Cycloadditions of Chiral Nitrones to Racemic 3-Substituted Butenes: A Direct Access with Kinetic Resolution to Enantiopure Dihydroxylated Amino Acids

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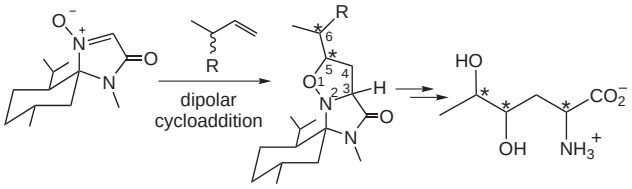
Abstract: 1,3-Dipolar cycloadditions of racemic 3-substituted 1-butenes to nitrones derived from (–)- or (+)-menthone occurred via *exo*-approach of the alkene onto the nitrone's less hindered face. This process afforded bicyclic spiroheterocycles as epimers, with selectivities ≤ 4:1, depending on the 3-substituent (R) on the alkene. The selectivity appeared to be influenced by hydrogen bonding (R = OH) or the bulkiness of the R group (R = OBz, Br), as a result of kinetic resolution. The cycloadducts obtained led, after a reductive step and cleavage of the chiral auxiliary, to enantiopure dihydroxylated non-natural amino acids in high overall yield.

Key words: 1,3-dipolar cycloadditions, nitrones, isoxazolidines, dihydroxy amino acid, kinetic resolution

Selectivity control is the corner stone for the chemical synthesis of elaborated molecules by economically viable processes with minimized impact on the environment. Much effort has led to improved synthetic methodologies and in particular to the development of concerted reactions[1,2] which may create simultaneously several chemical bonds and stereogenic centers under smooth conditions. [3+2] Cycloadditions of nitrones[3] to alkenes and related reactions of azomethine ylides[4] are attracting much interest,[5] due to the availability of structurally diverse dipoles[2d,6] and opportunities to further elaborate the resulting cycloadducts.

While working on the synthesis of *C*-glycosyl compounds as stable glycomimics,[7] we noticed a recent approach to *C*-glycosylated 4-hydroxy amino acids, based on the cycloaddition of the chiral nitrone (–)-**1** [derived from (–)-menthone] to C-1 allyl or C-1 vinyl carbohydrates.[8] Sugar-based cycloadducts were obtained with excellent selectivities (82–92% yield). As the subsequent removal of the chiral auxiliary occurred in high yield under smooth conditions and as stereoisomers can be formed by use of (+)-**1** [derived from (+)-menthone], this method appeared to have great potential for stereocontrolled synthesis.[9,10] As an application to the synthesis of non-natural amino acids, we considered racemic 3-substituted 1-butenes as dipolarophiles displaying an asymmetric allylic carbon close to the reaction center, so as to exploit the potential of cycloaddition with menthone-derived nitrones.

From the structures of the cycloadducts obtained, and in particular from the absolute configuration of the three asymmetric centers (C-3 and C-5 in the isoxazoline ring and C-6 on the alkyl chain, Scheme 1), it should be possible to establish the cycloaddition selectivity. Depending on the mode of approach (face selection, *endo*/*exo*-mode of approach) regio- and diastereoisomers may be formed, respectively. Racemization or equilibration may occur by heating over prolonged times,[9c] while identification of the cycloadducts by NMR spectroscopy may be problematic.[9a] Nevertheless, many reactions are reported to occur selectively, via a preferred transition state favored for steric or electronic reasons.[11]



Scheme 1 Nitrone cycloaddition as a route to dihydroxy amino acids

Commercially available 3-hydroxy-1-butene (**2a**) and its derivatives [3-*tert*-butyldimethylsilyloxy **2b**, 3-benzyloxy **2c**, 3-benzoyloxy **2d**, and 3-bromo-1-butene (**2e**)] appeared to be suitable.[12] Due to the cycloaddition conditions (several hours in refluxing toluene) and the use of volatile alkenes, dipolarophiles **2a**–**d** were added in excess (2–9 equiv); the reaction was stopped once all the nitrone (–)-**1** was consumed, as indicated by TLC.[13] The cycloadducts (Scheme 2) were separated by column chromatography and fully characterized. Indeed, 3-bromo-1-butene (**2e**) is not commercially available, while 1-bromo-2-butene (crotyl bromide) is available as a mixture of *cis*/*trans* isomers (ca. 15% and 70%) and 3-bromo-1-butene (ca. 15%), as shown by ^{1}H NMR spectroscopy of the purchased batch.[14] We found by serendipity that nitrone (–)-**1** and commercial crotyl bromide in excess (four experiments with 2.7, 6.0, 66.0, and 69.4 equiv, respectively) reacted with complete conversion of the nitrone within a few days (24 h/69 equiv; 72 h/2.7 equiv) in refluxing

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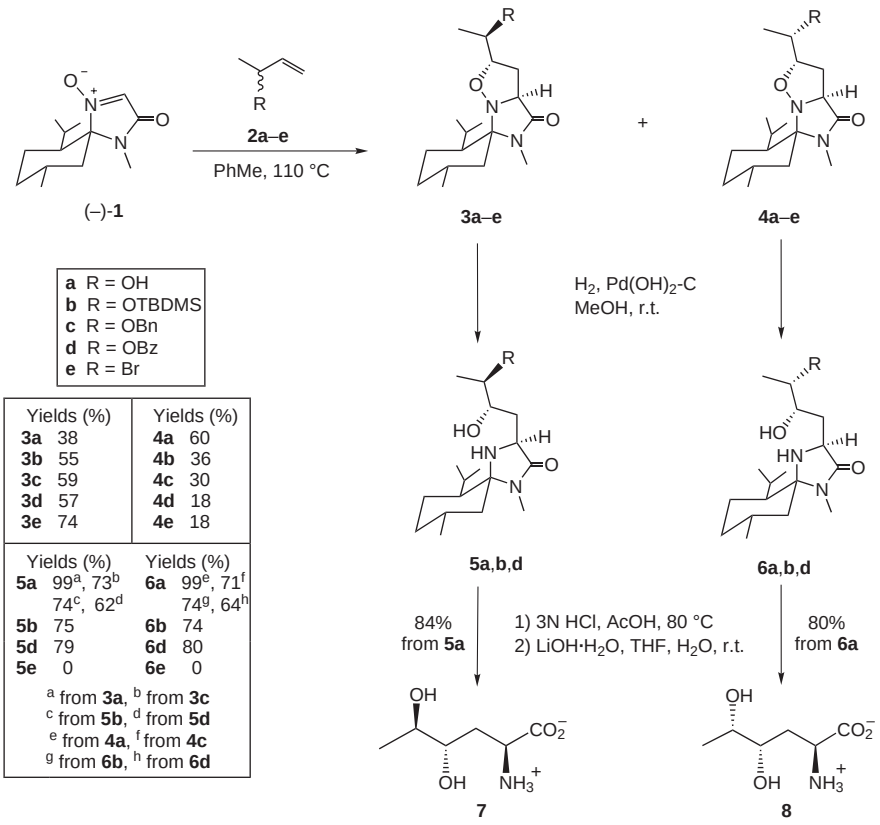
toluene to afford two major diastereoisomers **3e** and **4e** in 60–74% and 17–20% yields, respectively. Their structures were determined to be the cycloadducts derived from nitrone and **2e**, a dipolarophile more reactive than crotyl bromide, probably because of the higher accessibility of the monosubstituted double bond in **2e**. When using commercial crotyl bromide in large excess, a sufficient amount of **2e** was present in the reaction mixture for the reaction to occur. Otherwise, **2e** could result from in situ isomerization of crotyl bromide[15] over 72 hours at 110 °C. The cycloaddition of nitrone (–)-**1** to crotyl bromide was negligible, affording the corresponding product in trace amounts (< 4%).

Removal of the chiral auxiliary (Scheme 2) was achieved in three high-yielding steps: a) reductive cleavage of the N–O bond in the isoxazolidine ring of **3a**–**d** and **4a**–**d** [$Pd(OH)_2$/C (20%), H_2, 1 atm, MeOH];[16,17] b) acid-catalyzed hydrolysis of the imidazolidinones to liberate (–)-menthone; c) base-catalyzed hydrolysis of the resulting *N*-methylamides (two steps carried out in one-pot) to afford pure amino acids **7** and **8**, without racemization.[18] For the benzyloxy derivatives, the benzyl groups underwent hydrogenolysis concomitantly with N–O cleavage so that **3c** and **4c** led to **5a** (73%) and **6a** (71%). The brominated cycloadducts **3e** and **4e** were resistant towards N–O cleavage under various conditions [$Pd(OH)_2$/C (20%),[16] H_2, up to 10 atm, MeOH; SmI_2;[8b] Zn, AcOH[9b]], probably for steric reasons. The silyl and benzoyl groups in the isolated intermediates **5b**/**5d** and **6b**/**6d** were cleaved efficiently under standard conditions (TBAF, THF; NaOMe, MeOH respectively) to afford **5a** and **6a**, which were found to be identical in all respects (NMR spectra, optical rotations) with similar samples obtained from either **3a** and **4a** or **3c** and **4c**.

The cycloadducts obtained were stable compounds, in several cases amenable to crystallization, so that X-ray diffraction gave unambiguous proof of the structures for **3a**, **4a**, and **3e**.[19] The three rings were found to be roughly perpendicular at the spiro- and fused-junctions of the cycloadducts.

^{1}H NMR spectroscopy provided additional information, based on the vicinal coupling constants of the protons attached to the isoxazolidine ring and on the NOE experiments carried out with **3c**, **3d**, and **4c** in acetone-d_6. In one-dimensional NOE experiments (Figure 1), selective irradiation of 3-H induced enhancements of the vicinal protons were found to be higher for 4-H_{proR} compared to 4-H_{proS} (**3c**, **3d**, **4c**, 2.9:3.7: 2.3). Selective irradiation of 5-H enhanced the signal of 4-H_{proS} more compared to the effect exerted on 4-H_{proR} (**3c**, **3d**, **4c**, 2.9:7.3:3). These observations clearly indicated that the 3-H and 5-H protons attached to the isoxazolidine ring pointed in opposite directions. Selective irradiation of 3-H also enhanced the signals of the isopropyl protons, visible as doublets (Me) and as a multiplet (C*H*Me_2). These results showed conclusively the C-3–H bond pointed towards the isopropyl group (Figure 1); this was also observed in the solid state.[19] Further arguments came from analysis of the ^{1}H



Yields (%)		Yields (%)	
3a	38	**4a**	60
3b	55	**4b**	36
3c	59	**4c**	30
3d	57	**4d**	18
3e	74	**4e**	18

Yields (%)		Yields (%)	
5a	99[a], 73[b] 74[c], 62[d]	**6a**	99[e], 71[f] 74[g], 64[h]
5b	75	**6b**	74
5d	79	**6d**	80
5e	0	**6e**	0

[a] from **3a**, [b] from **3c**
[c] from **5b**, [d] from **5d**
[e] from **4a**, [f] from **4c**
[g] from **6b**, [h] from **6d**

Scheme 2 Access to enantiopure amino acids by cycloaddition

NMR spectra and the observed values of the vicinal couplings: $J_{3,4R}$ ca. 8–9 Hz, $J_{3,4S}$ < 2 Hz, $J_{4R,4S}$ ca. 12 Hz, $J_{4R,5}$ 8.7–11.7 Hz, $J_{4S,5}$ 4.5–6.0 Hz, $J_{5,6}$ 6.6–7.5 Hz, $J_{6,7}$ 6.0–6.6 Hz. Finally, the fact that **5a** (prepared from **3a** and **3c**) and **6a** (prepared from **4a** and **4c**) were found to be identical to samples prepared by desilylation (from **5b** and **6b**) and debenzoylation (from **5d** and **6d**) supported conclusively the structures proposed for the cycloadducts.

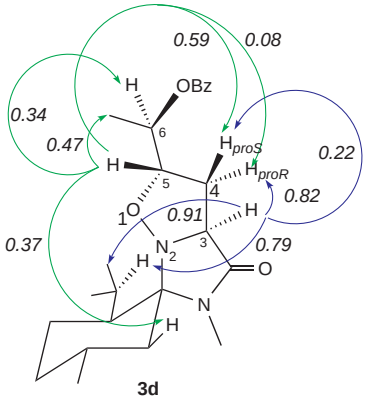


Figure 1 One-dimensional NOE observed for cycloadduct **3d**

The data collected clearly established the configurations at C-3 and C-5 as *S* for the ten cycloadducts considered. These observations indicated that the reaction proceeded with complete regioselectivity (due to steric control) and complete diastereoselectivity with regard to the isoxazolidine ring formation, with all products being formed via an anticipated *exo* approach of the alkene from the less hindered face of the nitrone (Figure 2).

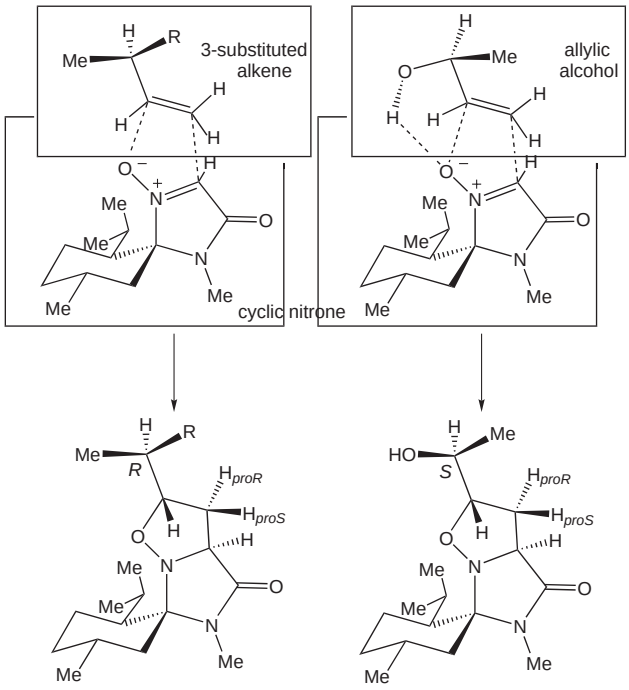


Figure 2 Normal (R ≠ OH) and H-bonded (R = OH) models for the cycloaddition transition state of nitrone (–)-**1** and alkenes in the *exo* approach

Therefore, the cycloadducts produced in the reactions studied were C-6 epimers (Scheme 2). Depending on the R substituent at C-6, the ratio of the 6*R*/6*S* products ranged from 2:3 (R = OH) to 1.5:1 (R = TBDMSO), 2:1 (R = OBn), 3:1 (R = OBz), 3:1 (R = Br). While the 6*S* epimer predominated when R was a hydroxyl group, 6*R* epimers were favored in the other cases studied, where the stereoselectivity increased according to the sequence TBDMSO < OBn < OBz < Br, thus suggesting steric control (Table 1). This can be seen from the models proposed for the approach/transition state (Figure 2), which favors conformers in which the hydrogen atom is closer to the nitrone moiety, while Me and R lie in uncrowded positions.[20] To account for the observed 6*S*-selectivity for 3-hydroxy-1-butene (**2a**) reacting in toluene with (–)-**1**, a hydrogen-bonded transition state is a reasonable model; this was previously invoked to explain both stereochemical and regiochemical trends in nitrile oxide cycloadditions with allylic alcohols.[21] Such favored approaches led to diastereoisomeric transition states with minimal activation energies associated with faster reaction rates. Kinetic resolution[22,23] could be achieved, in particular with brominated alkene **2e**, leading to C-6 epimeric cycloadducts with ca. 60% diastereomeric excess, which was shown to increase slightly with the amount of alkene **2e** used (Table 1).

Table 1 1,3-Dipolar Cycloadditions of Chiral Nitrone (–)-**1** with Racemic Alkenes **2a–e** in Toluene at 110 °C

Alkenes	R	Nitrone/ alkene ratio	Time (h)	**3a–e** (%)	**4a–e** (%)	de (%)
2a	OH	1:9	24	38	60	22
2b	OTBDMS	1:3	72	55	36	21
2c	OBn	1:5	48	59	30	33
2d	OBz	1:2	48	57	18	52
2e	Br	1:2.7	72	71	20	56
		1:6	48	60	17	56
		1:66	24	74	18	61
		1:69	24	70	18	59

Experiments performed with nitrone (+)-**1** fully confirmed the initial observations in terms of yields, regioselectivities, and diastereoselectivities and provided the corresponding enantiomers identical in all respects with those derived from (–)-**1**, except for their optical rotation. This was valid for the four γ,δ-dihydroxy amino acids **7**–**10** synthesized (Table 2).

In conclusion, 1,3-dipolar cycloadditions of menthone-based nitrones to a series of racemic 3-substituted 1-butenes afforded, via the *exo*-approach and completely controlled creation of two stereogenic centers, a series of epimeric isoxazolidines with a 6*R* or 6*S* configuration. Partial kinetic resolution due to one alkene enantiomer reacting at a faster rate accounted for the observed epimeric

Table 2 Optical Rotations of γ,δ-Dihydroxy Amino Acids **7**–**10**[a]

Amino acids	Optical rotations
7 (2*S*,4*S*,5*R*)	–23
8 (2*S*,4*S*,5*S*)	–27
9 (2*R*,4*R*,5*S*)	+22
10 (2*R*,4*R*,5*R*)	+28

[a] *c* = 1, H_2O.

ratio. Further manipulations of the cycloadducts led to four stereochemically defined non-natural γ,δ-dihydroxy-α-amino acids (2*S*,4*S*,5*R*; 2*S*,4*S*,5*S*; 2*R*,4*R*,5*S*; and 2*R*,4*R*,5*R*), as couples of enantiomers.

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(12) (a) Racemic 3-hydroxy-1-butene (**2a**) was purchased from Acros Organics. (b) For the preparation of **2b**, see: Hoeyer, T.; Kjaer, A.; Lykkesfeldt, J. *Collect. Czech. Chem. Commun.* **1991**, *56*, 1042. (c) For the preparation of **2c**, see: Bischofberger, N.; Waldmann, H.; Saito, T.; Simon, E. S.; Lees, W.; Bednarski, M. D.; Whitesides, G. M. *J. Org. Chem.* **1988**, *53*, 3457. (d) For the preparation of **2d** see: Yasui, K.; Fugami, K.; Tanaka, S.; Tamaru, Y. *J. Org. Chem.* **1995**, *60*, 1365.

(13) **General Procedure**: A mixture of nitrone (–)-**1** (1.5 mmol) and alkene **2a**–**e** (for nitrone/alkene ratio see Table 1) was stirred in toluene (10 mL) at 110 °C [monitored by TLC ($CHCl_3$–*i*-PrOH, 98:2)]. When the reaction was complete the solution was concentrated and the residue was purified by flash chromatography ($CHCl_3$–*i*-PrOH, 98:2) to afford the desired cycloadducts **3a**–**e** and **4a**–**e**. **Cycloadduct 3a**: $[\alpha]_D^{22}$ +65 (*c* 1, CH_2Cl_2); white solid; mp 97–100 °C (Et_2O). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.80 (d, 3 H, *J* = 6.6 Hz, CH_3), 0.86 (d, 3 H, *J* = 6.9 Hz, CH_3), 0.93 (d, 3 H, *J* = 6.3 Hz, CH_3), 0.93 (m, 1 H), 1.11 (d, 3 H, *J* = 6.6 Hz, CH_3), 1.25 (t, 1 H, *J* = 12.3 Hz), 1.39 (m, 1 H), 1.44 (m, 1 H), 1.64 (m, 2 H), 1.83 (m, 1 H), 1.99 (m, 1 H), 2.06 (dt, 1 H, *J* = 3.0 Hz, *J* = 12.3 Hz), 2.55 (m, 2 H), 2.74 (s, 3 H, NCH_3), 3.78 (dt, 1 H, *J* = 3.0 Hz, *J* = 6.9 Hz), 3.97 (dd, 1 H, *J* = 3.0 Hz, *J* = 7.5 Hz), 4.05 (dq, 1 H, *J* = 3.0 Hz, *J* = 6.6 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 18.4, 18.6, 22.2, 22.4, 24.1, 24.2, 25.9 (NCH_3), 29.3, 31.5, 34.5, 40.6, 47.9, 65.8, 68.0, 80.1, 88.9, 172.8 (C=O). MS (ESI): *m*/z = 311 $[M + H]^+$. Anal. Calcd for $C_{17}H_{30}N_2O_3$: C, 65.77; H, 9.74; N, 9.02; O, 15.46. Found: C, 65.66; H, 9.99; N, 8.83; O, 16.01. **Cycloadduct 3e**: $[\alpha]_D^{22}$ +59 (*c* 1, CH_2Cl_2); white crystals, mp 94–95 °C (Et_2O). ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.81 (d, 3 H, *J* = 6.9 Hz, CH_3), 0.85 (d, 3 H, *J* = 6.9 Hz, CH_3), 0.91 (d, 3 H, *J* = 6.6 Hz, CH_3), 0.93 (m, 1 H), 1.26 (t, 1 H, *J* = 12.3 Hz), 1.38 (m, 1 H), 1.44 (m, 1 H), 1.63 (m, 2 H), 1.72 (d, 3 H, *J* = 6.3 Hz, CH_3), 1.82 (m, 1 H), 1.98 (m, 1 H), 2.03 (dt, 1 H, *J* = 2.5 Hz, *J* = 12.6 Hz), 2.42 (ddd, 1 H, *J* = 7.2 Hz, *J* = 12.6 Hz, *J* = 9.0 Hz), 2.74 (s, 3 H, NCH_3), 2.86 (ddd, 1 H, *J* = 1.8 Hz, *J* = 5.4 Hz, *J* = 12.6 Hz), 3.92 (m, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 18.4, 22.2, 22.3, 23.1, 24.1, 24.2, 25.9 (NCH_3), 29.5, 34.5, 37.8, 40.7, 48.0, 48.8, 65.7, 80.8, 89.2, 172.5 (C=O). MS (ESI): *m*/*z* = 373 $[M + H]^+$, 395 $[M + Na]^+$, 767 $[2 M + Na]^+$. **Cycloadduct 4e**: $[\alpha]_D^{22}$ +54 (*c* 1, CH_2Cl_2); yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.83 (d, 3 H, *J* = 6.6 Hz, CH_3), 0.85 (d, 3 H, *J* = 6.6 Hz, CH_3), 0.92 (m, 1 H), 0.93 (d, 3 H,

J = 6.3 Hz, CH_3), 1.26 (t, 1 H, J = 12.3 Hz), 1.36 (m, 1 H), 1.39 (m, 1 H), 1.65 (m, 2 H), 1.67 (d, 3 H, J = 6.6 Hz, CH_3), 1.83 (m, 1 H), 2.05 (dt, 1 H, J = 2.5 Hz, J = 12.0 Hz), 2.11 (m, 1 H), 2.22 (ddd, 1 H, J = 9.0 Hz, J = 6.0 Hz, J = 12.3 Hz), 2.69 (ddd, 1 H, J = 5.1 Hz, J = 12.3 Hz), 2.75 (s, 3 H, NCH_3), 3.90 (ddd, 1 H, J = 5.1 Hz, J = 4.5 Hz), 4.02 (br d, 1 H, J = 9.0 Hz), 4.02 (dq, 1 H, J = 6.6 Hz, J = 7.2 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 18.3, 22.3, 22.3, 22.4, 24.1, 24.3, 26.0 (NCH_3), 29.6, 34.5, 36.1, 40.6, 47.8, 48.0, 66.6, 81.2, 90.0, 172.4 (C=O). MS (ESI): m/z = 373.1 $[M]^+$, 769.0 [2 M + Na]$^+$. HRMS (ESI): m/z calcd for $C_{17}H_{29}BrN_2O_2$ $[M]^+$: 373.1491; found: 373.1491.

(14) Sample purchased from Acros Organics.

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(17) **General Procedure**: A suspension of cycloadduct **3a**–**d** or **4a**–**d** (100 mg) and $Pd(OH)_2$/C (20%, 15 mg) was stirred in MeOH (10 mL) at r.t. under H_2 (1 atm). When the reaction was complete (TLC) ($CHCl_3$–*i*-PrOH, 98:2), the mixture was filtered over Celite, concentrated, and purified by flash chromatography ($CHCl_3$–*i*-PrOH, 98:2) to afford the desired spiro-imidazolidinones **5a**, **5b**, **5d** or **6a**, **6b**, **6d**. **Imidazolidinone 5a**: $[\alpha]_D^{22}$ +13 (*c* 1, CH_2Cl_2); colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.87 (d, 3 H, J = 6.9 Hz, CH_3), 0.89 (d, 3 H, J = 6.9 Hz, CH_3), 0.90 (m, 1 H), 0.93 (d, 3 H, J = 6.3 Hz, CH_3), 1.16 (d, 3 H, J = 6.3 Hz, CH_3), 1.38 (m, 2 H), 1.50 (m, 2 H), 1.58 (t, 1 H, J = 6.9 Hz), 1.68 (m, 2 H), 1.76 (m, 1 H), 1.81 (m, 1 H), 1.88 (ddd, 1 H, J = 2.1 Hz, J = 3.9 Hz, J = 13.1 Hz), 2.17 (br s, 1 H, OH), 2.76 (s, 3 H, NCH_3), 3.72 (m, 2 H), 3.83 (m, 1 H), 5.57 (br s, 1 H, NH). ^{13}C NMR ($CDCl_3$, 75 MHz): δ = 17.5, 18.4, 22.1, 22.2, 23.9, 24.6, 25.4 (NCH_3), 28.8, 34.0, 34.4, 46.6, 48.0, 58.3, 70.1, 73.4, 81.3, 174.6 (C = O). MS (ESI): m/z = 313 $[M + H]^+$, 647.0 [2 M + Na]$^+$. HRMS (CI, isobutane): m/z calcd for $C_{17}H_{32}N_2O_3$ $[M + H]^+$: 313.2491; found: 313.2490.

(18) **Typical Procedure**: A solution of 1,3-imidazolidinone **5a** (100 mg) and AcOH (25 mL) in aq HCl (3 N, 30 mL) was stirred at 80 °C for 2 h. The reaction mixture was then evaporated to dryness and $LiOH{\cdot}H_2O$ (200 mg) in THF–H_2O (1:1, 10 mL) was added. The resulting mixture was stirred at r.t. for 2 h, then concentrated to dryness and purified by reverse-phase flash chromatography (C_{18}) to afford the desired amino acid **7**. $[\alpha]_D^{22}$ –23 (*c* 1, H_2O); white solid; mp 194–195 °C (MeOH). ^{1}H NMR (D_2O, 300 MHz): δ = 1.12 (d, 3 H, J = 6.6 Hz, CH_3), 1.73 (m, 2 H, H-3), 3.50 (dd, 1 H, J = 4.8 Hz, J = 7.8 Hz, H-2), 3.65 (m, 1 H, H-4), 3.71 (m, 1 H, H-5). ^{13}C NMR (D_2O, 75 MHz): δ = 17.0 (CH_3), 35.7 (C-3), 53.4 (C-2), 70.8 (C-5), 72.5 (C-4), 181.3 (C=O). MS (ESI, negative mode): m/z = 162 $[M – H]^–$. HRMS (CI, isobutane): m/z calcd for $C_6H_{13}NO_4$ $[M + H]^+$: 164.0923; found: 164.0919.

(19) Crystallographic data for **3a**, **3e**, and **4a** have been deposited with the Cambridge Crystallographic Data Centre, under the following reference numbers: CCDC 606452 (**3a**); CCDC 601858 (**3e**); CCDC 606451 (**4a**). Copies of these data can be obtained on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (e-mail: deposit@ccdc.cam.ac.uk).

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