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Synthesis of a Sterically Congested α,α'-Iminodiacid

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Abstract: The synthesis of iminodiacid **2**, a derivative of valine, was found to be difficult at the point of attempting to functionalize the imino-nitrogen to form a tertiary amine. Nonetheless, a route was discovered starting from α-hydroxyisovaleric acid, ethanolamine and maleimide. After esterification, the α-triflate of α-hydroxyisovaleric acid was formed and used to sequentially alkylate the amino group of ethanolamine. Steric hindrance was reduced by tethering two of the amine substituents into lactone ring. This was followed by maleimide substitution of the hydroxyl group under Mitsunobu conditions. © 1997 Elsevier Science Ltd.

Iminodicarboxylic acids such as **1** are an interesting class of compounds which has been known for quite some time. For example, octopine[1], a natural product found in the octopus, was isolated almost 70 years ago. Since then, a number of iminodiacids have been isolated from a variety sources. In nature, these compounds are often associated with biologically active extracts. For example, histopine is found in crown gall tumors,[2] valinopine, epi-leucinopine and isoleucinopine are isolated from the poisonous mushroom *C. acromelalga*,[3] while BSF-A, produced by *B. squamosa*, is believed to be the toxin responsible for leaf blight of the onion.[4] Medicinally active derivatives such as certain ACE[5] and MMP inhibitors, incorporate this structure as well.[6] These compounds have become important synthetic targets with recent efforts directed at producing combinatorial libraries based on this compact yet highly functionalized scaffold.[7]

We became interested in this class of compounds as a template for the synthesis of bi-directional peptides. More specifically, we required compound **2**, a "valine-valine" α,α'-iminodiacid ((2*S*, 1'*S*)-*N*-(1'-carboxy-2'-methylpropyl)valine), to be recognized as a pair of N-terminal valine residues in the center of a bi-directional peptide. A maleimide moiety is also attached to provide a handle for bioconjugation or immobilization onto solid support via thioether formation.[8] In considering possible synthetic routes to **2**, it is important to point out that compound **2** is different from most of the iminodiacids reported in the literature in that the amine-nitrogen is tertiary and the amino acids are β-branched. These two factors contribute significantly to the difficulty of the synthesis (*vida infra*). No general synthetic approaches towards α,α'iminodiacids having both this level of substitution and this particular stereochemistry have been reported.[9,10]

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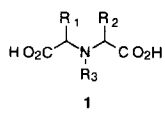
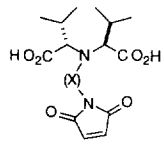
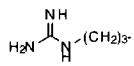
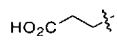
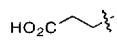
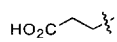


1

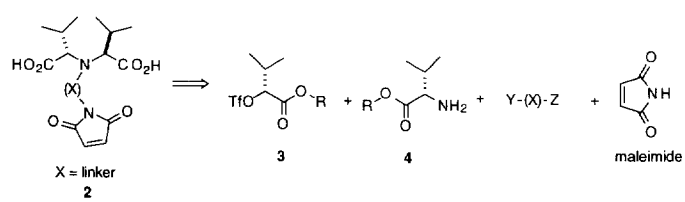


X = linker

2

compound	R_1	R_2
octopine		-Me
histopine		-Me
valinopine		
epi-leucinopine		
isoleucinopine		
BSF-A		-Me

The retro-synthesis is shown in scheme I. As can be seen, the starting materials necessary for the synthesis of **2** are; *L*-valine, the α-triflate of *D*-α-hydroxyisovaleric acid,[11] maleimide and a suitable bifunctional linker Y-(X)-Z. The forward synthesis is shown in scheme II.



X = linker

2

3

4

maleimide

Scheme I. Retrosynthesis of **2**

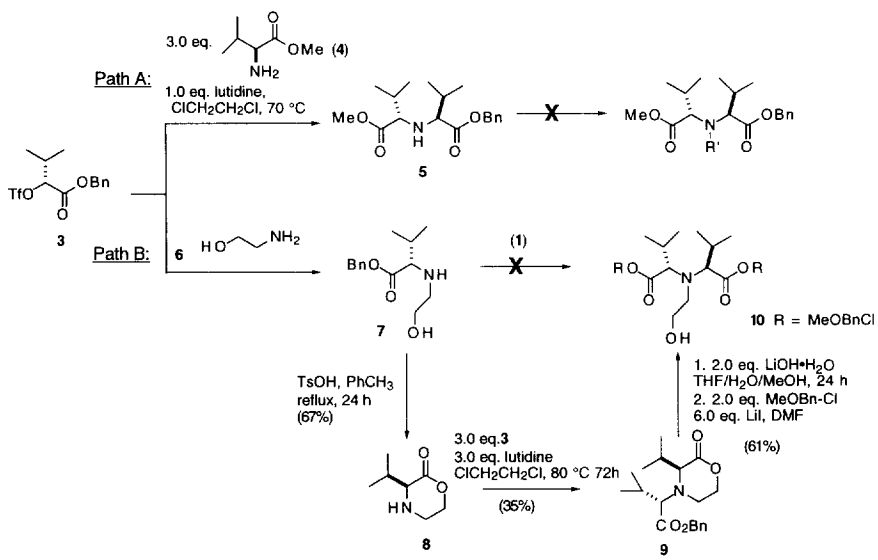
D-α-Hydroxyisovleric acid (not shown) was converted into the corresponding α-triflate benzyl ester (**3**) using literature procedures.[12] As shown in path A, this triflate was found to react, upon warming (70 °C), with

valine methyl ester (**4**) to give the corresponding *N*-carboxyalkyl amino acid intermediate (**5**) as a single diastereomer (NMR).[13] However, the nitrogen center of **5** proved to be unreactive towards further substitution. A number of acylating agents were screened including acetyl bromide and phosgene and in no case were we able to observe amide bond formation.[14]

The weak nucleophilicity of the central nitrogen of iminodiacids has been documented in the literature with *N*-carboxyalkyl valine being one of the least reactive.[15] As such, no precedent could be found for the N-alkylation or -acylation of *N*-(1-carboxy-2-methylpropyl)valine. In fact, previous researchers were unsuccessful in acylating the less sterically hindered *N*-(1-carboxymethyl)valine. Therefore path A was abandoned in favor of path B.

It was assumed that we could effect the synthesis of the sterically hindered tertiary amine by proceeding through a less sterically encumbered intermediate. Thus amine **7** was synthesized. However, attempts to alkylate this intermediates with triflate **3** under conditions similar to those used above (70 °C, $ClCH_2CH_2Cl$, lutidine) did not give any of the desired material. Instead, warming the reaction for extended periods of time resulted in decomposition of the triflate and alkylation of the hydroxyl group (<20%). It was apparent that the steric bulk around the amine needed further reduction.

This was accomplished by tethering the hydroxyethyl group of **7** to the carboxylic acid via a lactone ring. Lactonization also serves as a convenient method for protecting the hydroxyl group against alkylation. As shown in scheme II, **7** was converted by heating at reflux, in toluene, in the presence of TsOH to the corresponding lactone (**8**).[16]

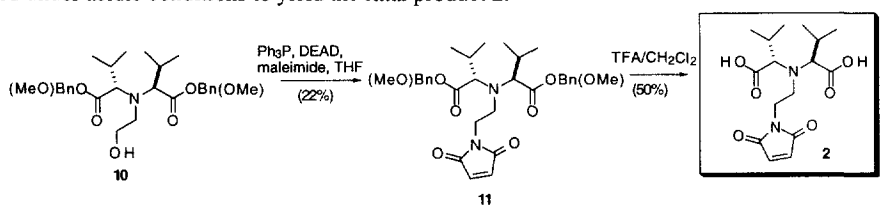


Scheme II. Synthesis of **10**

Although the rate of the reaction was slow, compound **8** was alkylated to the give **9** in modest yield (35%). The reaction required excess triflate (3 eq.) and extended reaction times (96 h, 80 °C). Under these conditions decomposition of the triflate was competitive with alkylation. Therefore, the triflate was added in two portions over the course of the reaction. After alkylation, the lactone and benzyl ester were simultaneously saponified using LiOH. The intermediate lithium carboxylate could be alkylated with *p*-MeOBnCl [17] in the in presence of LiI[18] to give **10**.

With compound **10** in hand the key steps in the synthesis of the unusual α,α'-iminodiacid, (2*S*, 1'*S*)-*N*-(1'-carboxy-2'-methylpropyl)valine, had been completed. To the best of our knowledge, this is the first synthesis of an α,α'-imidodiacid with this level of substitution and stereochemistry reported in the literature. The overall yield is modest due to the alkylation step, however, it is hoped that with further optimization this might prove to be a general route for the synthesis of derivatives with similar structure.

The conversion of **10** to the final target is demonstrated below. The hydroxyl group was displaced with maleimide under Mitsunobu conditions.[19] The yield for this reaction was unexpectedly low. This might be due to side reactions caused by intramolecular attack of the amino group. Others have observed such side reactions with ethanolamine substrates and it is possible that **10** behaves in a similar fashion.[20,21] Nonetheless, **11** was deprotected under acidic conditions to yield the final product **2.**



In summary, entry into a very challenging and little explored class of α,α'-iminodiacids has been established. The key bond formation was accomplished by the use of a morphilin-2-one intermediate to reduce steric hindrance about the central nitrogen of the emerging sterically-congested iminodiacid. Application of this methodology to other related-derivatives is currently under way.

EXPERIMENTAL SECTION

Reactants and reagents were purchased from appropriate commercial sources and used without further purification. All reactions were carried out under a N_2 atmosphere. ^1H NMR and ^{13}C NMR were recorded in $CDCl_3$ unless stated otherwise.

***(D)* α-(Trifluoromethylsulfonyloxy)-Isovaleric Acid, Benzyl Ester (3):** Benzyl (*D*)-α-hydroxyisovalerate (6.88 g, 33.1 mmol) was dissolved in 30 mL of CH_2Cl_2 and cooled to -78 °C. To this was added lutidine (4.60 mL, 39.5 mmol) followed by Tf_2O (6.68 mL, 39.7 mmol). After stirring 20 min. the

solution was allowed to warm to RT then transferred to a separatory funnel. The organic layer was washed with H_2O, separated, dried over Na_2SO_4, and the solvent was removed by evaporation on a rotary evaporator. The product was isolated by column chromatography (SiO_2, 1:1 hexanes/EtOAc) to give 10.9 g (97% yield) of **3** as an oil. ^{1}H NMR (300 MHz): δ 0.95 (d, 3 H, J = 6.9 Hz), 1.23 (d, 3 H, J = 7.3 Hz), 2.37 (m, 1 H), 4.98 (d, 1 H, J = 3.9 Hz), 5.25 (m, 2 H), 7.36 (s, 5 H). ^{13}C NMR (75 MHz): δ 16.2, 18.2, 31.2, 68.1, 87.9, 118.0(q), 128.7, 128.8, 134.4, 166.7. $[\alpha]_D$ = +36.7 (c = 1.0 $CHCl_3$)

(2*S*,*I'S*)–*N*–(1'–Methylcarboxy-2'-Methylpropyl)Valine, Benzyl Ester (5): Compound **3** (7.50 g, 22.1 mmol) was dissolved in 80 mL of $ClCH_2CH_2Cl$. To this was added lutidine (2.58 mL, 22.2 mmol) and valine methyl ester (8.90 g, 67.6 mmol). The resulting solution was warmed to 70 °C and allowed to stir overnight. After cooling to room temperature the reaction mixture was transferred to a separatory funnel, washed with pH 7.0 buffer, dried over Na_2SO_4 and the solvent was removed by evaporation on a rotary evaporator. The product was purified by column chromatography (SiO_2, 20:1 hexanes/EtOAc) to give 6.80 g (96% yield) of **5** as an oil. ^{1}H NMR (300 MHz): δ 0.90 (m, 12 H), 1.78 (br s, 1 H), 1.90 (m, 2 H), 2.96 (dd, 2 H, J = 6.1, 11.0 Hz), 3.65 (s, 3 H), 5.08 (d, 1 H, J = 12.2 Hz), 5.15 (d, 1 H, J = 12.2 Hz), 7.31 (br s, 5 H). ^{13}C NMR (75 MHz): δ 18.5, 18.6, 19.1, 19.1, 31.4, 51.4, 66.1, 66.3, 128.3, 128.4, 128.5, 135.8, 174.1, 174.7. HRMS (DCI) calcd for $C_{18}H_{28}NO_4$: 322.2018 $(M+H)^+$. Found: 322.2026.

(*S*) *N*-(2'-Hydroxyethyl)Valine Benzyl Ester (7): Compound **3** (33.9 g, 100 mmol) was dissolved in 250 mL of CH_2Cl_2 and ethanol amine (24.1 mL g, 400 mmol) added. The resulting solution was stirred overnight then transferred to a separatory funnel and washed with pH 7.0 buffer. The organic layer was separated, dried over Na_2SO_4, filtered and the solvent was removed by evaporation on a rotary evaporator to give 24.7 g (99% yield) of **7c** as an oil. This was used in subsequent reactions without further purification. ^{1}H NMR (300 MHz): δ 0.89 (d, 3 H, J = 4.0 Hz), 0.91 (d, 3 H, J = 4.0 Hz), 1.97 (m, 1 H), 2.56 (m, 1 H), 2.60 (br s, 1 H), 2.81 (m, 1 H), 3.06 (m, 2 H), 3.55 (m, 2 H), 5.15 (m, 2 H), 7.33 (s, 5 H). ^{13}C NMR (75 MHz): δ 18.4, 19.1, 31.5, 49.9, 60.6, 66.6, 66.9, 128.4, 128.5, 128.6, 135.6, 174.6. HRMS (ESI) calcd for $C_{14}H_{22}NO_3$ $(M+H)^+$: 252.1600. Found: 252.1594. $[\alpha]_D$ = -6.4 (c = 1.0 $CHCl_3$).

(*S*) 3-Isopropyl-Morphilin-2-one (8): In a 1000 mL round bottom flask fitted with a Dean-Stark trap compound **7c** (26.8 g, 107 mmol) was dissolved in 500 mL of $PhCH_3$. To this was added $TsOH•H_2O$ (30.4 g, 160 mmol) and the resulting suspension heated at reflux. After heating at reflux overnight the solution was allowed to cool to room temp. and the solvent removed by rotovap. The resulting oil was triturated with Et_2O then re-dissolved in CH_2Cl_2 and transferred to a separatory funnel. The organic solution was washed with sat'd $NaHCO_3$, H_2O, dried over Na_2SO_4, filtered and the solvent was removed by evaporation on a rotary evaporator. The product was purified by column chromatography (SiO_2, 1:2 hexanes/EtOAc) to give 10.3 g (67% yield) **8** as an oil. ^{1}H NMR (300 MHz): δ 0.86 (d, 3 H, J = 6.8 Hz), 0.90 (d, 3 H, J = 7.05 Hz), 1.66 (br s, 1 H), 2.29 (d sept, 1 H, J = 3.5, 10.4 Hz), 2.99 (m, 2 H), 3.44 (d, 1 H, J = 3.4 Hz), 4.23 (m, 2 H).

^{13}C NMR (75 MHz): δ 17.1, 18.9, 30.8, 42.2, 63.6, 69.9, 170.3. Anal. calcd for $C_7H_{13}NO_2$: C, 58.72; H, 9.15; N, 9.78. Found: C, 58.56; H, 9.35; N, 9.67. $[\alpha]_D$ = -14.63 (c = 1.0 $CHCl_3$).

Morphilin-2-one (9): Compound **8** (3.89 g, 11.47 mmol) was dissolved in 25 mL of $ClCH_2CH_2Cl$. To this was added **3** (0.820 g, 5.73 mmol) and lutidine (1.34 mL, 11.5 mmol) and the resulting solution warmed to 80 °C. After stirring overnight additional triflate (2.00 g) and lutidine (0.70 mL) were added and the reaction allowed to continue for 72 h more. The solution was then allowed to cool to room temperature, transferred to a separatory funnel and washed with dil. HCl, sat'd $NaHCO_3$, dried over Na_2SO_4 and the solvent was removed by evaporation on a rotary evaporator. Purification by column chromatography (SiO_2, 10:1 hexanes/EtOAc) gave 650 mg of **9** (35% yield). ^{1}H NMR (300 MHz): δ 0.84 (d, 3 H, *J* = 6.5 Hz), 0.95 (d, 3 H, *J* = 6.6 Hz), 0.96 (d, 3 H, *J* = 6.8 Hz), 1.07 (d, 3 H, *J* = 6.8 Hz), 2.01 (m, 2 H), 2.87 (m, 3 H), 3.44 (d, 1 H, *J* = 4.2 Hz), 4.27 (m, 2 H), 5.09 (d, 1 H, *J* = 12.0 Hz), 5.16 (d, 1 H, *J* = 12.0 Hz), 7.34 (s, 5 H). ^{13}C NMR (75 MHz): δ 17.5, 19.3, 19.8, 19.9, 27.1, 32.1, 41.8, 66.4, 67.4, 68.9, 70.1, 128.5, 128.6, 128.7, 135.5, 169.4, 171.0. ESI-MS calcd for $C_{19}H_{27}NO_4$: 333. Found: 334 $(M+H)^+$. Anal calcd for $C_{19}H_{27}NO_4$: C, 68.44; H, 8.16; N, 4.20. Found: C, 68.43; H, 8.16; N, 4.05.

(2*S*,1'*S*)-*N*-(1'-para-Methoxybenzylcarboxy-2'-Methylpropyl)-*N*-(2''-Hydroxyethyl)Valine, para-Methoxybenzyl Ester (10): Lactone **9** (2.25 g, 6.76 mmol) was dissolved in 10 mL of THF and $LiOH{\bullet}H_2O$ (0.590 g, 14.0 mmol)) added. 8 mL of H_2O was added and the LiOH was dissolved after which 10 mL of MeOH was added and the cloudy solution became clear. This mixture was allowed to stir overnight. The solvent was removed by evaporation on a rotary evaporator. The resulting residue dissolved in 4.0 mL of THF then added to Et_2O to form a percipitate. The solid was filtered and dried under vacuum.

The intermediate bis-lithiocarboxylate (1.30 g, 4.75 mmol) was dissolved in 15 mL of DMF to which was added para-methoxy benzyl chloride (1.39 mL, 9.48 mmol) and LiI (3.81 g, 28.5 mmol) [CAUTION: exothermic]. After stirring overnight the reaction mixture was transferred to a separatory funnel, washed with dil. $NaHCO_3$, H_2O, dried over Na_2SO_4 and the solvent was removed by evaporation on a rotary evaporator. The product (**10**) was purified by column chromatography (SiO_2, 5:1 hexanes/EtOAc) to give 1.45 g (61% yield). ^{1}H NMR (300 MHz): δ 0.74 (d, 6 H, *J* = 6.5 Hz), 0.78 (d, 6 H, *J* = 6.5 Hz), 1.97 (m, 2 H), 3.14 (m, 3 H), 3.25 (br s, 1 H), 3.55 (m, 2 H), 3.78 (s, 6 H), 4.96 (d, 2 H, *J* = 11.9 Hz), 5.03 (d, 2 H,*J* = 11.9 Hz), 6.85 (m, 4 H), 7.25 (m, 4 H). ^{13}C NMR (75 Mhz): δ 19.6, 19.8, 28.9, 50.5, 55.3, 61.8, 66.0, 68.7, 113.9, 127.6, 130.4, 159.7, 173.9. Anal calcd for $C_{28}H_{39}NO_7$: C, 67.04; H, 7.84,; N, 2.79. Found: C, 67.47; H, 7.83; N, 2.56. HRMS (ESI) calcd for 502.2805 $(M+H)^+$. Found: 502.2796.

(2*S*,1'*S*)-*N*-(1'-para-Methoxybenzylcarboxy-2'-Methylpropyl)-*N*-(2''-Maleimidoethyl)Valine, para-Methoxybenzyl Ester (11): Alcohol **10** (1.44g, 2.87 mmol) and Ph_3P (0.75 g, 2.87 mmol) were dissolved in 10 mL of THF and cooled to -78 °C. To this was added DEAD (0.45 mL, 2.87 mmol) dropwise. After 5 min. maleimide (0.28 g, 2.87 mmol) was added all at once. The ice-bath

was removed and the reaction mixture allowed to stir overnight. The solution was then concentrated by evaporation on a rotary evaporator and applied to a column (SiO_2) and eluted with 4:1 hexanes/EtOAc to give 360 mg (22% yield) of **11**. ^{1}H NMR (300 MHz): δ 0.75 (d, 6 H, *J* = 6.5 Hz), 0.85 (d, 6 H, *J* = 6.5 Hz), 2.04 (m, 2 H), 3.08 (d, 2 H, *J* = 10.6 Hz), 3.17 (m, 2 H), 3.53 (m, 2 H), 3.77 (s, 6 H), 4.88 (d, 2 H, *J* = 12.0 Hz), 5.02 (d, 2 H, *J* = 12.0 Hz), 6.62 (s, 2 H), 6.82 (d, 4 H, *J* = 8.5 Hz), 7.24 (d, 4 H, *J* = 8.5 Hz). ^{13}C NMR (75 MHz); δ 19.5, 19.9, 29.5, 37.9, 45.5, 55.2, 65.7, 70.4, 113.8, 127.9, 130.3, 134.1, 159.6, 170.6, 172.9. Anal calcd for $C_{32}H_{40}N_2O_8$: C, 66.19; H, 6.94; N, 4.82. Found: C, 66.18; H, 7.03; N, 4.73.

(2*S*,1'*S*)-*N*-(1'-Carboxy-2'-Methylpropyl)-*N*-(2''-Maleimidoethyl)Valine(2): Bis-ester **11** (70 mg, 0.12 mmol) was dissolved in 1.0 mL of CH_2Cl_2. To this was added anisole (0.13 mL, 1.2 mmol) followed by TFA (0.09 mL, 0.93 mmol) and the resulting solution stirred 1.5 h. The solvent was removed by rotovap and the resulting oil triturated with CH_2Cl_2. The crude product was triturated with hexanes to yield 20 mg of **2** as a solid, mp 200 °C (decomp.). ^{1}H NMR (CD_3OD, 300 MHz) δ 0.89 (d, 6 H, *J* = 6.5 Hz), 0.98 (d, 6 H, *J* = 6.5 Hz), 2.05 (m, 2 H), 3.10 (d, 2 H, *J* = 10.6 Hz), 3.20 (dd, 2 H, *J* = 8.4, 8.4 Hz), 3.57 (dd, 2 H, *J* = 8.4, 8.4 Hz), 6.79 (s, 2 H). ^{13}C NMR (CD_3OD, 75 MHz): δ 20.2, 20.7, 30.5, 38.9, 47.3, 71.3, 135.5, 172.6, 176.6. MS (HR FAB) calcd for $C_{16}H_{24}N_2O_6$•H^+ (MH^+): 341.1716. Found: 341.1717. $[\alpha]_D$ = -2.75 (c = 0.75 MeOH).

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9. A N-substituted 1'-carboxy-2'-methylpropyl)valine iminodiacid has been synthesized using the Ugi reaction. This reaction was selective for the *R,S*-diastereomer. See: (a) Yamada, T.; Motoyama, N.; Taniguchi, T.; Kazuta, Y.; Miyazawa, T.; Kuwata, S.; Matsumoto, K.; Sugiura, M.; *Chem. Lett.*, **1987**, 723. However, the diastereoselectivity of the Ugi reaction can be controlled to yield iminodiacids having the *S,S*-configuration. See: (b) Demharter, A.; Hörl, W.; Herdtweck, E.; Ugi, I. *Angew. Chem. Int. Ed.* **1996**, *35*, 173. (c) Ugi, I.; Demharter, A.; Hörl, W.; Schmid, T. *Tetrahedron* **1996**, *52*, 11657.

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14. The analogous *N*-(1-carboxy-2-phenylethyl)phenyalanine iminodiacid was synthesized and found to be resistant to acylation as well.

15. The acylation of *N*-(carboxymethyl)alanine, *N*-(carboxymethyl)leucine and *N*-(carboxymethyl)valine esters is accomplished in high to low yield (respectively) at 10 kbar. Yamada, T.; Manabe, Y.; Miyazawa, T.; Kuwata, S.; Sera, A. *Chem. Comm.* **1984**, 1500.

16. Kashima, C.; Harada, K. *Perkin Trans. I* **1988**, 1521.

17. The reaction was not successful without LiI.

18. The addition of base other than LiI to this reaction caused lactonization.

19. Walker, M. A. *Tetrahedron Lett.* **1994**, *35*, 665.

20. Unreacted maleimide and **10** were recovered from the reaction in 32% and 26% yield respectively. The rest of the reaction mixture consisted of a mixture of base-line (TLC) compounds which were not characterized.

21. The Mitsunobu reactions of alcohols of this type can lead to unexpected side reactions depending on the length of the tether linking the alcohol to the iminodiacid. For example see: Walker, M. A. *Tetrahedron Lett.* **1996**, *37*, 8133.

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