Supporting Information

Solid-Phase Intramolecular *N*-Acyliminium Pictet-Spengler Reactions as Crossroads to Scaffold Diversity

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General Methods. All solvents were of HPLC quality and stored over molecular sieves. Solid-phase peptide chemistry and solid-phase organic chemistry were routinely carried out using plastic-syringe technique. Flat bottom PE syringes were equipped with sintered teflon filters (50 μm pores), teflon tubing, and valves, which allow suction to be applied to the syringes below. For all reactions on solid support, $PEGA_{800}$ resin (0.4 mmol/g) was used. Prior to use, the resin was washed with methanol (× 6), DMF (× 6), and DCM (× 6). All commercially available reagents were used as received without further purification.

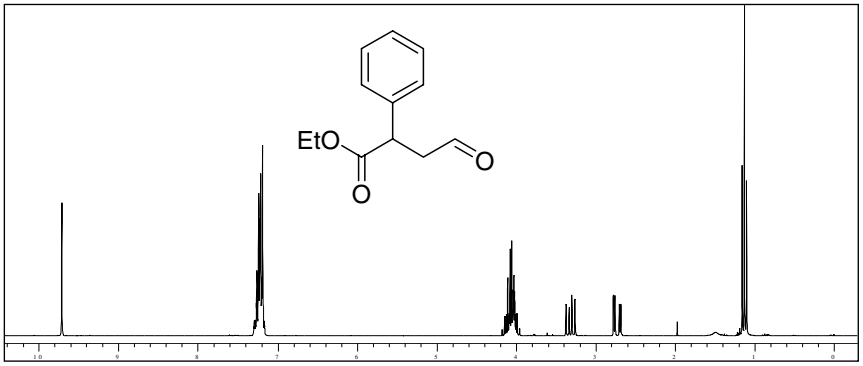
Analysis of all solid-phase reactions was performed after cleaving the products as their free acids from a resin sample. A small resin sample (<1 mg) was treated with 0.1 M aqueous NaOH (50 μL) for 2 h. After neutralization with 0.1 M HCl (50 μL), and addition of CH_3CN (100 μL), a sample (10 μL) was analyzed by analytical RP-HPLC on an HPLC system using a C-18 column (4.5 × 50 mm, 1 mL/min) with detection at 215 nm using a multiwavelength detector. Eluents A (0.1% TFA in water) and B (0.1% TFA in acetonitrile/water, 9:1) were used in a linear gradient (100% A → 100% B) in a run-time of 25 min. Collected fractions were analyzed by ESI MS on a QTOF mass spectrometer (mobile phase 50% CH_3CN (aq), 0.1 μL/min, sample conc. ~ 10 pmol/μL). All compounds on which HRMS (ESI) analysis was performed exhibited clean ^1H NMR spectra and one spot on TLC analysis, or a single peak on analytical RP-HPLC.

Material sufficient for ^1H NMR analysis was obtained by cleaving a resin sample (50-100 mg) as described above. Solution phase NMR spectra were recorded on a 250 MHz spectrometer (proton frequency 250.13 MHz) at 30 °C. ^1H (250 MHz) NMR spectra were recorded using $CDCl_3$, CD_3CN, or DMSO-d_6, as solvents, and chemical shifts were measured relative to the signals for $CHCl_3$ (7.26 ppm), CH_3CN (1.94

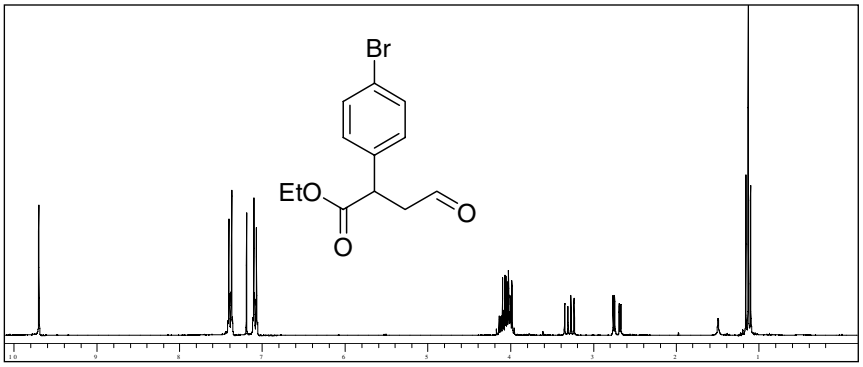
ppm), or DMSO (2.50 ppm), respectively, whereas ^{13}C (62.5 MHz) NMR spectra were recorded for all novel compounds synthesized in solution, and chemical shifts were measured relative to the signals for $CDCl_3$ (77.0 ppm), or CD_3CN (1.2 ppm). The spectral width for the phase-sensitive (States-TPPI) 1H/1H-NOESY (consult: Jeener, J.; Meier, B.H.; Bachmann, P.; Ernst, R.R. *J. Chem. Phys.* **1979**, *71*, 4546-4553) was 2 kHz with 2048 data points and 256 increments, each acquiered with 8 scans and with a relaxation delay of 1.5 sec. The mixing time was 800 ms. The zero filled data was multiplied with a squared shifted sine bell function prior to Fourier transform to a final matrix size of 2048 x 1024.

^{1}H NMR Spectra.

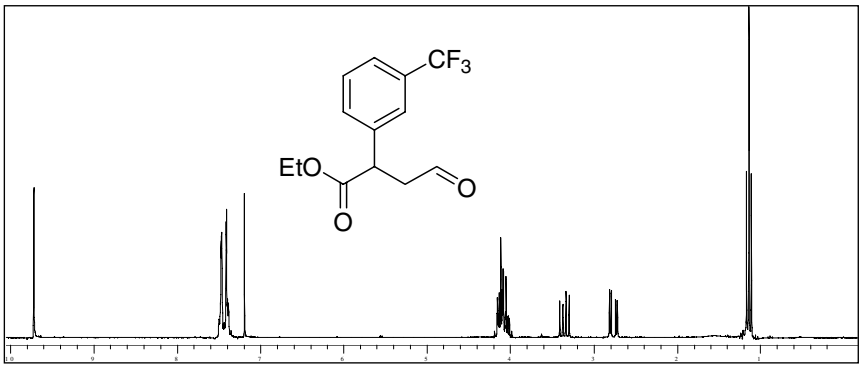
^{1}H NMR (250 MHz, $CDCl_3$) of Aldehyde **14a**:



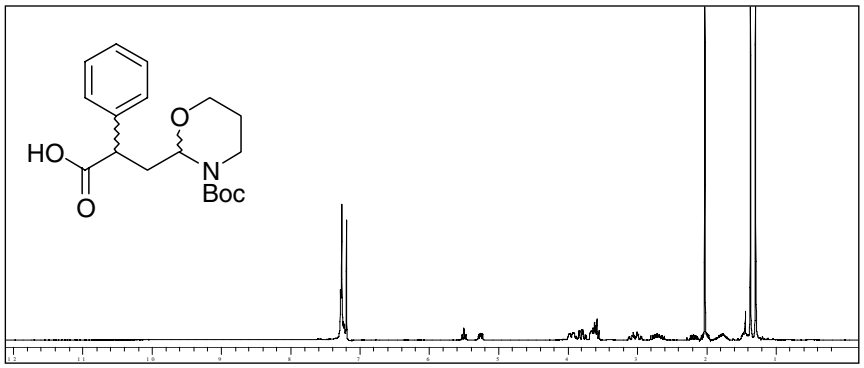
^{1}H NMR (250 MHz, $CDCl_3$) of Aldehyde **14b**:



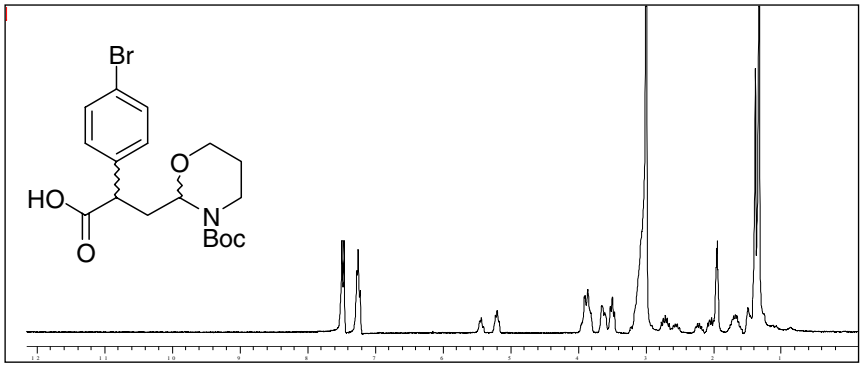
^{1}H NMR (250 MHz, $CDCl_3$) of Aldehyde **14c**:



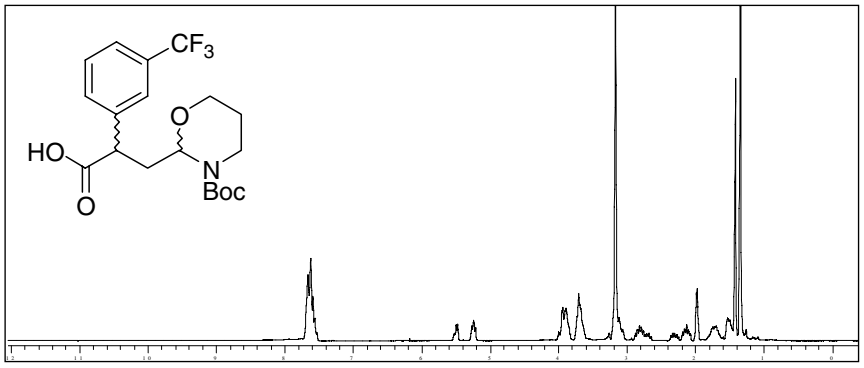
^{1}H NMR (250 MHz, CD_3CN) of masked aldehyde building block **2e**:



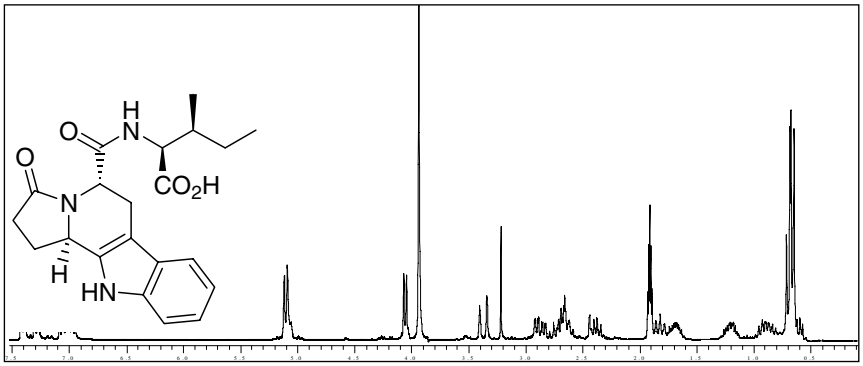
^{1}H NMR (250 MHz, CD_3CN) of masked aldehyde building block **2f**:



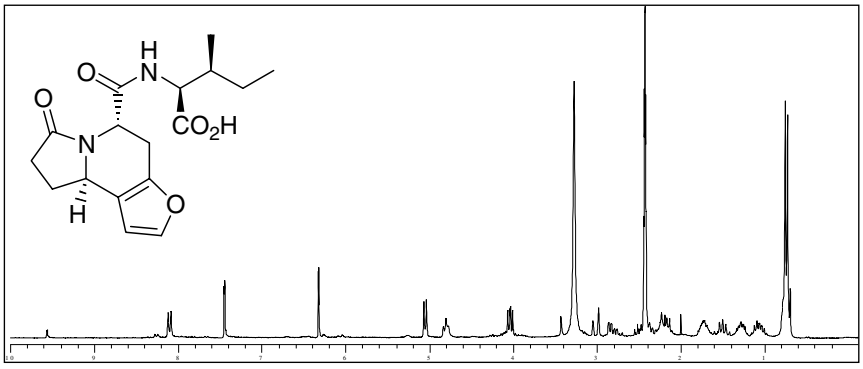
^{1}H NMR (250 MHz, CD_3CN) of masked aldehyde building block **2g**:



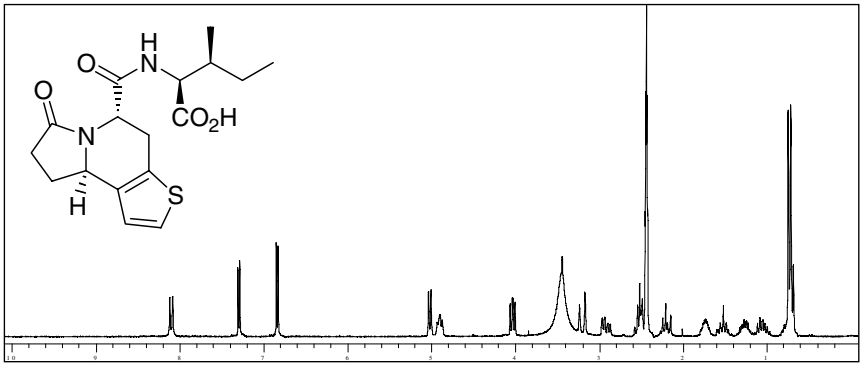
^{1}H NMR (250 MHz, CD_3CN) of Pictet-Spengler reaction product of *rac*-MABB1-Trp-Ile-OH (**4a**):



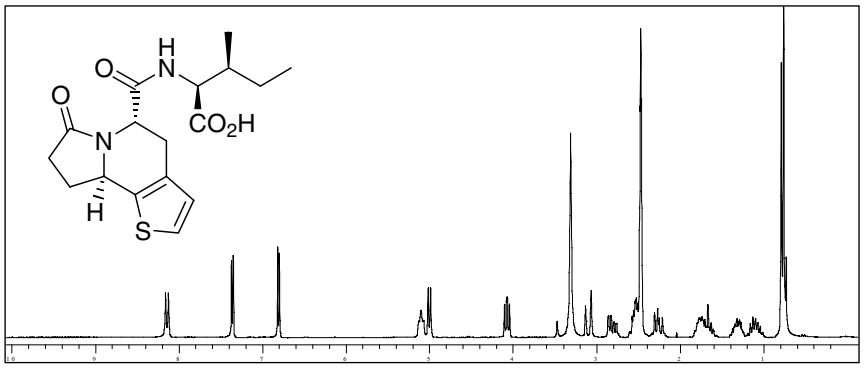
^{1}H NMR (250 MHz, DMSO-d_6) of Pictet-Spengler reaction product of *rac*-MABB1-(3-(2-furyl)Ala)-Ile-OH (**18a**):



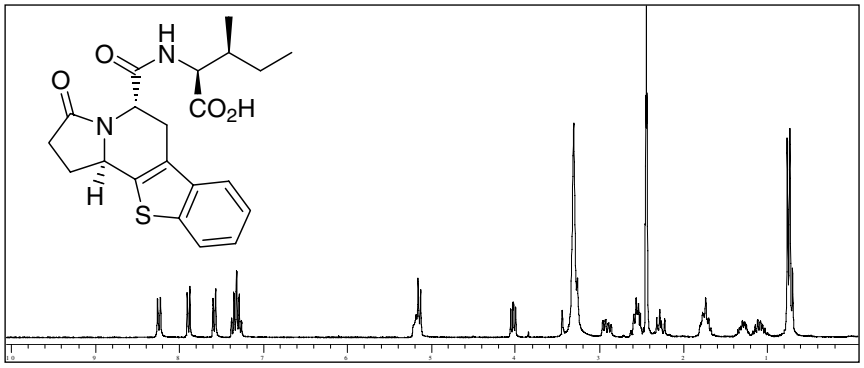
^{1}H NMR (250 MHz, DMSO-d_6) of Pictet-Spengler reaction product of *rac*-MABB1-(3-(2-thienyl)Ala)-Ile-OH (**18b**):



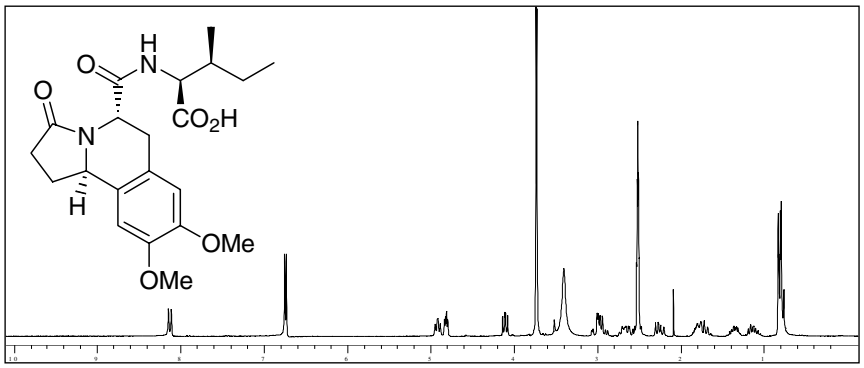
^{1}H NMR (250 MHz, DMSO-d_6) of Pictet-Spengler reaction product of *rac*-MABB1-(3-(3-thienyl)Ala)-Ile-OH (**18c**):



^{1}H NMR (250 MHz, DMSO-d_6) of Pictet-Spengler reaction product of *rac*-MABB1-(3-(3-benzothienyl)Ala)-Ile-OH (**18d**):

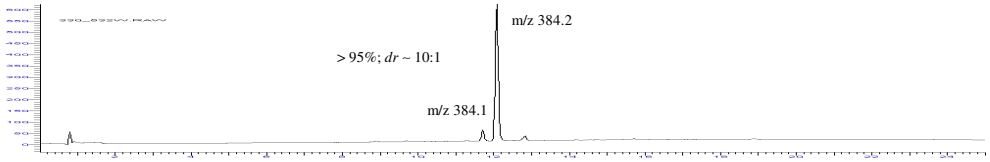


^{1}H NMR (250 MHz, DMSO-d_6) of Pictet-Spengler reaction product of *rac*-MABB1-(3-(3,4-dimethoxyphenyl)Ala)-Ile-OH (**18e**):

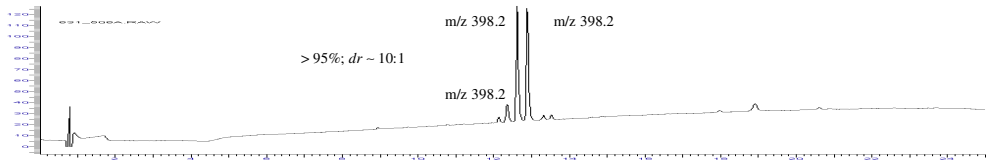


Analytical RP-HPLC Chromatograms.

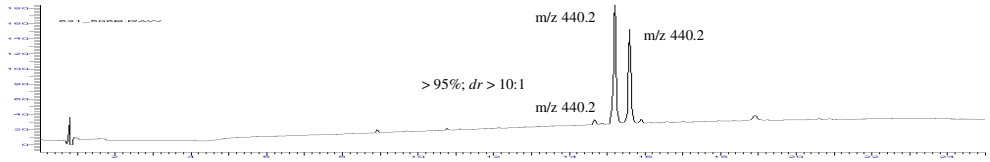
Pictet-Spengler reaction products of *rac*-MABB1-Trp-Ile-OH (**4a**):



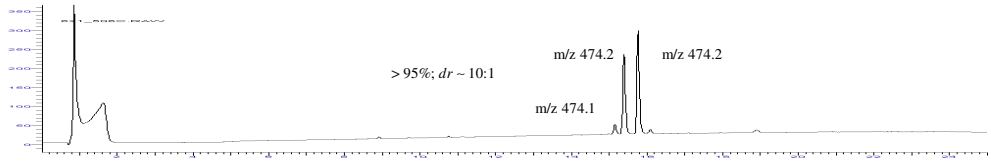
Pictet-Spengler reaction products of *rac*-MABB2-Trp-Ile-OH (**4b**):



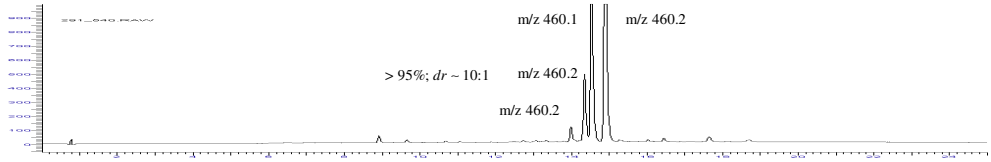
Pictet-Spengler reaction products of *rac*-MABB3-Trp-Ile-OH (**4c**):



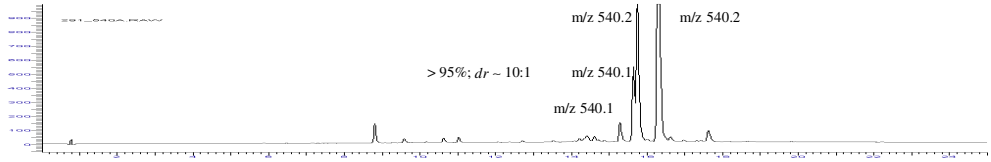
Pictet-Spengler reaction products of *rac*-MABB4-Trp-Ile-OH (**4d**):



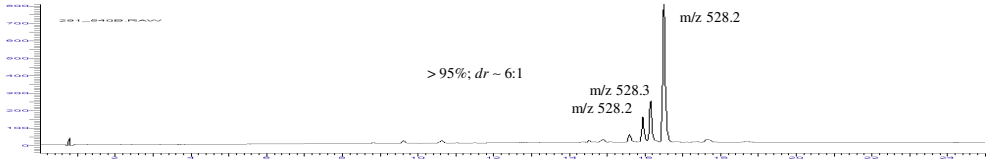
Pictet-Spengler reaction products of *rac*-MABB5-Trp-Ile-OH (**4e**):



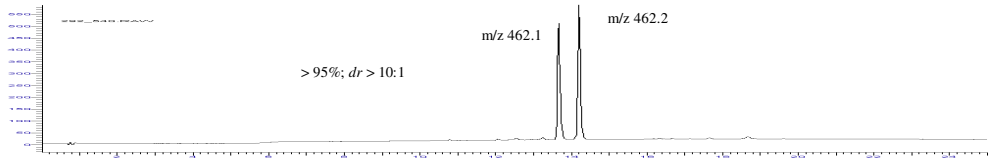
Pictet-Spengler reaction products of *rac*-MABB6-Trp-Ile-OH (**4f**):



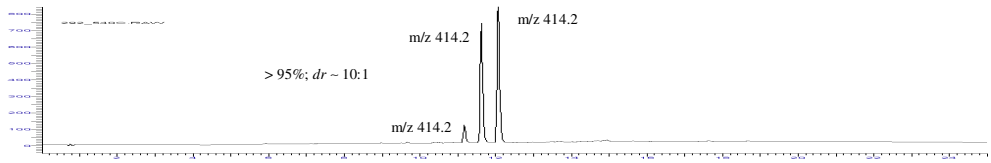
Pictet-Spengler reaction products of *rac*-MABB7-Trp-Ile-OH (**4g**):



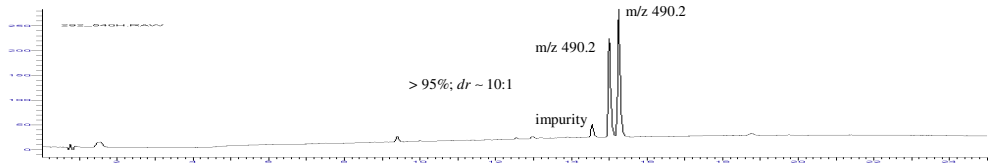
Pictet-Spengler reaction products of *rac*-MABB1-(5-Br-(D/L))Trp-Ile-OH (**16a**):



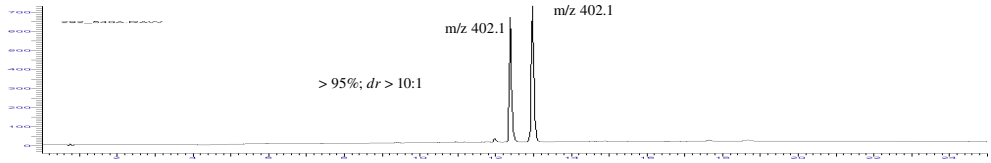
Pictet-Spengler reaction products of *rac*-MABB1-(5-MeO-(D/L))Trp-Ile-OH (**16b**):



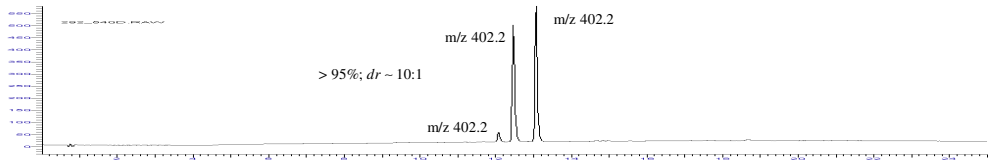
Pictet-Spengler reaction products of *rac*-MABB1-(5-BnO-(D/L))Trp-Ile-OH (**16c**):



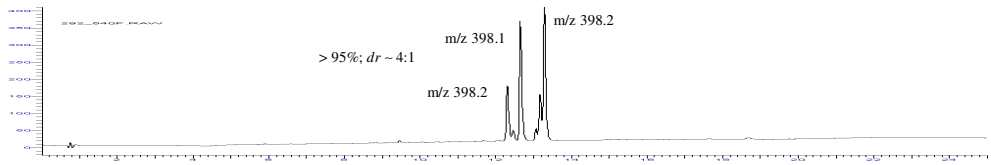
Pictet-Spengler reaction products of *rac*-MABB1-(5-F-(D/L))Trp-Ile-OH (**16d**):



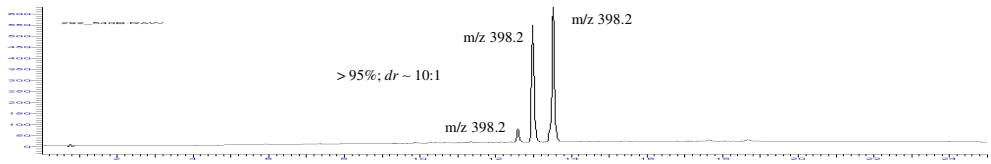
Pictet-Spengler reaction products of *rac*-MABB1-(6-F-(D/L))Trp-Ile-OH (**16e**):



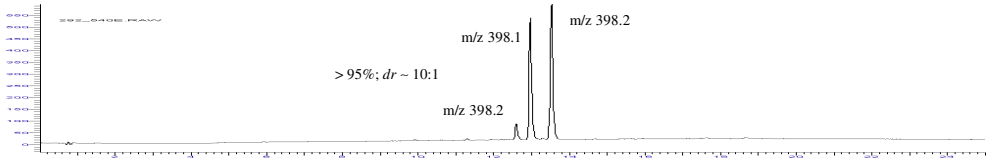
Pictet-Spengler reaction products of *rac*-MABB1-(4-Me-(D/L))Trp)-Ile-OH (**16f**):



Pictet-Spengler reaction products of *rac*-MABB1-(5-Me-(D/L))Trp-Ile-OH (**16g**):



Pictet-Spengler reaction products of *rac*-MABB1-(6-Me-(D/L))Trp-Ile-OH (**16h**):



Pictet-Spengler reaction products of *rac*-MABB1-(5-OH)Trp-Ile-OH (**16i**):