

# Supporting Information

## Efficiency in Isotetronic Acid Synthesis via a Diamine-Acid Couple Catalyzed Ethyl Pyruvate Homoaldol Reaction

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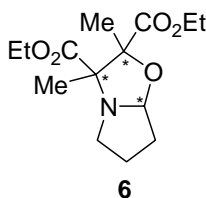
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### Experimental Section

All moisture-sensitive reactions were performed under a nitrogen atmosphere using oven-dried glassware. Solvents were dried over standard drying agent and freshly distilled prior to use. Commercially available powdered 4 Å molecular sieves (5 µm average particle size) were used without further activation. Reactions were monitored by TLC on silica gel 60 F<sub>254</sub> with detection by charring with sulfuric acid. Flash column chromatography was performed on silica gel 60 (230-400 mesh). Melting points were determined with a capillary apparatus. Optical rotations were measured at 20 ± 2 °C in the stated solvent; [α]<sub>D</sub> values are given in 10<sup>-1</sup> deg cm<sup>2</sup> g<sup>-1</sup>. <sup>1</sup>H (300 MHz) and <sup>13</sup>C (75 MHz) NMR spectra were recorded for CDCl<sub>3</sub> solutions at room temperature unless otherwise specified. Assignments were aided by homo- and heteronuclear two-dimensional experiments. The enantiomeric excess of the *tert*-butyldimethylsilyl enol ether **14** obtained under different organocatalytic conditions (Table 1) was determined by quantitative GC analysis using a Megadex DETTBSβ capillary column.

MALDI-TOF mass spectra were acquired using  $\alpha$ -cyano-4-hydroxycinnamic acid as the matrix. Aldol **2**, isotetronic acid **3**, and the *tert*-butyldimethylsilyl enol ether **14** are known compounds.<sup>6</sup>

*Abortive homoaldol reaction of ethyl pyruvate 1 under L-proline 4 catalysis (Scheme 2).*



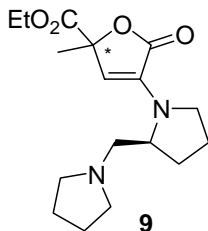
**1-oxapyrrolizidine (6).** To a stirred solution of L-proline **4** (93 mg, 0.81 mmol) in anhydrous DMSO (3 mL) ethyl pyruvate **1** (300  $\mu$ L, 2.70 mmol) was added dropwise. The mixture was stirred at room temperature for 16 h then the reaction flask connected to the high vacuum pump to remove unreacted **1** along with DMSO and give crude 1-oxapyrrolizidine **6** (218 mg, 95% with respect to **4**) as a 1:1 mixture of stereoisomers (**6a** and **6b**) of unassigned stereochemistry. MALDI-TOF MS: 285.3 ( $M^+ + H$ ).

These derivatives decompose on silica gel while  $CDCl_3$  affects their diastereomeric ratio in favor of **6b**.

**6a:**  $^1H$  NMR:  $\delta$  5.44 (dd, 1 H,  $J = 5.7$  Hz,  $J = 2.8$  Hz), 4.25-4.10 (m, 4 H, 2  $OCH_2CH_3$ ), 3.10-2.70 (m, 2 H) 2.20-1.70 (m, 4 H), 1.46 (s, 3 H,  $CH_3$ ), 1.34 (s, 3 H,  $CH_3$ ), 1.27 (t, 3 H,  $J = 7.1$  Hz,  $OCH_2CH_3$ ), 1.26 (t, 3 H,  $J = 7.1$  Hz,  $OCH_2CH_3$ ).  $^{13}C$  NMR:  $\delta$  173.4, 173.3, 99.2, 86.1, 74.8, 61.2, 61.1, 47.8, 30.8, 24.4, 21.5, 17.5, 13.9, 13.8.

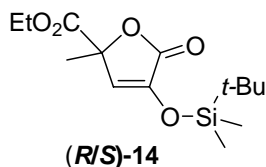
**6b:**  $^1H$  NMR:  $\delta$  5.32 (dd, 1 H,  $J = 5.5$  Hz,  $J = 1.6$  Hz), 4.15-4.00 (m, 4 H, 2  $OCH_2CH_3$ ), 3.10-2.70 (m, 2 H) 2.20-1.70 (m, 4 H), 1.55 (s, 3 H,  $CH_3$ ), 1.43 (s, 3 H,  $CH_3$ ), 1.21 (t, 3 H,  $J = 7.1$  Hz,  $OCH_2CH_3$ ), 1.20 (t, 3 H,  $J = 7.1$  Hz,  $OCH_2CH_3$ ).  $^{13}C$  NMR:  $\delta$  172.4, 172.0, 97.2, 86.1, 73.4, 61.2, 60.9, 48.0, 31.0, 24.5, 24.1, 16.8, 13.9, 13.7.

Abortive homoaldol reaction of ethyl pyruvate **1** under (*S*)-(+)-1-(2-pyrroldinylmethyl)-pyrrolidine **7** catalysis (Scheme 3).



**(2'*S*)-2-Methyl-5-oxo-4-(2'-(pyrrolidin-1''-ylmethyl)pyrrolidin-1'-yl)-2,5-dihydrofuran-2-carboxylic Acid Ethyl Ester (9).** To a stirred solution of (*S*)-(+)-1-(2-pyrroldinylmethyl)-pyrrolidine **7** (44  $\mu$ L, 0.27 mmol) in anhydrous DMSO (1 mL) ethyl pyruvate **1** (100  $\mu$ L, 0.90 mmol) was added dropwise. The mixture was stirred at room temperature for 16 h then the reaction flask connected to the high vacuum pump to remove unreacted **1**. The resulting residue was directly eluted from a column of silica gel with 9:1  $\text{CH}_2\text{Cl}_2$ -MeOH to afford the adduct **9** (63 mg, 45% with respect to **1**) as a 1:1 mixture of stereoisomers of unassigned stereochemistry.  $^1\text{H}$  NMR:  $\delta$  5.51 (s, 0.5 H, CH=C), 5.50 (s, 0.5 H, CH=C), 4.32-4.18 (m, 1 H), 4.20 (q, 1 H,  $J = 7.1$  Hz,  $\text{OCH}_2\text{CH}_3$ ), 4.19 (q, 1 H,  $J = 7.1$  Hz,  $\text{OCH}_2\text{CH}_3$ ), 3.43-3.30 (m, 1 H) 3.18-3.05 (m, 1 H), 2.86-2.63 (m, 4 H), 2.59 (d, 0.5 H,  $J = 6.8$  Hz), 2.54 (d, 0.5 H,  $J = 6.6$  Hz), 2.24-2.08 (m, 1 H), 1.97-1.75 (m, 8 H), 1.66 (s, 1.5 H,  $\text{CH}_3$ ), 1.65 (s, 1.5 H,  $\text{CH}_3$ ), 1.28 (t, 1.5 H,  $\text{OCH}_2\text{CH}_3$ ) 1.27 (t, 1.5 H,  $\text{OCH}_2\text{CH}_3$ ).  $^{13}\text{C}$  NMR:  $\delta$  170.2, **170.1**, 168.3, **168.2**, 135.5, **135.4**, 112.3, **112.0**, 83.3, **83.3**, 62.0, **62.0**, 58.3, **58.2**, 57.4, **57.3**, 54.3, **54.3**, 49.3, **49.2**, 29.1, **29.1**, 23.8, **23.5**, 23.4, **23.4**, 22.7, **22.7**, 14.0, **14.0**. MALDI-TOF MS: 323.4 ( $\text{M}^+ + \text{H}$ ).

Synthesis of racemic tert-butyl dimethylsilyl enol ether **14**.



In order to better evaluate the enantiomeric excess of the *tert*-butyldimethylsilyl enol ether **14** obtained under different organocatalytic conditions (Table 1) a racemic sample of **14** was prepared in the following way.

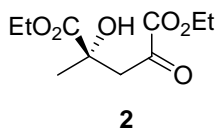
**(*R/S*)-4-(*tert*-Butyldimethyl-silanyloxy)-2-methyl-5-oxo-2,5-dihydrofuran-2-carboxylic Acid Ethyl Ester (*R/S*-14).** To a stirred solution of pyrrolidine (23  $\mu$ L, 0.27 mmol) in *i*-PrOH (1 mL) acetic acid (15  $\mu$ L, 0.27 mmol) was added in one portion. The solution was stirred at room temperature for 15 min then ethyl pyruvate **1** (100  $\mu$ L, 0.90 mmol) was added dropwise. The mixture was stirred for an additional 16 h then concentrated. The residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) then Amberlyst 15 (300 mg) was added. The suspension was shaken at room temperature for 48 h and then the resin was filtered off and washed thoroughly with CH<sub>2</sub>Cl<sub>2</sub>. The combined filtrates were concentrated and dried under high vacuum. The resulting residue (~77 mg) was dissolved in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (4 mL) then imidazole (184 mg, 2.70 mmol) and *tert*-butyldimethylsilyl chloride (271 mg, 1.80 mmol) were added sequentially. The mixture was stirred at room temperature for 12 h, then concentrated and eluted from a column of silica gel with 6:1 cyclohexane-Et<sub>2</sub>O to give ***R/S*-14** (46 mg, 35% with respect to **1**) as a clear colorless oil (see the corresponding chromatogram at the end of this Supporting Information). <sup>1</sup>H NMR:  $\delta$  6.24 (s, 1 H, CH=C), 4.22 (q, 2 H,  $J = 7.1$  Hz, OCH<sub>2</sub>CH<sub>3</sub>), 1.69 (s, 3 H, CH<sub>3</sub>), 1.28 (t, 3 H, OCH<sub>2</sub>CH<sub>3</sub>), 0.96 (s, 9 H, *t*-Bu), 0.25 (s, 6 H, (CH<sub>3</sub>)<sub>2</sub>Si). <sup>13</sup>C NMR:  $\delta$  169.0, 168.0, 143.1, 124.4, 81.6, 62.4, 25.4, 22.9, 18.3, 14.0, -4.9.

*Homoaldol reaction of ethyl pyruvate 1 under (*S*)-(+)-1-(2-pyrrodimethyl)-pyrrolidine 7/TFA couple catalysis (Scheme 4).*

To a stirred solution of (*S*)-(+)-1-(2-pyrrodimethyl)-pyrrolidine **7** (44  $\mu$ L, 0.27 mmol) in anhydrous DMSO (1 mL) trifluoroacetic acid (TFA) (21  $\mu$ L, 0.27 mmol) was added in one portion. The solution was stirred at room temperature for 15 min then ethyl pyruvate **1** (100  $\mu$ L, 0.90 mmol) was added dropwise. The mixture was stirred for an additional 16 h then the reaction flask

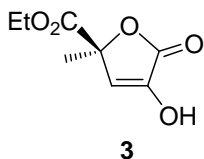
connected to the high vacuum pump to remove DMSO. The residue was dissolved in CH<sub>2</sub>Cl<sub>2</sub> (2 mL) then Amberlyst 15 (300 mg) was added in one portion. The suspension was shaken at room temperature for 3 h and then the resin was filtered off and washed thoroughly with CH<sub>2</sub>Cl<sub>2</sub>. The combined filtrates were concentrated and dried under high vacuum. A sample of the resulting residue was analyzed by <sup>1</sup>H NMR spectroscopy to determine the product distribution (mol %) which is reported in Table 1 (entry 1).

**(S)-2-Hydroxy-2-methyl-4-oxoglutarate (2).**



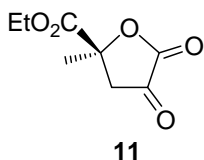
<sup>1</sup>H NMR: δ 4.32 (q, 2 H, *J* = 7.1 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 4.24 (q, 2 H, *J* = 7.1 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 3.57 (bs, 1 H, OH), 3.38 (d, 1 H, *J*<sub>3a,3b</sub> = 18.2 Hz, H-3a), 3.32 (d, 1 H, H-3b), 1.46 (s, 3H, CH<sub>3</sub>), 1.36 (t, 3 H, OCH<sub>2</sub>CH<sub>3</sub>), 1.28 (t, 3 H, OCH<sub>2</sub>CH<sub>3</sub>). <sup>13</sup>C NMR: δ 191.8, 175.3, 160.3, 72.0, 62.7, 62.2, 48.2, 26.7, 14.0, 13.9.

**(S)-Isotretroic acid (3).**



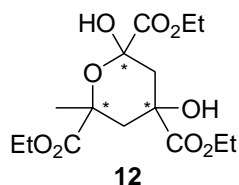
<sup>1</sup>H NMR: δ 6.25 (s, 1 H, CH=C), 4.23 (bs, 1 H, OH), 4.22 (q, 2 H, *J* = 7.1 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 1.72 (s, 3 H, CH<sub>3</sub>), 1.29 (t, 3 H, OCH<sub>2</sub>CH<sub>3</sub>). <sup>13</sup>C NMR: δ 169.1, 168.7, 142.6, 119.2, 83.1, 62.6, 22.8, 14.0.

**(S)-2-Methyl-4,5-dioxo-tetrahydrofuran-2-carboxylic Acid Ethyl Ester (11).**



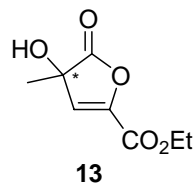
<sup>1</sup>H NMR: δ 4.25 (q, 2 H, *J* = 7.1 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 3.17 (d, 1 H, *J*<sub>3a,3b</sub> = 19.3 Hz, H-3a), 2.76 (d, 1 H, H-3b), 1.86 (s, 3 H, CH<sub>3</sub>), 1.29 (t, 3 H, OCH<sub>2</sub>CH<sub>3</sub>).

**Trimer (12).**



$^1\text{H}$  NMR:  $\delta$  5.02 (bs, 1 H, OH), 4.32-4.28 (m, 6 H, 3  $\text{OCH}_2\text{CH}_3$ ), 2.73 (dd, 1 H,  $J_{2\text{ax},2\text{eq}} = 14.3$  Hz,  $J_{2\text{eq},4\text{eq}} = 2.4$  Hz, H-2eq), 2.40 (d, 1 H, H-2ax), 2.08 (dd, 1 H,  $J_{4\text{ax},4\text{eq}} = 14.3$  Hz, H-4eq), 2.01 (d, 1 H, 4ax), 1.52 (s, 3 H,  $\text{CH}_3$ ), 1.38-1.25 (m, 9 H, 3  $\text{OCH}_2\text{CH}_3$ ).  $^{13}\text{C}$  NMR:  $\delta$  175.9, 173.3, 168.8, 95.6, 75.1, 71.6, 62.4, 62.1, 62.0, 40.0, 36.6, 28.6, 14.1, 14.0.

**4-Hydroxy-4-methyl-5-oxo-4,5-dihydrofuran-2-carboxylic Acid Ethyl Ester (13).**



$^1\text{H}$  NMR:  $\delta$  6.22 (s, 1 H,  $\text{CH}=\text{C}$ ), 4.23 (q, 2 H,  $J = 7.1$  Hz,  $\text{OCH}_2\text{CH}_3$ ), 1.81 (s, 3 H,  $\text{CH}_3$ ), 1.28 (t, 3 H,  $\text{OCH}_2\text{CH}_3$ ).

The above residue (~95 mg) was dissolved in anhydrous  $\text{CH}_2\text{Cl}_2$  (4 mL) then imidazole (184 mg, 2.70 mmol) and *tert*-butyldimethylsilyl chloride (271 mg, 1.80 mmol) were added sequentially. The mixture was stirred at room temperature for 12 h, then concentrated and eluted from a column of silica gel with 6:1 cyclohexane- $\text{Et}_2\text{O}$  to give **14** (72 mg, 53% with respect to **1**, 68% ee) as a clear colorless oil.

*Screening of protic acids and solvents in the homoaldol reaction of ethyl pyruvate 1 under (S)-(+)-1-(2-pyrrodimethyl)-pyrrolidine 7/protic acid catalysis (Table 1).*

To a stirred solution of (S)-(+)-1-(2-pyrrodimethyl)-pyrrolidine **7** (44  $\mu\text{L}$ , 0.27 mmol) in the stated anhydrous solvent (1 mL) the reported (Table 1) amount of protic acid was added in one portion. The solution was stirred at room temperature for 15 min then ethyl pyruvate **1** (100  $\mu\text{L}$ , 0.90 mmol) was added dropwise. The mixture was stirred for an additional 16 h (unless otherwise specified. See footnote in Table 1) then concentrated. The residue was dissolved in  $\text{CH}_2\text{Cl}_2$  (2 mL)

then Amberlyst 15 (300 mg) was added in one portion. The suspension was shaken at room temperature for 3 h and then the resin was filtered off and washed thoroughly with CH<sub>2</sub>Cl<sub>2</sub>. The combined filtrates were concentrated and dried under high vacuum. A sample of the resulting residue was analyzed by <sup>1</sup>H NMR spectroscopy to determine the product distribution (mol%) which is reported in Table 1.

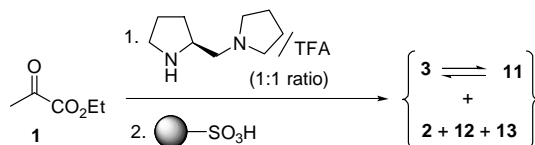
The above residue was dissolved in anhydrous CH<sub>2</sub>Cl<sub>2</sub> (4 mL) then imidazole (184 mg, 2.70 mmol) and *tert*-butyldimethylsilyl chloride (271 mg, 1.80 mmol) were added sequentially. The mixture was stirred at room temperature for 12 h, then concentrated and eluted from a column of silica gel with 6:1 cyclohexane-Et<sub>2</sub>O to give **14** (yields and ee% reported in Table 1) as a clear colorless oil.

**14** (Table 1 entry 4; 86% ee): 80 mg, 59%. [α]<sub>D</sub>: -83 (c 0.1, CH<sub>2</sub>Cl<sub>2</sub>); lit.<sup>6</sup>: [α]<sub>D</sub>: -84 (c 0.01, CH<sub>2</sub>Cl<sub>2</sub>, 96% ee).

*Effect of variation of 7/TFA couple (1:1 ratio) amount on the stereoselectivity of the homoaldol reaction of ethyl pyruvate 1.*

The results of this study are summarized in Table S1.

**Table S1.**



entry	7/TFA mol%	solvent	mol% <sup>a</sup>				yield% <sup>b</sup> (ee%) <sup>c</sup>
			2	3+11	$\frac{1}{2}$	13	14
1	20	<i>i</i> -PrOH	2 4	33+18	2 5	0	49 (74)
2	10	<i>i</i> -PrOH <sup>d</sup>	/	/	/	/	/
3	40	<i>i</i> -PrOH	5	55+21	1 3	6	35 (70)
4	50	<i>i</i> -PrOH	4	60+21	6	9	33 (66)
5	100	<i>i</i> -PrOH	8	61+31	0	0	27 (50)

<sup>a</sup>Determined by <sup>1</sup>H NMR analysis of the crude reaction mixture. <sup>b</sup>Isolated yield. <sup>c</sup>Determined by chiral GC. <sup>d</sup>Conversion of **1** <5%.

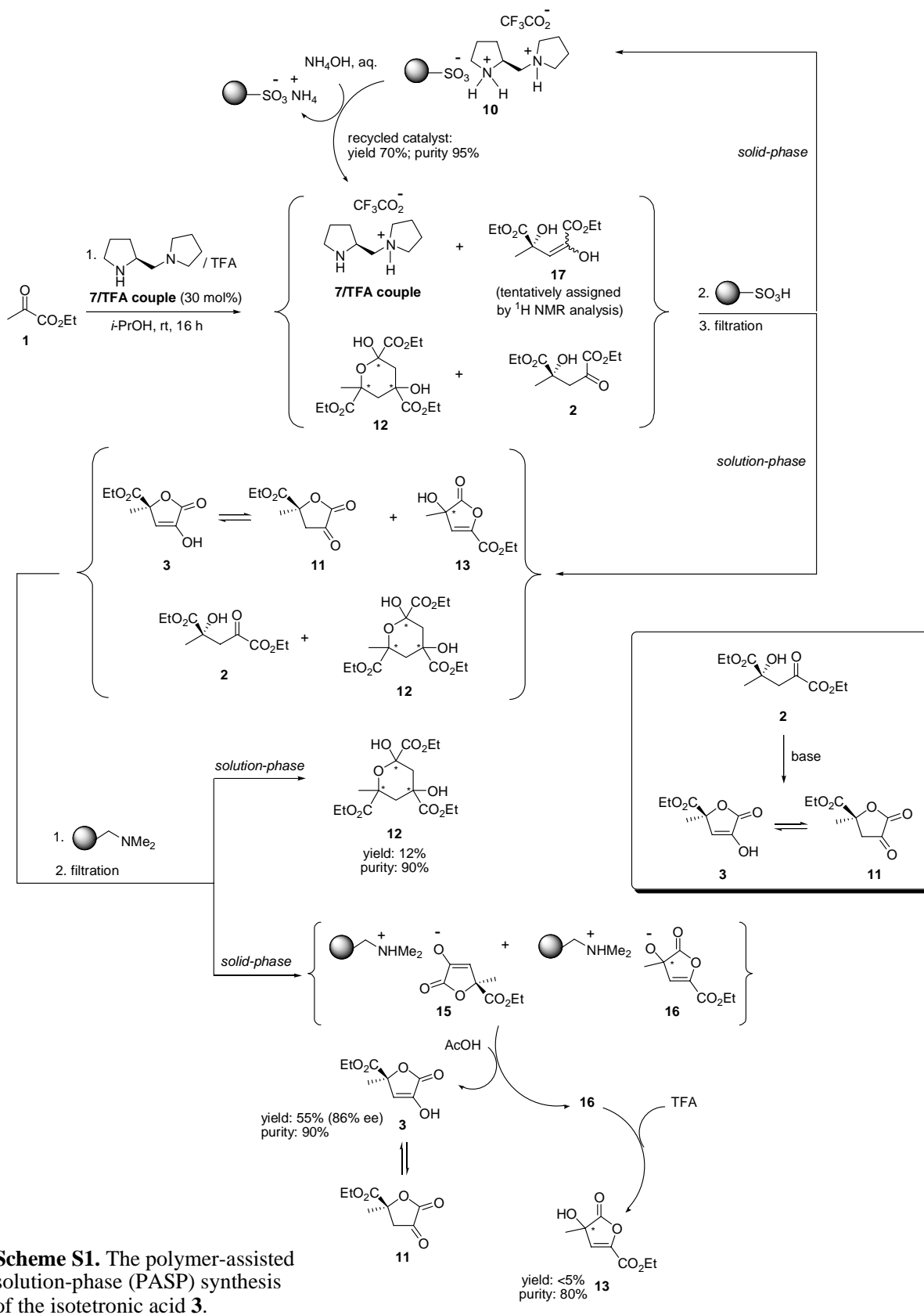
*The polymer-assisted solution-phase (PASP) synthesis of the isotetronic acid 3 (Scheme 5 and Scheme S1).*

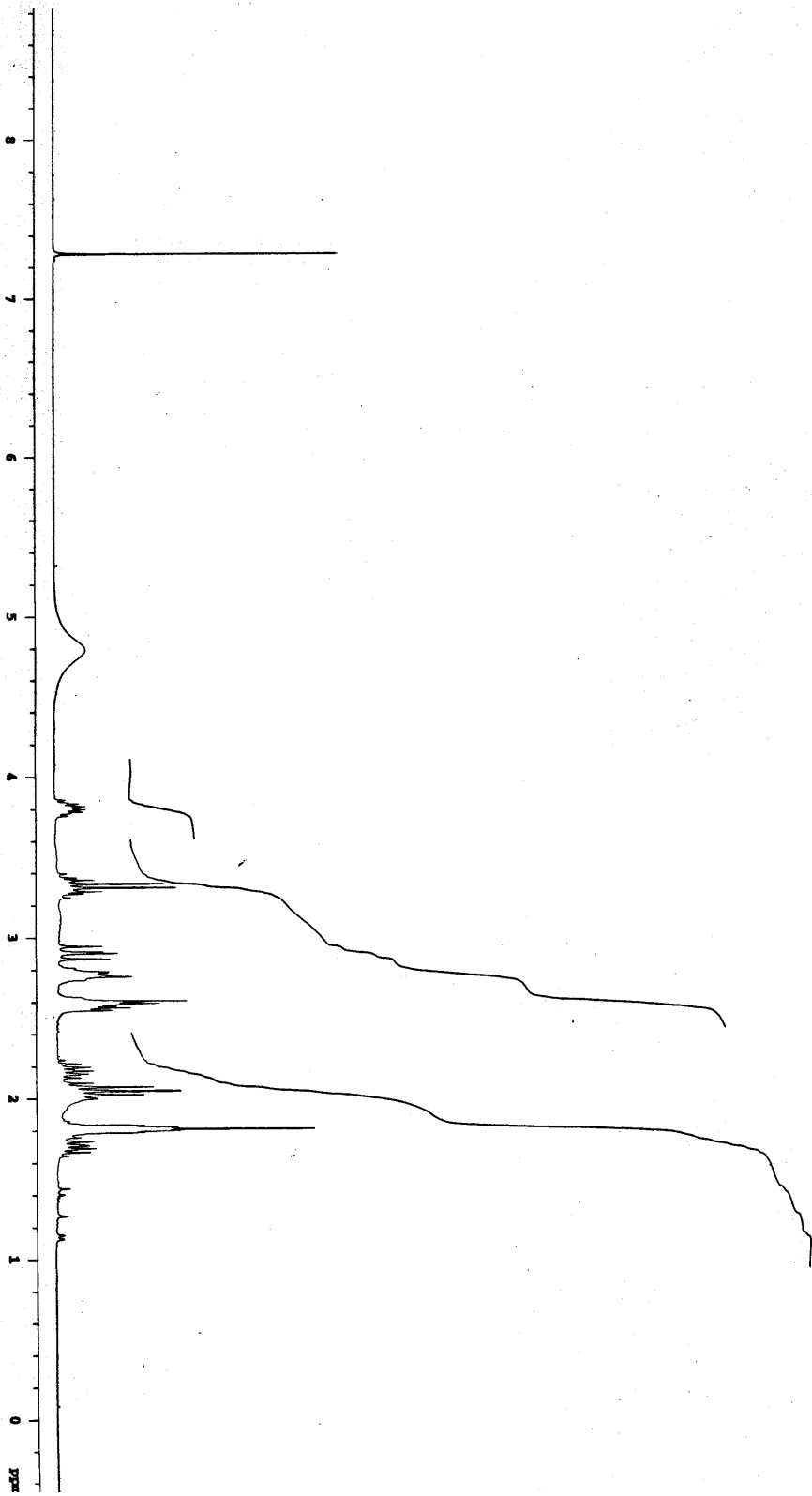
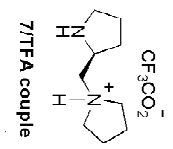
To a stirred solution of (*S*)-(+)-1-(2-pyrrodimethyl)-pyrrolidine **7** (220  $\mu$ L, 1.35 mmol) in *i*-PrOH (3 mL) trifluoroacetic acid (TFA) (103  $\mu$ L, 1.35 mmol) was added in one portion. The solution was stirred at room temperature for 15 min then ethyl pyruvate **1** (500  $\mu$ L, 4.50 mmol) was added dropwise. The mixture was stirred for an additional 16 h then concentrated. The residue was dissolved in  $\text{CH}_2\text{Cl}_2$  (8 mL) then Amberlyst 15 (1.5 g) was added in one portion. The suspension was shaken at room temperature for 3 h and then the resin was filtered off and washed thoroughly with  $\text{CH}_2\text{Cl}_2$ . The combined filtrates were concentrated and dried under high vacuum to give a crude material (466 mg).

*Recycling of the catalyst.* The polymer was suspended in a 28%  $\text{NH}_4\text{OH}$  aqueous solution (10 mL) and the resulting mixture shaken at room temperature for 12 h. The resin was then filtered off and washed thoroughly with MeOH. The combined filtrates were concentrated to give the (*S*)-(+)-1-(2-pyrrodimethyl)-pyrrolidine **7**/TFA couple (253 mg, 70% with respect to **7**) at least 95% pure as determined by  $^1\text{H}$  NMR analysis.

The crude material (466 mg) resulting from the treatment with Amberlyst 15 was instead dissolved in  $\text{CH}_2\text{Cl}_2$  (12 mL) then Amberlyst 21 (2.5 g) was added in one portion. The suspension was shaken at room temperature for 12 h and then the resin was filtered off and washed thoroughly with  $\text{CH}_2\text{Cl}_2$ . The combined filtrates were concentrated and dried under high vacuum to give the trimer byproduct **12** (62 mg, 12% with respect to **1**) at least 90% pure as determined by  $^1\text{H}$  NMR analysis. MALDI-TOF MS: 371.4 ( $\text{M}^+ + \text{Na}$ ). The polymer was suspended in  $\text{CH}_2\text{Cl}_2$  (6 mL) and then AcOH (4 mL) was added in one portion. The resulting mixture was shaken at room temperature for 16 h. The resin was then filtered off and washed thoroughly with  $\text{CH}_2\text{Cl}_2$ . The combined filtrates were concentrated to give the isotetronic acid **3** in equilibrium with its dicarbonyl form **11** (230 mg, 55%; 86% ee) at least 90% pure as determined by  $^1\text{H}$  NMR analysis.

The resin left after the treatment with AcOH was then suspended in CH<sub>2</sub>Cl<sub>2</sub> (8 mL) and then TFA (2 mL) was added in one portion. The resulting mixture was shaken at room temperature for 2 h. The resin was then filtered off and washed thoroughly with CH<sub>2</sub>Cl<sub>2</sub>. The combined filtrates were concentrated to give the lactone **13** (9 mg, ~1% with respect to **1**) at least 80% pure as determined by <sup>1</sup>H NMR analysis.

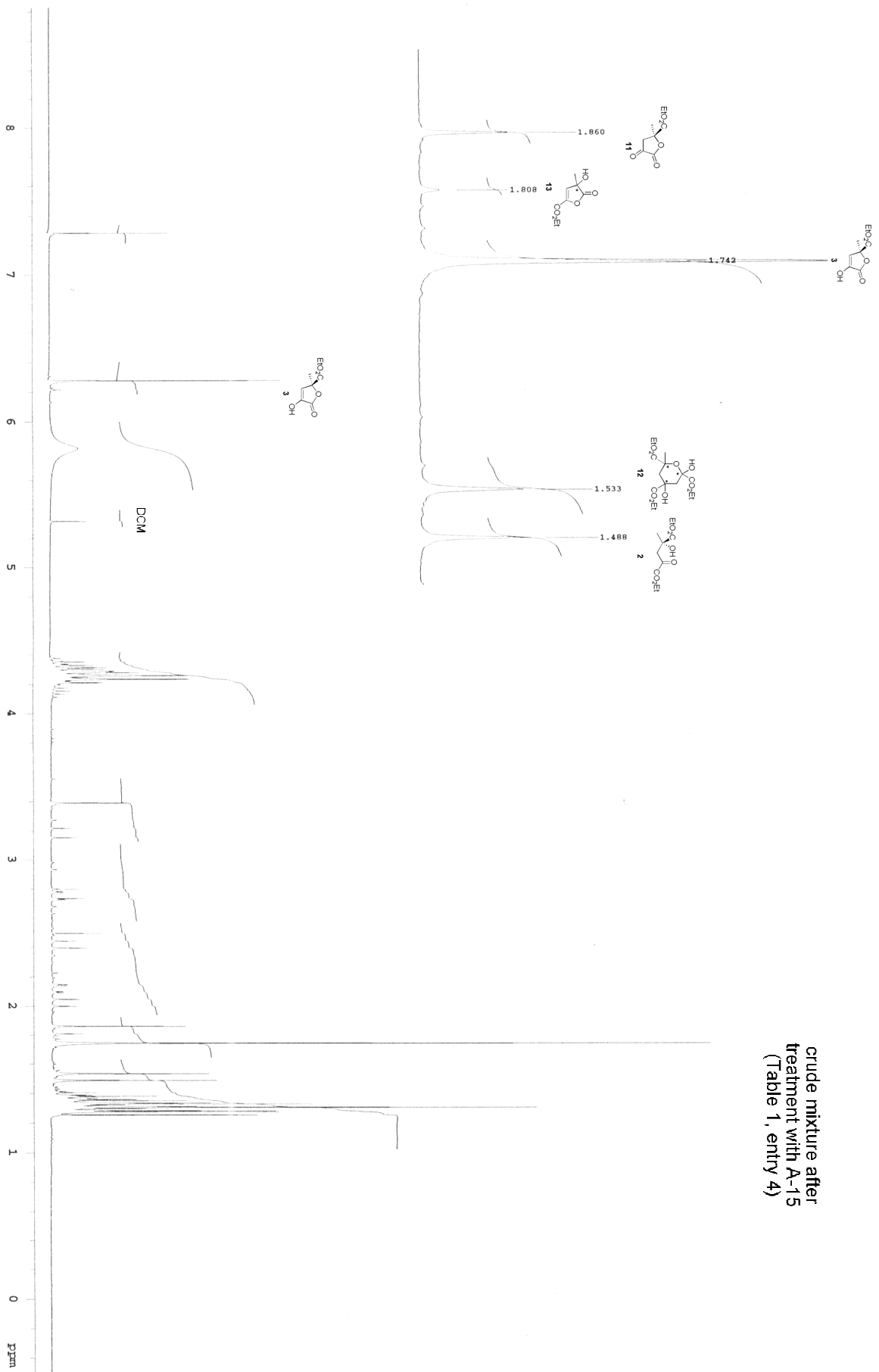


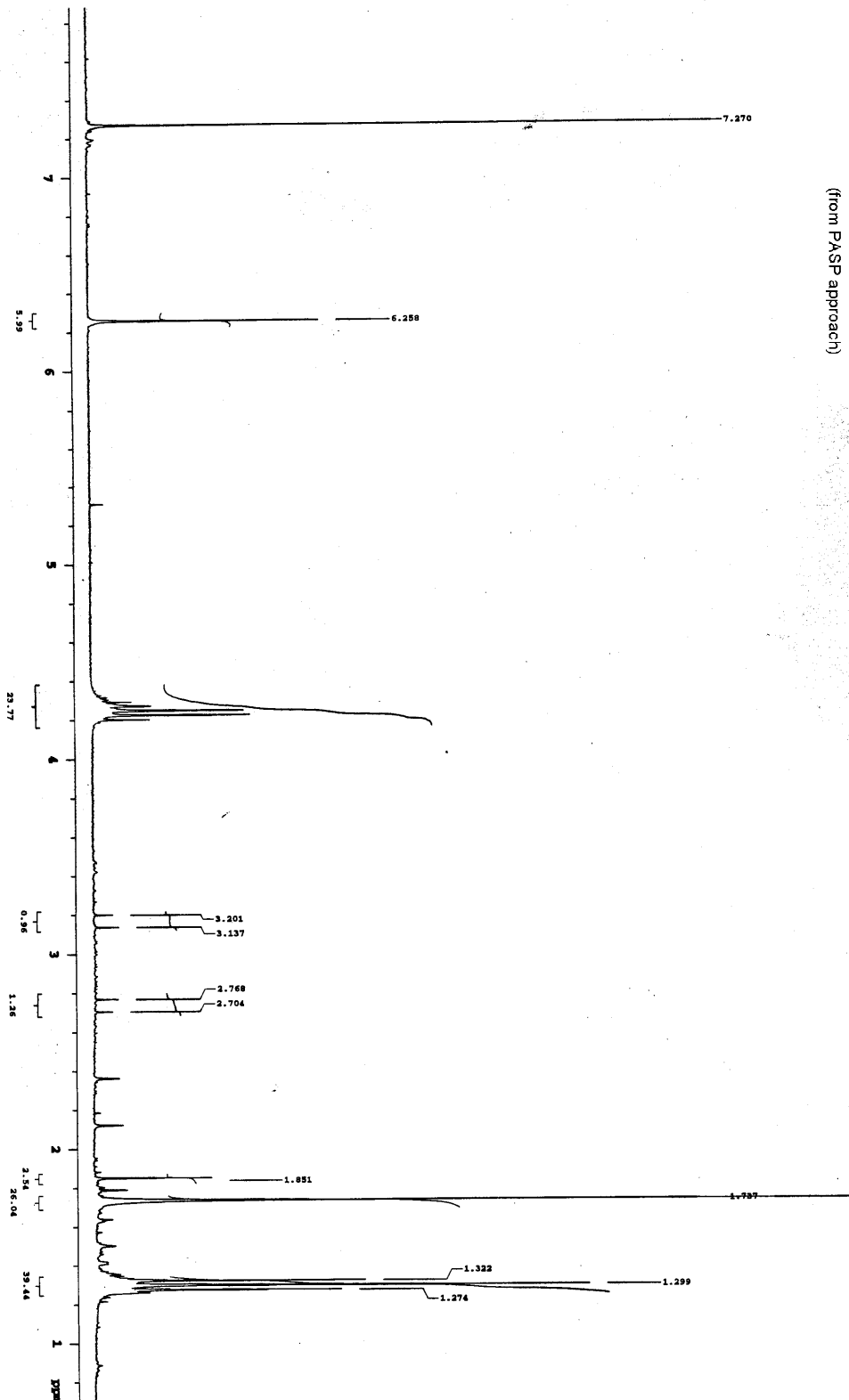
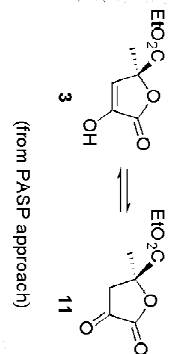


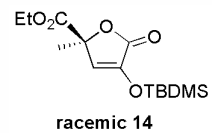
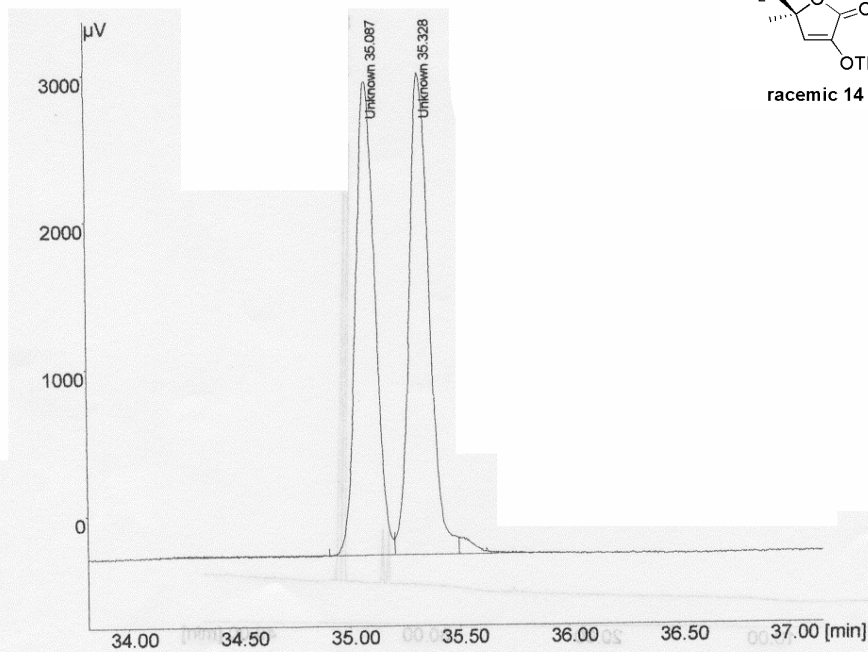
crude mixture before  
treatment with A-15  
(Table 1, entry 4)



crude mixture after  
treatment with A-15  
(Table 1, entry 4)







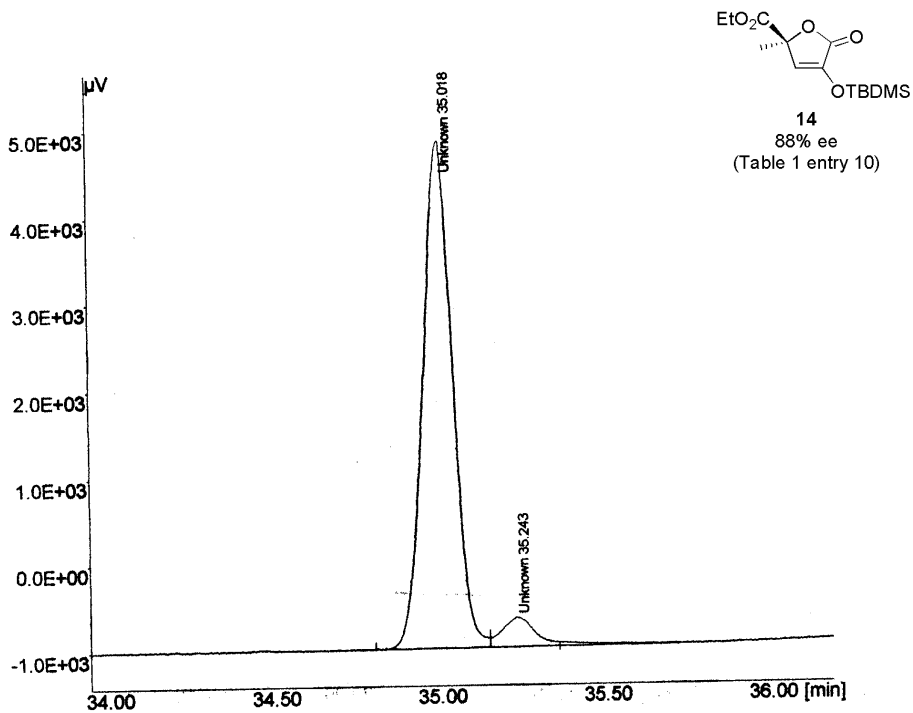
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 Group : FOGO  
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2		35.328	20296.567	51.030

Total Area of Peak = 39773.961 [ $\mu\text{V} \cdot \text{Sec}$ ]



File name : PDF 52080.CH1

Info :  
 ee prodotto siliato  
 90 ---- 2 gradi min --- 200

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2		35.243	2299.617	6.087

Total Area of Peak = 37779.225 [μV.Sec]