.1 Hz, 1 H), 4.74 (d, *J* = 11.0 Hz, 1 H), 4.76 (d, *J* = 11.0 Hz, 1 H), 5.37 (td, *J* = 5.0, 3.1 Hz, 1 H) ppm. ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 11.3, 16.5, 27.6, 34.5, 39.3, 68.9, 72.9, 73.7, 74.8, 75.9, 83.2, 85.3, 128.1–128.9 (15 C), 138.5, 138.6, 138.9, 178.7 ppm. IR (neat): $\tilde{\nu}$ = 3374, 3064, 3031, 2972, 2926, 2870, 1722, 1455, 1284, 1160, 1096 cm^{-1}. HRMS (ESI): calcd. for $C_{33}H_{42}NO_5$ $[M + H]^+$: *m*/*z* = 532.3063; found 532.3077.

(4*R*)-4-*C*-(1-Aminocyclopropyl)-3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-threofuranose (10): Colourless oil (0.165 g, 54%). R_f = 0.43 (diethyl ether/NEt_3, 98:2). $[\alpha]_D^{20}$ = –84.3 (*c* = 0.79, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz): δ = 0.41 (ddd, *J* = 9.7, 5.7, 4.2 Hz, 1 H), 0.56 (ddd, *J* = 9.7, 5.9, 4.2 Hz, 1 H), 0.69 (ddd, *J* = 9.8, 5.7, 4.2 Hz, 1 H), 0.73 (ddd, *J* = 9.8, 5.9, 4.2 Hz, 1 H), 1.33 (s, 3 H), 1.45 (s, 3 H), 2.07 (brs, 2 H, NH_2), 3.52 (d, *J* = 3.6 Hz, 1 H), 3.97 (d, *J* = 3.6 Hz, 2 H), 4.53 (d, *J* = 11.9 Hz, 1 H), 4.62 (d, *J* = 3.9 Hz, 1 H), 4.75 (d, *J* = 11.9 Hz, 1 H), 6.01 (d, *J* = 3.9 Hz), 7.20–7.30 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 11.4, 15.4, 26.7, 27.3, 32.8, 72.4, 82.6, 84.5, 85.2, 105.6, 111.8, 128.3 (2 C), 128.7, 129.0 (2 C), 137.6 ppm. IR (neat): $\tilde{\nu}$ = 3377, 2986, 2930, 2872, 1599, 1455, 1378, 1216, 1075, 1031 cm^{-1}. HRMS (ESI): calcd. for $C_{17}H_{24}NO_4$ $[M + H]^+$: *m*/*z* = 306.1705; found 306.1700.

1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)cyclopropylamine (11): Yellow oil (0.276 g, 55%). R_f = 0.12 (diethyl ether/NEt_3, 98:2). $[\alpha]_D^{20}$ = +7.3 (*c* = 3.9, $CHCl_3$). ^1H NMR ($CDCl_3$, 500 MHz): δ = 0.67 (m, 3 H), 0.78 (m, 1 H), 1.91 (brs, 2 H, NH_2), 3.70 (m, 1 H), 4.61 (m, 1 H), 4.64 (m, 1 H), 4.82 (m, 1 H), 5.80 (m, 2 H), 7.42–7.43 (m, 4 H), 7.49–7.51 (m, 2 H), 7.52–7.54 (m, 3 H), 7.97–8.02 (m, 4 H), 8.14–8.16 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 11.1, 14.4, 33.5, 64.6, 72.4, 73.6, 80.2, 88.0, 128.9–130.1 (15 C), 133.8 (3 C), 165.8, 165.9, 166.7 ppm. IR (neat): $\tilde{\nu}$ = 3385, 3064, 3009, 2954, 1717, 1602, 1452, 1315, 1268, 1123 cm^{-1}. HRMS (ESI): calcd. for $C_{29}H_{28}NO_7$ $[M + H]^+$: *m*/*z* = 502.1866; found 502.1863.

(1*S*)-1-*C*-(1-Amino-2-methylcyclopropyl)-1,2:3,4-di-*O*-isopropylidene-D-threitol (12): Treatment of the nitrile **1** (227 mg, 1 mmol) with *i*PrMgBr (1.1 mL, 2.2 mmol, 2 M in Et_2O) in the presence of $Ti(OiPr)_4$ (0.33 mL, 1.1 mmol) afforded **12a**–**b** (50 mg, 18%) as a 60:40 mixture of isomers and **12c**–**d** (110 mg, 41%) as a 78:32 mixture of isomers.

Isomer 12a: R_f = 0.42 (diethyl ether/NEt_3, 98:2). ^1H NMR ($CDCl_3$, 500 MHz): δ = 0.16 (t, *J* = 5.5 Hz, 1 H), 0.79–0.93 (m, 2 H), 1.14 (d, *J* = 6.4 Hz, 3 H), 1.39 (s, 3 H), 1.42 (s, 3 H), 1.43 (s, 3 H), 1.48 (s, 3 H), 1.79 (brs, 2 H, NH_2), 3.60 (d, *J* = 8.1 Hz, 1 H), 3.89 (t, *J* = 8.1 Hz, 1 H), 4.03–4.18 (m, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 14.2, 19.5, 21.2, 26.1, 26.6, 27.3, 27.7, 36.0, 66.6, 75.8, 76.8, 80.1, 109.1, 110.0 ppm.

Isomer 12b: R_f = 0.42 (diethyl ether/NEt_3, 98:2). ^1H NMR ($CDCl_3$, 500 MHz): δ = 0.41 (dd, *J* = 6.0, 5.7 Hz, 1 H), 0.79–0.93 (m, 2 H), 1.14 (d, *J* = 6.4 Hz, 3 H), 1.39 (s, 3 H), 1.42 (s, 3 H), 1.43 (s, 3 H), 1.48 (s, 3 H), 1.79 (brs, 2 H, NH_2), 3.84 (d, *J* = 8.4 Hz, 1 H), 3.98 (t, *J* = 8.4 Hz, 1 H), 4.03–4.18 (m, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 14.8, 20.3, 22.5, 26.2, 26.5, 27.1, 27.8, 35.6, 66.6, 73.8, 75.4, 81.9, 108.8, 109.7 ppm. IR (neat) of **12a** and **12b**: $\tilde{\nu}$ = 2984, 2929, 1454, 1375, 1070 cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{26}NO_4$ $[M + H]^+$: *m*/*z* = 272.1862; found 272.1866.

Isomer 12c: R_f = 0.12 (diethyl ether/NEt_3, 98:2). ^1H NMR ($CDCl_3$, 500 MHz): δ = 0.18 (t, *J* = 5.5 Hz, 1 H), 0.65 (dd, *J* = 9.4, 5.5 Hz, 1 H), 0.74–0.89 (m, 1 H), 1.17 (d, *J* = 6.0 Hz, 3 H), 1.38 (s, 3 H), 1.41 (s, 3 H), 1.43 (s, 3 H), 1.47 (s, 3 H), 1.77 (brs, 2 H, NH_2), 3.29 (d, *J* = 8.4 Hz, 1 H), 3.84 (t, *J* = 8.4 Hz, 1 Hz), 4.03–4.15 (m, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 13.1, 17.7, 18.5, 26.1, 26.6, 27.4, 27.7, 36.0, 66.6, 75.9, 77.0, 85.5, 109.0, 109.9 ppm.

Isomer 12d: R_f = 0.12 (diethyl ether/NEt_3, 98:2). ^1H NMR ($CDCl_3$, 500 MHz): δ = 0.32 (t, *J* = 4.6 Hz, 1 H), 0.74–0.89 (m, 2 H), 1.17 (d, *J* = 6.0 Hz, 3 H), 1.38 (s, 3 H), 1.41 (s, 3 H), 1.43 (s, 3 H), 1.47 (s, 3 H), 1.77 (brs, 2 H, NH_2), 3.32 (d, *J* = 8.0 Hz, 1 H), 3.91 (t, *J* = 8.0 Hz, 1 H), 3.98 (dd, *J* = 8.4, 4.0 Hz, 1 H), 4.03–4.15 (m, 2 H) ppm. ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 12.4, 16.1, 20.7, 26.1, 26.6, 27.4, 27.7, 36.0, 66.2, 76.0, 77.2, 85.3, 109.0, 109.9 ppm. IR (neat) of **12c** and **12d**: $\tilde{\nu}$ = 2987, 2932, 1373, 1249, 1218, 1159, 1069 cm^{-1}. HRMS (ESI): calcd. for $C_{14}H_{26}NO_4$ $[M + H]^+$: *m*/*z* = 272.1862; found 272.1867.

(1*S*)-1-*C*-(1-Amino-2-ethylcyclopropyl)-1,2:3,4-di-*O*-isopropylidene-D-threitol (13): Treatment of the nitrile **1** (227 mg, 1 mmol) with *n*BuMgBr (1.1 mL, 2.2 mmol, 2 M in Et_2O) in the presence of $Ti(OiPr)_4$ (0.33 mL, 1.1 mmol) afforded **13a**–**b** (60 mg, 21%) as a 66:34 mixture of isomers and **13c**–**d** (120 mg, 42%) as a 68:32 mixture of isomers.

Isomer 13a: R_f = 0.59 (diethyl ether/NEt_3 98:2). ^1H NMR ($CDCl_3$, 500 MHz): δ = 0.22 (t, *J* = 5.4 Hz, 1 H), 0.63 (dd, *J* = 9.1, 5.4 Hz, 1 H), 0.65–0.75 (m, 1 H), 1.00 (t, *J* = 7.2 Hz, 3 H), 1.38 (s, 3 H), 1.41 (s, 3 H), 1.43 (s, 3 H), 1.46 (s, 3 H), 1.49–1.59 (m, 2 H), 3.33 (d, *J* = 8.1 Hz, 1 H), 3.90 (t, *J* = 8.1 Hz, 1 H), 4.01–4.15 (m, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 14.5, 15.7, 16.4, 21.7, 26.1, 26.6, 27.4, 27.8, 36.3, 66.6, 76.0, 77.0, 85.4, 109.0, 109.9 ppm.

Isomer 13b: R_f = 0.59 (diethyl ether/NEt_3, 98:2). ^1H NMR ($CDCl_3$, 500 MHz): δ = 0.37 (t, *J* = 5.2 Hz, 1 H), 0.65–0.75 (m, 2 H), 1.00 (t, *J* = 7.2 Hz, 3 H), 1.39 (s, 3 H), 1.41 (s, 3 H), 1.43 (s, 3 H), 1.48 (s, 3 H), 1.49–1.59 (m, 2 H), 3.36 (d, *J* = 8.4 Hz, 1 H), 3.97 (dd, *J* = 8.4, 3.7 Hz, 1 H), 4.01–4.15 (m, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 14.5, 14.9, 16.4, 21.7, 26.1, 26.6, 27.4, 27.8, 36.3, 66.3, 75.7, 77.0, 85.1, 109.0, 109.9 ppm. IR (neat) of **13a** and **13b**: $\tilde{\nu}$ = 2986, 2931, 1375, 1219, 1157, 1069 cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{28}NO_4$ $[M + H]^+$: *m*/*z* = 286.2018; found 286.2029.

Isomer 13c: R_f = 0.26 (diethyl ether/NEt_3, 98:2). ^1H NMR ($CDCl_3$, 500 MHz): δ = 0.17 (t, *J* = 5.5 Hz, 1 H), 0.79 (dd, *J* = 9.1, 5.5 Hz, 1 H), 0.82–0.92 (m, 1 H), 1.02 (t, *J* = 7.4 Hz, 3 H), 1.38 (s, 3 H), 1.41 (s, 3 H), 1.44 (s, 3 H), 1.48 (s, 3 H), 1.50–1.57 (m, 2 H), 1.92 (brs, 2 H, NH_2), 3.60 (d, *J* = 8.3 Hz, 1 H), 3.90 (t, *J* = 8.3 Hz, 1 H), 4.03–4.15 (m, 3 H) ppm. ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 14.2, 17.9, 22.9, 26.2, 26.6, 27.3, 27.7, 29.3, 36.0, 66.6, 75.7, 76.8, 80.1, 109.0, 110.0 ppm.

Isomer 13d: R_f = 0.26 (diethyl ether/NEt_3, 98:2). ^1H NMR ($CDCl_3$, 500 MHz): δ = 0.39 (t, J = 5.3 Hz, 1 H), 0.82–0.92 (m, 2 H), 1.02 (t, J = 7.4 Hz, 3 H), 1.38 (s, 3 H), 1.41 (s, 3 H), 1.44 (s, 3 H), 1.48 (s, 3 H), 1.50–1.57 (m, 2 H), 1.92 (br s, 2 H, NH_2), 3.83 (d, J = 8.4 Hz, 1 H), 3.98 (t, J = 8.4 Hz, 1 H), 4.03–4.15 (m, 3 H) ppm; ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 14.5, 21.1, 22.6, 26.2, 26.5, 27.1, 27.8, 30.7, 35.7, 66.6, 73.9, 75.4, 82.1, 108.7, 109.7 ppm. IR (neat) of **13c** and **13d**: $\tilde{\nu}$ = 2986, 2931, 1370, 1220, 1158, 1070 cm^{-1}. HRMS (ESI): calcd. for $C_{15}H_{28}NO_4$ $[M + H]^+$: m/z = 286.2018; found 286.2011.

(4*R*)-4-*C*-(1-Amino-2-ethylcyclopropyl)-3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-threofuranose (14): Treatment of the nitrile **3** (275 mg, 1 mmol) with *n*BuMgBr (1.1 mL, 2.2 mmol, 2 M in Et_2O) in the presence of Ti(O*i*Pr)$_4$ (0.33 mL, 1.1 mmol) afforded **14a–b** (56 mg, 17%) as a 65:35 mixture of isomers and **14c–d** (111 mg, 33%) as a 61:39 mixture of isomers.

Isomer 14a: R_f = 0.57 (diethyl ether/NEt_3, 98:2). ^1H NMR ($CDCl_3$, 500 MHz): δ = 0.33 (t, J = 5.3 Hz, 1 H), 0.80–0.95 (m, 2 H), 1.00 (t, J = 7.2 Hz, 3 H), 1.24–1.33 (m, 2 H), 1.34 (s, 3 H), 1.44 (s, 3 H), 2.49 (br s, 2 H, NH_2), 3.67 (d, J = 3.6 Hz, 1 H), 3.94 (d, J = 3.8 Hz, 1 H), 4.53 (d, J = 11.7 Hz, 1 H), 4.61 (d, J = 3.7 Hz, 1 H), 4.74 (d, J = 12.0 Hz, 1 H), 6.01 (d, J = 4.0 Hz, 1 H), 7.28–7.39 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 14.1, 18.6, 22.8, 26.9, 27.5, 28.6, 36.6, 72.5, 80.6, 82.6, 85.3, 105.6, 111.9, 128.4, 128.4, 128.5, 129.0 (2 C), 137.6 ppm.

Isomer 14b: R_f = 0.57 (diethyl ether/NEt_3, 98:2). ^1H NMR ($CDCl_3$, 500 MHz): δ = 0.51 (t, J = 5.0 Hz, 1 H), 0.80–0.95 (m, 2 H), 1.00 (t, J = 7.2 Hz, 3 H), 1.24–1.33 (m, 2 H), 1.34 (s, 3 H), 1.44 (s, 3 H), 2.49 (br s, 2 H, NH_2), 3.68 (d, J = 3.7 Hz, 1 H), 3.97 (d, J = 3.7 Hz, 1 H), 4.50 (d, J = 11.7 Hz, 1 H), 4.64 (d, J = 3.7 Hz, 1 H), 4.75 (d, J = 12.0 Hz, 1 H), 6.02 (d, J = 4.0 Hz, 1 H), 7.28–7.39 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 14.6, 21.7, 23.0, 26.7, 27.3, 28.2, 36.2, 72.4, 83.0, 83.7, 84.5, 104.9, 111.8, 128.4 (2 C), 128.6, 129.0 (2C), 137.6 ppm. IR (neat) of **14a** and **14b**: $\tilde{\nu}$ = 2960, 2930, 2870, 1455, 1374, 1216, 1165, 1075, 1029 cm^{-1}. HRMS (ESI): calcd. for $C_{19}H_{28}NO_4$ $[M + H]^+$: m/z = 334.2018; found 334.2031.

Isomer 14c: R_f = 0.10 (diethyl ether/NEt_3, 98:2). ^1H NMR ($CDCl_3$, 500 MHz): δ = 0.36 (t, J = 5.2 Hz, 1 H), 0.60–0.74 (m, 1 H), 0.94–1.01 (m, 1 H), 1.21 (t, J = 7.0 Hz, 3 H), 1.32 (s, 3 H), 1.45 (s, 3 H), 1.51–1.62 (m, 2 H), 2.24 (br s, 2 H, NH_2), 3.95 (d, J = 3.6 Hz, 1 H), 4.51 (d, J = 11.7 Hz, 1 H), 4.53 (d, J = 11.7 Hz, 1 H), 4.59 (d, J = 3.7 Hz, 1 H), 4.72 (d, J = 11.9 Hz, 1 H), 5.99 (d, J = 3.7 Hz, 1 H), 7.27–7.39 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 14.1, 16.7, 21.7, 26.7, 27.3, 28.1, 36.5, 72.4, 82.5, 84.3, 86.8, 105.6, 111.9, 127.3, 128.0, 128.2, 128.4, 128.5, 137.6 ppm.

Isomer 14d: R_f = 0.10 (diethyl ether/NEt_3, 98:2). ^1H NMR ($CDCl_3$, 500 MHz): δ = 0.51 (dd, J = 9.4, 5.0 Hz, 1 H), 0.60–0.74 (m, 1 H), 0.94–1.01 (m, 1 H), 1.21 (t, J = 7.0 Hz, 3 H), 1.32 (s, 3 H), 1.45 (s, 3 H), 1.51–1.62 (m, 2 H), 2.24 (br s, 2 H, NH_2), 3.44 (d, J = 3.7 Hz, 1 H), 3.99 (d, J = 3.7 Hz, 1 H), 4.60 (d, J = 3.7 Hz, 1 H), 4.71 (d, J = 11.9 Hz, 1 H), 4.73 (d, J = 11.9 Hz, 1 H), 6.00 (d, J = 3.7 Hz, 1 H), 7.27–7.39 (m, 5 H) ppm. ^{13}C NMR ($CDCl_3$, 62.5 MHz): δ = 14.0, 20.8, 21.1, 26.7, 27.3, 28.6, 36.3, 72.6, 82.3, 85.0, 86.4, 105.4, 111.8, 127.3 (2 C), 128.4 (3 C), 137.6 ppm. IR (neat) of **14c** and **14d**: $\tilde{\nu}$ = 2960, 2931, 2870, 1689, 1455, 1377, 1216, 1165 cm^{-1}. HRMS (ESI): calcd. for $C_{19}H_{28}NO_4$ $[M + H]^+$: m/z = 334.2018; found 334.2009.

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