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A flexible synthetic route to isoxazolidine β-proline analogs

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We dedicate this paper to Professor Justin Du Bois in honor of the 2007 Tetrahedron Young Investigator Award in recognition of his many important contributions to Organic Chemistry

ABSTRACT

The function and higher order structure of β-proline oligomers have been relatively unexplored compared to other foldamer classes due in part to synthetic challenges associated with substituted monomers. Here we report a flexible synthesis of di- and trisubstituted isoxazolidine β-proline monomers that enables access to a wide range of densely functionalized analogs suitably protected for solid-phase synthetic protocols. This strategy utilizes chiral isoxazolines as key intermediates and can readily provide single stereoisomers of the target molecules.

1. Introduction

Nonnatural molecules that mimic key protein structural motifs such as helices and β-turns have found widespread application as catalysts, sensors, materials, and as inhibitors of protein–protein interactions.[1–4] A key advantage of these so-called 'foldamers' compared to proteins is their often enhanced structural and proteolytic stability relative to their natural counterparts. Foldamers composed of β-amino acids, for example (Fig. 1), can adopt stable and predictable secondary structures, are resistant to proteolytic degradation, and can be more densely functionalized than their natural α-amino acid counterparts.[5,6] Further, it was recently demonstrated that β-amino acid foldamers can assemble into higher order structures, a critical step toward proteomimetics that mimic the structure *and* function of natural proteins.[7–12]

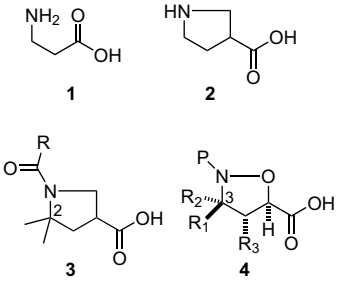

Figure 1. Structural classes of β-amino acids. **1**: β-amino acid skeleton; **2**: β-proline monomer; oligomers of **2** populate multiple rotamer states; **3**: disubstituted β-proline; oligomers of **3** adopt regular structure; **4**: trisubstituted isoxazolidine β-proline analog.

One class of β-peptides that has been less studied includes oligomers composed of β-prolines (Fig. 1); however, the monomeric units have been utilized in a number of applications.[13–16] Early solution studies of unfunctionalized β-proline oligomers (4 or more subunits) suggested the existence of multiple rotameric states, precluding thorough structural characterization.[17,18] However, the introduction of two substituents at C2 of the β-proline (**3**) leads to a strong preference for the *Z*-amide bond isomer.[19] Indeed, CD analysis of the homooligomers of disubstituted β-prolines indicated the adoption of regular structure for the pentameric and hexameric species.[19] Although an exciting advance, a major roadblock for further implementing these more substituted β-proline oligomers is the synthetic difficulties associated with selectively installing a range of functional groups adjacent to the nitrogen and along the backbone. The standard approach employs 4-hydroxylproline as the starting material and uses alkylation to install a second functional group adjacent to the nitrogen.[19,20] This inherently limits the diversity of functional groups that can be installed as one is derived from the carboxylic acid moiety. Further, the incorporation of additional functional groups within the backbone, a substitution pattern important for other β-amino acid classes, would require a significantly more complicated synthetic route.

To address this need, we hypothesized that a flexible synthetic strategy could be developed for densely functionalized β-proline analogs in which one carbon has been replaced by an oxygen (**4**, Fig. 1), a substitution that should confer advantageous aqueous solubility properties while minimally perturbing the amide bond in the context of oligomers. An additional advantage is that the

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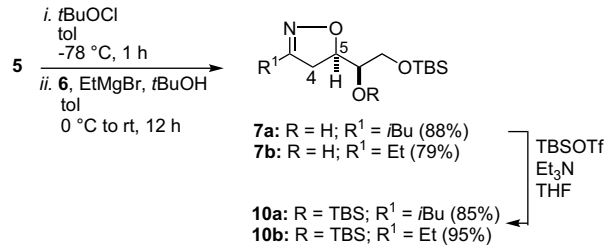
synthetic strategy employs chiral isoxazolines as the key intermediates; isoxazolines are readily accessible as single stereoisomers and as such have been employed as building blocks for other β-amino acid classes and complex targets such as polyketides.[21–29] Toward isoxazolidine β-prolines, a 1,3-dipolar cycloaddition using the conditions of Kanemasa and Carreira establishes the stereochemistry at C5 of isoxazoline **7** and introduces the first substituent adjacent to the nitrogen (Fig. 2).[30,31] Additional substitution at C4 of the isoxazoline ring of **7** can be incorporated by using a disubstituted double bond in the cycloaddition and/or through a separate alkylation step post-cycloaddition.[28] Selective nucleophilic attack at the C=N bond within **7** then provides the additional C3 substituent in **8**.[28,29] Finally, oxidative cleavage of the C5 diol moiety would provide the requisite carboxylic acid at this position (**9**). Here we describe the development and implementation of this synthetic strategy for a range of β-proline analogs, including those with substitution patterns not accessible by previous methodologies.



Scheme 1. Synthesis of the key isoxazoline intermediates.

2. Results and discussion

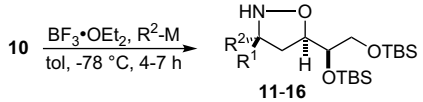
2.1. Disubstituted isoxazolidine β-prolines

The first step in the synthesis of disubstituted isoxazolidine β-prolines is a 1,3-dipolar cycloaddition between a nitrile oxide and a chiral allylic alcohol derived from glycidol (Scheme 1).[30,31–33] Consistent with previous reports, the cycloaddition proceeds in excellent yield with either an isobutyl (**5a**) or ethyl (**5b**) R^1 substituent.[28,29] Subsequent protection of the secondary alcohol as a silyl ether produced isoxazoline **10** in excellent yield.

Installation of the second functional group at C3 was accomplished by the combination of isoxazoline **10** with either a stabilized Grignard reagent (**11**, **13**, and **16**) or an organolithium reagent (**12**, **14**, **15**) in the presence of $BF_3\cdots Et_2O$ (Table 1). In all examples, the major diastereomer isolated results from addition to the *re* face of the C=N bond, with good (7:1) to excellent (>20:1) diastereomeric ratios observed. The relative stereochemistry was assigned by NOE analysis. In this way, a variety of alkyl, aryl, and heteroaryl functional groups can be positioned at C3. Protection of the secondary alcohol prior to this reaction is not a requirement, but the isolation and purification of the product are facilitated.

Conversion of isoxazolidines **11**–**16** to the β-proline analogs required only protection at N2 followed by unmasking of the C5 diol moiety and oxidative cleavage to the carboxylic acid (Fig. 3). Protection of the ring nitrogen with a group compatible with solid-phase synthesis was anticipated to be a challenging step. Due to significant steric hindrance and concomitant reduced nucleophilicity of the nitrogen, we have previously found that alkyl groups can only be added to that position using microwave-accelerated conditions.[34] However, it was possible to protect the nitrogen with a BOC, Fmoc or Cbz group, all commonly used in solid-phase peptide synthesis, without requiring forcing conditions. Installation of the Cbz group consistently provided the highest yields and is shown in Figure 3. The TBS groups were then removed in situ by addition of a fluoride source (TBAF). The resulting diols were oxidatively cleaved in a two-step procedure in which a $NaIO_4$ cleavage

Table 1
Nucleophile addition to isoxazoline **10**



Entry	R^1	R^2–M	Yield[a] (%)	dr[b]
11	^{i}Bu	BnMgBr	80	10:1
12	^{i}Bu	PhLi	60	7:1
13	^{i}Bu	allylMgCl	76	8:1
14	^{i}Bu	MeLi	64	7:1
15	^{i}Bu	thienylLi	73	20:1
16	Et	2-MethylallylMgCl	79	8:1

[a] Yield of the major diastereomer.
[b] Diastereomeric ratios determined by ^{1}H NMR spectral integration of the crude product mixture.

produced an intermediate aldehyde; due to instability of the aldehyde, this intermediate was immediately oxidized to the more stable carboxylic acid. This was accomplished by treatment with sodium perchlorate to cleanly produce the desired isoxazolidine β-proline analogs shown (**17**–**22**) in good overall yields (over the four steps shown) and with no detectable epimerization.

A key feature of this synthetic approach to β-prolines is that diverse functionality can be introduced at multiple stages, from choice of oxime in the cycloaddition step to late-stage modification of the C3 and N2 side chains. As a representative example, we prepared an amphipathic isoxazoldine β-proline, **26**, bearing a hydrophobic (isobutyl) and polar (hydroxyl) functional group at the carbon adjacent to the nitrogen (Scheme 2). From **13**, the nitrogen was protected with an Fmoc group in 92% yield. The double bond of isoxazolidine **23** was oxidatively cleaved and protected as the MOM ether; the MOM group is compatible with Fmoc solid-phase peptide synthesis. Subsequently the silyl ethers were selectively removed by treatment with 20% HCl in MeOH. In the final step the pendant diol of **25** was oxidatively cleaved to yield isoxazolidine β-proline **26** (Scheme 2). This monomer is suitable for use in solid-phase synthesis.

2.2. Synthesis of trisubstituted isoxazolidine β-prolines

As described earlier, we envisioned that one advantage of our synthetic strategy would be that it could be used to access

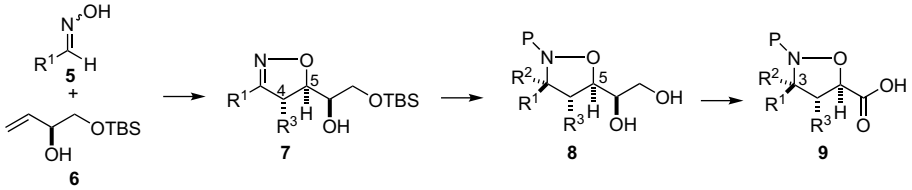


Figure 2. Isoxazoline strategy for the synthesis of di- and trisubstituted isoxazolidine β-prolines.

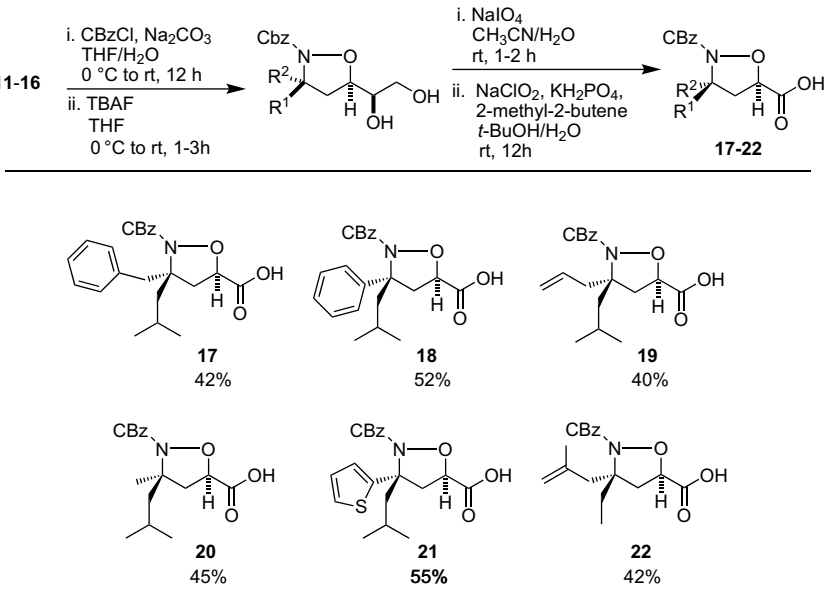
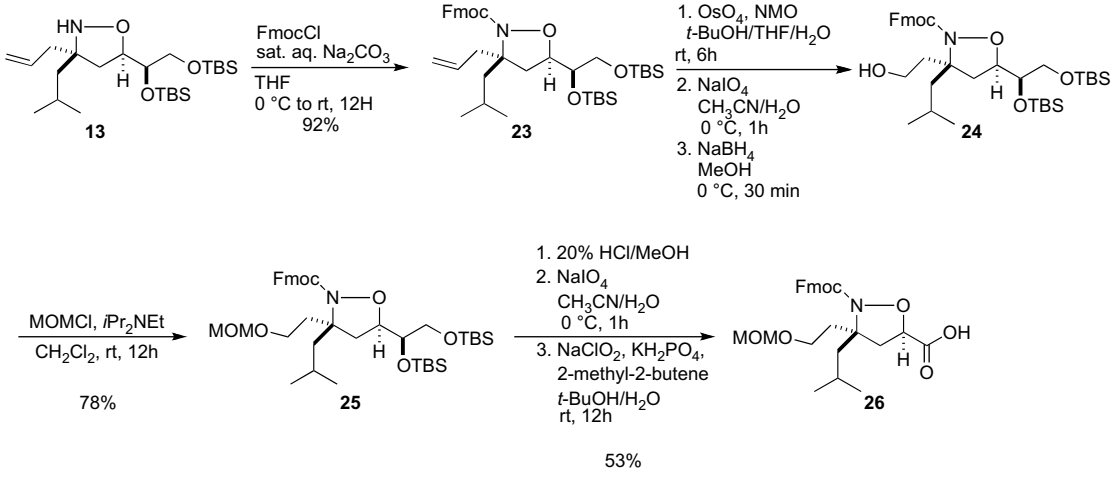


Figure 3. Conversion of isoxazolidines **11**–**16** to β-prolines.



Scheme 2. Synthesis of amphipathic isoxazolidine β-proline **26**.

trisubstituted β-proline analogs. Although not expected to strongly impact the conformational preferences of oligomers, functional groups at C4 of the isoxazolidine ring could be useful for *inter*-oligomer interactions, facilitating the formation of higher order assemblies. A *C*4 substituent can be introduced at the cycloaddition stage through the use of allylic alcohols containing disubstituted double bonds or via an alkylation reaction with the isoxazolidine. We elected the alkylation strategy for this study as it offers a more

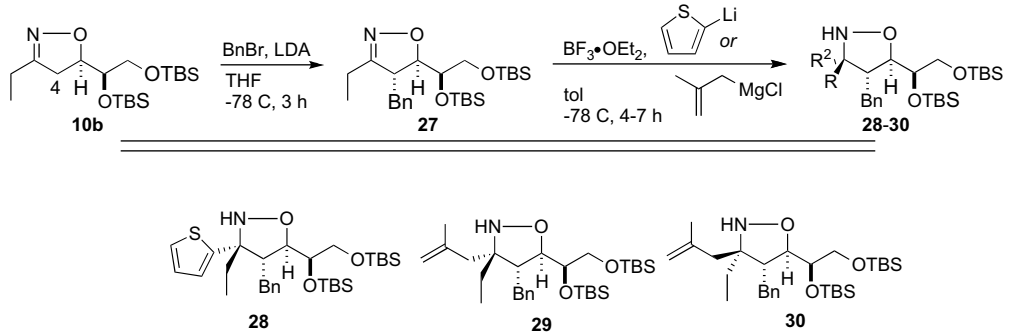


Figure 4. Nucleophile addition to *C*4 substituted isoxazolidines.

convergent synthesis (Fig. 4). Deprotonation of isoxazolidine **10b** with LDA and the addition of benzyl bromide proceeded in good yield (62%) to provide **27** as a single stereoisomer. Nucleophilic attack at the C=N bond proceeded with either an organolithium reagent (**28**) or a stabilized Grignard (**29**, **30**) reagent. The *C*4 and *C*5 substituents exert opposing steric effects in this reaction. In the case of **28**, the additional steric hindrance leads to an attenuated yield (55%) relative to the earlier example (Table 1, **15**), although only a single diastereomer was observed. In the second example, a better overall yield was obtained of a 1.2:1 mixture of diastereomers. In all cases, the relative stereochemistry was verified by NOESY carried out on *N*2-protected derivatives.

Conversion of isoxazolidines **28**–**30** to β-proline analogs occurred using the same reaction sequences as outlined in Figure 3. Despite the additional steric hindrance in these isoxazolidines, Cbz protection proceeded without incident as did the deprotection/oxidative cleavage sequence. Purification of the acids was, however, facilitated by in situ protection as the methyl ester. Although only three examples are presented here, these results suggest that the strategy should be utilizable for a wider range of substrates by variation of the oxime substituent in the initial cycloaddition, alternative alkylating agents, and the organometallic reagents used in Table 1.

3. Conclusions

Here we have described the preparation of isoxazolidine β-proline analogs functionalized with a variety of substituents. This was accomplished via a flexible synthetic route employing simple building blocks (oximes, allylic alcohols, organometallic nucleophiles) that should enable selective installation of wider range of functional groups than previously available. In addition, this strategy provides access to either enantiomer of a given β-proline monomer depending upon the choice of chiral allylic alcohol used in the initial cycloaddition step. We have previously described the biological activity of related isoxazolidines as transcriptional activators; given the likely structural preferences of oligomers of isoxazolidine β-prolines such as the ones shown here, transcriptional activators with enhanced function should now be accessible.[34–36]

4. Experimental section

4.1. General

Unless otherwise noted, starting materials were obtained from commercial suppliers and used without further purification. CH_2Cl_2, THF, benzene, and toluene were dried by passage through activated alumina columns and degassed by stirring under a dry N_2 atmosphere.[37] All reactions involving air- or moisture-sensitive compounds were performed under a dry N_2 atmosphere. $BF_3{\cdot}OEt_2$, Et_3N, $^iPr_2NH$, and MeOH were distilled from CaH_2. Purification by flash column chromatography was carried out with E. Merck Silica Gel 60 (230–400 mesh) according to the procedure of Still et al.[38] ^1H and ^{13}C NMR spectra were recorded in $CDCl_3$ at 500 MHz and 125 MHz, respectively, unless otherwise specified. IR spectra were measured as thin films on NaCl plates. Compounds **7a**, **10a**, and **11** have been reported previously.[35]

4.2. 2-(*tert*-Butyl-dimethyl-silanyloxy)-1-[(3-ethyl-4,5-dihydro-isoxazol-5-yl)]-ethanol (7b)

To a solution of oxime **5**, in which R=ethyl (480 mg, 6.6 mmol, 1.0 equiv), in toluene (33 mL) cooled in a dry ice–acetone bath and shielded from light was added ^{t}BuOCl (790 μL, 6.6 mmol, 1.0 equiv) dropwise over 20 min. The resulting mixture was stirred for 2 h with continued cooling at which time TLC analysis indicated complete consumption of starting material. In a separate flask, chiral allylic alcohol **6**[32,33] (1.7 g, 8.6 mmol, 1.3 equiv) in toluene (66 mL) was cooled in an ice–H_2O bath. To this solution was added ^{t}BuOH (2.1 mL, 22 mmol, 3.3 equiv) followed by dropwise addition of EtMgBr (10 mL of a 2.0 M solution in Et_2O, 20 mmol, 3.0 equiv) and the solution was stirred for 1 h with continued cooling. The solution of hydroximinoyl chloride was then transferred via cannula to the allylic alcohol solution and the mixture allowed to slowly warm to ambient temperature and stirred for 15 h. Satd NH_4Cl (10 mL) was added to the reaction mixture followed by further dilution with H_2O (40 mL). The organic and aqueous layers were separated and the aqueous extracted with CH_2Cl_2 (3×40 mL). The combined organic extracts were washed with brine (1×30 mL), dried over $MgSO_4$, filtered, and concentrated. Purification by flash chromatography yielded 1.4 g of isoxazoline **7b** as a colorless oil in 79% yield as a single stereoisomer. IR: 3365, 2929, 2857, 1115, 1059, 837 cm^{-1}; ^1H NMR: δ 0.06 (s, 6H), 0.88 (s, 9H), 1.15 (t, 3H, *J*=7.33), 2.32–2.57 (m, 2H), 2.95–2.98 (m, 2H), 3.56–3.73 (m, 3H), 4.62 (ddd, 1H, *J*=11.4, 7.7, 2.6); ^{13}C NMR: δ −5.5, −5.5, 10.8, 18.2, 21.2, 25.8, 38.9, 63.9, 73.0, 79.2, 160.6; HRMS (ESI) calcd for $[C_{13}H_{27}NO_3Si+Na]^+$: 296.1658, found: 296.1655.

4.3. 5-[1,2-Bis-(*tert*-butyl-dimethyl-silanyloxy)-ethyl]-3-ethyl-4,5-dihydro-isoxazole (10b)

To a solution of isoxazoline **7b** (1.4 g, 5.1 mmol, 1.0 equiv) in THF (26 mL) cooled in an ice–H_2O bath were added DMAP (63 mg, 0.51 mmol, 0.10 equiv) and Et_3N (1.6 mL, 11 mmol, 2.2 equiv). TBSOTf (2.6 mL, 11 mmol, 2.2 equiv) was then added dropwise and the solution slowly warmed to ambient temperature. Upon stirring for 2 h, TLC analysis indicated complete consumption of starting material. The mixture was again cooled in an ice–H_2O bath and diluted with satd NH_4Cl (15 mL). The solution was extracted with Et_2O (3×15 mL) and the combined organic extracts were washed with brine (1×20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. Purification of the crude product by flash chromatography (95:5 hexanes/EtOAc) yielded 1.9 g of isoxazoline **10b** in 95% yield as a colorless oil. IR: 2929, 2856, 1462, 1254, 1090, 835 cm^{-1}; ^1H NMR: δ 0.04 (s, 3H), 0.04 (s, 3H), 0.06 (s, 3H), 0.07 (s, 3H), 0.85 (s, 9H), 0.87 (s, 9H), 1.14 (t, 3H, *J*=7.3), 2.25–2.37 (m, 2H), 2.88 (d, 2H, *J*=9.3), 3.56 (dd, 1H, *J*=9.0, 1.7), 3.62–3.69 (m, 2H), 4.59–4.63 (m, 1H); ^{13}C NMR: δ −5.5, −4.9, −4.4, 10.7, 18.0, 18.2, 21.3, 25.7, 25.8, 38.2, 64.2, 74.2, 80.1, 159.4; HRMS (ESI) calcd for $[C_{19}H_{41}NO_3Si_2+Na]^+$: 410.2523, found: 410.2517.

4.4. 4-Benzyl-5-[1,2-bis-(*tert*-butyl-dimethyl-silanyloxy)-ethyl]-3-ethyl-4,5-dihydro-isoxazole (27)

$^iPr_2NH$ (760 μL, 5.4 mmol, 1.5 equiv) was added to 25 mL THF and the solution was cooled in an ice–H_2O bath. To the solution was added *n*-BuLi (3.4 mL of a 1.7 M solution in hexanes, 5.6 mmol, 1.6 equiv). The mixture was stirred for 10 min and transferred to a dry ice–acetone bath. A solution of isoxazoline **10b** (1.4 g, 3.6 mmol, 1.0 equiv) in 5 mL THF was added to the solution dropwise over 15 min and the mixture was stirred for 1 h with continued cooling. BnBr (1.4 mL, 11 mmol, 3.0 equiv) in 5 mL THF was subsequently added and the mixture continued to stir while being cooled until complete by TLC analysis (3 h). The mixture was diluted with satd aq NH_4Cl (10 mL) and extracted with Et_2O (3×20 mL). The combined organic extracts were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by flash chromatography (98:2 hexanes/EtOAc) to yield 1.1 g of isoxazoline **27** as a colorless oil in 62% yield. IR: 2929, 2856, 1462, 1254, 1090, 835 cm^{-1}; ^1H NMR: δ −0.04

(s, 6H), −0.02 (s, 3H), −0.02 (s, 3H), 0.82 (s, 9H), 0.83 (s, 9H), 1.14 (t, 3H, *J*=7.3), 2.10–2.20 (m, 1H), 2.34–2.43 (m, 1H), 2.65 (dd, 1H, *J*=9.9, 13.6), 3.01 (dd, 1H, *J*=5.5, 13.6), 3.17–3.21 (m, 1H), 3.35–3.45 (m, 2H), 3.52 (dd, 1H, *J*=6.9, 9.9), 4.33 (dd, 1H, *J*=2.9, 5.9), 7.13–7.15 (m, 2H), 7.19–7.30 (m, 3H); ^{13}C NMR: δ −5.5, −5.5, −4.8, −4.3, 10.7, 18.0, 18.3, 20.1, 25.8, 25.9, 37.6, 52.1, 63.7, 74.2, 76.7, 77.0, 77.3, 84.6, 126.7, 128.7, 128.9, 138.1, 161.5; HRMS (ESI) calcd for $[C_{26}H_{47}NO_3Si_2+Na]^+$: 500.2992, found: 500.2999.

4.5. General procedure for nucleophile addition to isoxazolines

To a solution of isoxazoline **10a** or **10b** (1.0 equiv) in toluene (final concentration 0.1–0.15 M) cooled in a dry ice–acetone bath was added $BF_3{\cdot}OEt_2$ (3.0 equiv) dropwise, and the resulting mixture was stirred with continued cooling for 30 min. A solution of organolithium reagent or Grignard reagent (6.0–8.0 equiv) was then added dropwise. The reaction mixture was allowed to stir with continued cooling until the starting material had been consumed as ascertained by TLC analysis, typically within 4 h. Saturated $NaHCO_3$ was added slowly to consume any remaining organolithium reagent or Grignard reagent, the solution was transferred to an ice–H_2O bath, and the mixture was extracted with EtOAc. The organic extracts were combined, washed with H_2O and brine, dried over Na_2SO_4, and concentrated in vacuo. The major and minor diastereomers were separated chromatographically and the major diastereomer was used in subsequent steps. In the case of the addition of methylallylmagnesium chloride to **27**, a 1.2:1 mixture of diastereomers was obtained and each was individually carried forward as depicted in Figure 5. The diastereomeric ratios were determined by spectral integration of the crude product mixture. However, in the case of **12**–**15**, there was significant spectral overlap and it was thus difficult to accurately ascertain diastereoselectivity at this stage. In these instances, the diastereoselectivity was assessed following protection of N2 (Fig. 3).

*4.5.1. 5-[1,2-Bis-(tert-butyl-dimethyl-silanyloxy)-ethyl]-3-isobutyl-3-phenyl-isoxazolidine (**12**)*

Prepared following the general procedure with addition of PhLi (2.3 mL of a 1.9 M solution in cyclohexane/ether, 4.3 mmol, 7.2 equiv) to **10a** (250 mg, 0.6 mmol, 1.0 equiv). Purification of the crude product mixture by flash column chromatography (9:1 hexanes/EtOAc and 2% NH_4OH) provided 180 mg of isoxazolidine **12** as a colorless oil in 60% yield (major diastereomer, dr 7:1). IR: 2954, 2929, 2858, 1472, 1255 cm^{-1}; ^{1}H NMR: δ −0.01 (d, 6H, *J*=5.2), 0.09 (d, 6H, *J*=6.5), 0.66 (d, 3H, *J*=6.6), 0.76 (d, 3H, *J*=6.6), 0.81 (s, 9H), 0.91 (s, 9H), 1.22 (br s, 1H), 1.52 (br s, 1H), 2.00 (br s, 1H), 2.03–2.24 (m, 1H), 2.74 (br s, 1H), 3.58–3.60 (m, 2H), 3.65–3.70 (m, 1H), 4.02–4.06 (m, 1H), 5.45 (br s, 1H), 7.16–7.22 (m, 1H), 7.29–7.31 (m, 2H), 7.49–7.51 (m, 2H); ^{13}C NMR (100 MHz): δ −5.2, −4.1, 18.3, 18.6, 23.7, 24.4, 25.1, 26.2, 46.5, 49.1, 64.9, 71.3, 75.9, 78.6, 126.5, 126.7, 128.2, 144.2; HRMS (ESI) calcd for $[C_{27}H_{51}NO_3Si_2+Na]^+$: 516.3305, found: 516.3302.

*4.5.2. 3-Allyl-5-[1,2-bis-(tert-butyl-dimethyl-silanyloxy)-ethyl]-3-isobutyl-isoxazolidine (**13**)*

Prepared following the general procedure with addition of allylmagnesium chloride (5 mL of a 2.0 M solution in THF, 10 mmol, 7.2 equiv) to **10a** (580 mg, 1.4 mmol, 1.0 equiv). Purification of the crude product mixture by flash column chromatography (15:1 hexanes/EtOAc and 2% NH_4OH) provided 490 mg of isoxazolidine **13** as a colorless oil in 76% yield (major diastereomer, dr 8:1). IR: 2955, 2930, 2858, 1472, 1255 cm^{-1}; ^{1}H NMR: δ −0.02 (d, 6H, *J*=1.8), 0.05 (br s, 6H), 0.84 (s, 9H), 0.86 (s, 9H), 0.88 (s, 3H), 0.90 (s, 3H), 1.30–1.44 (m, 2H), 1.75–1.82 (m, 2H), 2.13–2.19 (m, 2H), 2.30–2.36 (m, 1H), 3.53–3.57 (m, 2H), 3.66–3.68 (m, 1H), 4.23 (br s, 1H), 5.02–5.06 (m, 2H), 5.77–5.89 (m, 1H); ^{13}C NMR (100 MHz): δ −5.2, −4.4, −4.1, 18.2, 18.5, 24.2, 24.4, 24.5, 26.1, 40.1, 42.5, 43.7, 64.5, 67.6, 76.0, 78.9, 117.3, 135.4; HRMS (ESI) calcd for $[C_{24}H_{51}NO_3Si_2+Na]^+$: 480.3305, found: 480.3304.

*4.5.3. 5-[1,2-Bis-(tert-butyl-dimethyl-silanyloxy)-ethyl]-3-isobutyl-3-methyl-isoxazolidine (**14**)*

Prepared following the general procedure with addition of MeLi (3.1 mL of a 1.6 M solution in ether, 5.0 mmol, 7.2 equiv) to **10a** (290 mg, 0.7 mmol, 1.0 equiv). Purification of the crude product mixture by flash column chromatography (9:1 hexanes/EtOAc and 2% NH_4OH) provided 190 mg of isoxazolidine **14** as a colorless oil in 64% yield (major diastereomer, dr 7:1). IR: 2954, 2929, 2858, 1472, 1255 cm^{-1}; ^{1}H NMR: δ 0.01 (d, 6H, *J*=1.5), 0.05 (s, 6H), 0.85 (s, 9H), 0.86 (s, 9H), 0.89 (d, 3H, *J*=6.6), 0.90 (d, 3H, *J*=6.6), 1.13 (s, 3H), 1.30–1.35 (m, 1H), 1.39–1.44 (m, 1H), 1.77–1.86 (m, 2H), 2.01–2.10 (m, 1H), 3.54–3.57 (m, 2H), 3.66–3.69 (m, 1H), 4.30 (br s, 1H), 5.17 (br s, 1H); ^{13}C NMR (100 MHz): δ −5.2, −4.3, −4.2, 18.2, 18.6, 23.7, 24.2, 24.5, 25.2, 26.2, 44.5, 46.5, 64.6, 65.1, 75.9, 79.2; HRMS (ESI) calcd for $[C_{22}H_{49}NO_3Si_2+H]^+$: 432.3329, found: 432.3322.

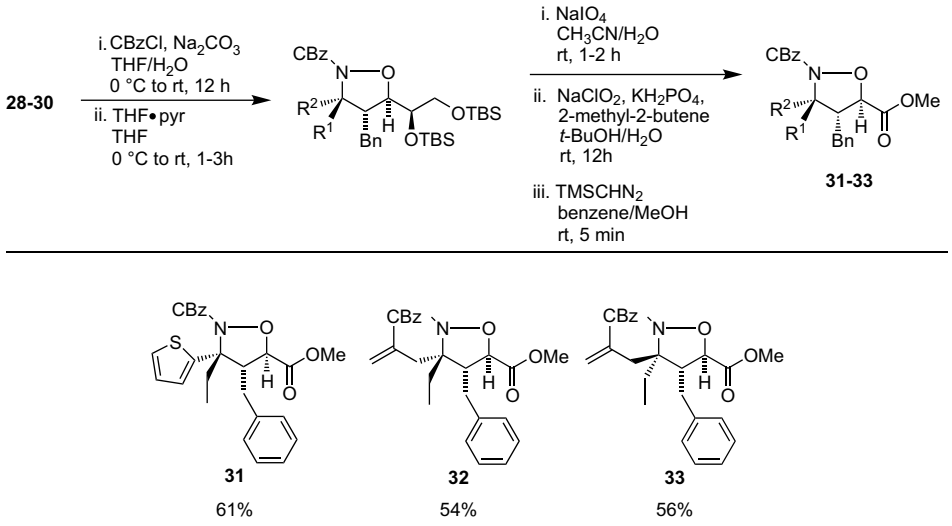


Figure 5. Generation of trisubstituted β-prolines.

*4.5.4. 5-[1,2-Bis-(tert-butyl-dimethyl-silanyloxy)-ethyl]-3-isobutyl-3-thiophen-isoxazolidine (**15**)*

2-Thienyllithium (4.3 mL of a 1 M solution in THF, 4.3 mmol, 7.2 equiv) was added to isoxazoline **10a** (250 mg, 0.6 mmol, 1.0 equiv). Purification of the crude product mixture by flash column chromatography (10:1 hexanes/EtOAc and 2% NH_4OH) provided 220 mg of isoxazolidine **15** as a colorless oil in 73% yield (major diastereomer, dr 20:1). IR: 2954, 2929, 2858, 1472, 1255 cm^{-1}; ^1H NMR: δ 0.02 (d, 6H, J=3.3), 0.12 (d, 6H, J=3.0), 0.83–0.85 (m, 6H), 0.86 (s, 9H), 0.93 (s, 9H), 1.40–1.55 (m, 1H), 1.64–1.86 (m, 2H), 2.25–2.29 (m, 1H), 2.75–2.90 (m, 1H), 3.59–3.65 (m, 2H), 3.70–3.74 (m, 1H), 4.29 (br s, 1H), 5.65 (br s, 1H), 6.92–6.96 (m, 2H), 7.17–7.19 (m, 1H); ^{13}C NMR (100 MHz): δ −5.2, −5.2, −4.3, −4.1, 18.2, 18.6, 23.9, 24.0, 25.3, 26.2, 46.1, 48.8, 64.8, 70.4, 76.1, 79.4, 123.9, 124.3, 126.7; HRMS (ESI) calcd for $[C_{25}H_{49}NO_3SSi_2+H]^+$: 500.3050, found: 500.3055.

*4.5.5. 5-[1,2-Bis-(tert-butyl-dimethyl-silanyloxy)-ethyl]-3-ethyl-3-(2-methyl-allyl)-isoxazolidine (**16**)*

Compound **16** was prepared following the general procedure using isoxazoline **10b** (800 mg, 2.1 mmol, 1.0 equiv) and the nucleophile 2-methylallylmagnesium chloride (30 mL of a 0.5 M solution in THF, 15 mmol, 7.2 equiv). Purification of the crude product by flash chromatography (95:5 hexanes/EtOAc) yielded 730 mg of the major diastereomer (dr 8:1) as a clear oil in 79% yield. ^1H NMR: δ 0.03 (s, 3H), 0.03 (s, 3H), 0.06 (s, 6H), 0.86 (s, 9H), 0.86 (s, 9H), 0.95 (apparent triplet, 3H, J=7.3), 1.35 (dd, 1H, J=13.2, 7.3), 1.62–1.69 (m, 1H), 1.82 (s, 3H), 1.84 (dd, 1H, J=13.2, 7.3), 2.05–2.15 (m, 2H), 2.26–2.29 (m, 1H), 3.56–3.59 (m, 2H), 3.67–3.71 (m, 1H), 4.21 (br s, 1H), 4.71 (s, 1H), 4.83 (s, 1H); ^{13}C NMR: δ −5.4, −5.4, −4.6, −4.4, 9.5, 18.0, 18.3, 24.4, 25.6, 25.9, 41.6, 41.7, 42.2, 64.6, 67.2, 68.1, 75.4, 113.9, 114.7; HRMS (ESI) calcd for $[C_{23}H_{49}NO_3Si_2+Na]^+$: 466.3149, found: 466.3145.

*4.5.6. 4-Benzyl-5-[1,2-bis-(tert-butyl-dimethyl-silanyloxy)-ethyl]-3-ethyl-3-thiophen-2-yl-isoxazolidine (**28**)*

Prepared following the general procedure by additional of 2-thienyllithium (3.9 mL of a 1 M solution, 3.9 mmol, 7.2 equiv) to isoxazoline **27** (260 mg, 0.54 mmol, 1.0 equiv). Purification of the crude product by flash chromatography (98:2 hexanes/EtOAc) gave 170 mg of **28** as a clear oil in 55% yield as a single diastereomer. ^1H NMR: δ −0.08 (s, 3H), −0.02 (s, 3H), 0.00 (s, 3H), 0.04 (s, 3H), 0.89 (s, 9H), 0.89 (s, 9H), 0.96 (t, 3H, J=6.8), 1.82 (br s, 1H), 1.96 (t, 1H, J=12.0), 2.54 (br s, 1H), 2.62–2.66 (m, 1H), 2.78–2.80 (m, 2H), 3.44 (dd, 1H, J=9.8, 5.4), 3.59 (t, 1H, J=9.0), 4.16 (d, 1H, J=7.3), 7.01–7.03 (m, 1H), 7.05–7.06 (m, 3H), 7.16–7.19 (m, 1H), 7.22–7.25 (m, 2H), 7.36 (d, 1H, J=4.9); ^{13}C NMR: δ −5.5, −5.4, −4.6, −4.5, 9.5, 17.9, 18.3, 25.9, 25.9, 30.8, 37.1, 56.7, 64.0, 72.1, 75.2, 84.2, 124.5, 124.7, 125.7, 126.3, 128.5, 128.9, 139.7, 144.5; HRMS (ESI) calcd for $[C_{30}H_{51}NO_3SSi_2+Na]^+$: 584.3026, found: 584.3032.

*4.5.7. Compounds **29** and **30***

Prepared according to the general procedure by addition of 2-methylallylmagnesium chloride (12 mL of a 0.5 M solution in THF, 6.0 mmol, 7.2 equiv) to isoxazoline **27** (400 mg, 0.83 mmol, 1.0 equiv). A 1.2:1 diastereomeric ratio of products was determined by spectral integration of the crude product mixture. Purification by flash chromatography (98:2 hexanes/EtOAc) yielded 190 mg of diastereomer **29** and 160 mg of diastereomer **30**, each as colorless oils, for a combined yield of 81%.

*4.5.7.1. 4-Benzyl-5-[1,2-bis-(tert-butyl-dimethyl-silanyloxy)-ethyl]-3-ethyl-3-(2-methyl-allyl)-isoxazolidine (**29**).* IR: 2928, 2857, 1471, 1254, 1093, 836 cm^{-1}; ^1H NMR: δ −0.17 (s, 3H), −0.13 (s, 3H), −0.06 (s, 3H), −0.04 (s, 3H), 0.81 (s, 9H), 0.84 (s, 9H), 1.08 (t, 3H, J=7.7), 1.28–1.36 (m, 1H), 1.70–1.79 (m, 1H), 1.91 (s, 3H), 2.18 (d, 1H, J=13.2), 2.36 (d, 1H, J=13.2), 2.47–2.53 (m, 1H), 2.56–2.64 (m, 2H), 2.97 (dd, 1H, J=12.5, 2.9), 3.34 (dd, 1H, J=9.5, 5.1), 3.58 (dd, 1H, J=9.5, 8.1), 4.06 (d, 1H, J=6.6), 4.75 (s, 1H), 4.87–4.88 (m, 1H), 5.34 (br s, 1H), 7.12–7.27 (m, 5H); ^{13}C NMR: δ −5.5, −5.4, −4.8, −4.4, 9.1, 17.9, 18.3, 24.9, 25.9, 26.0, 26.1, 36.7, 37.6, 53.7, 64.1, 68.5, 75.7, 76.7, 77.0, 77.3, 85.0, 113.9, 126.3, 128.6, 128.8, 140.3, 143.9; HRMS (ESI) calcd for $[C_{30}H_{55}NO_3Si_2+Na]^+$: 556.3618, found: 556.3615.

*4.5.7.2. 4-Benzyl-5-[1,2-bis-(tert-butyl-dimethyl-silanyloxy)-ethyl]-3-ethyl-3-(2-methyl-allyl)-isoxazolidine (**30**).* IR: 2953, 2928, 2857, 1471, 1254, 1093, 836 cm^{-1}; ^1H NMR: δ −0.15 (s, 3H), −0.07 (s, 3H), −0.01 (s, 3H), 0.00 (s, 3H), 0.84 (s, 9H), 0.89 (s, 9H), 1.03 (t, 3H, J=7.7), 1.51–1.59 (m, 1H), 1.64–1.73 (m, 1H), 1.89 (s, 3H), 2.28 (d, 1H, J=13.2), 2.33 (d, 1H, J=13.3), 2.51–2.68 (m, 3H), 3.02 (dd, 1H, J=12.5, 2.2), 3.37 (dd, 1H, J=9.5, 5.1), 3.49–3.53 (m, 1H), 4.12 (d, 1H, J=6.59), 4.91 (s, 1H), 5.02 (s, 1H), 7.16–7.22 (m, 3H), 7.25–7.28 (m, 2H); ^{13}C NMR: δ −5.5, −5.4, −4.7, −4.4, 8.1, 17.9, 18.3, 24.3, 24.9, 25.9, 25.9, 35.3, 40.5, 53.6, 64.0, 67.8, 75.1, 84.2, 115.9, 126.2, 128.6, 128.9, 140.3, 141.5; HRMS (ESI) calcd for $[C_{30}H_{55}NO_3Si_2+Na]^+$: 556.3618, found: 556.3615.

4.6. General procedure for Cbz protection, TBS deprotection, and oxidative cleavage

A solution of isoxazolidine (1.0 equiv) in THF (final concentration of 0.3 M) was cooled in an ice–H_2O bath. To the stirring solution were added CbzCl (3.0 equiv) and satd Na_2CO_3 (final concentration of 0.3 M) and the biphasic reaction mixture was stirred at rt for 12 h. The reaction mixture was then partitioned between H_2O and EtOAc, and the aqueous layer was extracted 3× with EtOAc. The combined organic extracts were dried over Na_2SO_4 and concentrated in vacuo. The crude mixture was passed through a short plug of SiO_2 (15:1 hexanes/EtOAc) and concentrated. The residue was dissolved in THF, cooled in an ice–H_2O bath, and 4 equiv TBAF (1 M in THF) or HF·Py (3.0 equiv) was added dropwise. HF·Py was used for the deprotection of isoxazolidines containing a *C*4 substituent (2**8**–**30**) as the deprotection with TBAF proceeded very slowly. After 1 h, the ice–H_2O bath was removed and the progress of the reaction was monitored by TLC analysis. Upon complete consumption of starting material, the reaction was then diluted with H_2O and extracted 3× with Et_2O or EtOAc. The organic extracts were combined, washed with H_2O and brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude diol was then used in the subsequent oxidative cleavage reactions after passing through a plug of silica to eliminate the nonpolar impurities (1:9 MeOH/CH_2Cl_2).

To a stirred solution of crude diol (1.0 equiv) dissolved in ^{t}BuOH/THF/H_2O (10:3:1, final concentration 0.2 M)[†] was added $NaIO_4$ (1.2 equiv). The reaction mixture was stirred at rt until the starting material was fully consumed as ascertained by TLC analysis. Two methods were effective for isolation of the aldehyde at this stage. In the first method, the reaction mixture was diluted with 5 mL $CHCl_3$ and filtered through a layer of Celite. Alternatively, the mixture was diluted with H_2O and extracted 3× with Et_2O; the combined organic extracts were washed with brine, dried over $MgSO_4$, and filtered. Concentration in vacuo of the combined filtrate from either procedure then provided a crude oil that was immediately dissolved in ^{t}BuOH (0.1 M) and 2-methyl-2-butene (47 equiv). A solution of $NaClO_2$ (9.2 equiv) and KH_2PO_4 (7.0 equiv) in H_2O was added dropwise to give a pale yellow mixture. The reaction mixture was stirred at rt until TLC analysis indicated complete consumption of starting material, typically within 3 h. The mixture was diluted

[†] A 1:1 mixture of CH_3CN/H_2O can also be used.

with satd $NaHCO_3$ and EtOAc. The aqueous layer was then extracted with EtOAc and the combined organic extracts were dried over Na_2SO_4, filtered, and concentrated to provide the crude product mixture. The compounds were purified using flash chromatography. Isoxazolidines containing a substituent at the C4 position were isolated as the methyl ester. The methyl ester was generated by treatment of the crude acid (1.0 equiv) in benzene (0.05 M) and MeOH (0.15 M) with $TMSCHN_2$ (10 equiv). The resulting mixture was stirred for 10 min, at which time TLC analysis indicated complete consumption of starting material. The solvent was removed by rotary evaporation and the product purified by flash chromatography.

4.6.1. 3-Benzyl-3-isobutyl-isoxazolidine-2,5-dicarboxylic acid 2-benzyl ester (**17**)

Prepared following the general procedure on 0.05 mmol scale. Purification of the crude product mixture by flash column chromatography (1:9 MeOH/CH_2Cl_2 and 2% acetic acid) provided 8.3 mg of acid **17** as a colorless oil in 42% overall yield over two steps. IR: 3388, 2956, 2929, 2870, 1694, 1455, 1350 cm^{-1}; ^1H NMR (CD_3OD): δ 0.85 (d, 3H, J=6.3), 0.92 (d, 3H, J=6.2), 1.74–1.81 (m, 2H), 1.82–1.90 (m, 1H), 2.46–2.54 (m, 1H), 2.66–2.73 (m, 1H), one set of benzylic CH_2 buried under CD_3OD around 3.30, 3.60 (br s, 1H), 5.11–5.24 (m, 2H, rotamers), 7.04–7.06 (m, 2H), 7.16–7.17 (m, 3H), 7.30–7.40 (m, 5H); ^{13}C NMR (100 MHz) (CD_3OD): δ 22.7, 24.3, 41.3, 42.3, 45.4, 67.3, 68.7, 75.5, 126.7, 128.1, 128.3, 128.4, 128.5, 130.5, 136.3, 136.6, 153.0; HRMS (ESI) calcd for $[C_{23}H_{27}NO_5+Na]^+$: 420.1787, found: 420.1782.

4.6.2. 3-Isobutyl-3-phenyl-isoxazolidine-2,5-dicarboxylic acid 2-benzyl ester (**18**)

Prepared following the general procedure on 0.12 mmol scale. Purification of the crude product mixture by flash column chromatography (1:9 MeOH/CH_2Cl_2 and 2% acetic acid) provided 24 mg of acid **18** as a colorless oil in 52% overall yield from **12**. IR: 3388, 2956, 2929, 2870, 1700, 1447, 1346 cm^{-1}; ^1H NMR (CD_3OD): δ 0.84 (d, 3H, J=6.6), 0.94 (d, 3H, J=6.6), 1.81–1.89 (m, 1H), 2.18–2.25 (m, 2H), 2.64–2.70 (m, 1H), 2.81–2.87 (m, 1H), 4.49–4.52 (m, 1H), 5.02–5.03 (m, 2H, rotamers), 7.11–7.15 (m, 2H), 7.21–7.28 (m, 8H); ^{13}C NMR (100 MHz) (CD_3OD): δ 23.2, 24.2, 24.4, 29.5, 44.6, 53.6, 67.1, 70.8, 125.0, 127.0, 128.0, 128.1, 128.2, 128.3, 136.1, 145.1, 153.7; HRMS (ESI) calcd for $[C_{22}H_{25}NO_5+Na]^+$: 406.1630, found: 406.1638.

4.6.3. 3-Isobutyl-3-methyl-isoxazolidine-2,5-dicarboxylic acid 2-benzyl ester (**20**)

Prepared following the general procedure on 0.06 mmol scale. Purification of the crude product mixture by flash column chromatography (1:9 MeOH/CH_2Cl_2 and 2% acetic acid) provided 8.7 mg of acid **20** as a colorless oil in 45% overall yield from **14**. IR: 3388, 2956, 2929, 2870, 1698, 1447, 1346 cm^{-1}; ^1H NMR (CD_3OD): δ 0.89 (d, 3H, J=6.3), 0.94 (d, 3H, J=6.6), 1.43 (s, 3H), 1.69–1.74 (m, 2H), 1.82–1.85 (m, 1H), 2.49–2.53 (m, 1H), 2.60–2.64 (m, 1H), 4.68 (t, 1H, J=7.7), 5.18 (s, 2H), 7.31–7.42 (m, 5H); ^{13}C NMR (100 MHz) (CD_3OD) (some aromatic peaks overlap): δ 22.8, 23.8, 23.9, 24.6, 45.0, 46.5, 66.0, 67.1, 74.7, 128.1, 128.3, 136.3, 154.2, 173.5; HRMS (ESI) calcd for $[C_{17}H_{23}NO_5+Na]^+$: 344.1474, found: 344.1467.

4.6.4. 3-Isobutyl-3-thiophen-2-yl-isoxazolidine-2,5-dicarboxylic acid 2-benzyl ester (**21**)

Prepared following the general procedure on 0.05 mmol scale. Purification of the crude product mixture by flash column chromatography (1:9 MeOH/CH_2Cl_2 and 2% acetic acid) provided 10.7 mg of acid **21** as a colorless oil in 55% overall yield from **15**. IR: 3401, 2956, 2929, 1705, 1400, 1329 cm^{-1}; ^1H NMR (CD_3OD): δ 0.86 (s, 3H), 0.88 (s, 3H), 1.73–1.84 (m, 1H), 2.17–2.34 (m, 2H), 2.88–2.99 (m, 2H), 5.14 (s, 2H), 6.87–6.89 (m, 1H), 6.97–6.99 (m, 1H), 7.17–7.19 (m, 2H), 7.24–7.27 (m, 4H); ^{13}C NMR (100 MHz) (CD_3OD): δ 23.1, 23.8, 24.9, 46.2, 46.5, 68.3, 69.6, 77.2, 124.4, 124.7, 126.4, 128.3, 128.3, 128.4, 135.5, 147.8; HRMS (ESI) calcd for $[C_{20}H_{23}NO_5S+Na]^+$: 412.1195, found: 412.1201.

4.6.5. (3S,5R)-3-Ethyl-3-(2-methyl-allyl)-isoxazolidine-2,5-dicarboxylic acid 2-benzyl ester (**22**)

Compound **22** was prepared according to the general procedure from isoxazolidine **16** (44 mg, 0.10 mmol, 1.0 equiv). Purification by flash chromatography (95:5 CH_2Cl_2/MeOH+2% acetic acid) of the crude product yielded 14 mg of **22** as a colorless oil in 42% yield. IR: 2927, 2363, 1696, 1559, 1456 cm^{-1}; ^1H NMR (CD_3OD): δ 0.89 (t, 3H, J=7.3), 1.74 (s, 3H), 1.78–1.85 (m, 1H), 1.97–2.04 (m, 1H), 2.37 (d, 1H, J=13.7), 2.50 (dd, 1H, J=12.7, 7.3), 2.69 (d, 1H, J=13.7), 2.82 (dd, 1H, J=12.9, 8.1), 4.53–4.56 (m, 1H), 4.82 (s, 1H), 4.95 (s, 1H), 5.22 (s, 2H), 7.33–7.41 (m, 3H), 7.43–7.45 (m 2H); ^{13}C NMR: δ 8.6, 24.2, 32.0, 42.3, 45.7, 68.5, 69.5, 85.7, 117.2, 129.5, 129.6, 129.7, 143.2, 166.7; HRMS (ESI) calcd for $[C_{18}H_{23}NO_5+Na]^+$: 356.1474, found: 356.1472.

4.6.6. 4-Benzyl-3-ethyl-3-thiophen-2-yl-isoxazolidine-2,5-dicarboxylic acid 2-benzyl ester 5-methyl ester (**31**)

Isoxazolidine **28** (67 mg, 0.12 mmol, 1.0 equiv) was treated according to the general procedure to yield 34 mg of **31** as a colorless oil in 61% yield. IR: 2950, 1710, 1454, 1327, 697 cm^{-1}; ^1H NMR (CD_3OD): δ 0.93 (t, 3H, J=7.2), 2.09 (d, 1H, J=14.3, 9.6), 2.14 (dd, 1H, J=14.1, 7.0), 2.40–2.49 (m, 1H), 2.54 (dd, 1H, J=14.5, 5.5), 3.26–3.33 (m, 4H), 4.41 (d, 1H, J=9.4), 4.94 (s, 2H), 6.91 (dd, 1H, J=3.9, 1.2), 6.93–6.96 (m, 3H), 7.00–7.02 (m, 2H), 7.07–7.09 (m, 1H), 7.11–7.14 (m, 2H), 7.15–7.18 (m, 3H), 7.31 (dd, 1H, J=5.1, 1.2); ^{13}C NMR: δ 7.7, 29.2, 34.1, 52.3, 53.7, 67.5, 71.2, 78.9, 124.8, 125.0, 126.7, 126.8, 128.0, 128.0, 128.3, 128.4, 128.8, 137.4, 145.2, 169.5; HRMS (ESI) calcd for $[C_{26}H_{27}NO_5S+Na]^+$: 488.1508, found: 488.1507.

4.6.7. 4-Benzyl-3-ethyl-3-(2-methyl-allyl)-isoxazolidine-2,5-dicarboxylic acid 2-benzyl ester 5-methyl ester (**32**)

Isoxazolidine **29** (43 mg, 0.08 mmol, 1.0 equiv) was treated according to the general procedure to yield 19 mg of **32** as a colorless oil in 54% yield. IR: 3468, 2923, 2852, 1695, 1455, 1348, 1115 cm^{-1}; ^1H NMR (CD_3OD): δ 0.93 (t, 3H, J=7.3), 1.65–1.72 (m, 1H), 1.76 (s, 3H), 2.31–2.38 (m, 1H), 2.41 (d, 1H, J=14.2), 2.66 (d, 1H, J=13.7), 2.93 (dd, 1H, J=13.9, 10.0), 3.02 (dd, 1H, J=13.7, 5.4), 3.19–3.23 (m, 1H), 3.40 (s, 3H), 4.44 (d, 1H, J=9.3) (two protons buried under MeOH), 5.11 (d, 1H, J=12.2), 5.19 (d, 1H, J=12.2), 7.22–7.25 (m, 3H), 7.30–7.43 (m, 7H); HRMS (ESI) calcd for $[C_{26}H_{31}NO_5+Na]^+$: 460.2100, found: 460.2093.

4.6.8. 4-Benzyl-3-ethyl-3-(2-methyl-allyl)-isoxazolidine-2,5-dicarboxylic acid 2-benzyl ester 5-methyl ester (**33**)

Isoxazolidine **30** (37 mg, 0.07 mmol, 1.0 equiv) was treated according to the general procedure to yield 17 mg of **33** as a colorless oil in 56% yield. IR: 3469, 2924, 2852, 1695, 1455, 1348, 1115 cm^{-1}; ^1H NMR: δ 0.95 (t, 3H, J=7.6), 1.67–1.74 (m, 4H), 2.02–2.09 (m, 1H), 2.24 (d, 1H, J=14.6), 2.67 (dd, 1H, J=13.7, 10.7), 2.93 (dd, 1H, J=13.7, 4.9), 3.03 (d, 1H, J=14.6), 3.26 (s, 3H), 3.31–3.36 (m, 1H), 4.28 (d, 1H, J=9.8), 4.72 (s, 1H), 4.95 (s, 1H), 5.21 (s, 2H), 7.11–7.38 (m, 10H); ^{13}C NMR: δ 10.1, 22.5, 23.2, 29.0, 33.7, 37.0, 44.9, 54.5, 68.5, 70.7, 81.2, 117.1, 127.9, 129.7, 129.7, 130.3, 141.9, 163.9; HRMS (ESI) calcd for $[C_{26}H_{31}NO_5+Na]^+$: 460.2100, found: 460.2098.

4.7. (9*H*-Fluoren-9-yl)methyl 3-allyl-3-isobutyl-5-(2,2,3,3,8,8,9,9-octamethyl-4,7-dioxa-3,8-disiladecan-5-yl)isoxazolidine-2-carboxylate (23)

To a stirred solution of **13** (73, mg, 0.16 mmol, 1.0 equiv) in THF (530 μL) cooled in an ice–H_2O bath was added FmocCl (170 mg, 0.64 mmol, 4.0 equiv) followed immediately by satd Na_2CO_3 (530 μL) and the mixture was allowed to slowly warm to rt. Upon

stirring for 12 h TLC analysis indicated complete consumption of starting material. The reaction mixture was diluted with H_2O (5 mL) and extracted with Et_2O (3×5 mL). The combined organic extracts were washed with brine (10 mL), dried over Na_2SO_4, filtered, and concentrated. The crude mixture was purified by flash chromatography (96:4 hexanes/EtOAc) to yield 100 mg of **23** as a colorless oil in 92% yield. ^{1}H NMR: δ 0.03 (s, 3H), 0.04 (s, 3H), 0.08 (s, 3H), 0.10 (s, 3H), 0.10 (s, 3H), 0.86 (s, 18H), 1.24–1.28 (m, 1H), 1.47–1.50 (m, 1H), 1.56–1.61 (m, 1H), 1.66–1.73 (m, 1H), 2.12–2.23 (m, 2H), 2.54 (br s, 1H), 3.59–3.66 (m, 2H), 3.68–3.71 (m, 1H), 4.09–4.13 (m, 1H), 4.24 (apparent triple, 1H, J=7.08), 4.39–4.43 (m, 1H), 4.47–4.51 (m, 1H), 4.97–5.04 (m, 2H), 5.61–5.71 (m, 1H), 7.27 (m, 2H), 7.36 (m, 2H), 7.63 (dd, 2H, J=2.9, 7.3), 7.73 (d, 2H, J=7.8); ^{13}C NMR (100 MHz): δ −5.5, −5.4, 4.7, 4.6, 18.2, 18.3, 23.1, 24.1, 25.0, 25.8, 25.9, 39.9, 42.2, 45.5, 47.1, 65.2, 66.8, 67.6, 73.5, 76.7, 77.0, 77.3, 79.7, 118.6, 119.8, 125.2, 127.1, 127.6, 133.6, 141.3, 144.1, 144.1, 152.1; HRMS (ESI) calcd for $[C_{39}H_{61}NO_5Si_2+Na]^+$: 702.3986, found: 702.4001.

4.8. (9*H*-Fluoren-9-yl)methyl 3-allyl-3-isobutyl-5-((*R*)-2,2,3,3,8,8,9,9-octamethyl-4,7-dioxa-3,8-disiladecan-5-yl)isoxazolidine-2-carboxylate (25)

To a stirred solution of **23** in ^{t}BuOH (7.5 mL), THF (2.0 mL), and H_2O (500 μL) cooled in an ice–H_2O bath were added NMO (150 mg, 1.3 mmol, 1.2 equiv) and OsO_4 (1.0 mL of a 2.5 wt% solution in ^{t}BuOH). The reaction mixture was stirred for 6 h at which point TLC analysis indicated complete consumption of starting material. Na_2SO_3 (25 mg) was then added and the solution was stirred for 1 h. The mixture was then diluted with H_2O (10 mL) and extracted with EtOAc (3×20 mL). The combined organic extracts were washed with brine (25 mL), dried over Na_2SO_4, filtered, and concentrated. The crude material was dissolved in CH_3CN (5.5 mL) and H_2O (0.5 mL), cooled in an ice–H_2O bath, and $NaIO_4$ (280 mg) was added to the solution. The mixture was stirred for 1 h at which point TLC analysis indicated complete consumption of starting material. The reaction mixture was diluted with H_2O (10 mL) and extracted with Et_2O (3×15 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude material was then dissolved in 11 mL MeOH and cooled in an ice–H_2O bath. $NaBH_4$ was added to the solution and after 30 min TLC analysis indicated complete consumption of starting material. The reaction mixture was diluted with H_2O (10 mL) and extracted with Et_2O (3×20 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude material was purified by flash chromatography (elution in 60:40 hexanes/EtOAC) to give 450 mg of product as a colorless oil in 60% yield. To a solution of product (500 mg, 0.73 mmol, 1.0 equiv) in CH_2Cl_2 (7.3 mL) cooled in an ice–H_2O bath was added ^{i}Pr$_2$NEt (380 μL, 2.2 mmol, 3.0 equiv) followed by dropwise addition of MOMCl (170 μL, 2.2 mmol, 3.0 equiv). The reaction mixture was allowed to slowly warm to rt. After 12 h TLC analysis indicated complete consumption of starting material. The reaction mixture was diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (3×10 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude product was purified by flash chromatography (elution in 80:20 hexanes/EtOAc) to yield 480 mg of isoxazolidine **25** as a colorless oil in 90% yield. ^{1}H NMR: 0.04 (s, 3H), 0.04 (s, 3H), 0.09 (s, 3H), 0.11 (s, 3H), 0.81 (d, 3H, J=6.4), 0.85 (d, 3H, J=2.9), 0.87 (s, 9H), 0.87 (s, 9H), 1.46–1.60 (m, 2H), 1.65–1.73 (m, 1H), 1.82–1.91 (m, 1H), 2.00 (br s, 1H), 2.24–2.26 (m, 1H), 2.33 (dd, 1H, J=6.1, 12.5), 3.30 (s, 3H), 3.42–3.51 (m, 3H), 3.71 (dd, 1H, J=5.6, 11.0), 4.09–4.15 (m, 1H), 4.23 (apparent triplet, 1H, J=6.6), 4.40 (dd, 1H, J=6.6, 10.0), 4.48–4.52 (m, 3H), 7.27 (apparent triplet, 2H, J=7.3), 7.37 (apparent triplet, 2H, J=7.3), 7.62 (dd, 2H, J=4.2, 7.1), 7.73 (d, 2H, J=7.3); ^{13}C NMR: δ −5.5, −5.41, −4.7, −4.6, 18.2, 18.3, 23.2, 24.1, 25.1, 25.8, 25.9, 37.2, 40.8, 45.7, 47.1, 55.3, 64.1, 65.3, 66.8, 66.9, 73.6, 76.7, 77.0, 77.3, 79.9, 96.5, 119.9, 125.1, 127.1, 127.6, 127.6, 141.3, 141.3, 144.0, 152.2; HRMS (ESI) calcd for $[C_{40}H_{65}NO_7Si_2+Na]^+$: 750.4197, found: 750.4181.

4.9. 2-(((9*H*-Fluoren-9-yl)methoxy)carbonyl)-3-isobutyl-3-(2-(methoxymethoxy)ethyl)isoxazolidine-5-carboxylic acid (26)

A 40% solution of HCl in MeOH (2 mL) was cooled in an ice–H_2O bath and then added to a solution of **25** (58 mg, 0.08 mmol, 1.0 equiv) in 2 mL MeOH that was also cooled in an ice–H_2O bath. Upon stirring 30 min ESI-MS analysis of the reaction mixture indicated complete consumption of starting material. The reaction mixture was diluted with H_2O (5 mL) and extracted with EtOAc (3×5 mL). The combined organic extracts were washed with H_2O (10 mL) and brine (10 mL), dried over Na_2SO_4, filtered, and concentrated. The crude material was dissolved in CH_3CN (400 μL) and H_2O (400 μL), cooled in an ice–H_2O bath, and $NaIO_4$ (21 mg, 0.08 mmol, 1.2 equiv) was added to the solution. Upon stirring for 1 h TLC analysis indicated complete consumption of starting material. The reaction mixture was diluted with H_2O (5 mL) and extracted with Et_2O (3×5 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated. The crude material was dissolved in ^{t}BuOH (400 μL) and 2-methyl-2-butene was added to the solution. A solution of KH_2PO_4 (76 mg, 0.56 mmol, 7.0 equiv) and $NaOCl_2$ (67 mg, 0.745 mmol, 0.2 equiv) in H_2O (230 μL) was then added dropwise to the isoxazolidine solution. The reaction mixture was stirred for 12 h at which point TLC analysis indicated complete consumption of starting material. The reaction mixture was diluted with H_2O (5 mL) and extracted with EtOAC (3×5 mL). The combined organic extracts were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by flash chromatography (elution in 80:20 CH_2Cl_2/MeOH) to yield 21 mg of **26** as a colorless oil in 53% yield. ^{1}H NMR (CD_3OD): δ 1.57 (d, 3H, J=6.6), 1.64 (d, 3H, J=6.6), 1.86–1.94 (m, 1H), 2.04–2.20 (m, 2H), 2.24–2.40 (m, 2H), 3.44 (dd, 1H, J=5.9, 12.9), 3.66 (dd, 1H, J=8.6, 12.5), 4.26 (s, 3H), 5.24–5.26 (m, 1H), 5.39–5.44 (m, 3H), 5.76 (dd, 1H, J=3.3, 10.7), 5.92 (dd, 1H, J=3.7, 10.7), 7.28–7.33 (m, 2H), 7.36–7.40 (m, 2H), 7.60 (dd, 2H, J=4.9, 6.8), 7.80 (dd, 2H, J=2.7, 7.4); HRMS (ESI) calcd for $[C_{27}H_{33}NO_7+Na]^+$: 506.2155, found: 506.2147.

References and notes

1. Gellman, S. H. *Acc. Chem. Res.* **1999**, *31*, 173–180.
2. Hill, D. J.; Mio, M. J.; Prince, R. B.; Hughes, T. S.; Moore, J. S. *Chem. Rev.* **2001**, *101*, 3893–4012.
3. Bautista, A. D.; Craig, C. J.; Harker, E. A.; Schepartz, A. *Curr. Opin. Chem. Biol.* **2007**, *11*, 685–692.
4. Seebach, D.; Hook, D. F.; Glattli, A. *Biopolymers* **2006**, *84*, 23–37.
5. Seebach, D. M.; Matthews, J. L. *Chem. Commun.* **1997**, 2015–2022.
6. Cheng, R. P.; Gellman, S. H.; DeGrado, W. F. *Chem. Rev.* **2001**, *101*, 3219–3232.
7. Qiu, J. X.; Petersson, E. J.; Matthews, E. E.; Schepartz, A. *J. Am. Chem. Soc.* **2006**, *128*, 11338–11339.
8. Raguse, T. L.; Lai, J. R.; LePlae, P. R.; Gellman, S. H. *Org. Lett.* **2001**, *3*, 3963–3966.
9. Cheng, R. P.; DeGrado, W. F. *J. Am. Chem. Soc.* **2002**, *124*, 11564–11565.
10. Goodman, J. L.; Molski, M. A.; Qiu, J.; Schepartz, A. *Chembiochem* **2008**, *9*, 1576–1578.
11. Goodman, J. L.; Petersson, E. J.; Daniels, D. S.; Qiu, J. X.; Schepartz, A. *J. Am. Chem. Soc.* **2007**, *129*, 14746–14751.
12. Daniels, D. S.; Petersson, E. J.; Qiu, J. X.; Schepartz, A. *J. Am. Chem. Soc.* **2007**, *129*, 1532–1533.
13. Larsson, O. M.; Thorbek, P.; Krogsgaard-Larsen, P.; Schousboe, A. *J. Neurochem.* **1981**, *37*, 1509–1516.
14. Mitsumori, S.; Zhang, H.; Ha-Yeon Cheong, P.; Houk, K. N.; Tanaka, F.; Barbas, C. F., 3rd. *J. Am. Chem. Soc.* **2006**, *128*, 1040–1041.
15. Zhang, H.; Mitsumori, S.; Utsumi, N.; Imai, M.; Garcia-Delgado, N.; Mifsud, M.; Albertshofer, K.; Cheong, P. H.; Houk, K. N.; Tanaka, F.; Barbas, C. F., 3rd. *J. Am. Chem. Soc.* **2008**, *130*, 875–886.
16. Min, J. Z.; Toyo'oka, T.; Kato, M.; Fukushima, T. *Biomed. Chromatogr.* **2005**, *19*, 43–50.
17. Huck, B. R.; Langenhan, J. M.; Gellman, S. H. *Org. Lett.* **1999**, *1*, 1717–1720.

18. Sandvoss, L. M.; Carlson, H. A. *J. Am. Chem. Soc.* **2003**, *125*, 15855–15862.
19. Huck, B. R.; Fisk, J. D.; Guzei, I. A.; Carlson, H. A.; Gellman, S. H. *J. Am. Chem. Soc.* **2003**, *125*, 9035–9037.
20. Huck, B. R.; Gellman, S. H. *J. Org. Chem.* **2005**, *70*, 3353–3362.
21. Martin, S. F.; Dupre, B. *Tetrahedron Lett.* **1983**, *24*, 1337–1340.
22. Kozikowski, A. P. *Acc. Chem. Res.* **1984**, *17*, 410–416.
23. Muri, D.; Lohse-Fraefel, N.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2005**, *44*, 4036–4038.
24. Curran, D. *J. Am. Chem. Soc.* **1982**, *104*, 4024–4026.
25. Fader, L. D.; Carreira, E. M. *Org. Lett.* **2004**, *6*, 2485–2488.
26. Curran, D. P.; Zhang, J. C. *J. Chem. Soc., Perkin Trans. 1* **1991**, 2613–2625.
27. Asaoka, M.; Abe, M.; Mukuta, T.; Takei, H. *Chem. Lett.* **1982**, 215–218.
28. Fuller, A. A.; Chen, B.; Minter, A. R.; Mapp, A. K. *J. Am. Chem. Soc.* **2005**, *127*, 5376–5383.
29. Minter, A. R.; Fuller, A. A.; Mapp, A. K. *J. Am. Chem. Soc.* **2003**, *125*, 6846–6847.
30. Bode, J. W.; Fraefel, N.; Muri, D.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2001**, *40*, 2082–2085.
31. Kanemasa, S.; Nishiuchi, M.; Kamimura, A.; Hori, K. J. *J. Am. Chem. Soc.* **1994**, *116*, 2324–2339.
32. Davoille, R. J.; Rutherford, D. T.; Christie, S. D. R. *Tetrahdron Lett.* **2000**, *41*, 1255–1259.
33. Wang, J. C.; Just, G. *J. Org. Chem.* **1999**, *64*, 8090–8097.
34. Minter, A. R.; Brennan, B. B.; Mapp, A. K. *J. Am. Chem. Soc.* **2004**, *126*, 10504–10505.
35. Buhrlage, S. J.; Brennan, B. B.; Minter, A. R.; Mapp, A. K. *J. Am. Chem. Soc.* **2005**, *127*, 12456–12457.
36. Casey, R. J.; Desaulniers, J. P.; Hojfeldt, J. W.; Mapp, A. K. *Bioorg. Med. Chem.*, in press, doi:10.1016/j.bmc.2008.02.045.
37. Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518–1520.
38. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923–2925.