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Synthesis and Stereochemistry of Some Thiazolidines Related to 6-(Hydroxyethyl)-Penams.

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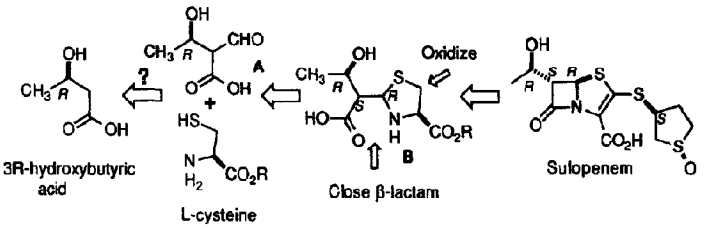
Abstract: L-Cysteine and D-penicillamine esters reacted with (R,R)- or (S,S)-2-t-butyl-5-dimethylamino-methylene-6-methyl-[1,3]dioxan-4-one **3** to provide thiazolidines with high stereospecificity. The major products were potential precursors for cis-β-lactams.

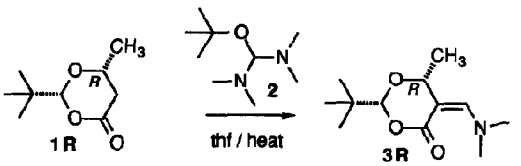
Several years ago, we started to examine alternate approaches to sulopenem[1], (5R, 6S)-6-(1(R)-hydroxyethyl)-2-[(cis-(1R)-oxo-(3S)-thiolanyl)thio]-2-penem, using three starting materials that were readily available from the "chiral pool": 3R-hydroxybutyric acid, L-cysteine, and D-methionine[2]. In this paper, stereospecific syntheses of some thiazolidines derived from 3-hydroxybutyric acid and either L-cysteine or D-penicillamine are described as part of our approach to the penem nucleus.



Our strategy for the penem nucleus followed the classical approach of Sheehan[3], first making an optically active thiazolidine **B** from cysteine and a formylated-derivative **A** of 3-hydroxy-butyric acid. The butyrate carboxylic acid and the thiazolidine nitrogen in **B** would then need to be coupled to form the β-lactam of the penam system[4]. Finally, Pummerer oxidation alpha to sulfur would provide functionality for the introduction of the thiolane sidechain[5].

For the protection of the acid and hydroxyl groups in 3-hydroxy-butyric acid, we turned to the dioxanone chemistry of Seebach[6]. 2R-(t-Butyl)-6R-methyl-1,3-dioxan-4-one **1** was prepared according to the modification described by Schreiber[7]. Enamine **3R** was formed with Bredereck's reagent[8] **2** in tetrahydrofuran solution in moderate yields (35-57%) and was isolated in pure form as a low melting solid by flash chromatography[9]. The material was best used immediately since it tended to darken upon exposure to air. No enamine formation was seen with benzyl 3R-(t-butyldimethylsilyloxy)butyrate and neat reagent **2**, while t-butyl 3R-(t-

butyldimethylsilyloxy)thiobutyrate was converted to N,N-dimethyl 3R-(t-butyldimethyl-silyloxy)-butyramide. The successful enamine formation with cyclic acetal **1R** may be due to the increased acidity of the methylene protons due to the "ring effect" as seen also for Meldrum's acid[10].



Dioxanone enamine **3R** was reacted with L-cysteine ethyl ester hydrochloride in pyridine at room temperature which gave one product **4** as a crystalline solid in 41% yield. The structure was determined by X-ray crystal analysis (Figure 1)[11]. In **4**, the C5 and C8 stereochemistry (penam numbering) were the desired configuration while C6 had the wrong R-stereochemistry. The C6 stereochemistry was expected since the three substituents on the six-membered ring were all equatorial. The thiazolidine ring was 2,4-cis-substituted. Compound **4** was a precursor to a cis-β-lactam. One key feature from the X-ray was the bifurcated hydrogen bond between the thiazolidine NH and the two carbonyl groups.

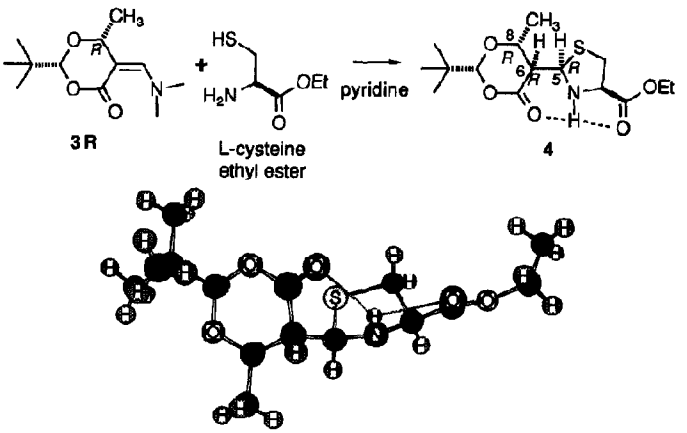
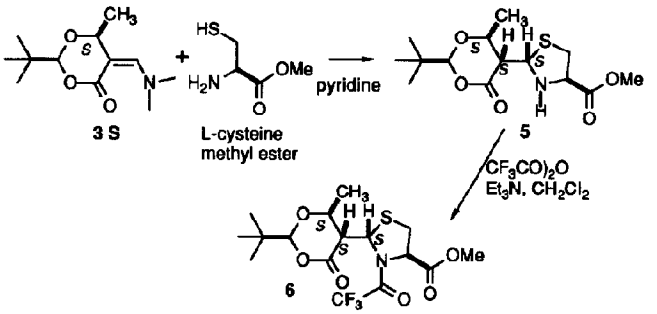


Figure 1. Structure of compound **4** showing hydrogen bonds.

If the methyl group in **3R** controlled C6 and L-cysteine controlled C5, then **3S** should give the desired trans-β-lactam precursor, while the hydroxyethyl configuration could be inverted later in the synthesis. *2S-tert-Butyl-5-dimethylaminomethylene-6S-methyl-[1,3]dioxan-4-one* (**3S**)was reacted with L-cysteine methyl ester hydrochloride in pyridine and again one isomer **5**

was isolated in 29% yield as an oil. Since we were not able to prove the absolute stereochemistry unequivocally by nmr methods, the thiazolidine **5** was converted to its trifluoroacetamide derivative **6** with trifluoroacetic anhydride and triethylamine in methylene chloride. Only one isomer was produced and based on the experiments described below we believe that no rearrangement of the thiazolidine center has occurred.



The X-ray structure of amide **6** showed that the two newly formed stereocenters were both S which would give a cis-β-lactam if the ring could be closed (Figure 2). In this instance, C6 was correct, C5 and C8 were wrong and the thiazolidine was 2, 4-trans-substituted.

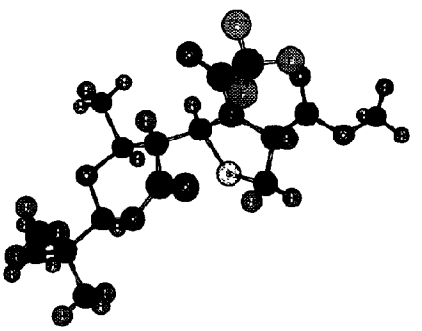
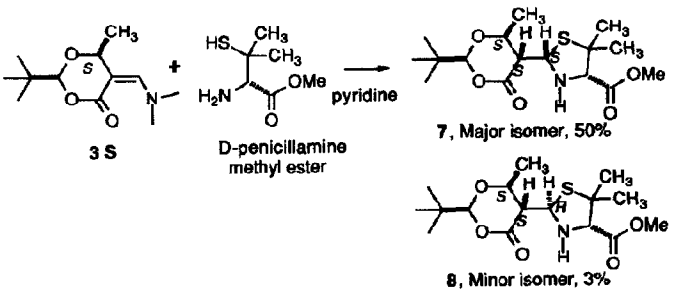


Figure 2. Structure of compound **6**.

Since D-cysteine esters were not readily available commercially, D-penicillamine methyl ester hydrochloride was used in the condensation with enamine **3S** as a model study even though further conversion to a penem was not possible.



Not surprisingly the major product **7** (50% yield) exhibited a bifurcated hydrogen bond in its single crystal X-ray structure (Figure 3) since it had absolute stereochemistry which was the opposite of that in **4** at each center. However, in this experiment, a small amount of a second isomer **8** was isolated (3% yield) which by X-ray analysis had the desired C5 and C6 stereochemistry for a trans-penam (Figure 4)! Interestingly, in the X-ray structure of minor isomer **8** no hydrogen bond was seen and the rings were rotated so that the nitrogen lone pair rather than the sulfur atom was turned toward the dioxanone methyl group to reduce steric crowding.

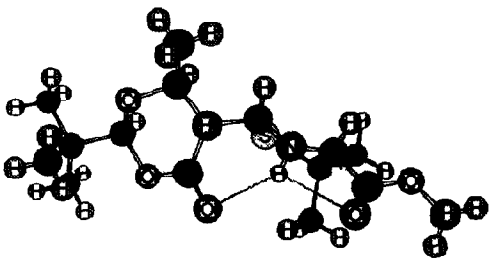


Figure 3. Structure of compound **7** showing hydrogen bonds.

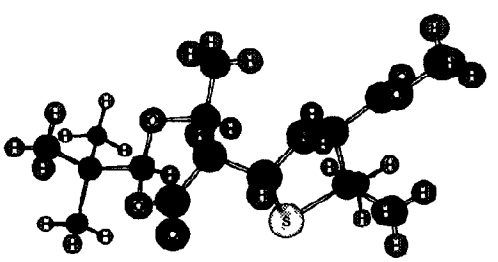
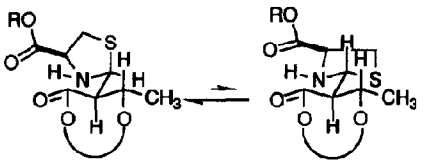


Figure 4. Structure of compound **8**.

It has been reported that cysteine-derived thiazolidines diastereomeric at C2 (thiazolidine numbering) equilibrate readily in deuteriochloroform solution[4,5]. We found that minor isomer **8** slowly converted to the major isomer **7** in $CDCl_3$ while **7** was stable. The addition of a small amount of pyridine to **8** in $CDCl_3$ completely inhibited the rearrangement.

The methyl group on the acetal moiety controlled the stereochemistry of the new asymmetric centers. The X-ray structures of two of these compounds, **4** and **7**, showed bifurcated hydrogen bonds that probably stabilized the structures. Looking at the two possible thiazolidine isomers with the hydrogen bonds in place, there would be a strong preference for the observed stereochemistry to avoid steric interaction of the methyl group and the thiazolidine sulfur atom (Figure 5).



cis-β-lactam precursor trans-β-lactam precursor

Figure 5. Showing steric interactions with hydrogen bonds in place.

Based on the penicillamine results where minor isomer **8** with the desired stereochemistry was isolated and found to be converted to the undesired major isomer **7** in $CDCl_3$ and the stereochemistry of the L-cysteine-derived thiazolidines **4** and **6**, the cis-β-lactam precursors were both the kinetic and the thermodynamic products of these thiazolidine formations and the N-acyl derivatives were likely formed without rearrangement.

In conclusion, we were seeking a formylated derivative of 3-hydroxybutyric acid and wanted to determine the stereochemistry of thiazolidine formation with L-cysteine and D-penicillamine. In the event, the methyl group on dioxanone-enamine **3** controlled both new stereocenters and provided potential precursors for cis-β-lactams. Since thiazolidine formation was highly stereospecific, R-hydroxybutyrate provided the crucial R-configuration at C5 (penem numbering). D-Cysteine should be used for positioning the ester group on the convex side of the bicyclic nucleus during cis-β-lactam closure. The C6 stereochemistry might be inverted by base catalyzed equilibration to provide a trans-β-lactam.

EXPERIMENTAL

Melting points were determined on a Thomas Hoover capillary melting point apparatus and were uncorrected. NMR spectra were obtained on a Brucker WM 300 (300 MHz) spectrometer in deuteriochloroform ($CDCl_3$). Mass spectra were determined with a Finnigan

4510 mass spectrometer. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Elemental analyses were performed by either the Analytical Chemistry Department, Pfizer Central Research or Schwarzkopf Microanalytical Laboratory, Woodside, NY.

2R-tert-Butyl-5-dimethylaminomethylene-6R-methyl-[1,3]dioxan-4-one (3R):

2R-(t-Butyl)-6R-methyl-1,3-dioxan-4-one[12] **1R** (16 g, 93 mmol), prepared by the method of Schreiber,[7] and t-butoxy-bis-(dimethylamino)methane (33 mL, 159 mmol) were combined in dry tetrahydrofuran (100 mL) and heated to 60°C for 4 h. The reaction mixture was evaporated in vacuo to an oil and chromatographed over flash silica gel with a solvent mixture of 70:30:0.5, chloroform: ethyl acetate: triethylamine. The desired product was isolated as an oil that slowly crystallized. The yield was 7.4 g, 35%. $[\alpha]_D$ –20.8 (c = 1.08, chloroform). IR (KBr) 1688, 1592 cm^{-1}. ^1H NMR ($CDCl_3$) δ 7.40 (s, 1), 5.0 (q, 1), 4.70 (s, 1), 2.95 (s, 6, NMe_2), 1.28 (d, 3), 0.95 (s, 9). ^{13}C NMR δ 170.12, 150.17, 103.85, 95.48, 89.35, 70.54, 61.00, 60.96, 43.32, 34.36, 24.16, 23.77. Mass spectrum *m/e* 227.1540 (M), exact mass calcd. 227.1521, 142 (M – ($(CH_3)_3CCO$). This material would darken upon exposure to air and was used immediately in the next step. The yields for repeat runs varied between 35 - 57%.

2S-t-Butyl-5-dimethylaminomethylene-6S-methyl-[1,3]dioxan-4-one (3S):

This was prepared in the same manner starting with 3S-hydroxybutyric acid and exhibited the same spectral properties. The optical rotation was not recorded since the material we prepared contained 5-10% of the 2,6-trans isomer.

2R-(2R-tert-Butyl-4R-methyl-6-oxo-[1,3]dioxan-5R-yl) - thiazolidine - 4R - carboxylic acid ethyl ester (4):

2R-tert-Butyl-5-dimethylaminomethylene-6R-methyl-[1,3]dioxan-4-one **3R** (10 g, 44 mmol) was dissolved in dry pyridine (80 mL). L-Ethyl cysteine hydrochoride (12 g, 66 mmol) was added and the solution was stirred at room temperature for 24 h. The reaction was evaporated in vacuo and the crude mixture was flash chromatographed over silica gel with chloroform as the eluant. The product fractions were combined and evaporated to an oil which was crystallized from hexanes, 6 g, 41% yield. mp 92-3°C; $[\alpha]_D$ +15.2 (c = 0.40, chloroform). IR (KBr) 3293, 1732 cm^{-1}. ^1H NMR ($CDCl_3$) δ 4.97 (s, 1), 4.60 (d, 1), 4.33 (t, 1), 4.26 (q, 2), 3.80-3.72 (m, 2), 3.30 (dd, 1), 3.04 (d, 1, J = 10 Hz, H6) 2.78 (dd, 1), 1.38 (d, 3), 1.31 (t, 3), 0.97 (s, 9). ^{13}C NMR (methyl ester) δ 170.13, 168.87, 108.34, 74.81, 67.73, 66.01, 60.91, 52.59, 50.22, 38.13, 35.14, 23.856, 19.90. Mass spectrum (methyl ester) *m/e* 317.1297 (M), exact mass calcd. 317.1297, 232 (M – ($(CH_3)_3CCHO$), 146 (M – $C_9H_{15}O_3$ - dioxanone). Anal. Calcd. for $C_{15}H_{25}NO_5S$: C, 54.38; H, 7.55; N, 4.23. Found: C, 54.54; H, 7.71; N, 4.04.

2S-(2S-tert-Butyl-4S-methyl-6-oxo-[1,3]dioxan-5S-yl) - thiazolidine - 4R - carboxylic acid methyl ester (5):

2S-t-Butyl-5-dimethylaminomethylene-6S-methyl-[1,3]dioxan-4-one **3S** (5.3 g, 23 mmol) was dissolved in dry pyridine (50 mL) and stirred under nitrogen at room temperature while L-

cysteine methyl ester hydrochloride (5 g, 29 mmol) was added in one portion. The reaction was stirred for 48 h, then was concentrated in vacuo. The crude oil was stirred with ethyl acetate to precipitate pyridine hydrochloride which was filtered. The filtrate was concentrated in vacuo and the product was isolated by flash chromatography over silica gel with 80% hexanes / 20% ethyl acetate. The material was isolated as an oil, 2.1 g, 29% yield. $[\alpha]_D$ –92.1 (c = 1.04, chloroform). IR ($CHCl_3$) 3309, 1742, 1721 cm^{-1}. ^1H NMR ($CDCl_3$) δ 4.98 (s, 1), 4.73 (d, 1, J = 2.2 Hz, H2'), 4.52 (d, 1, J = 5.7 Hz), 3.79 - 3.68 (m with s at 3.73, 4), 3.39 (d, 1, J = 10.6 Hz, H5'), 3.03 (dd, 1, J = 2.2 Hz and 8.5 Hz, H5), 3.00 (dd, 1, J = 6.6 Hz and 10.6 Hz, H5'), 1.38 (d, 3), 0.95 (s, 9). ^{13}C NMR δ 171.50, 169.49, 108.35, 75.26, 67.91, 65.38, 60.83, 52.55, 50.48, 37.35, 35.09, 23.85, 19.92. Mass spectrum *m/e* 318 (M + 1), 232 (M – $((CH_3)_3CCHO)$, 146 (M – $C_9H_{15}O_3$ - dioxanone).

2S-(2S-tert-Butyl-4S-methyl-6-oxo-[1,3]dioxan-5S-yl)-3-(2,2,2-trifluoro-acetyl)-thiazolidine-4R-carboxylic acid methyl ester (6):

Methyl 2S-(2S-tert-butyl-4S-methyl-6-oxo-[1,3]dioxan-5S-yl)-thiazolidine-4R-carboxylate **5** (0.25 g, 0.8 mmol) and triethylamine (0.15 mL, 1.1 mmol) were dissolved in dry methylene chloride (10 mL) and cooled to 0^0C. Trifluoroacetic anhydride (0.15 mL, 1.1 mmol) in methylene chloride (3 mL) was added dropwise over 2 min. After 0.5 h, the reaction was complete by tlc. The reaction was washed with water, sodium bicarbonate solution and brine. The solution was dried over magnesium sulfate and evaporated to a crude solid that was chromatographed over silica gel with chloroform and then crystallized from hexanes; 0.172 g, 52% yield. mp 134-9^0C; $[\alpha]_D$ –58.8 (c = 0.62, chloroform). IR (KBr) 1756, 1730, 1696 cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.22 (d, 1, J = 6.4 Hz), 5.12 (d, 1, J = 1.8 Hz), 4.95 (s, 1), 3.80 - 3.67 (m with singlet at 3.78, 5), 3.53 (dd, 1), 3.23 (d, 1, J = 11.6), 3.75 (d, 3, J = 6.08 Hz), 0.93 (s, 9). ^{13}C NMR δ 169.97, 167.49, 117.62, 108.18, 74.39, 64.01, 63.56, 63.43, 63.29, 60.70, 53.53, 49.99, 35.11, 34.64, 34.48, 23.97, 23.83, 23.69, 23.69, 19.15. Mass spectrum *m/e* 414 (M + 1), 238 (M – $((CH_3)_3CCHO)$, 242 (M – $C_9H_{15}O_3$ - dioxanone). Anal. Calcd. for $C_{16}H_{22}F_3NO_6S$: C, 46.49; H, 5.36; N, 3.39. Found: C, 46.56; H, 5.35; N, 3.40.

2S-(2S-tert-Butyl-4S-methyl-6-oxo-[1,3]dioxan-5S-yl)-5,5-dimethyl-thiazolidine-4S-carboxylic acid methyl ester (7) and 2R-(2S-tert-Butyl-4S-methyl-6-oxo-[1,3]dioxan-5S-yl)-5,5-dimethyl-thiazolidine-4S-carboxylic acid methyl ester (8):

As described in an earlier example, 2S-t-butyl-5-dimethylaminomethylene-6S-methyl-[1,3]dioxan-4-one **3S** (4 g, 17.6 mmol) and D-penicillamine methyl ester hydrochloride (4.3 g, 21.5 mmol) were reacted in dry pyridine (40 mL). The major product **7** was isolated by chromatography over silica gel with 20% ethyl acetate in hexanes followed by crystallization from hexanes, 3 g, 50% yield. mp 104-6^0C; $[\alpha]_D$ –15.5 (c = 0.96, chloroform). IR (KBr) 3314, 1748, 1725 cm^{-1}. ^1H NMR ($CDCl_3$) δ 4.92 (s, 1), 4.68 (bd, 1, J = 10Hz), 3.78 (s, 3), 3.67-3.51 (m, 2), 3.01 (dd, 1, J = 2.4, 10 Hz), 1.65 (s, 3), 1.36 (d, 1, J = 6 Hz), 1.22 (s, 3), 0.96 (s, 9). ^{13}C NMR δ 168.85, 108.24, 89.26, 74.66, 74.29, 65.57, 60.31, 59.95, 52.14, 50.46, 35.12, 28.62,

27.32, 23.86, 19.85. Mass spectrum *m/e* 346 (M + 1), 260 (M – ((CH3)3CCHO), 174 (M – C9H15O3 - dioxanone). Anal. Calcd. for $C_{16}H_{27}NO_5S$: C, 55.63; H, 7.88; N, 4.05. Found: C, 55.52; H, 7.83; N, 4.05.

A less polar material was isolated as a white solid from the column chromatography of the D-penicillamine methyl ester reaction. This was recrystallized from hexanes to provide the trans β-lactam precursor **8**; 0.2 g, 3% yield. mp 131-33°C; $[\alpha]_D$ +96.4 (c = 0.33, CH_2Cl_2). IR (KBr) 3352, 1726, 1681 cm^{-1}. ^1H NMR ($CDCl_3$) δ 5.30 (d,1, J = 4.7 Hz), 4.98 (s, 1), 4.24-4.17 (m, 1), 3.76 (s, 3), 3.69 (s, 1), 2.80 (dd, 1, J = 4.7 and 8.3 Hz), 1.62 (s, 3), 1.43 (d, 3, J = 6.1), 1.21 (s, 3), 0.94 (s, 9). mass spectrum *m/e* 346 (M + 1), 260 (M – ((CH3)3CCHO), 174 (M – C9H15O3 - dioxanone). Anal. Calcd. for $C_{16}H_{27}NO_5S$: C, 55.63; H, 7.88; N, 4.05. Found: C, 55.54; H, 7.75; N, 3.85.

REFERENCES AND NOTES:

1. Volkmann, R. A.; Kelbaugh, P. R.; Nason, D. M.; Jasys, V. J. *J. Org.Chem.*, **1992**, *57*, 4352.
2. For the synthesis of the thiolane sidechain from D-methionine see : Urban, F. J.; Breitenbach, R.; Vincent, L. A. *J. Org.Chem.*, **1990**, *55*, 3670.
3. Sheehan, J. C.; Henery-Logan, K. R. *J. Amer. Chem. Soc.*, **1959**, *81*, 3089.
4. A more recent application of this strategy to the synthesis of penam 3-carboxylic acid and its alkyl analogues has been described by Chiba, T.; Sakaki, J-I.; Kobayashi, S.; Furuya, T.; Inukai, N.; and Kaneko, C. *Chem. Pharm. Bull.* **1989**, *37*, 877.
5. Similar selective oxidations can be found in the work of Baldwin. Baldwin, J.E.; Freeman, R. T.; Lowe, C.; Schofield, C. J.; Lee, E. *Tetrahedron*, **1989**, *45*, 4537 and references therein.
6. Seebach, D.; Imwinkelried, R.; Stucky, G. *Angew. Chem. Int. Ed. Engl.*, **1986**, *25*, 178.
7. Schreiber, S. L.; Reagan, J. *Tet. Lett.*, **1989**, *27*, 2945.
8. Bredereck, H.; Simchen, G.; Rebsdat, S.; Kantlehner, W.; Horn, P.; Wahl, R.; Hoffmann, H.; Grieshaber, P. *Chem. Ber.* **1968**, *101*, 41.
9. The enamine was one isomer by nmr, but the absolute stereochemistry was not determined.
10. Arnett, E. M.; Harrelson, J. A. *J. Amer. Chem. Soc.*, **1987**, *109*, 809.
11. The figures were plotted in Chem3D Plus™ (Cambridge Scientific Computing, Inc.) using the experimentally determined coordinates. Atomic coordinates have deposited for each X-ray structure with the Cambridge Crystallographic Data Centre.
12. Seebach, D.; Imwinkelried, R.; Stucky, G., *Angew. Chem. Int. Ed. Engl.*, **1986**, *25*, 178.

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