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Diastereoselective Ritter Reactions of Chiral Cyclic *N*-Acyliminium Ions: Synthesis of Pyrido- and Pyrrolo[2,3-*d*]oxazoles and 4-Hydroxy-5-*N*-acylaminopyrrolidines and 5-Hydroxy-6-*N*-acylaminopiperidines

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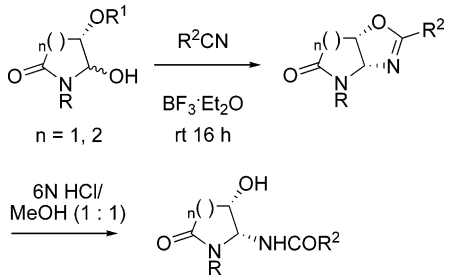
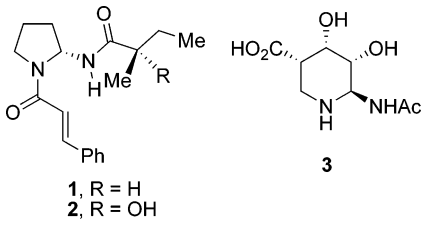


Pyrido- and pyrrolo[2,3-*d*]oxazoles can be conveniently prepared in high yield from the Ritter reaction of nitriles and in situ generated chiral cyclic *N*-acyliminium ions. *cis*-4-Hydroxy-5-acylaminopyrrolidines and *cis*-5-hydroxy-6-acylaminopiperidines can be readily obtained by acid hydrolysis of these bicyclic heterocyclic compounds, respectively.

The 2-acylaminopyrrolidine and -piperidine structural motif is found in several biologically active natural and synthetic products. For example, odorine **1**,[1] (+)-odorinol **2**,[1] and its enantiomer (−)-odorinol[2] and the aglains[3] are 2-acylaminopyrrolidine alkaloids isolated from *Aglaia odorata* Lour. (+)-Odorinol **2** showed significant inhibitory activity on P-388 lymphocytic leukemia cell growth.[2] The naturally occurring *N*-iminosugar, siastatin B **3**, has neuraminidase and β-glucuronidase inhibition activities,[4] while related 2-acetamidopiperidine derivatives show antimetastatic activity on tumor cells[5] and inhibition of tumor cell heparanase,[6] heperan sulfate 2-*O*-sulfotransferase,[7] *N*-acetylhexosaminidases,[8] influenza virus neuraminidase,[9] and glucosidases.[10]



The incorporation of the 2-acylamino group in these molecules often requires a multistep sequence, and thus, a more direct route would be desirable.[8,11] We report here that these types of substituted heterocycles can be conveniently prepared in a highly diastereoselective manner from the Ritter reaction of nitriles and chiral cyclic *N*-acyliminium ions generated in situ from the (5*S*)-hydroxy-2-pyrrolidinone and (6*S*)-hydroxy-2-piperidone derivatives **4**/**5** and **6**, respectively.

Treatment of (4*S*)-**4**[12] in a solution of the nitriles **7a**−**c** at rt with $BF_3{\cdot}Et_2O$ (3 equiv) for 16 h followed by a mild basic workup (saturated aqueous $NaHCO_3$ solution) and purification by column chromatography resulted in formation of the pyrrolo[2,3-*d*]oxazoles **8a**−**c** in excellent yields (86−93%, Scheme 1, Table 1, entries 1−3). Treatment of (4*S*)-**4** with the nitrile **7d** (3 equiv) at rt in nitromethane solution with $BF_3{\cdot}Et_2O$ (3 equiv) for 16 h resulted in formation of the pyrrolo[2,3-*d*]oxazole **8d** in 91% yield (Scheme 1, Table 1, entry 4). Interestingly, treatment of the *O*-benzyl ether analogue of **4**, (4*S*)-**5**,[13] with the nitriles **7b**,**c** also resulted in formation of the pyrrolo[2,3-*d*]oxazoles **8b**,**c** in high yields (87% and 80%, respectively, Table 1, entries 5 and 6). The corresponding *N*-benzylamides **10b**,**c** were also isolated in yields of 77% and 63%, respectively (Scheme 1).

The 6-membered ring hemiaminal (5*S*)-**6** (dr = 3:1) was prepared from the known *N*-PMB-(3*S*)-hydroxyglutarimide[14,15] by $NaBH_4$ reduction.[16] The major trans isomer of (5*S*)-**6** could be selectively crystallized from the mixture and its structure was estabilished by X-ray crystallographic analysis (Supporting Information). Treatment of the diol (5*S*)-**6** (dr = 3:1) with the

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(12) Prepared from the known (3*S*)-hydroxysuccinimide (Kočalka, P.; Pohl, R.; Rejmam, D.; Rosenberg, I. *Tetrahedron* **2006**, *62*, 5763−5774) by $NaBH_4$ reduction.
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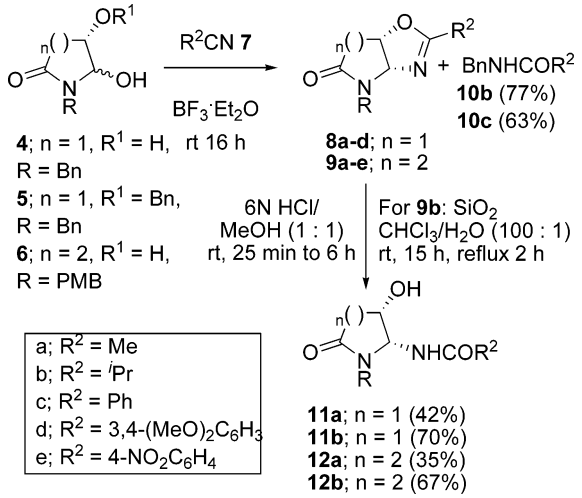
TABLE 1

entry	starting material	product (yield, %)
1	**4**	**8a** (93)
2	**4**	**8b** (90)
3	**4**	**8c** (86)
4	**4**	**8d** (91)[a]
5	**5**	**8b** (87)
6	**5**	**8c** (80)
7	**6**	**9a** (99)
8	**6**	**9b** (91)
9	**6**	**9c** (58)[b]
10	**6**	**9d** (79)[a]
11	**6**	**9e** (0)

[a] $MeNO_2$ as solvent, 3 equiv of **7d**. [b] Starting **6** was also isolated in 21% recovered yield.

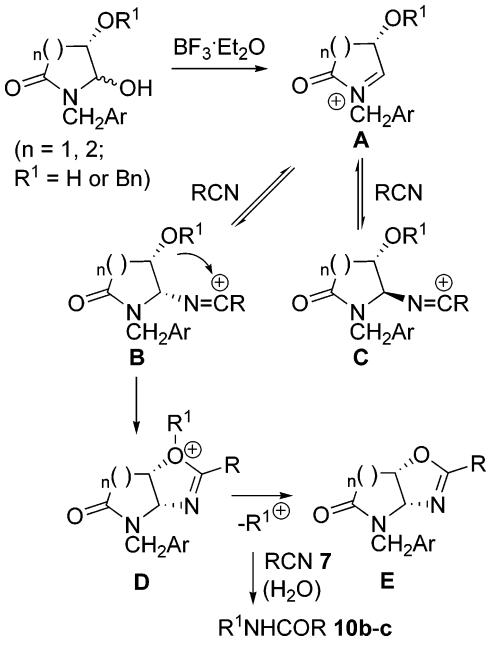
SCHEME 1



nitriles **7a**−**d**, under similar conditions to that of (4*S*)-**4** (BF_3·Et_2O (5 equiv), rt for 16 h, and finally at reflux for 30 min to 3 h), resulted in formation of the corresponding pyrido[2,3-*d*]-oxazoles **9a**−**d** in good to excellent yields (Table 1, entries 7−10). The use of the less nucleophilic 4-nitrobenzonitrile (**7e**) resulted in only recovered starting hemiaminal **6** (Table 1, entry 11).

Acid hydrolysis of **8a**,**b** with 6 N HCl/MeOH (1:1) at rt for 25 min provided the corresponding *cis*-hydroxyamides **11a**,**b**, respectively, in respective yields of 42% and 70%, Scheme 1. This method was less efficient (35−30% yields) for the synthesis of corresponding 6-membered ring analogues **12a**,**b** from the acid hydrolysis of **9a**,**b** (Scheme 1). This hydrolysis method also gave several other minor uncharaterizable products by TLC analysis. A much improved yield of 67% for **12b** was achieved by hydrolysis using silica gel and $CHCl_3/H_2O$ (100 : 1) at rt for 16 h and then at reflux for 2 h. An analogus acid hydrolysis (6 N HCl/MeOH (1:1) at rt) of the aromatic derivatives **8c**,**d** or **9c**,**d** gave only recovered starting material, whereas more forcing conditions (50 °C) resulted in a complex mixture of products. The stereochemistry of the products **11a** and **11b** was determined to be cis based on their the coupling constants $J_{4,5}$, which were 5.0 and 5.6 Hz, respectively. On related systems, $J_{4,5}$ is typically 0−2.5 Hz for the trans isomers and 6.0−7.5 Hz for the corresponding cis isomers.[17a,b] The highly crystalline hydroxy amides **12a**,**b** were shown to have also have the cis stereochemistry from their single-crystal X-ray structural analysis (Supporting Information).

SCHEME 2



These reactions are notable for providing products with high cis diastereoselectivities. Typically, the addition of nucleophiles to the iminium ions generated in situ from **4**−**6** show modest diastereoselectivities.[13,17] To rationalize the high diastereoselectivities and the stereochemical outcomes of these reactions we suggest that attack of the nitriles **7a**−**d** on the intermediate *N*-acyliminium ion **A** (Ritter reaction)[18,19] is reversible and gives a mixture of the Ritter intermediates **B** and **C** (Scheme 2). Because of its cis stereochemistry, intermediate **B** more readily cyclizes to the oxazolidine cationic intermediate **D**. Deprotonation or *O*-debenzylation of **D** gives the oxazolidine **E**. When R^1 in **D** is Bn, the benzyl cation that is formed undergoes a

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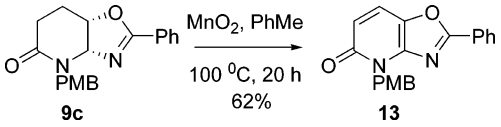
(19) Ritter-like reactions using nitriles, and the related Holy reaction using cyanamide, has been employed on sugar acetals and related compounds, providing analogous bicyclic sugar oxazolines. See: (a) Gordon, D. M.; Danishefsky, S. J. *J. Org. Chem.* **1991**, *56*, 3713−3715. (b) Blanco, J. L. J.; Rubino, E. M.; Mellet, C. O.; Fernandez, J. M. G. *Synlett*, **2004**, 2230−2232. (c) Jenkinson, S. F.; Jones, N. A.; Moussa, A.; Stewart, A. J.; Heinz, T.; Fleet, G. W. J. *Tetrahedron Lett.* **2007**, *48*, 4441−4444 and references cited therein.

SCHEME 3



Ritter reaction with the nitriles **7b**,**c** to give the *N*-benzyl amides **10b**,**c**, respectively (Scheme 2). The optical rotations of compounds **9a**−**d** and **12a**,**b** were notably small or essentially zero, suggesting that **6** may have undergone racemization under the reaction conditions. This was confirmed by converting **12b** to its (*S*)- or (*R*)-Mosher's esters by treating samples of **12b** with (*R*)- or (*S*)-Mosher's acid chloride, respectively. ^{1}H NMR analysis of these derivatives indicated essentially a 1:1 mixture of diastereomers were produced.[20] In contrast, the optical rotations of compounds **8a**−**d** and **11a**,**b** were relatively large in magnitude. ^{1}H NMR analysis of the analogous Mosher's esters of **11b** indicated high enantiomeric purity (95% ee). It seems likely therefore that hemiaminal **6** undergoes ring-opening to the corresponding α-hydroxy aldehyde−secondary amide (PMBN(H)COCH$_2$CH$_2$CH(OH)CHO) which undergoes racemization, through a Lewis acid-catalyzed enolization process of the α-hydroxy aldehyde moiety, prior to recyclization back to **6** and then the subsequent Ritter reaction. This does not seem to be a problem in the 5-membered ring series.

Under oxidative reaction conditions (MnO_2, toluene at reflux), the pyrido[2,3-*d*]oxazole **9c** was converted to the oxazolo[4,5-*b*]pyridin-5(4*H*)-one **13** in 62% yield (Scheme 3). The analogous pyrrolo[2,3-*d*]oxazole **8c**, however, failed to provide the corresponding oxidized product when exposed to the same reaction conditions.

In conclusion, pyrido- and pyrrolo[2,3-*d*]oxazoles can be conveniently prepared in high yield from the Ritter reaction of nitriles and chiral cyclic *N*-acyliminium ions. *cis*-4-Hydroxy-5-acylaminopyrrolidines and *cis*-5-hydroxy-6-acylaminopiperidines can be readily obtained by acid hydrolysis of these bicyclic heterocyclic compounds, respectively. The compounds derived from the 6-membered hemiaminal **6** are obtained in racemic form.

Experimental Section

General Procedures. Unless stated otherwise, $CDCl_3$ was used as a solvent for all ^{1}H NMR (500 MHz) and ^{13}C NMR (125 Mz) measurements. All IR spectra were determined as neat samples. All solutions were dried over anhydrous $MgSO_4$. Petrol refers to the hydrocarbon fraction of boiling point 40−60 °C.

(3a*R*,6a*S*)-4-Benzyl-2-methyl-6,6a-dihydro-3a*H*-pyrrolo[2,3-*d*]oxazol-5(4*H*)-one (8a). To a solution of diol **4** (0.10 g, 0.483 mmol) in acetonitrile (3 mL) at 0 °C was added dropwise BF_3·Et_2O (0.192 g, 1.35 mmol). The reaction mixture was warmed to rt and stirred for 16 h. Saturated $NaHCO_3$ solution (10 mL) was added, and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined extracts were dried, filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography (EtOAc as eluent) to give the title compound (0.103 g, 93%) as a colorless waxy solid: R_f 0.22 (EtOAc); $[\alpha]^{23}_D$ + 21.0 (*c* 0.19, $CHCl_3$); ν_{max}/cm^{-1}1680, 1433, 1308, 1227, 1065, 1024; δ_H 7.34−7.32 (5H, m, Ar*H*), 5.38 (1H, d, *J* = 7.5 Hz), 5.07 (1H, d, *J* = 14.5 Hz), 4.90 (1H, t, *J* = 7.5 Hz), 4.02 (1H, d, *J* = 14.5 Hz), 2.85 (1H, dd, *J* = 7.5, 18.5 Hz), 2.69 (1H, d, *J* = 18.5 Hz), 2.03 (3H, s); δ_C 170.7, 168.8, 135.9, 128.7, 128.6, 127.7, 83.2, 74.48, 44.3, 37.5, 14.1; MS (EI) *m*/*z* 230 (M$^{+\bullet}$,100%); HRMS (EI) calcd for $C_{13}H_{14}N_2O_2$ (M$^{+\bullet}$) 230.1055, found 230.1057.

(±)-(5*S*,6*S*)-4-(4-Methoxybenzyl)-3a,4,7,7a-tetrahydro-2-isopropyloxazolo[4,5-*b*]pyridin-5(6*H*)-one (9b). To a suspension of the diol **6** (150 mg, 0.597 mmol) in isobutyronitrile (10 mL) was added BF_3·OEt_2 (375 μL, 2.984 mmol), and the resulting homogeneous solution was stirred at rt for 16 h upon which TLC analysis indicated an incomplete reaction so the solution was heated at reflux for 30 min. The reaction was quenched at 0 °C with saturated $NaHCO_3$ (10 mL) and brine (50 mL) and then allowed to stir for 10 min. The resulting mixture was extracted with EtOAc (3 × 70 mL), dried, and concentrated in vacuo to yield the crude product. Flash chromatography (Et_2O, R_f = 0.31) of the crude product yielded **9b** (164 mg, 0.543 mmol, 91%) as a colorless oil: ν_{max}/cm^{-1} 2971, 1655, 1514, 1248, 752; δ_H 7.41 (2H, d, *J* = 8.5 Hz), 6.85 (2H, d, *J* = 8.5 Hz), 5.48 (1H, d, *J* = 14.8 Hz), 5.31 (1H, d, *J* = 9.2 Hz), 4.68−4.72 (1H, m), 3.95 (1H, d, *J* = 14.8 Hz), 3.79 (3H, s), 2.63 (1H, app sept, *J* = 7.0 Hz) 2.39−2.46 (1H, m), 2.23−2.30 (1H, m), 2.18 (1H, ddd, *J* = 14.5, 6.4 and 3.0 Hz), 1.88 (1H, app, tt, *J* = 14.3 and 3.7 Hz), 1.21 (3H, t, *J* = 7.0 Hz), 1.20 (3H, t, *J* = 7.0 Hz); δ_C 174.9, 171.2, 159.0, 129.6, 129.2, 114.0, 78.5, 74.9, 55.2, 46.5, 28.3, 27.1, 25.0, 19.6, 19.5; MS (EI) *m*/*z* 302 (M$^+$) 100; HRMS (EI) calcd for $C_{17}H_{22}N_2O_3$ (M$^+$) 302.1630, found 302.1623.

(±)-*N*-((2*R*,3*S*)-1-Benzyl-3-hydroxy-5-oxopyrrolidin-2-yl)acetamide (11a). To a solution of oxazoline **8a** (0.020 g, 0.086 mmol) in MeOH (1 mL) at rt was added dropwise 6 N HCl (1 mL). The reaction mixture was stirred at rt for 25 min, concentrated in vacuo, then diluted with water (5 mL) and basified with solid $NaHCO_3$ to pH 9. The aqueous layer was extracted with EtOAc (3 × 10 mL), dried (Na_2SO_4), filtered, and concentrated in vacuo. The crude product was purified by flash column chromatography (5% MeOH in EtOAc as eluent) to give the title compound (0.009 g, 42%) as a white solid: R_f 0.24 (5% MeOH in EtOAc); mp 190−193 °C; $[\alpha]^{23}_D$ −160 (*c* 0.075 MeOH); ν_{max}/cm^{-1} 3318, 1577, 1653, 1541, 1446, 1434, 1378, 1275, 1157; δ_H (MeOH-d_4) 7.31−7.24 (5H, m), 5.55 (1H, d, *J* = 5.0 Hz), 4.57 (1H, d, *J* = 15.0 Hz), 4.39 (1H, br q, *J* = 6.5 Hz), 4.23 (1H, d, *J* = 15.0 Hz), 2.68 (1H, dd, *J* = 6.5, 17.5 Hz), 2.46 (1H, dd, *J* = 5.0, 17.5 Hz), 1.88 (3H, s); δ_C (MeOH-d_4) 174.9, 173.9, 138.2, 129.5, 129.1, 128.5, 67.6, 65.8, 45.0, 39.6, 22.6; MS (EI) *m*/*z* 248 (M$^{+\bullet}$, 45); HRMS (EI) calcd for $C_{13}H_{16}N_2O_3$ (M$^{+\bullet}$) 248.1160, found 248.1158.

(±)-(5*S*,6*S*)-*N*-1-(4-Methoxybenzyl)-3-hydroxy-6-oxopiperidin-2-yl)isobutyramide (12b). Method 1. To a solution of the oxazoline **9b** (92 mg, 0.304 mmol) in MeOH/H_2O (10 mL of a 9:1 v/v mixture) was added three drops of concentrated hydrochloric acid, and the solution was stirred at rt for 6 h. The volatiles were removed in vacuo, and the residue was purified by column chromatography [EtOAc to 4% MeOH/EtOAc (R_f = 0.31)] to yield **12b** (35 mg, 0.090 mmol, 30%) as a colorless solid.

Method 2. To a solution of the oxazoline **9b** (75 mg, 0.248 mmol) in chloroform (20 mL) were added silica gel (2 g) and water (200 μL), and the resulting suspension was stirred vigorously for 15 h. TLC analysis indicated only starting material so the reaction was heated at reflux for 2 h. The reaction was cooled, and the volatiles were removed in vacuo. The silica gel was filtered and washed with EtOAc/MeOH (100 mL of a 2:1 v/v), and then the volatiles were removed. Column chromatography of the crude residue from the silica gel yielded **12b** (53 mg, 0.165 mmol, 67%) showing spectroscopic data consistent with the amide prepared from method 1 above. The starting oxazoline **9b** was also recovered (15 mg, 0.0496 mmol, 20%): mp 169−173 °C; ν_{max}/cm^{-1} 3288, 2966, 1652, 1615, 1541, 1513, 1468, 1244, 1176, 1033; δ_H 7.17 (2H, d, *J* = 8.6 Hz), 6.83 (2H, d, *J* = 8.6 Hz), 6.37 (1H, d, *J* = 8.8 Hz), 5.47 (1H, dd, *J* = 8.8, 4.1 Hz), 4.84 (1H, d, *J* = 14.6 Hz), 4.02 (1H, d, *J* = 14.6 Hz), 4.00−4.03 (1H, m), 3.76 (3H, s), 3.19 (1H, br s), 2.58 (1H, app dt, *J* = 18.1 and 5.4 Hz), 2.40−2.50 (1H, m),

(20) The ^{1}H NMR spectra of the (*S*)- or (*R*)-Mosher's ester derivatives of **12b** both showed two sets of doublet peaks (1:1 ratio) for the benzylic methylene signals CH_ACH_BPMP (see the Supporting Information).

2.36 (1H, app sept, $J = 6.9$ Hz), 1.85−1.95 (2H, m), 1.14 (3H, d, $J = 6.9$ Hz), 1.13 (3H, d, $J = 6.9$ Hz); δ_C (MeOH-d_4)174.9, 171.2, 158.9, 129.5, 129.2, 114.0, 78.5, 74.9, 55.2, 46.5, 28.3, 27.1, 25.0, 19.6, 19.5; MS (ESI$^-$) *m*/*z* 319.2 (M − H)$^-$, 100; HRMS (ESI$^+$) calcd for $C_{17}H_{25}N_2O_4$ (M + H)$^+$ 321.1814, found 321.1821.

4-(4-Methoxybenzyl)-2-phenyloxazolo[4,5-*b*]pyridin-5(4*H*)-one (13). To a solution of the oxazoline **9c** (48 mg, 0.143 mmol) in anhydrous toluene (10 mL) was added activated manganese(IV) dioxide (146 mg of 85% activity, 1.43 mmol, 10 equiv), and the suspension was heated at 100 °C for 16 h. TLC analysis indicated an incomplete reaction so a further portion of manganese(IV) dioxide (146 mg, 10 equiv) was added and the mixture then heated at reflux for 4 h, whereupon TLC analysis showed complete consumption of the oxazoline (the product is fluorescent and the oxazoline is not). The reaction was filtered through a short plug of silica (5 cm) and eluted with EtOAc, and the volatiles were removed in vacuo. The crude product was purified by column chromatography [10% EtOAc/petrol to 50% EtOAc/Petrol ($R_f = 0.29$)] yielding **13** (28.5 mg, 0.086 mmol, 62%) as a pale yellow solid: mp 120−122 °C. δ_H 8.16 (2H, dd, $J = 7.5$ and 1.5 Hz), 7.62 (1H, d, $J = 9.5$ Hz), 7.59 (2H, d, $J = 9.0$ Hz), 7.50−7.56 (4H, m), 6.82 (2H, d, $J = 9.0$ Hz), 6.44 (1H, d, $J = 9.5$ Hz), 5.44 (2H, s) and 3.76 (3H, s); δ_C 163.1, 161.6, 159.2, 133.7, 133.1, 131.8, 130.7, 129.0, 128.8, 127.2, 126.4, 124.3, 116.6, 113.8, 55.2, 45.8; MS (EI) *m*/*z* 332 (M$^+$), 100; HRMS (EI) calcd for $C_{20}H_{16}N_2O_3$ (M$^+$) 332.1160, found 332.1155.

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Supporting Information Available: Full experimental procedures and characterization data as well as copies of the ^{1}H NMR and ^{13}C NMR spectra of all new compounds. Crystal/refinement data and ORTEP plots of compounds **6**, **12a**, and **12b** (CCDC nos. 668234, 668235, and 668236). This material is available free of charge via the Internet at http://pubs.acs.org.

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