Supplementary Material

# Versatile, Diastereoselective Additions of Silyl Ketene Acetals, Allyl Tributylstannane, and $Me_3SiCN$ to *N*-Acyl Pyrazolines: Asymmetric Synthesis of Densely Functionalized Pyrazolidines

F.M. Guerra, Michael R. Mish and E.M. Carreira

Laboratorium für Organische Chemie
Eidgenissiche Technische Hochschule
Universitätstrasse 16
CH-8092, Zürich Switzerland

**General Procedures**

All reagents and reaction solvents were used as obtained from commercial sources except where additional purification prior to use is noted. Non-aqueous reactions were performed in flame-dried glassware under an atmosphere of dry nitrogen. Organic solutions were concentrated by rotary evaporation at temperatures between 25˚C and 35˚C. Acetic anhydride, benzoyl chloride and titanium tetrachloride were fractionally distilled before use. Tetrahydrofuran, toluene, methylene chloride and acetonitrile were dried and purified through activated alumina columns as described by Grubbs et. al.[1]prior to use. Flash chromatography was performed using silica gel 60 (230-400 mesh, 0.04-0.063 mm) from Fluka at rt and 0.2 to 0.5 bar air pressure. Thin layer chromatography was performed using Merck 0.25mm silica gel 60 F plates. Visualization was accomplished via the use of UV fluorescence at 254 nm or ceric ammonium molybdate (CAM) solution. Melting points were obtained using a Buchi 510 apparatus with open capillary tubes and are uncorrected. Infra red spectra were obtained with a Perkin-Elmer Paragon 1000 Fourier Transform single beam spectraphotometer. The samples were prepared as thin films on NaCl plates and are reported in absorption maxima in $cm^{-1}$. $^{1}H$, and $^{13}C$ NMR spectra were obtained using a Varian Gemini 200 or 300 operating at either 200 or 300 MHZ for $^{1}H$-NMR, or a Varian Mercury 300 operating at 300 MHz for $^{1}H$ and 75 MHz for $^{13}C$ NMR. $^{1}H$-NMR spectra are referenced to residual protio solvent signals. $^{1}H$-NMR data is reported as follows : chemical shift (δ, ppm), multiplicity, integration, and coupling constant. Data for $^{13}C$-NMR are reported in terms of chemical shift (δ, ppm). Elemental analyses were performed by the Mikrolabor für Organische Chemie at ETH-Zürich. High resolution mass spectra were obtained by the ETHZ mass spectroscopy facilities.

**Assignment of pyrazolidine stereochemistry**

In the case of pyrazolidine **8**, the stereochemistry of addition was determined by single crystal X-ray analysis. In the cases of pyrazolidines **7** and **9**, the NOE enhancements shown in Figure 1 were observed. Assignment of the stereochemistry of addition for additional products was made by analogy.

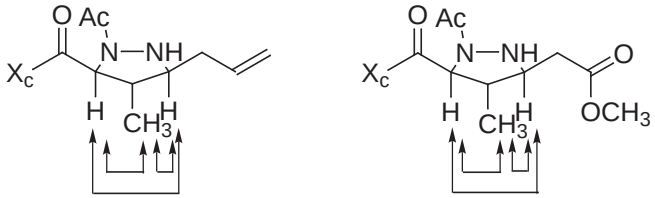
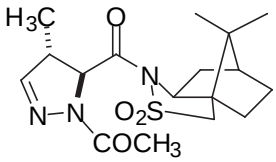



**Figure 1.** NOE Enhancements observed in pyrazolines **9a** and **9c**.

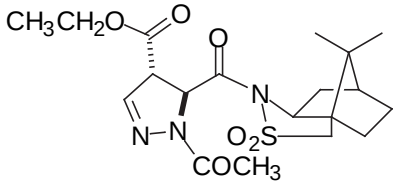
**General Procedure for the synthesis of N-acetylated pyrazolines 6**, **16**, and **25**.

To a 0.05 M solution of the pyrazoline in $CH_2Cl_2$ at 23˚ C is added 10.0 eq. dry acetic anhydride, followed by 0.10 eq toluenesulfonic acid monohydrate. The reaction is stirred under $N_2$ at 23˚ C. Upon completion of the reaction (2h-6h), the reaction mixture is poured into a volume of saturated sodium bicarbonate solution equal to the volume of $CH_2Cl_2$ used. After stirring for 30 min, this mixture is extracted 3x with $CH_2Cl_2$ and dried over $Na_2SO_4$. Solvent removal gives the unpurified product as a white powder. Flash

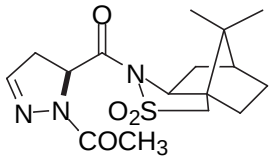
chromatography (2:1 hexanes/EtOAc) furnishes the N-acetylated product as a crystalline solid.



*N*-Acyl Pyrazoline **6**, obtained as a crystalline solid, 94 %
**m.p.** = 174-175˚C
**[α]$_D^{23.1}$** +100.5 ˚ (c = 0.49, $CHCl_3$)
**$^1$H NMR** (300 MHz, $CDCl_3$) d 6.73 (1H, s), 4.95 (1H, d, J = 4.5 Hz), 3.85 (1H, dd, J = 7.7, 4.8 Hz) 3.53 (1H, d, J=13.7 Hz), 3.41 (1H, d, J = 13.7 Hz), 3.28 (1H,m), 2.27 (3H,s), 2.2 (1H, m) 2.05-1.85 (4H, bm) 1.52-1.32 (8H, m) 0.93 (3H,s)
**$^{13}$C NMR**(75 MHz, $CDCl_3$) 168.9, 168.3, 149.8, 65.1, 62.8, 52.9, 49.1, 47.8, 46.8, 44.2, 37.5, 32.4, 26.4, 21.1, 20.2, 19.8, 16.8
**IR** (thin film, $cm^{-1}$) 2961, 2883, 1698, 1667, 1604, 1410, 1330, 1284, 1216, 1167, 1136, 1066, 735, 538
**HRMS** calcd. for $C_{17}H_{25}N_3O_4S$ $(M+1)^+$ 368.1644, found 368.1642.



*N*-Acyl pyrazoline **16**, obtained as a crystalline solid, 76 %.
**m.p** = 158-160 ˚C
**[α]$_D^{26.0.}$** + 321.3˚ (c = 0.81, $CHCl_3$)
**$^1$H NMR** (200 MHz,$CDCl_3$) : δ 6.90 (d, 1H, J= 2.0 Hz), δ 5.79 (d, 1H, J = 5.8 Hz), δ 4.27 (1H, d, J = 5.0 Hz), δ 4.16 (1H, δ, J = 5.8 Hz), δ 3.93 (1H, dd, J = 7.9, 5.0), δ 3.57 (1H, d , J = 13.7) δ 3.50 (1H, d, J=13.7), δ 2.35 (3H, s), δ 2.3-1.8 (6H, m), δ 1.7-1.2 (8H, m), δ 1.00 (s, 3H)
**$^{13}$C NMR** (75 MHz, $CDCl_3$) :δ 168.7, 167.2, 166.4, 140.7, 65.40, 62.56, 59.45, 57.70, 53.09, 49.31, 47.95, 44.73, 37.82, 32.82, 26.48, 21.20, 20.69, 19.93, 14.07 ;
**IR** (thin film, $cm^{-1}$) : 2961 , 2248, 1744, 1701, 1672, 1595, 1409, 1369, 1242, 1213, 1185, 1166, 1136, 1120, 993, 963, 646.;
**HRMS** calc. for $C_{19}H_{27}O_6S$ Anal. calcd. for $C_{19}H_{27}N_3O_6S$ (M +Na ) 448.1518, found : 448.1515.

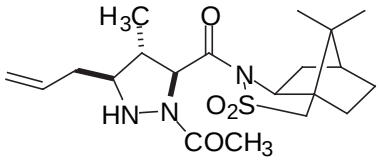


*N*-Acyl pyrazoline **25**, obtained as a crystalline solid,80 %.
**m.p**.= 168˚C.
**[α]$_D^{29.3}$** + 17.9 ˚ (c = 0.09, $CHCl_3$)

**$^1$H NMR** (200 MHz,$CDCl_3$) δ 6.851 (1H, t, J = 1.6 Hz), 5.33 (1H,dd, J = 12.0, 7.4 Hz) 3.91 (1H, m), 3.51 (1H, d, J=13.7 Hz) 3.40 (1H, d, J = 13.7 Hz) 3.16 (1H, ddd, J = 18.6, 11.6, 1.6 Hz) 2.97 (1H, ddd, J = 18.6, 7, 1.6 Hz), 2.33 (3H,s), 2.24 (1H,m), 2.1-1.85 (5H, m), 1.48-1.31 (4H, m), 1.00 (3H,s)
**$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 186.9, 166.4, 142.7, 62.9, 53.5, 50.6, 46.7, 45.5, 42.1, 36.9, 35.8, 35.3, 31.0, 30.2, 29.1, 24.1, 18.7, 18.1, 17.4
**IR** (thin film, $cm^{-1}$) 2960, 2358, 2244, 1702, 1661, 1605, 1412, 1358, 1329, 1272, 1237, 1221, 1166, 1119, 1067, 976, 668, 483.
**HRMS** calcd. for $C_{16}H_{23}N_3O_4S$ ( M + Na) 376.1307, found 376.1302.

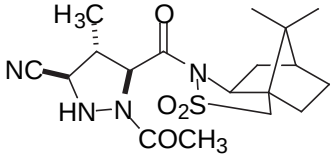
**General Procedure for the $TiCl_4$-promoted addition of nucleophiles to N-acetyl pyrazolines 6-8 to give N-acetyl pyrazolidines 9a-11c .**

To a 0.05 to 0.10 M solution of the *N*-acetyl pyrazoline in $CH_2Cl_2$ or toluene, cooled to –78˚ C, under an atmosphere of $N_2$ is added via syringe 1.2 eq $TiCl_4$ as a 1.0 M solution in $CH_2Cl_2$. The cold bath is removed and the reaction is allowed to stir for a period of 15 min. The reaction is recooled to –78˚C and 2.1 to 4.0 eq of nucleophile is added neat to the reaction solution via syringe. The cold bath is removed and the reaction is allowed to reach 23˚ C with stirring. Upon warming, the yellow color of the reaction solution turns dark brown. The reaction is monitored by TLC for progression to the product which is, in all cases studied, of lower $R_f$ than the starting N-acetyl pyrazoline. After completion of the reaction, (4-24 h), the reaction is diluted with additional reaction solvent and washed with aq. sodium bicarbonate solution. The aq. layer is extracted with additional reaction solvent, and the combined organic layers are washed with brine and dried over $Na_2SO_4$. Solvent is removed by rotary evaporation and the residue subjected to flash chromatography on silica gel (1:1 hexanes/EtOAc to 2:1 hexanes/EtOAc) to provide the pure *N*-acetyl pyrazolidine products.




Pyrazolidine **7**, obtained as a colorless oil, 71 %.
**$[\alpha]_D$** $^{23.1}$ 100.5 ˚ (c = 0.49, $CHCl_3$)
**$^1$H NMR** (300 MHz, $CDCl_3$) δ 5.81 (1H, m), 5.15 (1H, d, J = 16.2 Hz), 5.11 (1H, d, J = 9.3 Hz), 4.75 (1H, d, J = 6.1 Hz), 3.97 (1H, dd, J = 7.6, 4.9 Hz), 3.52 (1H, d, J = 13.7 Hz) 3.42 (1H, d, J = 13.7 Hz), 2.81 (1H, ddd, J = 7.6, 7.6, 5.1 Hz), 2.52-2.13 (3H, bm),2.14 (3H,s), 1.94-1.8 (3H,bm), 1.5-1.25 (8H,bm), 0.97 (3H,s)
**$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 172.4, 169.9, 133.4, 118.1, 66.8, 65.3, 65.1, 53.0, 48.9, 47.9, 46.8, 44.5, 44.5, 38.4, 34.5, 32.7, 26.5, 21.2, 20.4, 19.9,16.3
**IR** (thin film,$cm^{-1}$) : 3242, 3071, 2959, 1690, 1651, 1483, 1393, 1333, 1275, 1237, 1214, 1167, 1136, 1066, 1041, 992, 918, 857, 763, 733
**HRMS** calcd. for $C_{20}H_{31}N_3O_4S$ $(M+1)^+$ 410.2113, found 410.2115.

Pyrazolidine **8**, obtained as a crystalline solid, 91 %.



**m.p.** =124˚C

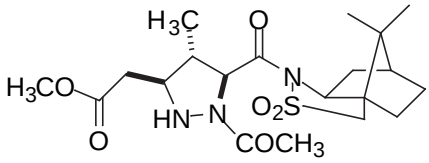
**[α]$_D$** $^{32.4}$ + 60.0˚ (c=2.15, $CHCl_3$)

**$^1$H NMR** (300 MHz, $CDCl_3$) δ 5.07 (1H, d, J = 10.8 Hz), 4.81 (1H, d, J = 4.8 Hz), 3.94 (1H, m), 3.62 (1H, dd, J = 10.5, 7.2 Hz), 3.54 (1H, d, J = 13.8 Hz), 3. 44 (1H, d, J = 13.8 Hz), 2.90 (1H, m), 2.18-1.82 (7H, m), 1.34-1.23 (5H, m), 1.24 (3H, s), 0.96 (3H,s);

**$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 170.2, 170.0, 116.2, 65.4, 63.9, 55.6, 53.2, 49.1, 48.0, 47.97, 44.5, 38.0, 32.7, 26.5, 21.3, 20.5, 20.0, 16.5

**IR** (thin film, $cm^{-1}$) 3246, 2962, 2251, 1702, 1650, 1469, 1393, 1327, 1276, 1215, 1135, 1063, 913, 732.

**Combustion analysis** : anal. calcd. for $C_{18}H_{26}N_4O_4S$: C, 54.80, H, 6.64, N, 14.20. Found : C, 54.78, H, 6.69, N, 14.04.




Pyrazolidine **9** obtained as a colorless oil, 85 %.

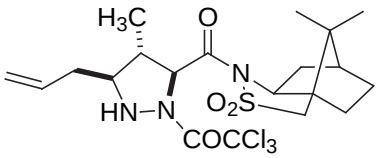
**[α]$_D$** $^{32.4}$ +45.0 (c=1.09, $CHCl_3$)

**$^1$H NMR** (300 MHz, $CDCl_3$) δ 4.71 (2H, m), 3.94 (1H, m), 3.70 (3H, s), 3.52 (1H, d, J = 13.8 Hz), 3.44 (1H, d, J = 13.8 Hz), 3.18 (1H,m), 2.65 (2H, d, J = 6 Hz), 2.36 (1H,m), 2.27-2.13 (4H, m), 2.02-1.86 (4H, m), 1.44-1.22 (5H,m), 0.96 (3H,s)

**$^{13}$C NMR** (75 MHz, CDCl3) δ 171.7, 171.6, 169.8, 65.43, 65.40, 65.41, 53.3, 52.0, 49.1, 48.0, 46.8, 44.6, 38.2, 35.6, 32.8, 26.6, 21.3, 20.5, 20.0, 17.0

**IR** (thin film, $cm^{-1}$) 3234, 2958, 2360, 2340, 1735, 1696, 1647, 1391, 1328, 1274, 1215, 1166, 1134, 1064, 993, 913, 731

**HRMS** calcd for $C_{20}H_{31}N_3O_4S$ (M +H) 442.2012, found : 442.2006.




**Pyrazolidine 11.** Product obtained as white crystals, 62%.

**m.p.** 168-170 °C ($CH_2Cl_2$)

**[α]$_D$**$^{27.1}$ 29.0° (c = 0.33, $CHCl_3$)

**IR** (thin film)

ν 3240, 1961, 1694, 1682, 1336, 1136, 830, 813, 539

**$^1$H NMR** (300 MHz, $CDCl_3$)

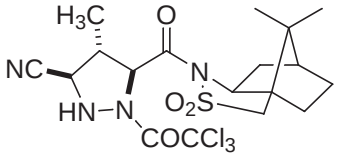
δ 5.78 (1H, m), 5.17 (1H, d, *J* = 17.8 Hz), 5.11 (1H, d, *J* =10.5 Hz), 4.88 (1H, d, *J* =5.6 Hz), 4.40 (1H, d, *J* =12.3 Hz), 3.91 (1H, dd, *J* =7.6, 5.0 Hz), 3.54 (1H, d, *J* =13.8 Hz),

3.44 (1H, d, *J* =13.8 Hz), 2.89 (1H, m), 2.56-1.80 (7H, m), 1.7-1.6 (1H, m), 1.5-1.3 (1H, m), 1.28 (3H, d, *j* =6.6 Hz), 1.23 (3H, s), 0.95 (3H, s)

**$^{13}$C NMR** (75MHz, $CDCl_3$)

δ 171.1, 158.9, 133.1, 118.2, 92.2, 67.8, 67.1, 65.2, 53.0, 49.0, 47.9, 46.2, 44.3, 38.3, 34.4, 32.6, 26.5, 20.5, 19.9, 16.6

**HRMS** calculated for $C_{20}H_{28}N_3O_4Cl_3S$ ($M^+$) 511.0866 found 511.0864.




**Pyrazolidine 12.** Product obtained as white crystals, 51%.

**m.p.** 213-215 °C ($CH_2Cl_2$)

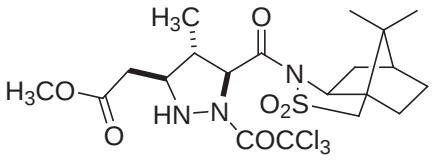
**[**$\alpha]_D^{27.7}$ 46.5° (c = 0.36, $CHCl_3$)

**IR** (thin film)ν 3250, 2961, 2884, 2252, 1694, 1681, 1545, 1392, 1329, 1277, 1136, 833, 814, 537

**$^1$H NMR** (300 MHz, $CDCl_3$) δ 5.10 (1H, d, *J* =10.9 Hz), 5.00 (1H, d, *J* =4.5 Hz), 3.94 (1H, dd, *J* =7.5, 4.9 Hz), 3.69 (1H, dd, *J* =10.9, 7.1 Hz), 3.57 (1H, d, *J* = 13.8 Hz), 3.47 (1H, d, *J* =13.8 Hz), 2.96 (1H, m), 2.2-1.8 (6H, m), 1.45-1.35 (1H, m), 1.45 (3H, d, *J* =6.9 Hz), 1.23 (3H, s), 0.97 (3H, s)

**$^{13}$C NMR** (75MHz,$CDCl_3$)δ 169.0, 159.0, 115.3, 91.4, 66.1, 65.4, 55.6, 53.1, 49.3, 48.0, 46.9, 44.4, 38.0, 32.7, 26.5, 20.5, 19.9, 16.8;

**HRMS** calculated for $C_{18}H_{23}N_4O_4Cl_3S$ ($M^+$) 496.0506 found 496.0502.




**Pyrazolidine 13.** Product obtained as a colorless oil, 68%.

**[**$\alpha]_D^{27.6}$ 34.7° (c = 0.36, $CHCl_3$)

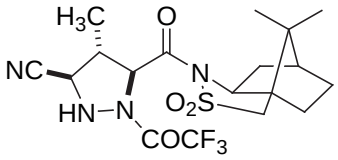
**IR (thin film)** ν 3250, 2959, 1738, 1732, 1694, 1682, 1332, 1276, 1238, 1167, 1136, 833, 814, 537

**$^1$H NMR** (300 MHz, $CDCl_3$) δ 4.89 (1H, d, *J* =4.5 Hz), 3.94 (1H, dd, *J* =7.3, 5.0 Hz), 3.70 (3H, s), 3.57 (1H, d, *J* = 13.8 Hz), 3.47 (1H, d, *J* = 13.8 Hz), 3.32 (1H, t, *J* =6.2 Hz),

2.72 (1H, d, *J* =6.4 Hz), 2.40 (1H, d, *J* =11.7, 6.2 Hz), 2.20-1.7(6H, m), 1.65-1.40(2H, m), 1.34 (3H, d, *J* =6.9), 1.27 (3H, s), 0.98 (3H, s)

**$^{13}$C NMR** (75MHz, $CDCl_3$) δ 171.0, 169.9, 158.7, 92.0, 67.7, 65.3, 64.2, 53.1, 51.9, 49.1, 47.9, 45.8, 44.3, 38.1, 35.1, 32.6, 26.5, 20.5, 19.9, 17.2

**HRMS** calculated for $C_{20}H_{28}N_3O_6Cl_3S$ $(M+1^+)$ 543.0764 found 543.0764.




**Pyrazolidine 15.** Product obtained as colorless crystals, 85%.

**m.p.** 100-102 °C ($CH_2Cl_2$)

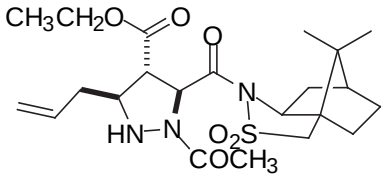
**[**$\alpha]_D^{23.2}$ 49.6° (c = 0.39, $CHCl_3$)

**IR** (thin film) ν 3251, 3062, 2960, 2887, 2306, 2252, 1714, 1704, 1694, 1455, 1393, 1069,995, 854, 742, 705, 536

**$^1$H NMR** (300 MHz, $CDCl_3$) δ 5.32 (1H, d, *J* =10.2 Hz), 4.90 (1H, d, *J* = 4.8 Hz), 3.93 (1H, dd, *J* = 7.5 Hz, 5.0 Hz), 3.73 (1H, dd, *J* = 10.1, 6.7 Hz), 3.57 (1H, d, *J* = 13.8 Hz), 3.47 (1H, d, *J* = 13.8 Hz), 2.96 (1H, dd, *J* = 11.8, 6.7 Hz), 2.20-1.81 (6H, m), 1.51-1.45 (1H,m), 1.41 (3H, d, *J* = 6.9 Hz), 1.20 (3H, s), 0.95 (3H, s)

**$^{13}$C NMR** (75MHz, $CDCl_3$) δ 168.1, 155.2 (q, *J* =38.3 Hz), 115.7 (q, *J* = 287.0 Hz), 115.5, 65.4, 64.9, 55.7, 53.0, 49.3, 47.9, 46.6, 44.4, 37.8, 32.6, 26.4, 20.4, 19.8, 16.4;

**HRMS** calculated for $C_{18}H_{23}N_4O_4F_3S$ $(M^+)$ 448.1392 found 448.1388.




Pyrazolidine **17**, obtained as a colorless oil, 60 %.

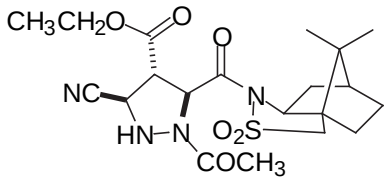
**[**$\alpha]_D^{32.2}$ +88.7 ˚ (c=0.42, $CHCl_3$)

**$^1$H NMR** (300 MHz, $CDCl_3$) : δ 5.80 (1H,m), 5.39 (1H, d, J = 5.3 Hz), 5.20 (2H, m), 4.43 (1H, d, J = 11.5 Hz), 4.20 (2H, m), 4.05 (1H,bm), 3.45 (3H,m), 3.10 (1H,m), 2.56 (2H,m), 2.22 (4H, m), 2.1-1.8 (4H, bm), 1.42-1.25 (8H, m), 0.97 (3H,s);

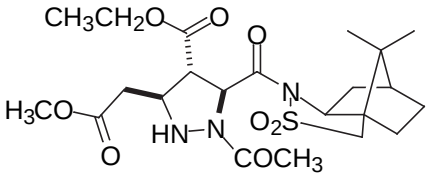
**$^{13}$C NMR** (75MHz, $CDCl_3$) : δ 174.0, 170.7, 132.9, 119.2, 64.7, 61.9, 61.0, 56.2, 54.2, 53.0, 49.4, 48.0, 45.1, 38.8, 35.9, 35.0, 33.0, 26.4, 21.4, 20.9, 20.0, 17.2.

**IR** (thin film, $cm^{-1}$) 3230, 2960, 2359, 2340, 1733, 1683, 1652, 1483, 1394, 1334, 1276, 1220, 1167, 1136, 1068, 1040, 995, 913.

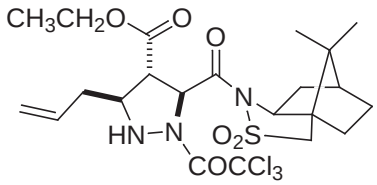
**HRMS** Calcd. for $C_{22}H_{33}N_3O_6S$ ( M + Na) 490.1988, found 490.1983.



Pyrazolidine **18**, obtained as a colorless oil, 91 %.
**[α]$_D^{32.4}$** + 79.1 ˚ (c=1.33, $CHCl_3$)
**$^1$H NMR** (300MHz, $CDCl_3$) : d 5.41 (1H, d, J = 3.9 Hz), 5.07 (1H, d, J = 9.3 Hz), 4.28-4.21 (3H, m), 4.00 (1H,m), 3.70 (1H,m), 3.52 (1H, d, J = 13.8 Hz), 3.42 (1H, d, J = 13.8 Hz), 2.24-215 (4H, bm), 2.06 (1H,m), 1.90 (2H, bm), 1.44-1.192 (8H, m), 0.97 (3H,s).
**$^{13}$C NMR** (75 MHz, $CDCl_3$) : δ 170.4, 169.0, 168.5, 115.5, 65.3, 62.9, 60.9, 60.5, 55.5, 53.07, 52.3, 49.3, 48.0, 44.9, 38.2, 32.9, 21.3, 20.8, 19.9, 14.0.
**IR** (thin film, cm$^{-1}$) : 3240, 2963, 2362, 2254, 1738, 1703, 1661, 1470, 1393, 1373, 1332, 1275, 1215, 1195, 1167, 1136, 1067, 1039.
**HRMS** calcd. for $C_{20}H_{28}N_4O_6S$ (M + Na) 475.1627, found 475.1620.



Pyrazolidine **19**, obtained as a colorless oil, 73 %.
**[α]$_D^{32.4}$** +83.1 (c=0.695, $CHCl_3$)
**$^1$H NMR** (300 MHZ, $CDCl_3$) : δ 5.33 (1H, d, J = 4.5 Hz), 4.83 (1H, d, J = 9.3 Hz), 4.19 (2H, q, J = 7.2 Hz), 3.98 (1H, m), 3.73 (4H, m), 3.50 (1H, d, J = 13.8 Hz), 3.39 (1H, d, J = 13.8 Hz), 3.15 (1H, m), 2.76 (2H, m), 2.00 (1H, m), 2.15 (3H, s), 2.08-1.83 (4H, m), 1.43-1.28 (8H,m), 0.97 (3H,s).
**$^{13}$C NMR** (75 MHz, $CDCl_3$): δ 171.2,170.8, 169.5,169.0, 65.2, 61.9, 61.7, 61.4, 55.7, 53.0, 52.0, 49.1, 47.914, 44.9, 38.2, 35.9, 32.9, 26.5, 21.4, 20.8, 19.9, 14.1 ;
**IR** (thin film, cm $^{-1}$) : 3244, 2959, 2353, 2340, 1736, 1696, 1655, 1394, 1331, 1275, 1217, 1166, 1135, 1068, 1040.
**HRMS** Calcd. for $C_{22}H_{33}N_3O_8S$ (M + Na): 522.1886, found 522.1881.

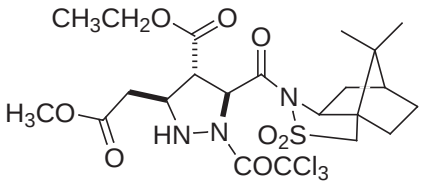


**Pyrazolidine 21.** Product obtained as a colorless oil, 62%.

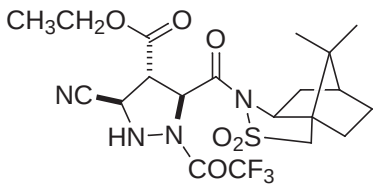
$[\alpha]_D^{25.9}$ 49.6° (c = 1.15, $CHCl_3$)

**IR** (thin film) ν 3240, 3078, 2960, 1739, 1732, 1694, 1682, 1336, 1280, 1167, 1137, 834, 814,736, 536

**$^{1}$H NMR** (300 MHz, $CDCl_3$) δ 5.79 (1H, m), 5.59 (1H, d, *J* =5.1 Hz), 5.20 (1H, d, *J* =16.6 Hz), 5.15 (1H, d, *J* =9.9 Hz), 4.5 (1H, d, *J* =11.4 Hz), 4.21 (2H, m), 3.94 (1H, dd, *J* =7.5, 4.9 Hz), 3.52 (1H, d, *J* =13.7 Hz), 3.41 (1H, d, *J* =13.7 Hz), 3.50-3.40 (1H,m), 3.07 (1H, dd, *J* =7.1, 5.5 Hz), 2.51 (2H, m), 2.28-1.90 (1H, m), 2.1-1.8 (3H, m), 1.7-1.6 (1H, m), 1.40-1.35 (2H, m), 1.27 (3H, t, *J* =7.2 Hz), 1.25 (3H, s), 0.96 (3H, s)
**$^{13}$C NMR** (75MHz, $CDCl_3$) δ 170.6, 169.5, 159.0, 132.6, 119.6, 92.3, 65.6, 65.4, 64.7, 62.2, 55.8, 53.3, 49.6, 48.3, 45.1, 38.7, 35.0, 33.2, 26.8, 21.2, 20.3, 14.5
**HRMS** calculated for $C_{22}H_{31}N_3O_6Cl_3S$ $(M+1^+)$ 570.0992 found 570.0999.




**Pyrazolidine 22.** Product obtained as a colorless oil, 60%.
$[\alpha]_D^{25.7}$ 54.3° (c = 0.75, $CHCl_3$)
**IR (thin film)** ν 3249, 2960, 1738, 1732, 1694, 1682, 1336, 1278, 1167, 1137, 1071, 1071, 1025, 814, 736, 536, 471
**$^{1}$H NMR** (300 MHz, $CDCl_3$) δ 5.53 (1H, d, *J* =4.3 Hz), 5.00 (1H, d, *J* =9.2 Hz), 4.23 (2H, q, *J* =7.1 Hz), 3.93 (1H, dd, *J* =7.6, 4.7 Hz), 3.8 (1H, m), 3.69 (3H, s), 3.54 (1H, d, *J* =13.7 Hz), 3.42 (1H, d, *J* =13.7 Hz), 3.19 (1H, t, *J* =4.5 Hz), 2.90 (1H, dd, *J* =16.8, 6.9 Hz), 2.80 (1H, dd, *J* =16.8, 5.9 Hz), 2.30-2.20 (1H, m), 2.08-1.80 (3H, m), 1.40-1.28 (2H, m), 1.29 (3H, t, *J* =7.2 Hz), 1.27 (3H, s), 0.97 (3H, s)
**$^{13}$C NMR** (75MHz, $CDCl_3$) δ 170.3, 170.2, 167.7, 158.1, 91.5, 65.1, 64.0, 61.8, 61.6, 54.5, 52.7, 51.8, 49.0, 47.7, 44.5, 37.8, 34.9, 32.6, 26.2, 20.6, 19.7, 13.8
**HRMS** calculated for $C_{22}H_{30}N_3O_8Cl_3S$ $(M^+)$ 601.0819 found 601.0811 $(M+1^+)$ 456.0318 found 456.0311.

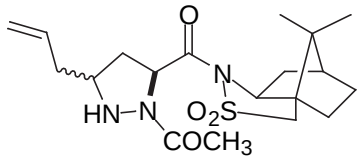



**Pyrazolidine 24**. Product obtained as a colorless oil, 81%.
**$[\alpha]_D^{23.3}$** 71.4 °C (c = 0.40, $CHCl_3$)
**IR** (thin film) ν 3244, 2964, 2258, 1739, 1704, 1698, 1336, 1283, 1248, 1197, 1138, 1069, 536

**$^{1}$H NMR** (300 MHz, $CDCl_3$) δ 5.60 (1H, d, *J* = 3.4 Hz), 5.15 (1H, d, *J* = 8.3 Hz), 4.35-4.20 (3H, m), 3.97 (1H, dd, *J* = 7.6, 4.7 Hz), 3.72 (1H, t, *J* = 3.9 Hz), 3.56 (1H, d, *J* = 13.8 Hz), 3.46 (1H, d, *J* =13.8 Hz), 2.3-2.15 (1H, m), 2.1-1.8 (3H, m), 1.30 (3H, t, *J* = 7.2 Hz), 1.22 (3H, s), 0.97 (3H, s)

**$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 168.1, 165.8, 155.0 (q, *J* = 39.1 Hz), 115.5 (q, *J* = 286.8 Hz), 114.7, 65.4, 63.1, 61.7, 54.3, 52.9, 52.6, 49.3, 47.9, 44.6, 37.7, 32.7, 26.3, 20.6, 19.8, 13.8

**HRMS** calculated for $C_{20}H_{26}N_4O_6F_3S$ ($M+1^+$) 507.1525 found 507.1516.

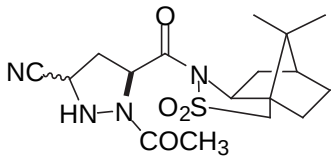



Pyrazolidine **26**, obtained as an inseparable mixture of diastereomers in a 1:1 ratio, 74 % combined yield.

**$^{1}$H NMR** (300 MHz, $CDCl_3$): δ 5.81 (2H,m), 5.30 (1H, dd, J = 19.5, 12.0 Hz), 5.12 (6H,m), 4.40 (1H,bs), 4.08 (1H,m), 3.90 (3H,m), 3.50 (7H,m), 3.20 (2H,m), 3.08 (1H,d, J= 6.3 Hz), 2.89 (1H,m), 2.74(1H,m), 2.42-1.85 (12H, cm), 1.71(2H,m)1.31 (10H,cm), 0.96 (6H,s).

**$^{13}$C NMR** (75MHz, $CDCl_3$) δ 171.9,170.7,134.8, 133.8, 118.7, 118.1, 65.5, 60.3, 59.4, 58.2, 53.3, 49.4, 48.2, 44.9, 39.6, 38.7, 38.2, 37.0, 35.7, 33.0, 26.8, 21.6, 21.6, 20.8, 20.2 . δ IR (thin film, $cm^{-1}$) 3222, 2950, 2341, 1694, 1642, 1480, 1448, 1395, 1330, 1273, 1220, 1135, 1067, 917, 780, 730.

**HRMS** calcd. for $C_{19}H_{29}N_3O_4S$ (M + Na) 418.1776, found 418.1815.



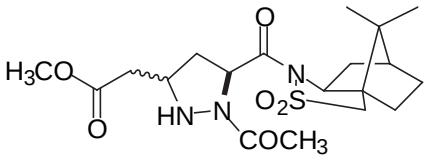

Pyrazolidine **27**, obtained as an inseparable mixture of diastereomers, in a 1.5:1 ratio, 79 % combined yield.

**$^{1}$H NMR** (300 MHz, $CDCl_3$) Non-integer proton values indicate a resonance belonging to or including the minor diasteromer:δ 5.37 (0.7H, dd, J = 8.1, 6.9 Hz), 5.21 (1H, dd, J = 8.7, 7.5 Hz),4.87 (0.7H,d, J = 6.8 Hz), 4.79 (1H, d, J = 11.7 Hz), 4.34 (0.7H, m), 3.93 (2.7H, m), 3.55 (1.7H, d, J = 14.1 Hz), 3.43 (1.7H, m), 3.05-2.88 (1.7H, m), 2.55-2.31 (1.7H, m), 2.22-2.17 (6.8H, m), 2.05-1.88 (6H,m), 1.67-1.20 (8.2H, m), 0.976 (5.1H, s).

$^{13}$C NMR (75 MHz, $CDCl_3$): δ 170.8, 170.0, 117.8, 115.9, 70.9, 65.2, 64.9, 57.5, 56.6, 52.9, 52.8, 49.5, 49.2, 48.1, 47.8, 45.8, 44.6, 38.5, 38.3, 38.1, 37.8, 32.6, 26.3, 21.0, 20.5, 19.7 .

**IR** (thin film, $cm^{-1}$) 3238, 2962, 2252, 1669, 1652, 1488, 1394, 1328, 1273, 1240, 1215, 1167, 1135, 1066, 913, 730.

**HRMS** calcd. for $C_{17}H_{24}N_4O_4S$ (M + Na) 403.1416, found 403.1410.



Pyrazoline **28**, obtained as an inseparable mixture of diastereomers in a 1.5:1 ratio, 66 % combined yield.

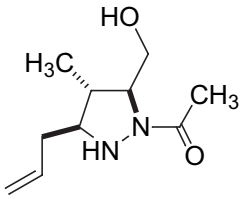
**$^{1}$H NMR** (300MHz, $CDCl_3$) Non-integer proton values indicate resonances belonging to or including the minor diastereomer : δ 5.13 (1.7H,m), 4.67(0.7H, d, J = 9.6 Hz), 4.38(1H,d, J = 16.4 Hz), 3.90 (1.7H, m), 3.75-3.65 (5.1H,m), 3.58-3.41 (3.4H, m), 2.92-2.61 (6H,m), 2.45-2.10 (8H,m), 2.05-1.74(8H,m), 1.55-1.20(9H,m), 0.97(5.1H,s).

**$^{13}$C** NMR (75MHz, $CDCl_3$) δ 171.6, 170.0, 65.2, 65.0, 59.1, 57.6, 56.9, 56.4, 53.1, 52.1, 49.2, 48.1, 45.7, 39.2, 38.5, 37.6, 37.5, 35.8, 32.7, 28.6, 26.6, 22.9, 21.2, 20.6, 20.0.

**IR** (thin film, cm $^{-1}$) 3244, 2954, 1736, 1696, 1664, 1480, 1435, 1396, 1291, 1274, 1235, 1216, 1166, 1135, 1065, 999.2, 978.5, 916.2.

**HRMS** calcd for $C_{19}H_{29}N_3O_6S$ (M + Na) 450.1675, found 450.1668.

**Reductive auxiliary removal with $NaBH_4$ to give the free alcohol.**



To a solution of 200 mg (1.0 eq, 0.47 mmol) N-acetyl pyrazolidine in 5 ml of a 10:1 solution of $THF/CH_3OH$ is added 9 mg (0.5 eq, 0.2 mmol) $NaBH_4$. After 2 h, TLC showed that an aproximately 1:1 ratio of starting material to lower $R_f$ spot existed as judged by visualization with CAM stain. An additional 9.0 mg $NaBH_4$ was added and after an additional 1 h, the reaction was seen to be complete via TLC analysis. The reaction was diluted with 50 ml diethyl ether and washed with 10 ml sodium bicarbonate solution. The aq. layer was extracted with 2x25 ml diethyl ether, and the combined organics washed with brine and dried over $Na_2SO_4$. Solvent removal via rotary evaporation followed by flash chromatography (EtOAc) furnished 77mg of the alcohol (84 %) as a colorless oil.

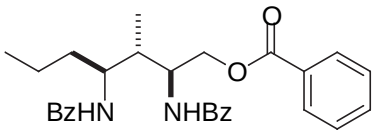
**$[\alpha]_D^{26.2}$**= - 85.0˚(c = 1.1, $CHCl_3$).

**$^{1}$H NMR** (300MHz, $CDCl_3$) δ 5.78 (1H,m), 5.11 (2H, m), 4.88 (1H,bs), 3.96 (1H, d, J = 12.9 Hz), 3.77 (2H,m), 3.50 (1H, dd, J = 11.1 , 8.1 Hz), 2.66 (1H,m), 2.40 (1H,m), 2.16 (4H,m), 1.54 (1H,m), 1.11 (3H, d, J = 6.3 Hz).

**$^{13}$C NMR** (75MHz, $CDCl_3$) d 174.2, 133.18, 118.3, 69.0, 65.3, 64.8, 44.4, 33.9, 21.5, 14.9 .

**IR** (thin film, cm $^{-1}$) 3375, 3219, 2958, 2929, 2875, 1623, 1495, 1435, 1417, 1184, 1072.2, 1041, 995, 968, 915, 668.

**HRMS** calcd for $C_{10}H_{18}N_2O_2$ (M + H) 199.1447, found 199.1445.



**Hydrogenation and Benzoylation to give diamine 29.**

To 7.0 mg (0.029 mmol, 1.0 eq) of the alcohol in 2 ml of a 1.6 M solution of aqueous HCl in methanol is added a weight equivalent of $PtO_2$. The open reaction flask is placed in a high pressure reaction apparatus which is charged with 5 atm $H_2$ and the heterogeneous reaction mixture stirred rapidly at 23˚ C. The reaction is allowed to continue in this manner for a period of 18 h to insure complete reaction has taken place. After this time, the reaction mixture is removed from the hydrogenation apparatus and filtered through celite. The filtrate is concentrated to furnish the presumed intermediate diammonium salt as a white solid. To this material is added $CH_2Cl_2$ (2 ml) and 6.0 eq (0.18 mmol, 25 µL) triethylamine followed by 3.0 eq. (0.09 mmol, 10 µL) benzoyl chloride. The reaction is monitored via TLC and after 1.5 h the reaction mixture is diluted with 10 ml $CH_2Cl_2$ and washed with 10 ml 1M aq. HCl solution, and then washed with 10 ml sat. aq. $Na_2(CO_3)_2$ solution. The organic layer is dried over $Na_2SO_4$ and solvent removed via rotary evaporation and high vacuum to give product as a white solid. Flash chromatography (3:1 hexanes/EtOAc) gives 11 mg pure product, 79 %.
**$[\alpha]_D^{25.2}$** = -2.19 ˚(c=2.16, $CHCl_3$)
**$^1$H NMR** ($CDCl_3$, 300 MHz) δ 8.00 (5H,cm), 7.45 (6H,cm), 7.02 (1H, d, J = 11.3 Hz), 4.75 (2H,m), 4.45 (1H,m), 4.28 (1H,m), 2.14 (1H,m), 1.66 (1H,m), 1.5-1.25 (4H, bm), 1.10 (3H, d, J = 6.9 Hz), 0.87 (3H, t, J = 13 Hz)
**$^{13}$C NMR** (75 MHz, $CDCl_3$) δ 167.9, 167.88, 167.6, 134.2, 134.1, 133.3, 131.7, 131.65, 129.8, 129.6, 128.7, 128.66, 128.5, 127.3, 127.1, 65.6, 51.9, 51.8, 38.6, 34.3, 19.6, 15.0, 13.9 .
**IR** (thin film, $cm^{-1}$) 3300, 3064, 2961, 2873, 1721, 1635, 1538, 1490, 1452, 1385, 1315, 1275, 1114, 1072, 1028, 911, 711.
**HRMS** calcd for $C_{29}H_{32}N_2O_4$ (M + Na) 492.2260, found 492.2272.