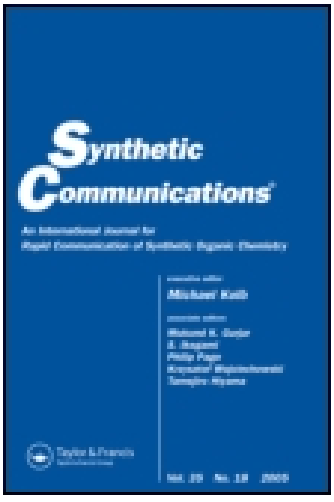

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New Route to *N*-Alkylated *trans*-Pyrrolidine Diols from 2,2,3,3-Tetramethoxybutane-Protected Dimethyl Tartrate

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Abstract: A short synthesis of some *trans*-pyrrolidine diols is described starting from (2*R*,3*R*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl[1,4]dioxane-2,3-dicarboxylic acid dimethyl ester **3**. The key step was the occurrence of a tandem azide reduction/cyclization sequence on mono-azide intermediate **6** upon catalytic hydrogenation. This method afforded both (3*R*,4*R*)-(+)-1-benzyl-3,4-pyrrolidinediol **9a** and (3*R*,4*R*)-(+)-1-allyl-3,4-pyrrolidinediol **9b** starting from **3**. Cytotoxicity tests were performed on compounds **9a** and **9b** using the brine shrimp bioassay, but each showed no activity, as were anti-oxidant tests using the stable free radical diphenylpicrylhydrazyl (DPPH).

Keywords: Alkylation, azidation, cyclization, dihydroxylated indolizidines

INTRODUCTION

trans-Dihydroxylated indolizidine alkaloids are a very important group of compounds from the pharmacological and medical point of view, given that in general they exhibit strong biological activities. Compounds such as (+)-lentiginosine, with potent amyloglucosidase inhibitory activity,[1] (−)-anisomycin[2,3] and (−)-deacetylanisomycin,[4] which show strong and selective

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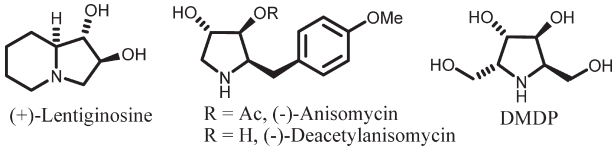
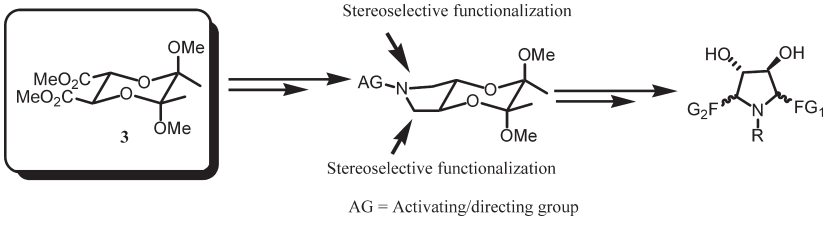


Figure 1. Biologically active *trans*-dihydroxylated indolizidine alkaloids.

activity against pathogenic protozoa and fungi, and 2,5-dideoxy-2,5-imino-D-mannitol (DMDP), which is an important glycosidase inhibitor[5] (Fig. 1), contain this structure as their core unit.

Although some strategies exist[6] for the construction of the *trans*-pyrrolidine 3,4-diol unit, perhaps the most efficient way of accessing this important structural unit is via tartaric acid, as it possesses the requisite relative stereochemistry. There is the classical method of Nagel,[7] which uses (+)-tartaric acid and involves a very cumbersome imide reduction to give the pyrrolidine in modest yields, or a similar method devised by Marson and Melling,[8] which involves condensing (3*R*,4*R*)-diacetoxysuccinic anhydride with amines followed by $NaBH_4/I_2$ reduction of the imide to the corresponding di-acetoxy pyrrolidine intermediate, followed by a two-stage hydrolytic workup to give *trans*-pyrrolidine 3,4-diols in only modest yields. Then there are less direct methods with increased functional group manipulation, for example, the method of McCaig et al.[9] starting from diethyl tartrate and involving expensive methoxymethyl (MOM) protection of the hydroxyl groups or the multistep method of Iida et al.[10] starting from 4-*O*-benzyl-2,3-*O*-bis(methoxymethyl)-*L*-threose.

Over the past 10 years, (2*R*,3*R*,5*R*,6*R*)-5,6-dimethoxy-5,6-dimethyl[1,4]-dioxane-2,3-dicarboxylic acid dimethyl ester **3**, which was originally unexpectedly prepared and used to form a 2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino) butane (DIOP) analog[11] and thereafter used successfully as a chiral template for the synthesis of a variety of biologically active targets,[12] something that had been predicted previously.[13] In our quest to obtain biologically active *trans*-dihydroxylated indolizidine alkaloids, particularly with functionality in the 2 and 5



Scheme 1. Our approach to substituted *trans*-dihydroxylated indolizidine alkaloids.

positions, we have considered the use of this building block as a starting point, particularly for the translation of the natural chirality of (+)-tartaric acid via so-called chirality memory effects[14] (Scheme 1).

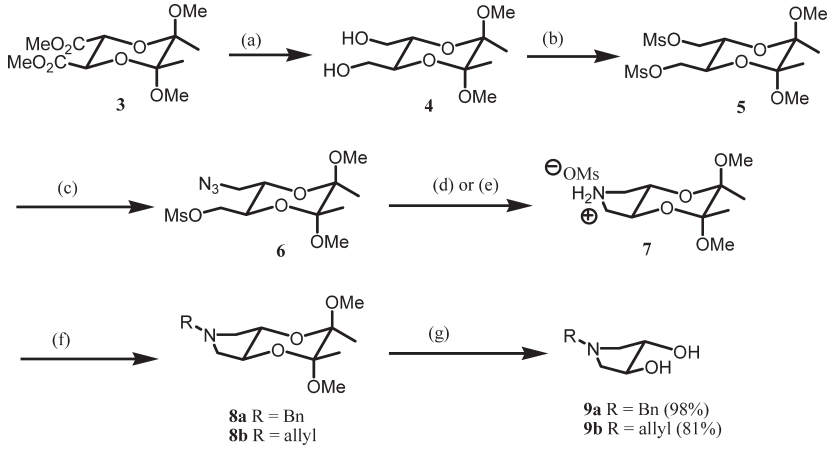
In this article we describe our preliminary results in the development of this strategy.

RESULTS AND DISCUSSION

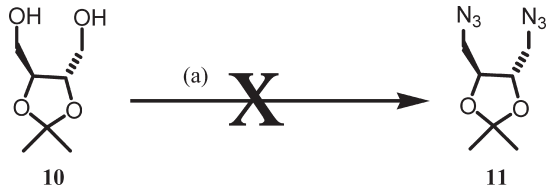
The strategy we selected involved converting the bis-acetal diester **3** to the corresponding dimesylate **5** because of the efficiency of these two steps (Scheme 2).[15] The azidation step predominantly gave the monoazide **6** with some of a known diazide derivative.[16] After some more experimentation, we optimized the yield of **6** to 51%.

To increase the yield, we also looked at using the bulky azide transfer reagent, diphenyl phosphoryl azide,[17] but this predominantly gave the starting material. The method of Thompson et al.,[18] which can directly substitute hydroxyl groups with azide groups, was evaluated. To probe this method, we carried out a model reaction with (+)-2,3-di-*O*-isopropylidene-*L*-threitol **10**,[19] but the reaction failed to give the desired diazide **11** (Scheme 3).

We then used catalytic hydrogenation to reduce the azide to the corresponding amine, but instead of getting the amine-mesylate **12**, gratifyingly we obtained the bicyclic chiral ammonium salt **7**, with the pyrollidine ring



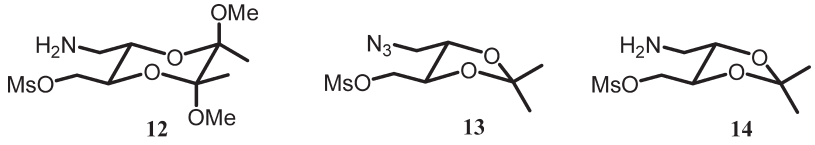
Scheme 2. (a) Ref. [15]; (b) Ref. [15]; (c) NaN_3, CH_3CN, reflux, 41% (with 24% diazide product[16]; (d) 5% Pd/C, H_2(g) (balloon), EtOAc (79%); (e) PPh_3, H_2O, THF (90%); (f) NEt_3 (4 eq), $PhCH_2Br$ (1.5 eq.; yield = 38%) or allylbromide (1.5 eq.; yield = 30%), DMF, 60 °C; (g) 6 M HCl, MeOH, 80 °C.



10 11

Scheme 3. (a) $(PhO)_2PON_3$, DBU, THF, rt.

in place. However, we have previously observed that other protected systems do not undergo this facile spontaneous cyclization in which the monoazide acetonide **13** was transformed exclusively to the corresponding cyclic monoamine acetonide **14**.[20] The spontaneous cyclization observed in the former case is most probably an indication of negligible or acceptable strain in the bicyclic pyrrolidine **7**.



12 13 14

As an alternative approach, we investigated the Staudinger azide reduction;[21] however, this also gave the cyclic product **7** in excellent yield.

The ammonium salt **7** was then alkylated with benzylamine and allyl bromide (these reactions were not optimized) to give the corresponding tertiary amines **8a** and **8b**, which were then hydrolyzed to give the corresponding *trans*-pyrrolidinediols, **9a** ($[\alpha]_D^{22} = +22.5$ [$c = 0.63$, MeOH], lit.[22] $[\alpha]_D^{20} = +33.6 \pm 3$ [$c = 1.05$, MeOH]) and **9b** ($[\alpha]_D^{23} = +11.9$ [$c = 0.31$, MeOH]), respectively.

The cytotoxicity (DL_{50}) of compounds **9a** and **9b** were evaluated using the brine shrimp bioassay (with *Artemia salina*).[23,24] However, no biological activity was recorded using this model system. Tests to evaluate the antioxidant activity of these compounds with the stable free radical diphenylpicrylhydrazyl (DPPH)[25] also were negative.[24]

We have demonstrated a simple and facile synthetic approach to alkylated *trans*-pyrrolidinediols using the diacetal-protected tartaric acid precursor **3**. In terms of chemical diversity, besides furnishing a plethora of useful tertiary *trans*-pyrrolidinediols, this approach should also give *trans*-pyrrolidinediol amides, carbamates, sulphonamides, and other derivatives upon reacting **7** (Scheme 2) with suitable electrophiles. We are currently testing these dihydroxylated indolizidines for antifungal activity and evaluating synthetic methodologies for the incorporation of functional groups in the 2 and 5 positions.

EXPERIMENTAL

General Methods

All reagents were obtained from Aldrich, Fluka, Alfa Aesar, or Acros. Solvents were dried using common laboratory methods. The dimesylate compound **5** was prepared according to the literature procedure.[15]

Column chromatography was carried out on silica gel (sds, 70–200 μm), and flash chromatography with silica gel (Merck, 40–63 μm and sds, 40–63 μm). Thin-layer chromatography (TLC) was carried out on aluminium-backed Kiselgel 60 F_{254} plates (Merck). Plates were visualised either by UV light or with phosphomolybdic acid in ethanol.

Melting points were recorded on a Leica Galen III apparatus and on a Barnstead Electrothermal 9100 apparatus and are uncorrected. The ^{1}H NMR and ^{13}C NMR spectra were recorded on either a Bruker AMX300 (^{1}H: 300 MHz and ^{13}C: 75 MHz) or a Bruker Avance instrument (^{1}H: 400 MHz and ^{13}C: 100 MHz) using $CDCl_3$ as solvent and TMS as internal standard (for measurements made with the Bruker AMX300 instrument) and the signal from residual $CHCl_3$ as an internal standard (for the measurements made with the Bruker Avance instrument). Mass spectra were recorded on a VG Autospec M spectrometer using the FAB technique. Infrared spectra were recorded using a Perkin-Elmer Paragon 1000 instrument. Optical rotations were measured with a Perkin-Elmer 241 polarimeter using a 10-cm cell, and the concentrations are quoted in g/100 mL.

[(2*R*,3*R*,5*S*,6*S*)-5-Azidomethyl-2,3-dimethoxy-2,3-dimethyl-1,4-dioxan-6-yl]methyl Methanesulphonate (6)

A suspension of sodium azide (0.17 g, 2.62 mmol) in acetonitrile (30 mL) was added to a solution of the dimesylate **5** (0.97 g, 2.46 mmol) in acetonitrile (30 mL) at rt. The mixture was then heated to 40 °C over a 21-h period and then refluxed for another 3 h. The temperature was lowered to rt and stirred at this temperature for another 16 h. Sodium azide (0.161 g, 2.48 mmol) was added, and the suspension was refluxed for a further 4 h. The temperature was lowered to rt, water (20 mL) was added, and the mixture was extracted with CH_2Cl_2 (4 × 20 mL). The organic phase was dried ($MgSO_4$) and the solvent evaporated in vacuo to give the crude product mixture that existed as a colorless oil and was purified by silica column chromatography (EtOAc/hexane, 1/2), giving two bands.

Band 1

[(2*R*,3*R*,5*S*,6*S*)-5,6-bis(Azidomethyl)-2,3-dimethyl-2,3-dimethoxy-1,4-dioxane[16] as a white solid (0.096 g, 24%); mp 77.8–79.4 °C; υ_{max}(KBr) 2953, 2915,

2102, 1449, 1286, 1132 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.32 (s, 6H, CH_3), 3.19–3.23 (dd, $J = 13.5$, 2.8, 2H, C*H*HN_3), 3.31 (s, 6H, OCH_3), 3.33–3.39 (m, 2H, CH*H*N_3), 3.86–3.88 (t, $J = 2.8$, CHO) (agrees with that given in Ref. [16b]).

Band 2

Title compound **6** as a colorless oil that solidified later (0.343 g, 41%), mp 80.4–80.6 °C; ($[\alpha]_D^{22} = -114.5$ ($c = 1.53$, $CHCl_3$); υ_{max}(KBr) 2948, 2832, 2104, 1455, 1354, 1128 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm), 1.27 (s, 3H, CH_3), 1.29 (s, 3H, CH_3), 3.08 (s, 6H, SO_3CH_3), 3.25 (s, 3H, OCH_3), 3.26 (s, 3H, OCH_3), 3.29–3.40 (m, 2H, CH_2N_3), 3.92 (m, 2H, CHO), 4.20–4.35 (m, 2H, CH_2SO_3); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 17.2, 37.8, 48.1, 50.6, 67.7, 68.9, 99.1; FAB-MS m/z: 340.09 $[M + H]^+$, 308.07 $[M + H\text{-OMe}]^+$, 280.08 $[M + H\text{-}2 \times OMe]^+$.

(2*R*,3*R*,5*S*,6*S*)-2,3-Dimethoxy-2,3-dimethyl-hexahydro-1,4-dioxino[2,3-*c*]pyrrol-6-ium Mesylate (7)

Method A

Monoazide **6** (0.851 g, 2.51 mmol) was dissolved in EtOAc (25 mL) under a nitrogen atmosphere. Palladium (5%) on carbon (0.086 g) was added, and after 30 min, hydrogen was supplied using a balloon. After stirring for 22 h at rt, the reaction mixture was filtered and the solvent evaporated in vacuo to give the title compound **7** as a white solid (0.52 g, 79%), mp 154.3–154.4 °C; $[\alpha]_D^{23} = -43.4$. ($c = 0.59$, $CHCl_3$); ^1H NMR ($CDCl_3$, 400 MHz) δ (ppm): 1.32 (s, 6H, CH_3), 2.78 (s, 3H, SO_3CH_3) 3.15 (m, 2H, C*H*HN), 3.27 (m, 6H, OCH_3), 3.52–3.57 (m, 2H, CH*H*N), 4.10 (m, 2H, CHO); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 17.8, 39.1, 43.0, 48.2, 68.6, 77.1, 100.9; FAB-MS m/z: 218.12 [$C_{10}H_{20}NO_4^+$]. Anal. calcd. for $C_{11}H_{23}NO_7S$: C, 42.16; H, 7.41; N, 4.47; S, 10.3. Found: C, 42.28; H, 7.53; N, 4.38; S, 9.78.

Method B

Triphenylphosphine (1.15 g, 4.38 mmol) was added to the monoazide **6** (0.973 g, 2.87 mmol) dissolved in dry THF (7 mL) under a nitrogen atmosphere. After 15 min, water (1.8 mL) was added, and a small piece of boiling stone was added to check the liberation of nitrogen gas. The reaction mixture was kept at rt for 13 h, and thereafter the solvent was evaporated to give a white solid (0.35 g, 90%), mp 152.9–153.1 °C; υ_{max}(KBr) 3345, 2945, 1642, 1402, 1378, 1134 cm^{-1}.

6-Benzil-2,3-dimethoxy-2,3-dimethylhexahydro-[1,4]dioxino[2,3-*c*] pyrrole (8a)

The ammonium salt **7** (0.276 g, 0.881 mmol) was dissolved in DMF (3 mL) under an atmosphere of nitrogen. NEt_3 (0.5 mL, 3.523 mmol) and benzylbromide (0.16 mL, 1.32 mmol) were added slowly by syringe. The reaction mixture was heated at 60 °C for 45 h, and the reaction monitored by TLC. The reaction mixture was then cooled to rt, and then water (10 mL) and CH_2Cl_2 (10 mL) were added. The organic phase was separated, and the aqueous phase extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phase was washed with water (8 × 10 mL) to remove residual DMF. It was then dried ($MgSO_4$) and filtered, and the solvent evaporated in vacuo to give a brown oil. This was purified by flash chromatography on silica gel, using hexane/EtOAc (5:1) giving the title compound **8a** as a pale yellow oil (0.104 g, 38%); $[\alpha]_D^{23} = -169.3$ ($c = 1.52$, $CHCl_3$); ^{1}H RMN ($CDCl_3$, 400 MHz) δ (ppm): 1.34 [s, 6H (CH_3)], 2.80–2.93 [m, 4H (RCH_2N)], 3.28 [s, 6H (OCH_3)], 3.70–3.90 [m, 2H (CHO)], 4.09–4.11 [m, 2H ($PhCH_2N$)], 7.27–7.32 [s, 5H (Ar)]; ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ (ppm): 18.04, 47.85, 51.55, 61.53, 70.37, 100.71, 128.26, 138.94; υ_{max}(KBr) 3020, 2839, 1519, 1215, 1037, 758 cm^{-1}; FAB-MS m/z: 308.15 ($M^+ + 1$), 307.07 ($C_{17}H_{25}NO_4^+$).

6-Allyl-2,3-dimethoxy-2,3-dimethylhexahydro-[1,4]-dioxino[2,3-*c*] pirrole (8b)

The ammonium salt **7** (0.5 g, 1.6 mmol) was dissolved in DMF (6 mL) under an atmosphere of nitrogen. NEt_3 (0.9 mL, 6.38 mmol) and allylbromide (0.21 mL, 2.4 mmol) were added slowly by syringe. The reaction mixture was heated at 60 °C for 23 h, and the reaction was monitored by TLC. The reaction mixture was then cooled to rt, and then water (20 mL) and CH_2Cl_2 (20 mL) were added. The organic phase was separated, and the aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phase was washed with water (8 × 10 mL) to remove residual DMF. It was then dried ($MgSO_4$) and filtered, and the solvent was evaporated in vacuo to give a brown oil. This was purified by flash chromatography on silica gel, using hexane/EtOAc (2:1) to give the title compound **8b** as a pale yellow oil (0.121 g, 30%); $[\alpha]_D^{22} = -132.11$ ($c = 0.85$, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.32 [s, 6H (CH_3)], 2.78–2.84 [m, 4H (RCH_2N)], 2.96–3.01 [m, 2H ($NCH_2C{=}C$)], 3.27 [s, 6H (OCH_3)], 5.17–5.26 [m, 2H ($CH_2{=}C$)], 5.80–5.93 [m, 1H ($RCH{=}C$)]; ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ (ppm): 17.99, 48.02, 50.80, 59.82, 69.59, 100.84; υ_{max}(KBr) 3053, 2986, 1549, 1530, 1265, 1144, 748 cm^{-1}; FAB-MS m/z: 258.18 ($M^+ + 1$), 257.17 ($C_{13}H_{23}NO_4^+$), 242.15 ($C_{12}H_{20}NO_4^+$), 230.18 ($C_{11}H_{20}NO_4^+$).

(3*S*,4*S*)-(+)-1-Benzyl-3,4-pyrrolidinediol (9a)

Compound **8a** (0.143 g, 0.465 mmol) was dissolved in a solution of freshly prepared MeOH/6 M HCl (1/1, 16 mL), and the resulting solution was subsequently heated at 80 °C for 1 h. The temperature was lowered to 70 °C, and the reaction mixture was heated at this temperature overnight. Afterward the temperature was raised again to 80 °C for 4 h, after which it was lowered to ice temperature using an ice bath. Solid sodium carbonate was added until the pH reached 10. The solids were removed, and the solvent was evaporated in vacuo. The residue was extracted with CH_2Cl_2 (8×10 mL), the combined organic extracts were dried ($MgSO_4$), and the solvent was evaporated in vacuo to give a brownish oil, which was purified by silica-gel column chromatography with EtOAc to give the title compound as a brownish gum (0.088 g, 98%); $[\alpha]_D^{[22]} = +22.5$ ($c = 0.63$, MeOH), lit.[22] $[\alpha]_D^{20} = +33.6 \pm 3$ ($c = 1.05$, MeOH); ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 2.46–2.53 [m, 4H (RCH_2N)], 2.93–3.00 [m, 2H (C*H*OH)], 4.03–4.10 [m, 2H ($PhCH_2N$)], 7.20–7.40 [s, 5H (Ar)]; ^{13}C NMR ($CDCl_3$, 100.61 MHz) δ (ppm): 60.05, 60.16, 77.29, 128.36, 137.24.

(3*S*,4*S*)-(+)-1-Allyl-3,4-pyrrolidinediol (9b)

Compound **8b** (0.1 g, 0.389 mmol) was dissolved in a solution of freshly prepared MeOH/6 M HCl (1/1, 16 mL), and the resulting solution was subsequently heated at 80 °C for 1 h. The temperature was lowered to 70 °C, and the reaction mixture was heated at this temperature overnight. Afterward the temperature was raised again to 80 °C for 4 h, after which it was lowered to ice temperature using an ice bath. Solid sodium carbonate was added until the pH reached 10. The solids were removed, and the solvent was evaporated in vacuo. The residue was extracted with CH_2Cl_2 (8×10 mL), the combined organic extracts were dried ($MgSO_4$), and the solvent was evaporated in vacuo to give a yellowish sticky solid (0.045 g, 81%); $[\alpha]_D^{23} = +11.9$ ($c = 0.31$, MeOH); ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.30–2.34 [m, 4H (RCH_2N)], 2.73–2.78 [m, 2H ($NCH_2C{=}C$)], 2.94–3.08 [m, 2H (C*H*OH)], 5.05–5.19 [m, 2H ($CH_2C{=}C$)], 5.74–5.87 [m, 1H ($RCH{=}C$)]; ^{13}C NMR (DMSO-d_6, 100.61 MHz) δ (ppm): 58.68, 60.40, 77.20, 116.74, 135.75; υ_{max}(KBr) 3405, 2925, 2852, 1645, 1572, 1231, 1095, 998 cm^{-1}; FAB-MS m/z: 143.94 ($C_7H_{13}NO_2^+$), 125.09 ($C_7H_{11}NO^+$), 116.11 ($C_5H_{10}NO_2^+$), 107.19 ($C_7H_9N^+$).

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