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Tetrahedron: *Asymmetry* 18 (2007) 383–389
Tetrahedron: *Asymmetry*

Highly diastereoselective nucleophilic addition reactions of masked acyl cyanide reagents to *tert*-butanesulfiminides

Hisao Nemoto,* Hideki Moriguchi, Rujian Ma, Tomoyuki Kawamura, Masaki Kamiya and Masayuki Shibuya

Division of Pharmaceutical Chemistry, Institute of Health Biosciences, Graduate School of The University of Tokushima, 1-78, Sho-machi, Tokushima 770-8505, Japan

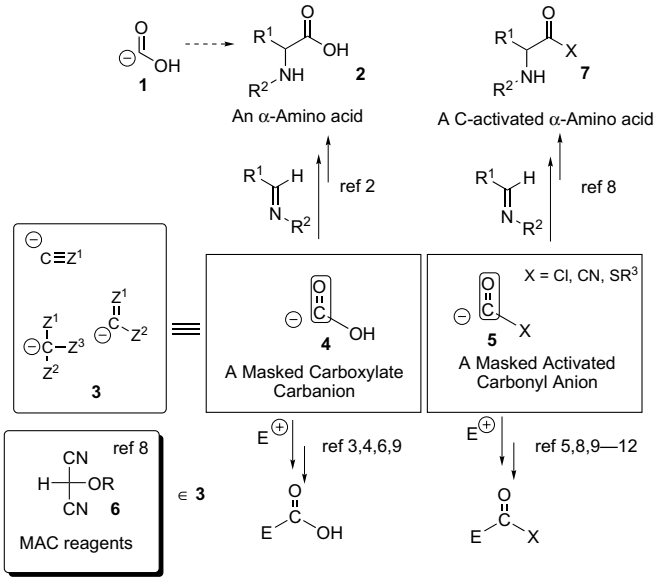
Received 19 December 2006; accepted 31 January 2007
Available online 26 February 2007

Abstract—Addition reactions of dicyanomethyl *tert*-butyldimethylsilyl ether (H–MAC–TBS) to optically active *tert*-butanesulfinimides afforded α-amino acid precursors in excellent yields and with high diastereoselectivities.

1. Introduction

Although the nucleophilic addition reaction of a naked carboxylate carbanion ($^{-}CO_2H$) **1** to imines may appear as a straightforward method for the synthesis of α-amino acids **2** (Scheme 1), the difficulty in the generation of **1**[1] because of the nature of carbonyl functionality has hindered the progress of this approach. Consequently, reagent **3**, a synthetic equivalent of **4**, has been used until now. The traditional methodology for preparing **2**, known as the Strecker synthesis,[2] involves hydrogen cyanide as the synthetic equivalent **3**. Subsequently, several modified methodologies that involve cyanides[2] or nitromethane[2a] have been reported.

Recently, a number of alternative reagents that can be classified as **3** have been reported; these include Seebach's and Manas' orthothioester,[3] Utimoto's dimethoxyacetonitrile,[4] Trost's alkoxydisulfones,[5] Dondoni's silylthiazole,[6] our MAC (masked acyl cyanide)[7] reagents **6**,[8] Katritzky's tris(benzotriazolyl)methane,[9] Yamakawa's α-chloromethylsulfoxides,[10] Wasserman's phosphoranylideneacetonitrile,[11] and Aggarwal's cyclic sulfone.[12] Nucleophilic addition reactions between these carbanion reagents and E^{+} have afforded various carbon–carbon bond formations. Moreover, in addition to serving as masked carbanion **4**, some of the above reagents[5,8,10–12] can also function as $^{-}$COX synthon **5** to afford C-activated species **7**, which



Scheme 1.

would allow subsequent amide or ester bond formations without condensation agents such as carbodiimides. To the best of our knowledge, however, only MAC reagents **6**[7,8,13–25] were successful in the formation of **7** via nucleophilic addition to the C=N double bond using **5**.

We have previously reported[8] on the reaction of MAC reagent **8** to N-sulfonylated imines **9** to afford the

* Corresponding author. Tel./fax: +81 88 633 7284; e-mail: nem@ph.tokushima-u.ac.jp

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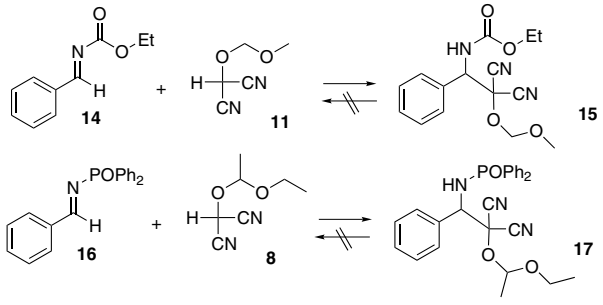
doi:10.1016/j.tetasy.2007.01.032

corresponding adduct **10**, quantitatively. Due to the reversible nature of the reaction (from **10** back to **8** and **9**), adduct **10** was isolated as **11** by protection using chloromethyl methyl ether (MOM–Cl). Subsequently, as shown in Scheme 2, adduct **11** was efficiently transformed to dipeptide derivatives **13** via **12** (corresponding to **7**) in excellent yields under mild conditions and without the use of any condensation reagents.[8,14]

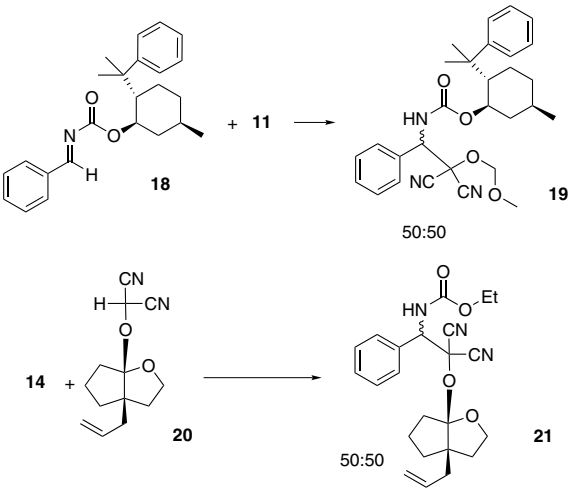
In contrast, as shown in Scheme 3, alkoxycarbonylated imine **14**[25] and phosphorous imine **16**[14] gave the corresponding adducts **15** and **17**, respectively, without the need for MOM protection.



Scheme 3.

Our first attempt to synthesize the optically active compounds, as shown in Scheme 4, involved alkoxycarbonylated imines. Unfortunately, the reactions using optically active imine **18** or a chiral MAC reagent **20**[26] did not exhibit any diastereoselectivity.[25] The lack of stereoselectivity can be attributed to (1) the large distance between the stereogenic center of the auxiliaries and the prochiral carbon and (2) the flexible conformation of the entire molecule. Furthermore, the preparation of N-alkoxycarbonylated *aliphatic* imines requires delicate control of the reaction temperature along with exhaustive removal of moisture,[27] such stringent conditions discourage the general applicability of this method for the synthesis of aliphatic α-amino acids.

Next, we turned our attention to reactions involving an optically active sulfinimide,[18,28] in which the distance



Scheme 4.

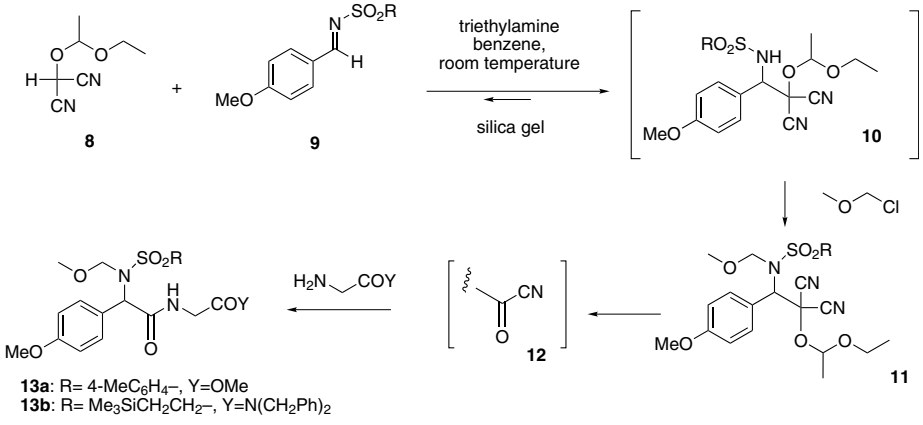
between the chiral auxiliary and the prochiral carbon is significantly shorter than in the case of Scheme 4. Additionally, the preparation of sulfinimides is well established.[29,30]

We have previously reported[18] on the reaction of (S_S)-*p*-toluenesulfinimide **22**[29] with MAC reagent **23**.[8,21] As shown in Scheme 5, our studies demonstrated the efficient formation of **24** via the coexistence of a tertiary amine and a Lewis acid. The Lewis acid affects the overall yield, the diastereoselectivity, and the configuration of the dominant diastereomer of the product.

2. Results and discussion

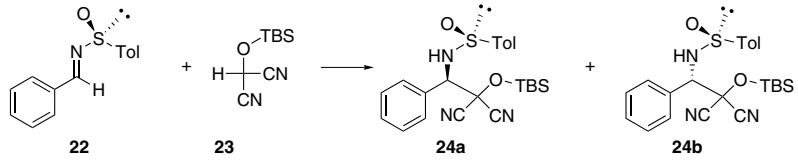
Herein, we report on the highly diastereoselective reaction of *tert*-butanesulfinimides using MAC reagents.[30] First, as shown in Scheme 6, we prepared **25** with an (*R*)-configuration via the asymmetric oxidation of *tert*-butyl disulfide, followed by treatment with ammonia and benzaldehyde.[31]

The reaction of **25** was initially carried out in dichloromethane (CH_2Cl_2) at room temperature with **23**

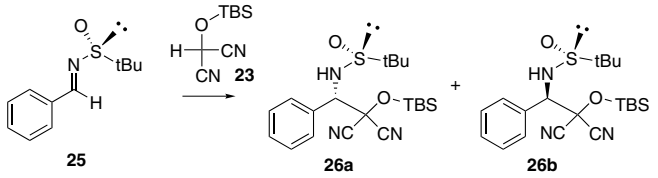


13a: R= 4-MeC_6H_4–, Y=OMe
13b: R= $Me_3SiCH_2CH_2$–, Y=N(CH_2Ph)$_2$

Scheme 2.



Scheme 5.

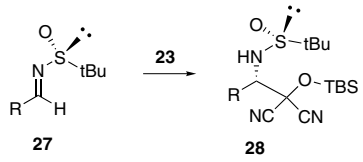


Scheme 6.

(1.5 equiv), diisopropylethylamine (DIEA, 3.0 equiv) as the base, and trimethylsilyl trifluoromethanesulfonate (TMSOTf, 2.0 equiv) as the Lewis acid (Table 1, entry 1). It is worth noting that these conditions were based upon the optimal conditions for the reaction of **22** to **24**.[18] After 1 h, **26a** was obtained in 45% chemical yield and with 100% diastereoselectivity. Our results also revealed the slow decomposition of **26a** along with the formation of unidentified polar materials in the presence of DIEA. Furthermore, in the presence of strong organic bases, such as triethylamine or DIEA, the MAC reagents were also slowly converted into an unidentifiable polar compound. Accordingly, by replacing DIEA (a strong base) with 2,6-lutidine (a weak base) the yield of **26a** increased to 67% (entry 2). When the 3 equiv of **23** was used for the reaction, the yield of **26a** was further improved to 99% (entry 3). Since the reaction of **22** in the presence of tin(II) trifluoromethanesulfonate ($Sn(OTf)_2$) afforded **24a**/**24b** with a ratio of 5:95,[18] the reaction of **25** was similarly carried out using $Sn(OTf)_2$-surprisingly, the ratio of **26a**:**26b** was 91:9 (entry 4). Presumably, the final diastereoselectivity was determined by the competing two transition states, the electronic interaction with $Sn(OTf)_2$, and the steric influence from either *tert*-butyl or 4-tolyl groups.

As listed in Table 2, the optimized reaction conditions (Table 1, entry 3) were applied to various *tert*-butanesulfinimides.[31] Although the reaction of the electron rich aromatic sulfinimide **27a** (entry 1) was slower than that of the electron deficient **27b** (entry 2), in both cases, **28** was obtained in excellent yield with 100% diastereoselectivity. The desired adduct **28c** was obtained from aliphatic sulfinimide **27c** in 73% yield with 100% diastereoselectivity (entry 3).

Table 2. The reaction of various *tert*-butanesulfinimides **27** with **23** (3.0 equiv), 2,6-lutidine (2.0 equiv), and TMSOTf (3.0 equiv) in CH_2Cl_2 at room temperature



Entry	sulfinimide **27**	Time (h)	Chemical yield (%) of **28**
1	**27a** (R = 4-$MeOC_6H_4$–)	3	89 (**28a**)
2	**27b** (R = 4-F_3C–C_6H_4–)	1	88 (**28b**)
3[a]	**27c** (R = $(CH_3)_2CH$–)	1	73 (**28c**)

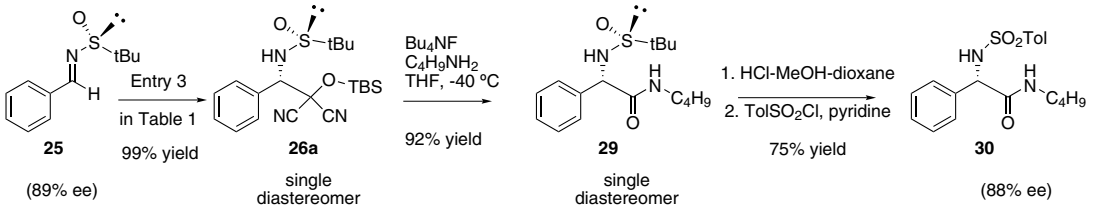
[a] 2,6-Lutidine (5.0 equiv) was used.

The absolute configuration of **26a** was determined by comparing its derivative **30** against a known compound,[18] as shown in Scheme 7. Deprotection of the TBS group of **26a**, followed by in situ amide bond formation with butylamine, gave **29** in 92% yield. Deprotection of the *tert*-butanesulfinyl group under acidic conditions,[30] followed by *p*-toluenesulfonylation, afforded **30** in 75% yield. Comparison between the $[\alpha]_D$ value of synthesized **30** $\{[\alpha]_D^{22} = +96.8$ (*c* 1.0, $CHCl_3$)$\}$ derived from **26a** and that of authentic (*R*)-**30** $\{[\alpha]_D^{22} = -109.4$ (*c* 1.4, $CHCl_3$)$\}$[18] revealed that the newly formed stereogenic center of **26a** had an (*S*)-configuration with an enantiomeric excess of **26a** being 88%. Apparently, the original enantiomeric excess of **25** (89% ee) was preserved in each chemical transformation during the formation of **30**.

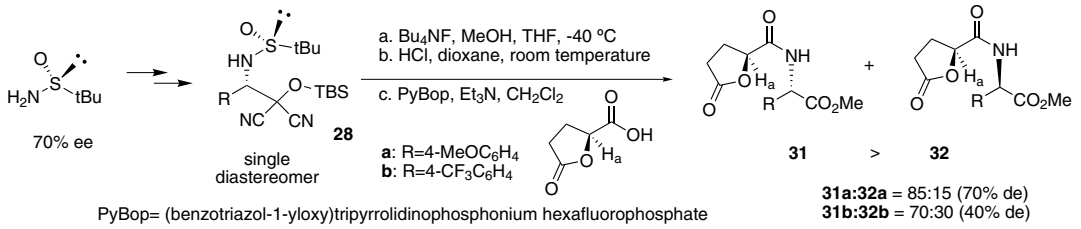
The transformation of adduct **28a** to **31a** is illustrated in Scheme 8. As shown in the ^1H NMR data (Fig. 1), and based on Kusumi's PGME method,[32] the H_a triplet signal at lower field was assigned to **31a**, whereas that at higher field was assigned to **32a**. The 85:15 ratio of **31a** to **32a** indicates that the benzylic position of **28a** has an (*S*)-configuration with 70% ee. The benzylic position of **28b** was also determined to be (*S*) since **31b** is favored over **32b**. In the case of **31b** and **32b**, however, the ratio of 70:30 was lower than expected. Simultaneous epimerization of the sulfur center and benzylic position can be ignored since

Table 1. The reaction of **25** and **23** with Lewis acid (3 equiv) and base (2 equiv) in CH_2Cl_2 at room temperature

Entry	Lewis acid	Base	**23**	Time (min)	Chemical yield (%)	**26a**:**26b**
1	TMSOTf	DIEA	1.5	30	46	100:0
2	TMSOTf	2,6-Lutidine	1.5	60	67	100:0
3	TMSOTf	2,6-Lutidine	3.0	15	99	100:0
4	$Sn(OTf)_2$	DIEA	3.0	10	27	91:9



Scheme 7.



Scheme 8.

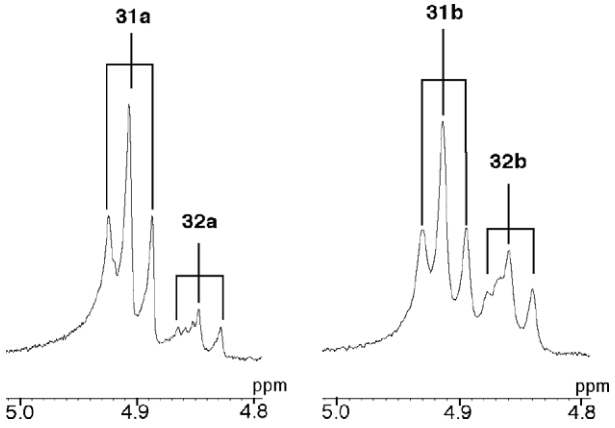


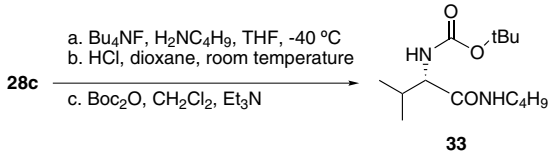
Figure 1. ^{1}H NMR of H_a of a mixture of **31** and **32** derived from **28** (70% ee).

27a (70% ee) resulted in a **31a/32a** ratio of 85:15. Epimerization remains a possibility during the final condensation (reaction step c) because the asymmetric center of **31b/32b** is triply activated by the 4-trifluoromethylphenyl, methoxycarbonyl, and acylated amino groups.[33]

As shown in Scheme 9, **28c** was transformed to the (*S*)-(−)-valine derivative **33** to assess the enantiomeric excess; ca. 69% ee was determined by comparing thespecific rotation of the synthesized derivative, $[\alpha]_D^{25} = -15.6$ (*c* 0.60, MeOH), to that of the pure (*S*)-enantiomer,[34] $[\alpha]_D^{25} = -22.7$ (*c* 2.2, MeOH). Thus, our results indicate that the chiral auxiliary, *tert*-butanesulfinyl group, gives comparable diastereoselectivities in all four cases, **25**, **27a**, **27b**, and **27c**.

3. Conclusion

The addition reaction of *tert*-butanesulfinimides with a MAC reagent afforded α-amino acid precursors in excellent yields, and with improved diastereoselectivities (over those obtained from 4-toluenesulfinimides).[18] The subsequent synthesis of an α-amino acid derivative with an aliphatic side chain was also successful. The results of our studies, in tandem with those of a previous study,[24] offer two practical methodologies for the preparation of optically active C-activated α-amino acid derivatives using MAC reagents.



Scheme 9.

4. Experimental

4.1. General

Melting points were measured with APPARATUS MODEL MP-20 (Yamato Kagaku) and uncorrected. Optical rotations were measured with DIP-370 (JASCO). IR spectra were recorded with 1720 Infrared Fourier Transform Spectrometer (Perkin–Elmer) or FT/IR420 (JASCO), and indicated with wavelength at cm^{-1}. ^{1}H NMR spectra were recorded with JMN-AL300, JMN-AL400, or GSX400 spectrometers (JEOL) at 300, 400, 400 MHz, respectively. ^{13}C NMR spectra were recorded with JMN-AL300, JMN-AL400, or GSX400 spectrometers (JEOL) at 75, 100, 100 MHz, respectively. Chemical shifts were indicated as a δ value at ppm with tetramethylsilane as an internal standard. Mass spectra were recorded with JMS-DX303 or JMS-SX102A Mass Spectrometer (JEOL). Unless noted, all the reactions were carried out under an argon atmosphere. Tetrahydrofuran (THF) was distilled over Na-benzophenone. Dichloromethane (CH_2Cl_2) was distilled over phosphorous pentoxide. Methanol (MeOH) was distilled over sodium methoxide.

4.2. Preparation of *tert*-butanesulfinimides

Preparations of **25** and **27a–c** were carried out using known procedure.[30] Since *tert*-butanesulfinimides **27a–c** were prepared from the same lot of (R_S)-2-methylpropane-2-sulfinamide (H_2N–SO^tBu) prepared from asymmetric oxidation of 1,2-di-*tert*-butyldisulfane (^{t}Bu–S–S–^{t}Bu),[30] (R_S)-**27b** was determined to be 69–71% ee.

(R_S)-2-Methyl-*N*-(4-benzylidene)propane-2-sulfinamide **25**: $[\alpha]_D^{22} = -108.6$ (*c* 1.0, $CHCl_3$), 89% ee {lit.[30] $[\alpha]_D^{22} = -122.0$ (*c* 1.0, $CHCl_3$)}.

(R_S)-2-Methyl-*N*-(4-methoxybenzylidene)propane-2-sulfinamide **27a**: $[\alpha]_D^{22} = -50.1$ (*c* 1.0, $CHCl_3$), 71% ee {lit.[30] $[\alpha]_D^{22} = -70.2$ (*c* 1.0, $CHCl_3$)}.

(R_S)-2-Methyl-*N*-(4-trifluoromethylbenzylidene)propane-2-sulfinamide **27b**: $[\alpha]_D^{22} = -78.2$ (*c* 1.0, $CHCl_3$).

(R_S)-2-Methyl-*N*-(2-methylpropylidene)propane-2-sulfinamide **27c** $[\alpha]_D^{22} = -179.2$ (*c* 1.0, $CHCl_3$), 69% ee {lit.[30] $[\alpha]_D^{22} = -259.4$ (*c* 1.0, $CHCl_3$)}.

4.3. General procedure for the nucleophilic addition of 23 to sulfinimides

To a solution of a *tert*-butanesulfinimide (0.50 mmol) and **23** (294 mg, 1.5 mmol) in CH_2Cl_2 (2.5 mL) were added TMSOTf (0.18 mL, 1.0 mmol) and 2,6-lutidine (0.17 mL, 1.5 mmol), and the mixture was stirred at room temperature. After the disappearance of either *tert*-butanesulfinimide or **23** was monitored by thin layer chromatography, the reaction mixture was poured into a saturated aqueous solution of ammonium chloride (NH_4Claq) and extracted with CH_2Cl_2 (30 mL × 3). The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with hexane/ethyl acetate to afford the corresponding adduct.

4.4. (R_S,2*S*)-*N*-(2-(*tert*-Butyldimethylsilyloxy)-2,2-dicyano-1-phenylethyl)-2-methylpropane-2-sulfinamide 26a

Colorless oil; FT-IR (neat): 2932, 2861, 2240, 1472, 1261, 1146, 1453, 1076 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.51–7.33 (m, 5H), 4.78 (d, $J = 7.6$ Hz, 1H), 4.06 (d, $J = 7.6$ Hz, 1H), 1.32 (s, 9H), 0.82 (s, 9H), 0.27 (s, 3H), 0.18 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 133.9 (C), 130.0 (CH), 128.9 (CH × 2), 128.2 (CH × 2), 114.5 (C), 114.0 (C), 68.7 (C), 67.0 (CH), 57.4 (C), 25.0 (CH_3 × 3), 22.6 (CH_3 × 3), 17.9 (C), −4.7 (CH_3), −5.0 (CH_3); EI-HRMS calcd for $C_{20}H_{31}N_3O_2SSi$ (M^+) 405.1906, found 405.1916.

4.5. (R_S,2*S*)-*N*-(2-(*tert*-Butyldimethylsilyloxy)-2,2-dicyano-1-(4-methoxyphenyl)ethyl)-2-methylpropane-2-sulfinamide 28a

Colorless oil; FT-IR (neat): 3324, 2958, 2861, 2360, 1612, 1517, 1471, 1256, 1077 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.35 (d, $J = 11.5$ Hz, 2H), 6.92 (d, $J = 11.5$ Hz, 2H), 4.78 (d, $J = 9.5$ Hz, 1H), 4.06 (d, $J = 9.5$ Hz, 1H), 3.81 (s, 3H), 1.31 (s, 9H), 0.85 (s, 9H), 0.28 (s, 3H), 0.22 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 160.6 (C), 129.3 (CH × 2), 125.9 (C), 114.4 (C), 114.2 (CH × 2), 114.1 (C), 68.7 (C), 66.4 (CH), 57.2 (C), 55.2 (CH_3), 25.0 (CH_3 × 3), 22.4 (CH_3 × 3), 17.9 (C), −4.7 (CH_3), −5.0 (CH_3); EI-HRMS calcd for $C_{21}H_{33}N_3O_3SSi$ (M^+) 435.2012, found 435.2018.

4.6. (R_S,2*S*)-*N*-(2-(*tert*-Butyldimethylsilyloxy)-2,2-dicyano-1-(4-(trifluoromethyl)phenyl)ethyl)-2-methylpropane-2-sulfinamide 28b

Colorless oil; FT-IR (neat): 2934, 2863, 2380, 1472, 1328, 1132, 1070 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.69 (d, $J = 10.5$ Hz, 2H), 7.57 (d, $J = 10.5$ Hz, 2H), 4.86 (d, $J = 11.0$ Hz, 1H), 4.11 (d, $J = 11.0$ Hz, 1H), 1.32 (s, 9H), 0.82 (s, 9H), 0.28 (s, 3H), 0.22 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 137.6 (C), 132.4 (q, $J_{C-F} = 33$ Hz, C–CF_3), 128.7 (CH × 2), 125.7 (q, $J_{C-F} = 4$ Hz, CH × 2), 124.3 (q, $J_{C-F} = 272$ Hz, CF_3), 114.0 (C), 113.7 (C), 68.2 (C), 66.7 (CH), 57.6 (C), 25.0 (CH_3 × 3), 22.5 (CH_3 × 3), 17.9 (C), −4.7 (CH_3), −4.9 (CH_3); EI-HRMS calcd for $C_{20}H_{30}F_3N_2O_2SSi$ [$(M-CN)^+$] 447.1749, found 447.1739.

4.7. (R_S,2*S*)-*N*-(1-(*tert*-Butyldimethylsilyloxy)-1,1-dicyano-3-methylbutan-2-yl)-2-methylpropane-2-sulfinamide 28c

Colorless oil; FT-IR (neat): 3348, 2960, 2932, 2862, 2360, 1472, 1261, 1086 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 3.70 (d, $J = 12.0$ Hz, 1H), 3.59 (dd, $J = 3.0$, 12.0 Hz, 1H), 2.45 (dsept, $J = 3.0$, 9.0 Hz, 1H), 1.32 (s, 9H), 1.17 (d, $J = 9.0$ Hz, 3H), 1.06 (d, $J = 9.0$ Hz, 3H), 0.95 (s, 9H), 0.41 (s, 3H), 0.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 115.1 (C), 114.5 (C), 68.1, 59.2 (C), 57.3 (C), 27.6 (CH), 25.1 (CH_3 × 3), 22.7 (CH_3 × 3), 21.1 (CH_3), 17.9 (C), 16.1 (CH_3), −4.7 (CH_3), −4.8 (CH_3); EI-HRMS calcd for $C_{16}H_{33}N_2O_2SSi$ [$(M-CN)^+$] 345.2032, found 345.2022.

4.8. (R_S,2*S*)-*N*-Butyl-2-(1,1-dimethylethylsulfinamido)-2-phenylacetamide 29

To a solution of **26a** (480 mg, 1.19 mmol) in THF (15 mL) cooled to −40 °C was added butylamine (0.24 mL, 2.37 mmol). To the solution was added tetrabutylammonium fluoride (Bu_4NF) (1.0 M in THF, 1.3 mL, 1.3 mmol) slowly at −40 °C. The resulting mixture was stirred for 1 h at −40 °C, poured into NH_4Claq and extracted with CH_2Cl_2 (30 mL × 3). The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with hexane/ethyl acetate (3:1) to afford **29** as a colorless oil (338.0 mg, 92% yield). FT-IR ($CHCl_3$): 2932, 2861, 1472, 1261, 1146, 1076, 846, 788 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 7.47–7.28 (m, 5H), 6.90 (br s, 1H), 5.06 (d, $J = 4.4$ Hz, 1H), 4.60 (d, $J = 4.4$ Hz, 1H), 3.30–3.20 (m, 2H), 1.51–1.40 (m, 2H), 1.37–1.22 (m, 2H), 1.20 (s, 9H), 0.88 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.9 (C), 138.4 (C), 128.4 (CH_2 × 2), 127.8 (CH), 127.4 (CH_2 × 2), 58.4 (C), 56.6 (CH), 39.4 (CH_2), 31.1 (CH_2), 22.6 (CH_3 × 3), 19.9

(CH_2), 13.6 (CH_3). Anal. Calcd for $C_{16}H_{26}N_2O_2S$: C, 61.90; H, 8.44; N, 9.02. Found: C, 61.55; H, 8.28; N, 8.88.

4.9. (2*S*)-*N*-Butyl-2-(4-methylphenylsulfonamido)-2-phenylacetamide 30

A solution of **29** (140 mg, 0.452 mmol) in a mixed solvent (3 M hydrochloric acid–MeOH–1,4-dioxane = 1:1:1 vol, 0.6 mL) was stirred for 15 min at room temperature. The resulting mixture was concentrated in vacuo. The residue was dissolved in pyridine (2 mL), and to the resulting solution was added 4-toluenesulfonyl chloride (258 mg, 1.35 mmol) in portions at room temperature. The reaction mixture was stirred for 2 h at room temperature, poured into water and extracted with CH_2Cl_2 (50 mL × 3). The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with chloroform/ethyl acetate (4:1) to afford **30** as a colorless solid (97.5 mg, 0.271 mmol, 60% yield). $[\alpha]_D^{22} = +96.8$ (*c* 1.0, $CHCl_3$); FT-IR (KBr): 3326, 3264, 2957, 1648, 1554, 1453, 1344, 1327, 1162, 1093 cm^{-1}; ^1H NMR (300 MHz): 7.59 (d, $J = 8.1$ Hz, 2H), 7.30–7.22 (m, 2H), 7.19 (d, $J = 8.1$ Hz, 2H), 7.16–7.10 (m, 3H), 5.88 (br d, $J = 4.7$ Hz, –SO_2NH, 1H), 5.61 (br, –CO*NH*, 1H), 4.70 (d, $J = 4.7$ Hz, 1H), 3.15 (dt, $J = 6.7$, 6.7 Hz, 2H), 2.39 (s, 3H), 1.41–1.27 (m, 2H), 1.27–1.11 (m, 2H), 0.84 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (75 MHz): 168.9 (C), 143.5 (C), 136.8 (C), 136.6 (C), 129.5 (CH × 2), 128.9 (CH × 2), 128.5 (CH × 2), 127.4 (CH), 127.2 (CH × 2), 60.5 (CH), 39.7 (CH_2), 31.2 (CH_2), 21.5 (CH_3), 19.8 (CH_2), 13.6 (CH_3). Anal. Calcd for $C_{19}H_{24}N_2O_3S$: C, 63.31; H, 6.71; N, 7.77. Found: C, 63.28; H, 6.89; N, 7.67.

4.10. Determination of the absolute configuration of 28a and 28b by the PGME method

To a mixture of **28** (0.11 mmol) and MeOH (0.013 mL, 0.33 mmol) in THF (2 mL) cooled to −40 °C was added Bu_4NF (1.0 M in THF, 0.11 mL, 0.11 mmol) slowly, and the mixture stirred for 1 h at −40 °C. The resulting solution was poured into NH_4Claq and extracted with CH_2Cl_2 (5 mL × 3). The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated in vacuo. The residue was dissolved in a mixed solvent (3 M hydrochloric acid–MeOH–1,4-dioxane = 1:1:1 vol, 0.3 mL). The solution was stirred for 15 min, and then concentrated in vacuo. To the residue dissolved in CH_2Cl_2 (1 mL) were added triethylamine (0.077 mL, 0.55 mmol), (*S*)-tetrahydrofuran-2-carboxylic acid (42.9 mg, 0.33 mmol), PyBop (172 mg, 0.33 mmol), and the mixture was stirred for 2 h at room temperature. The mixture was poured into hydrochloric acid (1 M) and extracted with CH_2Cl_2 (5 mL × 3). The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified roughly by silica gel column chromatography eluted with hexane/ethyl acetate (1:1) to afford a diastereomeric mixture of **31** and **32**. (**31a**/**32a**: 24.3 mg, 0.079 mmol, 72% overall yield, **31b**/**32b**: 26.5 mg, 0.077 mmol, 70% overall yield).

4.11. (*S*)-Methyl 2-(4-methoxyphenyl)-2-((*S*)-5-oxo-tetrahydrofuran-2-carboxamido)acetate 31a and (*R*)-methyl 2-(4-methoxyphenyl)-2-((*S*)-5-oxo-tetrahydrofuran-2-carboxamido)acetate 32a (85:15)

FT-IR ($CHCl_3$): 3334, 2956, 1788, 1746, 1683, 1611, 1514, 1251, 1177, 1031 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.38–7.35 (m, 2H), 7.24–7.08 (m, 1H), 7.00–6.84 (m, 2H), 5.56–5.46 (m, 1H), 4.91 (t, $J = 7.8$ Hz, 1H × 0.85), 4.85 (t, $J = 7.6$ Hz, 1H × 0.15), 3.81 (s, 3H × 0.15), 3.80 (s, 3H × 0.85), 3.74 (s, 3H × 0.85), 3.73 (s, 3H × 0.15), 2.75–2.21 (m, 4H); EI-HRMS calcd for $C_{15}H_{17}NO_6$ (M^+) 307.1056, found 307.1043.

4.12. (*S*)-Methyl 2-((*S*)-5-oxo-tetrahydrofuran-2-carboxamido)-2-(4-(trifluoromethyl)phenyl)acetate 31b and (*R*)-methyl 2-((*S*)-5-oxo-tetrahydrofuran-2-carboxamido)-2-(4-(trifluoromethyl)phenyl)acetate 32b (70:30)

FT-IR ($CHCl_3$): 3321, 2957, 1789, 1747, 1682, 1529, 1327, 1170, 1125, 1067 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.75–7.46 (m, 4H), 7.45–7.30 (m, 1H), 5.70–5.60 (m, 1H), 4.91 (t, $J = 7.8$ Hz, 1H × 0.70), 4.86 (t, $J = 7.8$ Hz, 1H × 0.30), 3.76 (s, 3H), 2.75–2.21 (m, 4H); EI-HRMS calcd for $C_{15}H_{14}F_3NO_5$ (M^+) 3345.0824, found 345.0838.

4.13. (*S*)-*tert*-Butyl 1-(butylamino)-3-methyl-1-oxobutan-2-ylcarbamate 33

To a mixture of **28c** (30.0 mg, 0.081 mmol) and MeOH (0.016 mL, 0.16 mmol) in THF (1 mL) cooled to −40 °C was added Bu_4NF (1.0 M in THF, 0.085 mL, 0.085 mmol), and the mixture was stirred for 1 h at −40 °C. The mixture was poured into NH_4Claq and extracted with CH_2Cl_2 (5 mL × 3). The combined organic layers were washed with brine, dried over magnesium sulfate and concentrated in vacuo. The residue was dissolved in a mixed solvent (3 M hydrochloric acid–MeOH–1,4-dioxane = 1:1:1 vol, 0.3 mL), and the mixture was stirred for 15 min at room temperature. The resulting mixture was concentrated in vacuo. The residue was poured into an aqueous solution of sodium hydroxide (10%), and extracted with CH_2Cl_2 (5 mL × 3). The combined organic layers were dried over potassium carbonate, and concentrated in vacuo. To a solution of the residue in THF (1 mL) were added triethylamine (0.034 mL, 0.24 mmol) and *tert*-butyl pyrocarbonate (Boc_2O) (35.4 mg, 0.16 mmol), and the mixture stirred for 12 h at room temperature. The mixture was poured into an aqueous solution of potassium hydrogen sulfate (5%), and extracted with CH_2Cl_2 (5 mL × 3). The combined organic layers were washed with brine, dried over magnesium sulfate, and concentrated in vacuo. The residue was purified by silica gel column chromatography eluted with hexane/ethyl acetate (2:1) to afford **33** (15.9 mg, 0.058 mmol, 72% yield). $[\alpha]_D^{25} = -15.7$ (*c* 0.60, MeOH) (69% ee) {lit. of (*S*)-**33**[33] $[\alpha]_D^{25} = -22.7$ (*c* 2.2, MeOH)}; FT-IR ($CHCl_3$): 3326, 2932, 2855, 1705, 1648, 1381, 1255, 853 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 5.95 (br, 1H, NH), 5.06 (br, 1H, NH), 3.83 (dd, $J = 6.5$, 8.8 Hz, 1H), 3.33–3.19 (m, 2H, NH–CH_2), 2.18–2.06 (m, 1H), 1.55–1.23 (m, 4H), 0.95 (d, $J = 6.8$ Hz, 3H), 0.92 (t, $J = 7.4$ Hz, 3H), 0.91 (d,

$J = 6.6$ Hz, 3H). Anal. Calcd for $C_{14}H_{28}N_2O_3$: C, 61.73; H, 10.36; N, 10.28. Found: C, 61.69; H, 10.34; N, 10.25.

Acknowledgement

This work was partly supported by a Grant-in-Aid for Scientific Research of the Ministry of Education, Culture, Sports, Science and Technology of Japan (Grant No. 18550094 in 2006–2007).

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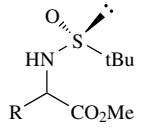

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