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Radical addition to oxime ethers for asymmetric synthesis of β-amino acid derivatives

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The diastereoselective alkyl radical addition to chiral oxime ethers was studied with a view to preparing enantiomerically pure α,β-dialkyl-β-amino acid derivatives. The phase transfer-catalyzed alkylation of Oppolzer's camphorsultam derivative of oxime ether proceeded smoothly to give the alkylated *N*-(β-oximino)acyl derivatives. In the presence of BF_3·OEt_2, radical addition to the oxime ethers proceeded using triethylborane as the radical initiator to give α,β-dialkyl-β-amino acid derivatives with excellent diastereoselectivity.

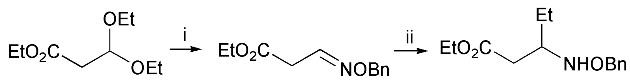
Introduction

The control of stereochemistry in free radical-mediated reactions has been of great importance in organic synthesis.[1] Asymmetric induction, particularly in intermolecular carbon–carbon bond-forming radical reactions of acyclic systems, is a subject of current interest.[1] Although a high degree of stereocontrol of radical reactions has been achieved in recent years, stereocontrol in radical addition to imine derivatives has not been widely studied.[2] Only three studies have been directed toward stereocontrol in the intermolecular carbon radical addition to imine derivatives.[3–5] Bertrand's and our groups recently reported studies on stereocontrol in the radical addition to activated imine derivatives such as glyoxylic oxime ethers and imines, which were successfully used for the novel asymmetric synthesis of α-amino acids.[3,4] More recently, Friestad and Qin reported diastereoselective radical addition to acylhydrazone.[5]

Among the different types of radical acceptors containing a carbon–nitrogen double bond, the oxime ethers are well known to be excellent radical acceptors because of the extra stabilization of the intermediate alkoxyaminyl radical provided by the lone pair on the adjacent oxygen atom.[6] However, studies on the radical reaction of oxime ethers have concentrated on intramolecular reactions,[6] and the difficulty of achieving the intermolecular construction of a carbon–carbon bond has remained unresolved.[7–10] Therefore, stereoselective carbon–carbon bond formation based on intermolecular carbon radical addition to oxime ethers is a challenging and promising task. We are interested in the stereoselective carbon–carbon bond-forming reactions based on the intermolecular carbon radical addition to a carbon–nitrogen double bond of acyclic oxime ethers.[4] In this paper, we describe full details of diastereoselective radical addition to unactivated oxime ethers bearing Oppolzer's camphorsultam for the synthesis of the enantiomerically pure β-amino acid derivatives.[11]

Results and discussion

Prior to exploring issues of stereocontrol, we first investigated the intermolecular carbon radical addition to achiral oxime ether **2** (Scheme 1). Oxime ether **2** was prepared from commercially available ethyl 3,3-diethoxypropionate and *O*-benzylhydroxylamine hydrochloride.[12] We recently reported the potential of BF_3·OEt_2 as a Lewis acid in achieving the intermolecular radical addition to unactivated oxime ethers.[10] To a



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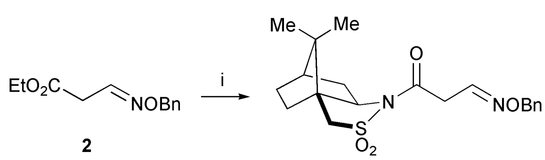
Scheme 1 *Reagents and conditions*: i, $BnONH_2$·HCl, *p*-TsOH, THF, 60 °C, 88%; ii, BF_3·OEt_2, Et_3B, CH_2Cl_2, 20 °C, 68%.

solution of oxime ether **2** and BF_3·OEt_2 in CH_2Cl_2 was added a commercially available 1.0 M solution of Et_3B in hexane, and then the reaction mixture was stirred at 20 °C. As indicated in our previous studies,[10] oxime ether **2** exhibits good reactivity in the presence of BF_3·OEt_2 to give the desired product **3** in 68% yield. This result suggests that the radical addition to oxime ethers is a highly promising approach to the synthesis of β-amino acids.[13] Additionally, it should be noted that the unactivated oxime ether having an acidic α-hydrogen reacted smoothly with a carbon radical. Nucleophilic addition to oxime ether **2** would be expected to be plagued by undesired deprotonation of the acidic α-hydrogen leading to the formation of a tautomer of the substrate.

The auxiliary of choice was Oppolzer's camphorsultam since it had shown good characteristics in our previous work on radical addition to glyoxylic oxime ethers.[4] Oxime ether **4** was readily prepared by treatment of ethyl 3-[*N*-(phenylmethoxy)-imino]propionate **2** with (1*S*)-(−)-2,10-camphorsultam in the presence of trimethylaluminium in boiling 1,2-dichloroethane (Scheme 2). The camphorsultam derivative of oxime ether **4** has



2 4

Scheme 2 *Reagents and conditions*: i, Me_3Al, (1*S*)-camphorsultam, CH_2ClCH_2Cl, reflux, 95%.

enough flexibility to allow access to a wide range of α,β-dialkyl-β-amino acids.

We next investigated the anionic alkylation of sultam compound **4** under several reaction conditions (Scheme 3, Table 1). The methylation of **4** using LiHMDS (5 equiv.) gave the undesired methylated product **5A** in 61% yield with 15% yield of the starting material **4** (Table 1, entry 1). The configuration of the newly-formed stereocenter of **5A** was not determined. Methylation of **4** using NaHMDS (2.5 equiv.) gave a similar result (entry 3). In the presence of MeOH (6 equiv.), methyl-

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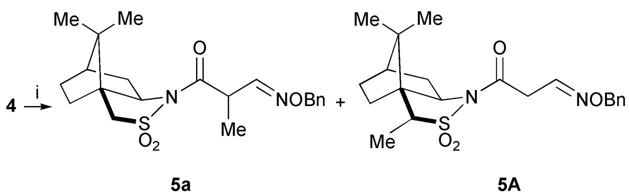
Table 1 Methylation of oxime ether **4**

Entry	Base (equiv.)	Additive (equiv.)	Yield (%) 5a	5A	4
1[a]	LiHMDS (5)	None		61	15
2[a]	LiHMDS (2)	None			90
3[a]	NaHMDS (2.5)	None		78	
4[a]	NaHMDS (1.5)	None			80
5[a]	NaHMDS (6)	MeOH (6)	19[b]		59
6[c]	5 M NaOH	Bu_4NBr (0.1)	85 (13.1 : 1 : 1.2)[b]		

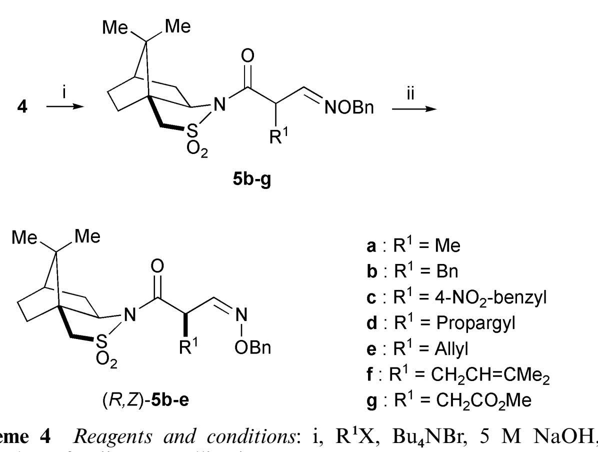
[a] Reaction was carried out with MeI in THF at −78 °C. [b] Combined yields; ratio of (*R*,*Z*)-, (*R*,*E*)-, (*S*,*Z*)-isomers was determined by ^{1}H NMR analysis after PTLC. [c] Reaction was carried out with MeI (1.5 equiv.) and Bu_4NBr (0.1 equiv.) in 5 M NaOH–CH_2Cl_2 at 20 °C.



Scheme 3 *Reagents and conditions*: i, Base, MeI.

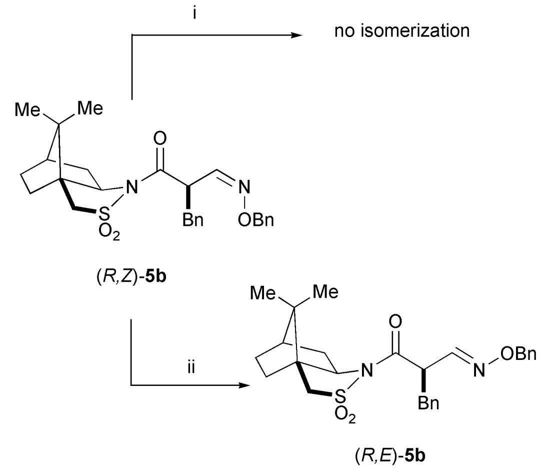
ation of **4** using NaHMDS (6 equiv.) gave the desired methylated product **5a** in 19% yield with 59% yield of the starting material **4** (entry 5). These results suggest that a weak base such as NaOMe is effective in the deprotonation of the acidic methylene in oxime ether **4**. The phase transfer-catalyzed reaction was an excellent method for the regioselective alkylation of the acidic methylene in oxime ether **4** with no detection of the undesired methylated product **5A** (entry 6). Methylation of sultam derivative **4** was carried out using MeI and tetrabutylammonium bromide as a phase-transfer catalyst in 5 M NaOH–CH_2Cl_2 at 20 °C. The desired methylated oxime ether **5a** was obtained in 85% combined yield in a 13.1 : 1 : 1.2 ratio of (*R*,*Z*)-, (*R*,*E*)-, and (*S*,*Z*)-isomers. The *E* : *Z* ratios of the oxime ether group were deduced by ^{1}H-NMR spectroscopy. In general, the signals due to the imino hydrogen of the *E*-oxime ether are shifted downfield by the influence of the alkoxy group of the oxime ether moiety.[14]

The phase transfer-catalyzed alkylation of sultam compound **4** using different alkylating reagents R^1X was studied (Scheme 4). The results are summarized in Table 2. All alkylations of



Scheme 4 *Reagents and conditions*: i, R^1X, Bu_4NBr, 5 M NaOH, CH_2Cl_2, 20 °C; ii, recrystallization.

sultam derivative **4** were carried out using alkyl bromides and tetrabutylammonium bromide (0.1 equiv.) as phase-transfer catalyst in 5 M NaOH–CH_2Cl_2 at 20 °C for 1 h. In the case of benzylation using benzyl bromide, the desired benzylated oxime ether **5b** was obtained in 99% combined yield in favor of the (*R*,*Z*)-isomer (Table 2, entry 1). The absolute configuration at the newly-formed chiral center of the major product of **5b** was determined to be *R* by X-ray analysis of (*R*,*Z*)-**5b**. The other diastereomerically pure alkylated products (*R*,*Z*)-**5c**, (*R*,*Z*)-**5d**, and (*R*,*Z*)-**5e** could also be obtained under similar reaction conditions after recrystallisation (entries 2–4). In contrast, oxime ethers **5a**, **5f**, and **5g** were obtained as an oil; thus, we could not separate (*R*,*Z*)-, (*R*,*E*)-, and (*S*,*Z*)-isomers by either medium-pressure column chromatography or recrystallisation (Table 1, entry 6 and Table 2, entries 5 and 6). The absolute configuration of major products **5a** and **5c**–**g** was assigned to be *R* since their ^{1}H NMR data showed similarity with that of (*R*,*Z*)-**5b**. Although no isomerization of the newly-formed chiral center of (*R*,*Z*)-**5b** was observed by treatment with tetrabutylammonium bromide (0.1 equiv.) in 5 M NaOH–CH_2Cl_2, (*R*,*Z*)-**5b** was isomerized to the more stable (*R*,*E*)-**5b** under acidic conditions (Scheme 5).



Scheme 5 *Reagents and conditions*: i, Bu_4NBr, 5 M NaOH, CH_2Cl_2, 20 °C; ii, 5% HCl, CH_2Cl_2, 20 °C.

As suggested by the studies on the camphorsultam derivative by Oppolzer's group,[15] the stereochemical feature of this alkylation reaction can be rationalized in terms of the stereoelectronic effect in the chelated (*Z*)-enolate anion of the conformationally restricted oxime ether **4** (Fig. 1).

We next investigated ethyl radical addition to the oxime ether **5a** by using triethylborane as an ethyl radical source (Scheme 6).

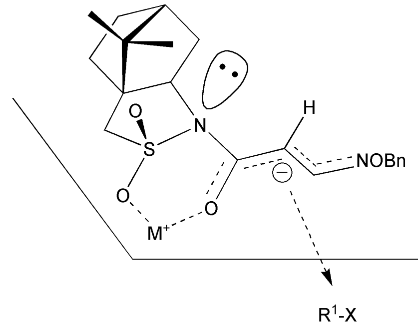


Fig. 1 Transition-state model for the alkylation of **4**.

Table 2 Alkylation of oxime ether **4**

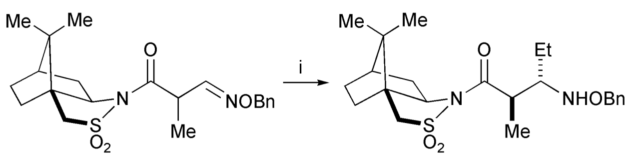
Entry	R^1X	Product	Yield (%)[a]	Ratio[b] $R,Z : R,E : S,Z$	Purity after recrystallisation[c]
1[d]	BnBr	**5b**	99	15.7 : 1.0 : 1.3	95% de
2[d]	4-NO_2-Benzyl Br	**5c**	98	7.6 : 1.0 : 1.0	95% de
3[d]	Propargyl Br	**5d**	99	9.7 : 1.2 : 1.0	95% de
4[d]	Allyl I	**5e**	97	8.5 : 1.4 : 1.3	95% de
5[e]	4-Bromo-2-methylbut-2-ene	**5f**	91	9.8 : 1.3 : 1.0	—
6[e]	Methyl bromoacetate	**5g**	47 (42)[f]	10.0 : 1.0 : —	—

[a] Combined yields. [b] Ratios were determined by ^{1}H NMR analysis after PTLC. [c] Diastereomeric purities of **5b–e** were determined after recrystallisation. The diastereomerically pure materials (*R*,*Z*)-**5b–e** were obtained in *ca.* 60–80% yields after recrystallisation. [d] Alkylation was carried out with R^1X (1.1 equiv.) and Bu_4NBr (0.1 equiv.) in 5 M NaOH–CH_2Cl_2 at 20 °C. [e] Alkylation was carried out with R^1X (1.5 equiv.) and Bu_4NBr (0.1 equiv.) in 5 M NaOH–CH_2Cl_2 at 20 °C. [f] Yield in parentheses is that for starting material.

Table 3 Ethyl radical addition to (*R*,*Z*)-**5b–e**

Entry	Oxime ether	Solvent	*T*/°C	Product	Yield (%)[a]	Selectivity[b]
1[c]	(*R*,*Z*)-**5b**	CH_2Cl_2	−78	**6bA**	95	>95% de
2[d]	(*R*,*Z*)-**5b**	CH_2Cl_2	20	**6bA**	99	>95% de
3[d]	(*R*,*Z*)-**5b**	Toluene	20	**6bA**	99	>95% de
4[c]	(*R*,*Z*)-**5c**	CH_2Cl_2	−78	**6cA**	66	>95% de
5[c]	(*R*,*Z*)-**5c**	Toluene	−78	**6cA**	72	>95% de
6[d]	(*R*,*Z*)-**5c**	Toluene	20	**6cA**	60	>95% de
7[c]	(*R*,*Z*)-**5d**	CH_2Cl_2	−78	**6dA**	43 (37)	>95% de
8[c]	(*R*,*Z*)-**5d**	Toluene	−78	**6dA**	31 (45)	>95% de
9[c]	(*R*,*Z*)-**5e**	CH_2Cl_2	−78	**6eA**	Complex mixture	
10[c]	(*R*,*Z*)-**5e**	Toluene	−78	**6eA**	Complex mixture	
11[e]	(*R*,*Z*)-**5b**	CH_2Cl_2	20	**6bA**	No reaction	

[a] Isolated yields; yield in parentheses is that for the recovered starting material. [b] Diastereoselectivities were determined by ^{1}H NMR analysis. [c] Radical addition at −78 °C was carried out with BF_3·OEt_2 (9 equiv.) and Et_3B (9 equiv.). [d] Radical addition at 20 °C was carried out with BF_3·OEt_2 (5 equiv.) and Et_3B (5 equiv.). [e] Radical addition at 20 °C was carried out with BF_3·OEt_2 (3 equiv.) and Et_2Zn (3 equiv.).



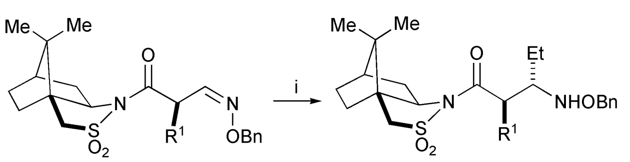
5a (*R*,*Z*:*R*,*E*:*S*,*Z* = 13.1:1:1.2)

6aA

Scheme 6 *Reagents and conditions*: i, BF_3·OEt_2, Et_3B, toluene, 20 °C, 70%.

In the presence of BF_3·OEt_2, the radical addition to the oxime ether **5a** proceeded smoothly to give the α,β-dialkyl-β-amino acid derivative, while no reaction occurred in the absence of BF_3·OEt_2. Although a mixture of (*R*,*Z*)-, (*R*,*E*)- and (*S*,*Z*)-isomers **5a** was used as the substrate, the ethylated product **6aA** was obtained as the major isomer in 70% isolated yield after separation of isomers.

The ethyl radical addition to other oxime ethers (*R*,*Z*)-**5b–5e** was also studied (Scheme 7). In the presence of BF_3·OEt_2, the



(*R*,*Z*)-**5b-e**

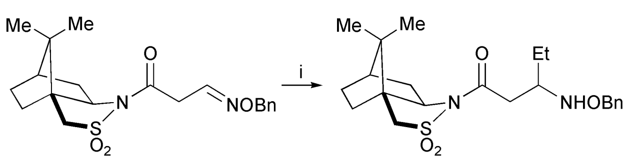
6bA-eA

b : R^1 = Bn, **c** : R^1 = 4-NO_2-benzyl, **d** : R^1 = Propargyl, **e** : R^1 = Allyl

Scheme 7 *Reagents and conditions*: i, BF_3·OEt_2, Et_3B.

reaction of (*R*,*Z*)-**5b** with triethylborane in CH_2Cl_2 proceeded smoothly within 15 min even at −78 °C to give a 95% yield of the ethylated product **6bA** (Table 3, entry 1). The diastereomeric purity of **6bA** was found to be not less than 95% de by ^{1}H NMR analysis of the crude products. The high diastereoselectivity and chemical yield were still maintained in the reaction at 20 °C (entry 2). In regard to the solvent effect, replacement of CH_2Cl_2 by a nonpolar aromatic solvent such as toluene was also effective in the radical reaction giving the ethylated product **6bA** in 99% yield with excellent diastereoselectivity (entry 3). The absolute configuration at the newly-formed stereocenter of the ethylated product **6bA** was determined to be *S* by X-ray analysis. Excellent diastereoselectivities were also observed in the radical addition to different radical acceptors (*R*,*Z*)-**5c** and **-5d** containing a 4-nitrobenzyl group or a carbon–carbon triple bond, respectively, to afford the ethylated products **6cA** and **6dA** with relatively low efficiency (entries 4–8). In contrast, the reaction of (*R*,*Z*)-**5e** did not give good results (entries 9 and 10). Although the ethyl radical addition to the oxime ether (*R*,*Z*)-**5b** was studied by using diethylzinc as the ethyl radical source, no reaction took place (entry 11).

In the case of the radical addition to the oxime ether **4**, the ethylated product **7** was obtained with low diastereoselectivity, probably because the approaching radical was too far away from the chiral sultam part (Scheme 8). Thus, the high stereo-



4

7

in toluene (84%, 5% de)
in CH_2Cl_2 (91%, 5% de)

Scheme 8 *Reagents and conditions*: i, BF_3·OEt_2, Et_3B, −78 °C.

control in the alkyl radical addition to (*R*,*Z*)-**5b**–**5d** would be regarded as the result of high 1,2-asymmetric induction.

In the case of (*R*,*Z*)-**5b**–**5d**, the conformer **A** minimizing $A^{1,3}$-strain effects would be favored (Fig. 2). Additionally, the stable conformation was also supported by the crystal structure

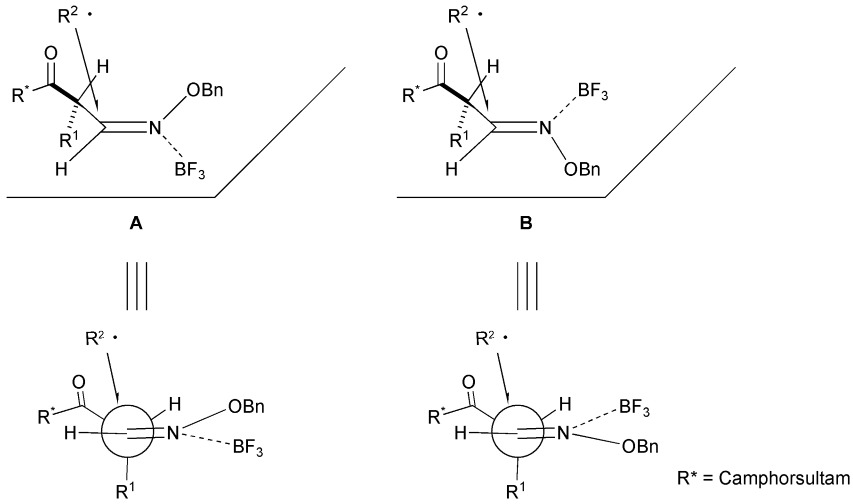
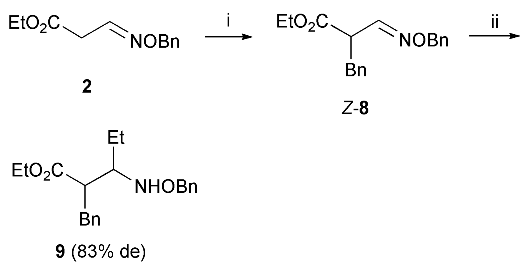


Fig. 2 1,2-Asymmetric induction.

resulting from X-ray analysis of (*R*,*Z*)-**5b**. Thus, ethyl radical addition took place predominantly from the less-hindered π-face of oxime ethers activated by BF_3, in which the bulky alkyl group (R^1) shields the opposite face. After the radical reaction in the presence of BF_3·OEt_2, isomerization of (*Z*)-**5** to (*E*)-**5** was observed in the recovered starting materials **5**. Thus, both (*Z*)- and (*E*)-isomers would be important for the radical reaction of **5**.

To explore the issues of 1,2-asymmetric induction,[16] we also studied the radical addition to simple oxime ether **8** (Scheme 9).

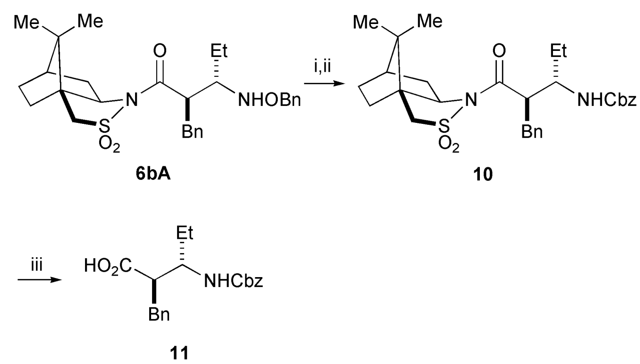


Scheme 9 *Reagents and conditions*: i, BnBr, Bu_4NBr, 5 M NaOH, CH_2Cl_2, 20 °C, 78%; ii, BF_3·OEt_2, Et_3B, CH_2Cl_2, 20 °C, 54%.

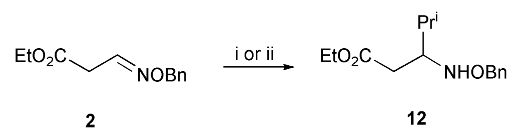
Benzylation of oxime ether **2** was run by using benzyl bromide and tetrabutylammonium bromide as a phase-transfer catalyst in 5 M NaOH–CH_2Cl_2 at 20 °C. The desired benzylated oxime ether (*Z*)-**8** was obtained in 78% yield. In the presence of BF_3·OEt_2, the reaction of (*Z*)-**8** with triethylborane proceeded smoothly to give a 54% yield of the ethylated product **9** in 83% de. The relative configuration of **9** was not determined. These results suggest that 1,2-asymmetric induction is responsible for diastereocontrol in the radical reaction of (*R*,*Z*)-**5a**–**5d**.

Hydrogenolysis of the benzyloxy group of **6bA** in the presence of $Pd(OH)_2$ in MeOH and subsequent protection of the resulting amine with benzyloxycarbonyl chloride gave **10** in 96% yield from **6bA** (Scheme 10). The removal of the sultam auxiliary by standard hydrolysis[17] afforded the enantiomerically pure α,β-dialkyl-β-amino acid **11** in 62% yield without any loss of stereochemical purity.

We next investigated radical reactions using different radical precursors. At first, isopropyl radical addition to oxime ether **2** was studied under different reaction conditions (Scheme 11). A modest chemical yield was obtained in the stannyl radical-mediated reaction of **2** using isopropyl iodide, Bu_3SnH, and Et_3B in the presence of BF_3·OEt_2. Free radical synthetic methods have largely relied on toxic organomercury or organotin chemistry. From economic and ecological points of view, we next investigated radical addition to oxime ether **2** in the absence of Bu_3SnH.[18] Even in the absence of Bu_3SnH, treatment of **2** with isopropyl iodide and Et_3B in toluene at 50 °C for 5 min gave the desired product **12** in 71% yield. The reaction proceeded *via* a route involving an iodine atom-transfer process between isopropyl iodide and an ethyl radical generated from Et_3B. In this reaction, Et_3B acts as a radical initiator and a radical terminator to trap the intermediate benzyloxyaminyl radical.[18] Thus, the radical chain reaction proceeds *via* the regeneration of the ethyl radical by a simple procedure, which does not require tedious workup to remove the tin residues from the reaction mixture.



Scheme 10 *Reagents and conditions*: i, H_2, $Pd(OH)_2$–C, MeOH, 20 °C; ii, CbzCl, Na_2CO_3, acetone–H_2O, 20 °C, 96% (2 steps); iii, LiOH, H_2O, THF, reflux, 62%.



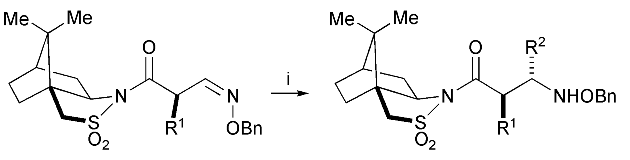
Scheme 11 *Reagents and conditions*: i, Bu_3SnH, BF_3·OEt_2, Pr^iI, Et_3B, CH_2Cl_2, 20 °C, 43%; ii, BF_3·OEt_2, Pr^iI, Et_3B, toluene, 50 °C, 71%.

In order to investigate the generality and practicality of the reaction, the present procedure was successfully extended to the radical addition reactions to (*R*,*Z*)-**5b**–**c** (Scheme 12). The isopropyl radical addition to (*R*,*Z*)-**5b** was run in toluene at 20 °C by using isopropyl iodide and Et_3B in the presence of BF_3·OEt_2 (Table 4, entry 1). As expected, the reaction proceeded smoothly in the absence of tin hydride to give a good yield of isopropylated product **6bB** with a high level of diastereoselectivity. In this reaction, the formation of the ethylated product **6bA** was not observed. Other secondary alkyl radicals also worked well under similar reaction conditions, allowing facile incorporation of a variety of structures into the oxime ether (entries 2–4). In the case of *sec*-butyl radical addition, a 1 : 1 diastereomeric ratio with regard the stereocenter on the *sec*-butyl group was observed, although the radical addition

Table 4 Alkyl radical addition to (*R*,*Z*)-**5b**–**c**[a]

Entry	Oxime ether	R^2	Product	Yield (%)[b]	Selectivity[c]
1	(*R*,*Z*)-**5b**	Pr^i	**6bB**	70	>95% de
2	(*R*,*Z*)-**5b**	*c*-Hexyl	**6bC**	57	>95% de
3	(*R*,*Z*)-**5b**	*c*-Pentyl	**6bD**	59	>95% de
4	(*R*,*Z*)-**5b**	Bu^s	**6bE**	50	>95% de
5	(*R*,*Z*)-**5b**	Bu^i	**6bF**	20 (39)[d]	>95% de
6	(*R*,*Z*)-**5c**	Pr^i	**6cB**	40 (16)	>95% de

[a] Radical addition was carried out with R^2I (30 equiv.), $BF_3{\cdot}OEt_2$ (9 equiv.) and Et_3B (9 equiv.) in toluene at 20 °C. [b] Isolated yields; yields in parentheses are for the recovered starting material. [c] Diastereoselectivities were determined by ^1H NMR analysis. [d] Ethylated product **6bA** was also obtained in 29% yield.



(*R*,*Z*)-**5b-c** **6bB-F**, **6cB**

b : R^1 = Bn
c : R^1 = 4-NO_2-benzyl,

B : R^2 = Pr^i
C : R^2 = *c*-Hexyl
D : R^2 = *c*-Pentyl
E : R^2 = Bu^s
F : R^2 = Bu^t

Scheme 12 *Reagents and conditions*: i, $BF_3{\cdot}OEt_2$, R^2I, Et_3B, toluene, 20 °C.

proceeded with high diastereoselectivity. Low chemical yield was obtained in the reaction using an unstable primary alkyl radical such as the isobutyl radical because of the competitive formation of a significant amount of the ethylated product **6bA** as a by-product, which was formed by the reaction with the ethyl radical generated from Et_3B (entry 5). Similar trends were observed in our previous studies of radical addition to activated glyoxylic oxime ethers.[4,17] The isopropyl radical addition to an oxime ether having a 4-nitrobenzyl group (*R*,*Z*)-**5c** also proceeded with excellent diastereoselectivity under similar reaction conditions (entry 6).

In conclusion, we have demonstrated that the stereocontrol in the intermolecular carbon radical addition to oxime ethers presents new opportunities for stereoselective synthesis of α,β-dialkyl-β-amino acid derivatives. In addition to the intermolecular radical reaction of glyoxylic oxime ether in the asymmetric synthesis of α-amino acids,[4] the radical reactions of unactivated oxime ethers disclosed a broader aspect of the utility of imine derivatives as a radical acceptor for the synthesis of various types of chiral amino compounds.

Experimental

Melting points are uncorrected. ^1H and ^{13}C NMR spectra were recorded at 500, 300, and 200 MHz and at 125, 75, and 50 MHz, respectively; chemical shifts are measured in ppm. IR spectra were recorded using FTIR apparatus. Mass spectra were obtained by the EI method. Preparative TLC separations were carried out on precoated silica gel plates (E. Merck $60F_{254}$). Medium-pressure column chromatography was performed using Lobar grösse B (E. Merck 310–25, Lichroprep Si60). Flash column chromatography was performed using E. Merck Kieselgel 60 (230–400 mesh). Optical rotations were recorded on a Jasco polarimeter with a path length of 1 cm; concentrations are quoted in mg (2 mL). $[\alpha]_D$ values are measured in 10^{-1} deg cm^2 g^{-1}.

Radical addition to oxime ether (2)

To a solution of **2** (60.0 mg, 0.271 mmol) in CH_2Cl_2 (3 mL) were added $BF_3{\cdot}OEt_2$ (0.068 mL, 0.542 mmol) and Et_3B (1.0 M in hexane, 0.678 mL, 0.678 mmol) under a nitrogen atmosphere at 20 °C. After being stirred at the same temperature for 15 min, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and then extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated at reduced pressure. Purification by preparative TLC (AcOEt–hexane 1 : 15, 2-fold development) afforded the alkylated products **3** (46.3 mg, 68%) as a colorless oil.

3-[(Phenylmethoxy)amino]pentanoic acid ethyl ester (3)

IR ($CHCl_3$) 3251, 2968, 1725, 1496 cm^{-1};^1H NMR ($CDCl_3$) δ 7.39–7.21 (5H, m), 4.69 (2H, s), 4.11 (2H, q, J = 7.1 Hz), 3.24 (1H, m), 2.53 (1H, dd, J = 15.6, 7.4 Hz), 2.44 (1H, dd, J = 15.6, 5.2 Hz), 1.71–1.32 (2H, m), 1.23 (3H, t, J = 7.1 Hz), 0.93 (3H, t, J = 7.5 Hz);^{13}C NMR ($CDCl_3$) δ 172.4, 137.8, 128.2, 127.6, 76.4, 60.2, 58.9, 36.6, 24.6, 14.0, 10.3. HRMS: Calcd for $C_{14}H_{21}NO_3$ (M^+): 251.1520. Found: 251.1501.

Synthesis of oxime ether (4)

To a solution of (1*S*)-(−)-2,10-camphorsultam (3.0 g, 13.9 mmol) and **2** (4.6 g, 20.8 mmol) in CH_2ClCH_2Cl (106 mL) was added Me_3Al (1.0 M in hexane, 20.8 mL, 20.8 mmol) under a nitrogen atmosphere at room temperature. After being heated at reflux for 9 h, the reaction mixture was diluted with 3% HCl and then extracted with CH_2Cl_2. The organic phase was washed with water, dried over $MgSO_4$, and concentrated at reduced pressure. Purification by flash chromatography (hexane–AcOEt 3 : 1) afforded **1** (5.1 g, 95%) as a colorless oil (2 : 3 mixture of (*E*)–(*Z*)-oxime ether).

(3a*S*,6*R*,7a*R*)-1,4,5,6,7,7a-Hexahydro-8,8-dimethyl-1-{1-oxo-3-[(phenylmethoxy)imino]propyl}-3*H*-3a,6-methano-2,1-benzisothiazole 2,2-dioxide (4)

$[\alpha]_D^{32}$ −84.5 (*c* 0.86, $CHCl_3$); IR ($CHCl_3$) 2964, 1698 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.58 (2/5H, t, J = 5.9 Hz), 7.38–7.25 (5H, m), 7.07 (3/5H, t, J = 4.7 Hz), 5.13 (6/5H, s), 5.08 (4/5H, s), 3.95–3.75 (11/5H, m), 3.68 (4/5H, d, J = 5.9 Hz), 3.49 (1H, br d, J = 13.8 Hz), 3.48 (1H, br d, J = 13.8 Hz), 2.2–1.8 (5H, m), 1.45–1.30 (2H, m), 1.14 (6/5H, s), 1.12 (9/5H, s), 0.96 (3H, s); ^{13}C NMR ($CDCl_3$) δ 167.3, 167.0, 143.7, 142.6, 137.6, 137.3, 128.3, 128.1, 127.9, 127.8, 127.7, 75.93, 75.86, 65.1, 52.72, 52.66, 48.5, 47.7, 44.51, 44.47, 38.14, 38.08, 36.1, 32.7, 32.5, 26.3, 20.6, 19.7. HRMS: Calcd for $C_{20}H_{26}N_2O_4S$ (M^+): 390.1612. Found: 390.1624.

Methylation of oxime ether (4)

For entry 1 in Table 1. To a solution of **4** (80.0 mg, 0.205 mmol) in THF (5 mL) was added LiHMDS (1 M in hexane, 1.08 mL, 1.08 mmol) under an argon atmosphere at −78 °C. After being stirred at the same temperature for 30 min, MeI (0.09 mL, 1.44 mmol) was added to the reaction mixture at −78 °C. After being stirred at the same temperature for 45 min, the reaction mixture was diluted with H_2O and then extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated at reduced pressure. Purification by preparative TLC (AcOEt–hexane 1 : 4, 2-fold development) afforded **5A** (51.9 mg, 61%) as a colorless oil and **4** (12.3 mg, 15%).

For entry 2 in Table 1. To a solution of **4** (80.0 mg, 0.205 mmol) in THF (5 mL) was added LiHMDS (1 M in hexane, 0.432 mL, 0.432 mmol) under an argon atmosphere at −78 °C. After being stirred at the same temperature for 15 min, MeI (0.05 mL, 0.72 mmol) was added to the reaction mixture at −78 °C. After being stirred at the same temperature for 15 min, the reaction mixture was diluted with H_2O and then extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated at reduced pressure. Purification by preparative TLC (AcOEt–hexane 1 : 4, 2-fold development) afforded **4** (72.0 mg, 90%).

For entry 3 in Table 1. To a solution of **4** (80.0 mg, 0.205 mmol) in THF (5 mL) was added NaHMDS (1 M in THF, 0.51 mL, 0.51 mmol) under an argon atmosphere at −78 °C. After being stirred at the same temperature for 30 min, MeI (0.038 mL, 0.615 mmol) was added to the reaction mixture at −78 °C. After being stirred at the same temperature for 30 min, the reaction mixture was diluted with H_2O and then extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated at reduced pressure. Purification by preparative TLC (AcOEt–hexane 1 : 4, 2-fold development) afforded **5A** (64.2 mg, 78%).

For entry 4 in Table 1. To a solution of **4** (80.0 mg, 0.205 mmol) in THF (5 mL) was added NaHMDS (1 M in THF, 0.31 mL, 0.31 mmol) under an argon atmosphere at −78 °C. After being stirred at the same temperature for 30 min, MeI (0.038 mL, 0.615 mmol) was added to the reaction mixture at −78 °C. After being stirred at the same temperature for 15 min, the reaction mixture was diluted with H_2O and then extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated at reduced pressure. Purification by preparative TLC (AcOEt–hexane 1 : 4, 2-fold development) afforded **4** (64.0 mg, 80%).

For entry 5 in Table 1. To a solution of **4** (80.0 mg, 0.205 mmol) in THF (5 mL) and CH_2Cl_2 (5 mL) were added MeOH (0.05 mL, 1.23 mmol) and NaHMDS (1 M in THF, 1.23 mL, 1.23 mmol) under an argon atmosphere at −78 °C. After being stirred at the same temperature for 15 min, MeI (0.08 mL, 1.23 mmol) was added to the reaction mixture at −78 °C. After being stirred at −40 °C for 1 h, the reaction mixture was diluted with H_2O and then extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated at reduced pressure. Purification by preparative TLC (AcOEt–hexane 1 : 4, 2-fold development) afforded **5a** (15.9 mg, 19%) and **4** (46.9 mg, 59%).

For entry 6 in Table 1. To a solution of **4** (80.0 mg, 0.205 mmol) in CH_2Cl_2 (5 mL) were added MeI (0.02 mL, 0.308 mmol), tetra-*n*-butylammonium bromide (6.8 mg, 0.023 mmol), and 5 M NaOH (0.2 mL) under a nitrogen atmosphere at 20 °C. After being stirred at the same temperature for 1 h, the reaction mixture was diluted with saturated aqueous NH_4Cl and then extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated at reduced pressure. Purification by preparative TLC (AcOEt–hexane 1 : 4, 2-fold development) afforded **5a** (70.3 mg, 85%).

(3a*S*,6*R*,7a*R*)-1,4,5,6,7,7a-Hexahydro-8,8-dimethyl-1-{2-methyl-1-oxo-3-[(phenylmethoxy)imino]propyl}-3*H*-3a,6-methano-2,1-benzisothiazole 2,2-dioxide (5a). (*R*,*Z* : *R*,*E* : *S*,*Z* = 13.1 : 1 : 1.2) as a colorless oil. $[\alpha]_D^{27}$ −95.9 (*c* 1.08, $CHCl_3$); IR ($CHCl_3$) 2964, 2884, 1694, 1456 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.59 (1/15.3H, d,*J* = 6.1 Hz), 7.40–7.21 (5H, m), 6.98 (13.1/15.3H, d, *J* = 5.9 Hz), 6.74 (1.2/15.3H, d, *J* = 5.3 Hz), 5.13 (2 × 13.1/15.3H, s), 5.11 (2 × 1.2/15.3H, s), 5.08 (2 × 1/15.3H, s), 4.62–4.30 (1H, m), 4.02 (1/15.3H, t, *J* = 6.4 Hz), 3.86 (1.2/15.3H, t, *J* = 6.4 Hz), 3.83 (13.1/15.3H, t, *J* = 6.4 Hz), 3.51 (1H, d, *J* = 13.9 Hz), 3.41 (1H, d, *J* = 13.8 Hz), 2.11–1.58 (5H, m), 1.48–1.22 (5H, m), 1.14 (3H, s), 0.97 (3 × 13.1/15.3H, s), 0.94 (3 × 1/15.3H, s), 0.92 (3 × 1.2/15.3H, s). HRMS: Calcd for $C_{21}H_{28}N_2O_4S$ (M^+): 404.1768. Found: 404.1759.

(3a*S*,6*R*,7a*R*)-1,4,5,6,7,7a-Hexahydro-3,8,8-trimethyl-1-{1-oxo-3-[(phenylmethoxy)imino]propyl}-3*H*-3a,6-methano-2,1-benzisothiazole 2,2-dioxide (5A). The configuration of the newly-formed stereocenter of **5A** was not determined. 1 : 2 mixture of (*E*)–(*Z*)-oxime ether as a colorless oil. $[\alpha]_D^{30}$ −53.6 (*c* 2.00, $CHCl_3$); IR ($CHCl_3$) 2964, 1697, 1454 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.59 (1/3H, t, *J* = 5.9 Hz), 7.39–7.22 (5H, m), 7.07 (2/3H, t, *J* = 4.8 Hz), 5.13 (4/3H, s), 5.08 (2/3H, s), 3.96–3.67 (3H, m), 3.46 (1H, q, *J* = 7.4 Hz), 2.12–1.73 (5H, m), 1.41 (3H, d, *J* = 7.4 Hz), 1.36–1.22 (2H, m), 1.12 (3/3H, s), 1.10 (6/3H, s), 0.94 (3H, s); ^{13}C NMR ($CDCl_3$) δ 167.6, 167.3, 143.8, 142.7, 137.6, 137.3, 128.2, 128.1, 127.8, 127.7, 127.6, 75.9, 75.8, 63.2, 57.03, 56.97, 52.0, 48.3, 44.6, 38.0, 37.9, 36.1, 32.5, 29.3, 25.8, 20.6, 19.7, 12.8. HRMS: Calcd for $C_{21}H_{28}N_2O_4S$ (M^+): 404.1768. Found: 404.1763.

General procedure for the alkylation of 4 (Table 2)

To a solution of **4** (7.7 mmol) in CH_2Cl_2 (190 mL) were added alkyl bromide (8.5 mmol), tetra-*n*-butylammonium bromide (0.77 mmol), and 5 M NaOH (7.5 mL) under a nitrogen atmosphere at 20 °C. After being stirred at the same temperature for 1 h, the reaction mixture was diluted with saturated aqueous NH_4Cl and then extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated at reduced pressure. Purification by flash column chromatography (AcOEt–hexane 1 : 4) afforded the alkylated products **5b**–**g**. The diastereomerically pure products (*R*,*Z*)-**5b**–**e** were obtained by recrystallisation from hexane–AcOEt.

(3a*S*,6*R*,7a*R*)-1,4,5,6,7,7a-Hexahydro-8,8-dimethyl-1-{(2*R*,3*Z*)-1-oxo-3-[(phenylmethoxy)imino]-2-(phenylmethyl)propyl}-3*H*-3a,6-methano-2,1-benzisothiazole 2,2-dioxide [(*R*,*Z*)-5b]. Colorless crystals. Mp 121–122 °C (AcOEt–hexane); $[\alpha]_D^{23}$ −90.0 (*c* 0.98, $CHCl_3$); IR ($CHCl_3$) 2960, 1691 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.36–7.12 (10H, m), 6.86 (1H, d, *J* = 6.4 Hz), 5.11 (1H, d, *J* = 8.1 Hz), 5.10 (1H, d, *J* = 8.1 Hz), 4.94 (1H, br m), 3.68 (1H, br m), 3.38 (1H, d, *J* = 13.7 Hz), 3.32 (1H, d, *J* = 13.7 Hz), 3.12 (1H, dd, *J* = 13.2, 8.4 Hz), 3.06 (1H, dd, *J* = 13.2, 6.8 Hz), 1.92 (1H, dd, *J* = 13.5, 8.0 Hz), 1.84–16.5 (4H, m), 1.26 (2H, br m), 0.87 (3H, s), 0.72 (3H, s); ^{13}C NMR ($CDCl_3$) δ 170.5, 147.0, 137.7, 136.8, 129.2, 128.2, 128.1, 127.6, 127.4, 126.7, 75.8, 64.8, 52.8, 48.0, 47.4, 44.8, 44.5, 38.1, 37.1, 32.6, 26.2, 20.4, 19.6. HRMS: Calcd for $C_{27}H_{32}N_2O_4S$ (M^+): 480.2081. Found: 480.2084. Anal. Calcd for $C_{27}H_{32}N_2O_4S$: C, 67.47; H, 6.71; N, 5.83; S, 6.67. Found: C, 67.65; H, 6.82; N, 5.82; S, 6.84%. Crystal data of (*R*,*Z*)-**5b**: ‡ $C_{27}H_{32}N_2O_4S$, space group monoclinic, $P2_1$ with a = 11.103 (11), b = 11.982 (14), c = 9.962 (12) Å, V = 1251.6 (2) Å^3, final R value 0.0297 for 3012 reflections

(3a*S*,6*R*,7a*R*)-1,4,5,6,7,7a-Hexahydro-8,8-dimethyl-1-{(2*R*,3*Z*)-2-[(4-nitrophenyl)methyl]-1-oxo-3-[(phenylmethoxy)imino]propyl}-3*H*-3a,6-methano-2,1-benzisothiazole 2,2-dioxide [(*R*,*Z*)-5c]. Colorless crystals. Mp 130–132 °C (AcOEt–hexane); $[\alpha]_D^{24}$ −86.9 (*c* 1.54, $CHCl_3$); IR ($CHCl_3$) 2964, 1690 cm^{-1}; ^1H NMR δ 8.05 (2H, d, *J* = 8.4 Hz), 7.40–7.22 (7H,

‡ CCDC reference number 135458. See http://www.rsc.org/suppdata/ob/b2/b208823a/ for crystallographic files in .cif or other electronic format.

m), 6.87 (1H, d, $J = 6.6$ Hz), 5.11 (1H, d, $J = 12.8$ Hz), 5.06 (1H, d, $J = 12.8$ Hz), 5.08–4.96 (1H, m), 3.82–3.73 (1H, m), 3.43 (1H, d, $J = 14.0$ Hz), 3.38 (1H, d, $J = 14.0$ Hz), 3.22 (1H, dd, $J = 13.2$, 8.3 Hz), 3.12 (1H, dd, $J = 13.2$, 6.8 Hz), 2.05–1.68 (5H, m), 1.40–1.22 (2H, m), 0.89 (3H, s), 0.68 (3H, s); ^{13}C NMR ($CDCl_3$) δ 169.9, 146.9, 146.0, 144.5, 137.3, 130.2, 128.2, 127.8, 127.7, 123.4, 76.0, 65.0, 52.8, 48.2, 47.4, 44.4, 44.0, 38.0, 36.6, 32.6, 26.1, 20.1, 19.5. HRMS: Calcd for $C_{27}H_{31}N_3O_6S$ (M^+): 525.1931. Found: 525.1953. Anal. Calcd for $C_{27}H_{31}N_3O_6S$: C, 61.70; H, 5.94; N, 7.99; S, 6.10. Found: C, 61.75; H, 5.91; N, 8.05; S, 6.21%.

(3a*S*,6*R*,7a*R*)-1,4,5,6,7,7a-Hexahydro-8,8-dimethyl-1-{(2*R*)-1-oxo-2-[(*Z*)-(phenylmethoxy)iminomethyl]pent-4-ynyl}-3*H*-3a,6-methano-2,1-benzisothiazole 2,2-dioxide [(*R*,*Z*)-5d]. Colorless crystals. Mp 101–103 °C (AcOEt–hexane); $[a]_D^{24}$ −89.4 (c 1.12, $CHCl_3$); IR ($CHCl_3$) 2964, 1697 cm^{-1}; ^{1}H NMR δ 7.70–7.25 (5H, m), 7.01 (1H, d, $J = 5.9$ Hz), 5.14 (2H, s), 4.67 (1H, br q, $J = 6.1$ Hz), 3.90–3.83 (1H, m), 3.49 (1H, d, $J = 13.7$ Hz), 3.42 (1H, d, $J = 13.7$ Hz), 2.84 (1H, ddd, $J = 17.0$, 5.6, 2.7 Hz), 2.74 (1H, ddd, $J = 17.0$, 6.4, 2.7 Hz), 2.18–1.80 (6H, m), 1.44–1.22 (2H, m), 1.17 (3H, s), 0.96 (3H, s); ^{13}C NMR ($CDCl_3$) δ 169.2, 146.1, 137.5, 128.2, 127.7, 127.6, 79.0, 76.0, 71.4, 65.0, 52.8, 48.4, 47.6, 44.4, 41.2, 38.0, 32.5, 26.3, 20.5, 20.4, 19.7. HRMS: Calcd for $C_{23}H_{28}N_2O_4S$ (M^+): 428.1768. Found: 428.1740. Anal. Calcd for $C_{23}H_{28}N_2O_4S$: C, 64.46; H, 6.59; N, 6.54; S, 7.48. Found: C, 64.62; H, 6.61; N, 6.58; S, 7.56%.

(3a*S*,6*R*,7a*R*)-1,4,5,6,7,7a-Hexahydro-8,8-dimethyl-1-{(2*R*)-1-oxo-2-[(*Z*)-(phenylmethoxy)iminomethyl]pent-4-enyl}-3*H*-3a,6-methano-2,1-benzisothiazole 2,2-dioxide [(*R*,*Z*)-5e]. Colorless crystals. Mp 105–108 °C (AcOEt–hexane); $[a]_D^{25}$ −98.9 (c 0.92, $CHCl_3$); IR ($CHCl_3$) 2964, 1692, 1455 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.42–7.20 (5H, m), 6.90 (1H, d, $J = 6.2$ Hz), 5.88 (1H, m), 5.14 (2H, s), 5.15–4.98 (1H, m), 4.68 (1H, dd, $J = 6.5$, 13 Hz), 3.83 (1H, t, $J = 6.2$ Hz), 3.50 (1H, d, $J = 13.7$ Hz), 3.40 (1H, d, $J = 13.8$ Hz), 2.73–2.46 (2H, m), 2.08–1.78 (6H, m), 1.47–1.20 (2H, m), 1.14, 0.96 (each 3H, s); ^{13}C NMR ($CDCl_3$) δ 170.5, 147.2, 133.4, 128.1, 127.7, 127.5, 118.0, 75.8, 65.0, 52.9, 48.2, 47.6, 44.5, 42.3, 38.2, 35.6, 32.7, 26.2, 20.6, 19.7. HRMS: Calcd for $C_{23}H_{30}N_2O_4S$ (M^+): 430.1924. Found: 430.1945. Anal. Calcd for $C_{23}H_{30}N_2O_4S$: C, 64.16; H, 7.02; N, 6.51; S, 7.45. Found: C, 63.94; H, 6.94; N, 6.45; S, 7.60%.

(3a*S*,6*R*,7a*R*)-1,4,5,6,7,7a-Hexahydro-8,8-dimethyl-1-{5-methyl-1-oxo-2-[(phenylmethoxy)iminomethyl]hex-4-enyl}-3*H*-3a,6-methano-2,1-benzisothiazole 2,2-dioxide [(*R*,*E*)-5f]. *R*,*Z* : *R*,*E* : *S*,*Z* = 9.8 : 1.3 : 1 as a colorless oil. $[a]_D^{29}$ −59.6 (c 1.44, $CHCl_3$); IR ($CHCl_3$) 2962, 1692, 1455 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.51 (1.3/12.1H, d, $J = 6.8$ Hz), 7.48–7.21 (5H, m), 6.85 (9.8/12.1H, d, $J = 6.3$ Hz), 6.69 (1/12.1H, d, $J = 6$ Hz), 5.12 (2 × 9.8/12.1H, s), 5.10 (2 × 1/12.1H, s), 5.08 (2 × 1.3/12.1H, s), 5.04–4.97 (1/12.1H, m), 4.64 (9.8/12.1H, br q, $J = 6.9$ Hz), 3.99 (1.3/12.1H, br q, $J = 6.9$ Hz), 3.94–3.77 (1H, m), 3.54–3.34 (2H, m), 2.73–2.34 (2H, m), 2.15–1.79 (6H, m), 1.63, 1.57 (each 3H, s), 1.43–1.24 (2H, m), 1.14, 0.95 (each 3H, br s). HRMS: Calcd for $C_{25}H_{34}N_2O_4S$ (M^+): 458.2238. Found: 458.2227.

(3a*S*,6*R*,7a*R*)-1,4,5,6,7,7a-Hexahydro-8,8-dimethyl-1-{3-(methoxycarbonyl)-1-oxo-2-[(phenylmethoxy)iminomethyl-]propyl}-3*H*-3a,6-methano-2,1-benzisothiazole 2,2-dioxide [(*R*,*Z*)-5g]. *R*,*Z* : *R*,*E* = 10 : 1 as a colorless oil. $[a]_D^{30}$ −47.1 (c 0.52, $CHCl_3$); IR ($CHCl_3$) 2959, 1737, 1692, 1455 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.56 (1/11H, d, $J = 7.5$ Hz), 7.40–7.25 (5H, m), 6.81 (10/11H, d, $J = 7.5$ Hz), 5.15 (2 × 10/11H, s), 5.00 (2 × 1/11H, s), 4.85–4.74 (1H, m), 3.95–3.85 (1H, m), 3.65 (3H, s), 3.52, 3.42 (each 1H, br d, $J = 15$ Hz), 2.96 (1H, br dd, $J = 7.5$, 15 Hz), 2.81(1H, br dd, $J = 6$, 15 Hz), 2.2–1.8 (5H, m), 1.64–1.2 (2H, m), 1.21, 0.98 (each 3H, s). HRMS: Calcd for $C_{23}H_{30}N_2O_6S$ (M^+): 462.1822. Found: 462.1825.

Ethyl radical addition to oxime ethers

General procedure for ethyl radical addition to 5 at 20 °C (Scheme 6, Table 3). To a solution of **5** (0.083 mmol) in toluene or CH_2Cl_2 (2 mL) were added $BF_3·OEt_2$ (0.052 mL, 0.417 mmol) and Et_3B (1.0 M in hexane, 0.417 mL, 0.417 mmol) at 20 °C. After being stirred at the same temperature for 15 min, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and then extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated at reduced pressure. Purification by preparative TLC (AcOEt–hexane 1 : 3) afforded the alkylated products **6**.

General Procedure for Ethyl Radical Addition to 5 or 4 at −78 °C (Table 3, Scheme 8). To a solution of **5** or **4** (0.208 mmol) in toluene or CH_2Cl_2 (8 mL) were added $BF_3·OEt_2$ (0.078 mL, 0.625 mmol) and Et_3B (1.0 M in hexane, 0.625 mL, 0.625 mmol) under a nitrogen atmosphere at −78 °C, and then air was passed into the solution. After being stirred at the same temperature for 3 min, $BF_3·OEt_2$ (0.078 mL, 0.625 mmol) and Et_3B (0.625 mL, 0.625 mmol) were added twice, and then air was passed into the solution. After being stirred at the same temperature for 3 min, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and then extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated at reduced pressure. Purification by preparative TLC (AcOEt–hexane 1 : 3) afforded the alkylated products **6** and **7** from **5** and **4**, respectively.

(3a*S*,6*R*,7a*R*)-1,4,5,6,7,7a-Hexahydro-8,8-dimethyl-1-{(2*R*,3*S*)-2-methyl-1-oxo-3-[(phenylmethoxy)amino]pentyl}-3*H*-3a,6-methano-2,1-benzisothiazole 2,2-dioxide (6aA). A colorless oil. $[a]_D^{28}$ −62.5 (c 0.69, $CHCl_3$); IR ($CHCl_3$) 3290, 2965, 1688, 1455 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.45–7.20 (5H, m), 6.15–5.72 (1H, br s), 4.68 (2H, s), 3.87 (1H, t, $J = 6.3$ Hz), 3.55–3.1 (3H, m), 2.95 (1H, dt, $J = 12.6$, 4.5 Hz), 2.09–1.63 (6H, m), 1.5–1.32 (3H, m), 1.28 (3H, d, $J = 7.1$ Hz), 1.15 (3H, s), 0.97 (3H, s), 0.94 (3H, t, $J = 7.4$ Hz); ^{13}C NMR ($CDCl_3$) δ 175.5, 138.1, 128.2, 127.5, 76.2, 64.9, 63.2, 53.0, 48.1, 47.6, 44.5, 42.3, 38.3, 32.7, 26.3, 23.2, 20.7, 19.7, 15.3, 10.8. HRMS: Calcd for $C_{23}H_{34}N_2O_4S$ (M^+): 434.2237. Found: 434.2220.

(3a*S*,6*R*,7a*R*)-1,4,5,6,7,7a-Hexahydro-8,8-dimethyl-1-{(2*R*,3*S*)-1-oxo-3-[(phenylmethoxy)amino]-2-(phenylmethyl)-pentyl}-3*H*-3a,6-methano-2,1-benzisothiazole 2,2-dioxide (6bA). Colorless crystals. Mp 136–137 °C (AcOEt–hexane); $[a]_D^{28}$ −6.8 (c 1.07, $CHCl_3$); IR ($CHCl_3$) 2965, 1679 cm^{-1}; ^{1}H NMR δ 7.40–7.20 (10H, m), 6.32 (1H, br m), 4.730 (1H, d, $J = 12.0$ Hz), 4.725 (1H, d, $J = 12.0$ Hz), 3.65 (2H, m), 3.29 (2H, br s), 3.11 (1H, dd, $J = 13.4$, 4.4 Hz), 3.09 (1H, m), 2.95 (1H, dd, $J = 13.4$, 10.7 Hz), 2.00–1.50 (7H, m), 1.29–1.16 (2H, m), 1.01 (3H, t, $J = 7.4$ Hz), 0.81 (3H, s), 0.43 (3H, s); ^{13}C NMR ($CDCl_3$) δ 174.0, 138.3, 138.0, 129.5, 128.2, 128.1, 127.5, 126.3, 76.5, 65.0, 62.8, 52.9, 48.3, 47.6, 47.3, 44.5, 38.3, 35.2, 32.7, 26.2, 23.1, 20.2, 19.6, 11.0. HRMS: Calcd for $C_{29}H_{38}N_2O_4S$ (M^+): 510.2550. Found: 510.2522. Anal. Calcd for $C_{29}H_{38}N_2O_4S$: C, 68.21; H, 7.50; N, 5.49; S, 6.28. Found: C, 67.99; H, 7.48; N, 5.35; S, 6.50. data of **6bA**:§ $C_{29}H_{38}N_2O_4S$, space group monoclinic, $P2_1$ with a = 12.240 (15), b = 20.564 (14), c = 10.904 (16) Å, V = 2737.1 (6) Å^3, final R value 0.0416 for 6927 reflections.

(3a*S*,6*R*,7a*R*)-1,4,5,6,7,7a-Hexahydro-8,8-dimethyl-1-{(2*R*,3*S*)-2-[(4-nitrophenyl)methyl]-1-oxo-3-[(phenylmethoxy)-amino]pentyl}-3*H*-3a,6-methano-2,1-benzisothiazole 2,2-dioxide (6cA). A colorless oil. $[a]_D^{28}$ −3.3 (c 1.02, $CHCl_3$); IR ($CHCl_3$) 2966, 1680 cm^{-1}; ^{1}H NMR δ 8.06 (2H, br d, $J = 8.8$ Hz), 7.40–

§ CCDC reference number 135459. See http://www.rsc.org/suppdata/ob/b2/b208823a/ for crystallographic files in .cif or other electronic format.

7.22 (7H, m), 6.22 (1H, br m), 4.72 (2H, br s), 3.80–3.62 (2H, m), 3.31 (2H, s), 3.23 (1H, dd, J = 13.4, 4.6 Hz), 3.14–2.98 (2H, m), 2.14–1.40 (7H, m), 1.32–1.10 (2H, m), 1.01 (3H, t, J = 7.4 Hz), 0.80 (3H, s), 0.32 (3H, s); ^{13}C NMR (CDCl$_3$) δ 173.2, 146.7, 146.4, 137.8, 130.5, 128.2, 127.6, 123.3, 76.5, 65.2, 63.0, 52.9, 48.1, 47.7, 47.2, 44.3, 38.3, 35.5, 32.7, 26.1, 23.1, 19.7, 19.4, 11.0. HRMS: Calcd for $C_{29}H_{37}N_3O_6S$ (M$^+$): 555.2401. Found: 555.2402.

(3a*S*,6*R*,7a*R*)-1,4,5,6,7,7a-Hexahydro-8,8-dimethyl-1-{(2*R*)-1-oxo-2-[(1*S*)-1-(phenylmethoxy)aminopropyl]pent-4-ynyl}-3*H*-3a,6-methano-2,1-benzisothiazole 2,2-dioxide (6dA). Colorless crystals. Mp 101–102 °C (AcOEt–hexane); $[a]^{23}_{D}$ −149.5 (c 0.24, CHCl$_3$); IR (CHCl$_3$) 2965, 1694 cm^{-1}; ^{1}H NMR δ 7.40–7.20 (5H, m), 5.95 (1H, br m), 4.67 (2H, s), 3.90 (1H, dd, J = 7.6, 5.1 Hz), 3.49 (1H, d, J = 13.7 Hz), 3.45 (1H, d, J = 13.7 Hz), 3.50–3.40 (1H, m), 3.15 (1H, td, J = 8.5, 4.4 Hz), 2.80 (1H, ddd, J = 17.3, 7.2, 2.7 Hz), 2.69 (1H, ddd, J = 17.3, 4.4, 2.7 Hz), 2.20–1.32 (10H, m), 1.19 (3H, s), 0.97 (3H, s), 0.96 (3H, t, J = 7.4 Hz); ^{13}C NMR (CDCl$_3$) δ 172.5, 137.9, 128.2, 127.6, 80.4, 77.1, 76.4, 70.9, 65.2, 61.0, 53.1, 48.2, 47.7, 45.9, 44.5, 38.3, 32.7, 26.4, 23.0, 20.7, 19.8, 19.0, 10.8. HRMS: Calcd for $C_{25}H_{34}N_2O_4S$ (M$^+$): 458.2237. Found: 458.2209. Anal. Calcd for $C_{25}H_{34}N_2O_4S$: C, 65.47; H, 7.47; N, 6.11; S, 6.99. Found: C, 65.18; H, 7.43; N, 6.00; S, 7.08%.

(3a*S*,6*R*,7a*R*)-1,4,5,6,7,7a-Hexahydro-8,8-dimethyl-1-{1-oxo-3-[(phenylmethoxy)amino]pentyl}-3*H*-3a,6-methano-2,1-benzisothiazole 2,2-dioxide (7). 9 : 10 mixture of diastereomers as a colorless oil. $[a]^{31}_{D}$ −63.1 (c 3.39, CHCl$_3$); IR (CHCl$_3$) 2964, 1693 cm^{-1}; ^{1}H NMR δ 7.40–7.20 (5H, m), 5.83 (1H, br m), 4.68 (18/19H, s), 4.66 (20/19H, s), 3.89–3.78 (1H, m), 3.53–3.30 (3H, m), 3.05–2.70 (2H, m), 2.18–1.25 (9H, m), 1.13 (27/19H, s), 1.11 (30/19H, s), 0.950 (27/19H, s), 0.945 (30/19H, s), 0.933 (30/19H, t, J = 6.4 Hz), 0.930 (27/19H, t, J = 6.4 Hz); ^{13}C NMR (CDCl$_3$) δ 170.72, 170.67, 137.90, 137.86, 128.24, 128.18, 128.1, 127.5, 76.20, 76.15, 65.0, 58.7, 58.6, 52.84, 52.77, 48.2, 47.5, 44.5, 38.3, 38.2, 37.61, 37.56, 32.7, 26.3, 24.8, 24.7, 20.7, 20.6, 19.7, 10.3, 10.2. HRMS: Calcd for $C_{22}H_{32}N_2O_4S$ (M$^+$): 420.2081. Found: 420.2107.

(3*Z*)-3-[(Phenylmethoxy)imino]-2-(phenylmethyl)propanoic acid ethyl ester (8)

According to the general procedure for the alkylation of **4**, compound **8** was prepared as a colorless oil. IR (CHCl$_3$) 3024, 1729, 1455 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.42–7.11 (10H, m), 6.84 (1H, d, J = 6.8 Hz), 5.09 (2H, s), 4.2 (1H, q, J = 7.1 Hz), 4.08 (2H, q, J = 7.1 Hz), 3.14 (1H, dd, J = 7.3, 14.1 Hz), 3.02 (1H, dd, J = 7.3, 13.8 Hz), 1.15 (3H, t, J = 7.1 Hz); ^{13}C NMR (CDCl$_3$) δ 171.1, 147.7, 137.5, 137.5, 128.9, 128.33, 128.26, 127.8, 127.7, 126.7, 76.0, 60.9, 44.0, 36.0, 13.9. HRMS: Calcd for $C_{19}H_{21}NO_3$ (M$^+$): 311.1520. Found: 311.1530.

3-[(Phenylmethoxy)amino]-2-(phenylmethyl)pentanoic acid ethyl ester (9)

To a solution of **8** (109 mg, 0.351 mmol) in toluene (8 mL) were added BF_3·OEt_2 (0.130 mL, 1.05 mmol) and Et_3B (1.0 M in hexane, 1.05 mL, 1.05 mmol) at 20 °C. After being stirred at the same temperature for 15 min, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and then extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated at reduced pressure. Purification by preparative TLC (CHCl$_3$) afforded the alkylated products **9** (64.5 mg, 54%) as a colorless oil. For the major isomer of **9**: IR (CHCl$_3$) 2966, 1724, 1454 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.39–7.13 (10H, m), 5.8 (1H, br s, NH), 4.70, 4.64 (each 1H, d, J = 11.6 Hz), 4.01 (2H, q, J = 7.2 Hz), 3.18–3.02 (1H, m), 3.02–2.82 (3H, m), 1.64–1.24 (2H, m), 1.09 (3H, t, J = 7.2 Hz), 0.94 (3H, t, J = 7.3 Hz); ^{13}C NMR (CDCl$_3$) δ 173.9, 139.6, 137.8, 128.8, 128.3, 128.2, 127.6, 126.0, 76.0, 63.5, 60.0, 48.7, 34.5, 21.8, 13.9, 11.0. HRMS: Calcd for $C_{21}H_{27}NO_3$ (M$^+$): 341.1990. Found: 341.2001.

Synthesis of β-amino acid 11

(3a*S*,6*R*,7a*R*)-1,4,5,6,7,7a-Hexahydro-8,8-dimethyl-1-{(2*R*,3*S*)-1-oxo-3-[(phenylmethoxy)carbonylamino]-2-(phenylmethyl)pentyl]-3*H*-3a,6-methano-2,1-benzisothiazole 2,2-dioxide (10). A suspension of 20% $Pd(OH)_2$–C (2.13 mg) in MeOH (2 mL) was stirred under a hydrogen atmosphere (1 atm) at 20 °C for 40 min. To this suspension was added a solution of **6bA** (50.0 mg, 0.10 mmol) in MeOH (2 mL). After being stirred under a hydrogen atmosphere at the same temperature for 1 h, the reaction mixture was filtered and the filtrate was concentrated at reduced pressure to afford the crude amine. To a solution of the resulting crude amine in acetone (4 mL) was added a solution of Na_2CO_3 (20.8 mg, 0.20 mmol) in H_2O (0.3 mL) under a nitrogen atmosphere at 20 °C. After benzyloxycarbonyl chloride (33.4 mg, 0.20 mmol) in acetone (0.5 mL) was added to the reaction mixture at 20 °C, the reaction mixture was stirred at the same temperature for 1 h. After the reaction mixture was concentrated at reduced pressure, the resulting residue was diluted with CH_2Cl_2 and water, and then extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated at reduced pressure. Purification by preparative TLC (hexane–AcOEt 3 : 1) afforded **10** (50.9 mg, 96%) as colorless crystals. Mp 158–160 °C (AcOEt–hexane); $[a]^{21}_{D}$ −18.8 (c 0.98, CHCl$_3$); IR (CHCl$_3$) 3434, 3032, 2965, 1719, 1512, 1456 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 7.45–7.10 (10H, m, Ar), 5.16 (1H, d, J = 12.3 Hz), 5.05 (1H, d, J = 12.1 Hz), 4.80–4.64, 4.20–3.92 (each 1H, m), 3.60–3.44 (1H, m), 3.32 (2H, s), 3.04–2.88 (2H, m), 2.20–1.48 (8H, m), 1.32–1.20 (2H, m), 0.95 (3H, t, J = 7.3 Hz), 0.82, 0.48 (each 3H, s); ^{13}C NMR (CDCl$_3$) δ 172.4, 156.3, 137.6, 129.4, 128.2, 127.9, 126.4, 77.1, 66.6, 65.1, 54.4, 52.9, 50.9, 47.7, 47.3, 44.5, 38.3, 36.1, 32.6, 26.4, 26.2, 20.3, 19.6, 10.8. HRMS: Calcd for $C_{30}H_{38}N_2O_5S$ (M$^+$): 538.2500. Found: 538.2517.

(α*R*)-α-{(1*S*)-1-[(Phenylmethoxy)carbonylamino]propyl}-benzenepropanoic acid (11). A solution of **10** (33.5 mg, 0.07 mmol) in 1 M LiOH–THF (1 : 1, 4 mL) was stirred at reflux for 3 h. After the reaction mixture was concentrated at reduced pressure, the resulting residue was acidified with dilute HCl, and then extracted with CH_2Cl_2. The organic phase was dried over Na_2SO_4 and concentrated at reduced pressure. Purification by preparative TLC (hexane–AcOEt 3 : 1) afforded **11** (71 mg, 73%) as a white powder. $[a]^{25}_{D}$ −23.7 (c 1.18, CHCl$_3$); IR (CHCl$_3$) 2969, 1716 cm^{-1}; ^{1}H NMR δ 7.45–7.13 (10H, m), 5.12 (1H, d, J = 12.4 Hz), 5.06 (1H, d, J = 12.4 Hz), 4.94 (1H, br d, J = 10.0 Hz), 3.87 (1H, m), 3.10–2.75 (4H, m), 1.68 (1H, m), 1.42 (1H, m), 0.95 (3H, t, J = 7.1 Hz); ^{13}C NMR (CDCl$_3$) δ 177.3, 156.2, 138.6, 136.3, 128.6, 128.4, 128.1, 128.0, 126.4, 77.1, 66.8, 54.0, 51.6, 34.4, 24.9, 10.6. HRMS: Calcd for $C_{20}H_{23}NO_4$ (M$^+$): 341.1626. Found: 341.1630.

Isopropyl radical addition to oxime ether 2

Reaction in the presence of Bu_3SnH. To a solution of **2** (80.0 mg, 0.362 mmol) in CH_2Cl_2 (4 mL) were added isopropyl iodide (0.720 mL, 7.24 mmol), Bu_3SnH (0.097 mL, 0.362 mmol), and Et_3B (1.0 M in hexane, 0.850 mL, 0.905 mmol) at 20 °C. After being stirred at the same temperature for 1 min, BF_3·OEt_2 (0.090 mL, 0.724 mmol) was added at 20 °C. After being stirred at the same temperature for 15 min, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and then extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated at reduced pressure. Purification by preparative TLC (AcOEt–hexane 1 : 15, 2-fold development) afforded **12** (41.6 mg, 43%) as a colorless oil.

Reaction in the absence of Bu_3SnH. To a solution of **2** (80.0 mg, 0.362 mmol) in CH_2Cl_2 (4 mL) were added isopropyl iodide

(0.720 mL, 7.24 mmol), BF_3·OEt_2 (0.090 mL, 0.724 mmol), and Et_3B (1.0 M in hexane, 0.850 mL, 0.905 mmol) at 50 °C. After being stirred at the same temperature for 5 min, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and then extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated at reduced pressure. Purification by preparative TLC (AcOEt–hexane 1 : 15, 2-fold development) afforded **12** (68.6 mg, 71%) as a colorless oil.

4-Methyl-3-[(phenylmethoxy)amino]pentanoic acid ethyl ester (12). IR ($CHCl_3$) 3250, 2964, 1725, 1454 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.23–7.41 (5H, m), 6.2–5.5 (1H, m), 4.67 (2H, s), 4.11 (2H, q, J = 7 Hz), 3.15 (1H, m), 2.42 (2H, m), 1.92 (1H, m), 1.23 (3H, t, J = 7 Hz), 0.94, 0.90 (each 3H, d, J = 7 Hz); ^{13}C NMR ($CDCl_3$) δ 172.9, 137.9, 128.3, 128.2, 127.6, 76.1, 62.6, 60.2, 33.9, 28.9, 19.1, 18.1, 14.0. HRMS: Calcd for $C_{15}H_{23}N_1O_3$ (M^+): 265.1627. Found: 265.1652.

General procedure for alkyl radical addition to (*R*,*Z*)-5b,c (Table 4)

To a solution of (*R*,*Z*)-**5b**,**c** (2.08 mmol) in toluene (15 mL) were added alkyl iodide (62.5 mmol), BF_3·OEt_2 (6.25 mmol), and Et_3B (1.0 M in hexane, 6.25 mmol) at 20 °C. After being stirred at the same temperature for 3 min, BF_3·OEt_2 (6.25 mmol) and Et_3B (6.25 mmol) were added twice. After being stirred at the same temperature for 3 min, the reaction mixture was diluted with saturated aqueous $NaHCO_3$ and then extracted with CH_2Cl_2. The organic phase was dried over $MgSO_4$ and concentrated at reduced pressure. Purification by preparative TLC (AcOEt–hexane 1 : 4) afforded the alkylated products **6bB**–**6bF**,**6cB**.

(3a*S*,6*R*,7a*R*)-1,4,5,6,7,7a-Hexahydro-8,8-dimethyl-1-{(2*R*,3*S*)-4-methyl-1-oxo-3-[(phenylmethoxy)amino]-2-(phenylmethyl)pentyl}-3*H*-3a,6-methano-2,1-benzisothiazole 2,2-dioxide (6bB). A colorless oil. $[\alpha]_D^{27}$ +1.7 (*c* 1.16, $CHCl_3$); IR ($CHCl_3$) 2964, 1679 cm^{-1}; ^1H NMR δ 7.39–7.09 (10H, m), 6.55 (1H, br m), 4.76 (1H, d, J = 11.5 Hz), 4.72 (1H, d, J = 11.5 Hz), 3.76–3.67 (2H, m), 3.30 (1H, d, J = 13.5 Hz), 3.28 (1H, d, J = 13.5 Hz), 3.12–3.05 (3H, m), 2.18–2.11 (1H, m), 1.88 (1H, dd, J = 13.5, 7.5 Hz), 1.83–1.73 (1H, m), 1.67–1.55 (3H, m), 1.30–1.20 (2H, m), 1.28 (6H, t, J = 5.5 Hz), 0.81 (3H, s), 0.38 (3H, s); ^{13}C NMR ($CDCl_3$) δ 174.0, 138.8, 138.1, 129.5, 128.3, 128.2, 128.1, 127.5, 126.3, 75.7, 65.5, 65.2, 53.0, 47.8, 47.7, 47.4, 44.5, 38.3, 34.6, 32.8, 29.2, 26.4, 20.5, 20.3, 20.2, 19.7. HRMS: Calcd for $C_{30}H_{40}N_2O_4S$ (M^+): 524.2706. Found: 524.2721.

(3a*S*,6*R*,7a*R*)-1-{(2*R*,3*S*)-3-Cyclohexyl-1-oxo-3-[(phenylmethoxy)amino]-2-(phenylmethyl)propyl}-1,4,5,6,7,7a-hexahydro-8,8-dimethyl-3*H*-3a,6-methano-2,1-benzisothiazole 2,2-dioxide (6bC). A colorless oil. $[\alpha]_D^{28}$ −10.1 (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 2930, 1679 cm^{-1}; ^1H NMR δ 7.38–7.09 (10H, m), 6.55 (1H, br m), 4.75 (1H, d, J = 11.5 Hz), 4.70 (1H, d, J = 11.5 Hz), 3.77–3.66 (2H, m), 3.30 (1H, d, J = 13.5 Hz), 3.27 (1H, d, J = 13.5 Hz), 3.14 (1H, dd, J = 3.5, 7.5 Hz), 3.06 (2H, d, J = 8.0 Hz), 2.11–2.04 (1H, m), 1.92–1.56 (10H, m), 1.32–1.10 (7H, m), 0.81 (3H, s), 0.39 (3H, s); ^{13}C NMR ($CDCl_3$) δ 174.1, 138.8, 138.1, 129.4, 128.3, 128.2, 127.5, 126.3, 75.7, 65.2, 64.8, 53.0, 47.8, 47.4, 47.3, 44.5, 38.9, 38.3, 34.6, 32.8, 30.53, 30.46, 26.7, 26.51, 26.48, 26.38, 20.2, 19.7. HRMS: Calcd for $C_{33}H_{44}N_2O_4S$ (M^+): 564.3020. Found: 564.3002.

(3a*S*,6*R*,7a*R*)-1-{(2*R*,3*S*)-3-Cyclopentyl-1-oxo-3-[(phenylmethoxy)amino]-2-(phenylmethyl)propyl}-1,4,5,6,7,7a-hexahydro-8,8-dimethyl-3*H*-3a,6-methano-2,1-benzisothiazole 2,2-dioxide (6bD). A colorless oil. $[\alpha]_D^{28}$ −12.2 (*c* 1.36, $CHCl_3$); IR ($CHCl_3$) 2960, 1679 cm^{-1}; ^1H NMR δ 7.39–7.10 (10H, m), 6.70 (1H, br m), 4.77 (1H, d, J = 11.5 Hz), 4.72 (1H, d, J = 11.5 Hz), 3.73–3.66 (2H, m), 3.30 (1H, d, J = 13.5 Hz), 3.27 (1H, d, J = 13.5 Hz), 3.18 (1H, dd, J = 2.5, 9.5 Hz), 3.15–3.07 (2H, m), 2.36–2.26 (1H, m), 2.05–1.97 (1H, m), 1.92–1.84 (2H, m), 1.82–1.20 (12H, m), 0.81 (3H, s), 0.37 (3H, s); ^{13}C NMR ($CDCl_3$) δ 173.8, 138.9, 138.2, 129.5, 128.3, 128.2, 128.1, 127.5, 126.3, 75.9, 65.2, 64.8, 53.1, 49.3, 47.9, 47.4, 44.5, 41.8, 38.3, 34.2, 32.8, 31.4, 30.1, 26.4, 25.2, 25.0, 20.2, 19.7. HRMS: Calcd for $C_{32}H_{42}N_2O_4S$ (M^+): 550.2863. Found: 550.2885.

(3a*S*,6*R*,7a*R*)-1,4,5,6,7,7a-Hexahydro-8,8-dimethyl-1-{(2*R*,3*S*)-4-methyl-1-oxo-3-[(phenylmethoxy)amino]-2-(phenylmethyl)hexyl}-3*H*-3a,6-methano-2,1-benzisothiazole 2,2-dioxide (6bE). 1 : 1 mixture of diastereomers, with regard the *sec*-butyl group, as a colorless oil. $[\alpha]_D^{26}$ −4.1 (*c* 1.04, $CHCl_3$); IR ($CHCl_3$) 2964, 1681 cm^{-1}; ^1H NMR δ 7.38–7.09 (10H, m), 6.45 (1H, br m), 4.73 (1/2H, d, J = 11.5 Hz), 4.716 (1/2H, d, J = 11.5 Hz), 4.715 (1/2H, d, J = 11.0 Hz), 4.712 (1/2H, d, J = 11.0 Hz), 3.75–3.64 (2H, m), 3.33–3.28 (2H, m), 3.26 (1/2H, t, J = 5.5 Hz), 3.20 (1/2H, dd, J = 8.0, 3.5 Hz), 3.13 (1/2H, dd, J = 8.0, 3.5 Hz), 3.09–2.99 (3/2H, m), 1.96–1.56 (7H, m), 1.35–1.20 (3H, m), 1.10 (3/2H, d, J = 7.0 Hz), 1.05 (3/2H, d, J = 6.5 Hz), 0.95 (3H, br t, J = 7.5 Hz), 0.81 (3H, br s), 0.40 (3/2H, s), 0.38 (3/2H, s); ^{13}C NMR ($CDCl_3$) δ 174.1, 138.9, 138.6, 138.15, 138.13, 129.5, 129.4, 128.3, 128.19, 128.16, 128.11, 127.52, 127.48, 126.4, 126.3, 75.8, 75.7, 65.3, 65.2, 64,2, 64.0, 53.06, 53.04, 48.1, 47.84, 47.81, 47.76, 47.6, 47.4, 44.51, 44.48, 38.29, 38.28, 36.4, 35.7, 35.3, 34.6, 32.8, 27.1, 26.4, 26.0, 20.2, 19.7, 16.2, 15.8, 12.1, 11.4. HRMS: Calcd for $C_{31}H_{42}N_2O_4S$ (M^+): 538.2863. Found: 538.2861

(3a*S*,6*R*,7a*R*)-1,4,5,6,7,7a-Hexahydro-8,8-dimethyl-1-{(2*R*,3*S*)-4,4-dimethyl-1-oxo-3-[(phenylmethoxy)amino]-2-(phenylmethyl)pentyl}-3*H*-3a,6-methano-2,1-benzisothiazole 2,2-dioxide (6bF). A colorless oil. $[\alpha]_D^{29}$ −17.3 (*c* 1.20, $CHCl_3$); IR ($CHCl_3$) 2960, 1682 cm^{-1}; ^1H NMR δ 7.38–7.09 (10H, m), 6.21 (1H, br m), 4.71 (2H, s), 3.64 (1H, br m), 3.32–3.23 (3H, m), 3.12 (1H, dd, J = 13.5, 5.0 Hz), 2.97 (1H, dd, J = 13.5, 10.5 Hz), 1.91–1.46 (7H, m), 1.33–1.18 (3H, m), 0.95 (3H, d, J = 6.0 Hz), 0.89 (3H, d, J = 6.5 Hz), 0.81 (3H, s), 0.92–0.77 (1H, m), 0.44 (3H, br s); ^{13}C NMR ($CDCl_3$) δ 174.0, 138.4, 138.2, 129.6, 128.3, 128.24, 128.18, 127.6, 126.4, 76.5, 65.2, 59.3, 53.0, 49.4, 47.7, 47.4, 44.6, 39.7, 38.4, 35.8, 32.8, 26.4, 24.9, 23.3, 22.3, 20.4, 19.8. HRMS: Calcd for $C_{31}H_{42}N_2O_4S$ (M^+): 538.2863. Found: 538.2855.

(3a*S*,6*R*,7a*R*)-1,4,5,6,7,7a-Hexahydro-8,8-dimethyl-1-{(2*R*,3*S*)-4-methyl-2-[(4-nitrophenyl)methyl]-1-oxo-3-[(phenylmethoxy)amino]pentyl}-3*H*-3a,6-methano-2,1-benzisothiazole 2,2-dioxide (6cB). A yellow oil. $[\alpha]_D^{27}$ +10.5 (*c* 0.57, $CHCl_3$); IR ($CHCl_3$) 2964, 1681 cm^{-1}; ^1H NMR δ 8.06 (2H, d, J = 8.5 Hz), 7.42–7.20 (7H, m), 6.36 (1H, br m), 4.73 (2H, s), 3.80–3.68 (2H, m), 3.31 (3H, s), 3.30–3.07 (3H, m), 2.20–2.15 (1H, m), 1.97–0.68 (6H, m), 1.12 (3H, d, J = 6.6 Hz), 1.11 (3H, d, J = 6.9 Hz), 0.80 (3H, s), 0.33 (3H, br s); ^{13}C NMR ($CDCl_3$) δ 173.2, 146.9, 146.7, 137.9, 130.3, 128.2, 128.0, 127.5, 123.3, 75.7, 65.4, 65.2, 52.9, 47.9, 47.3, 44.3, 38.2, 34.7, 32.6, 28.8, 26.2, 20.4, 19.9, 19.6, 19.5. HRMS: Calcd for $C_{30}H_{39}N_3O_6S$ (M^+): 569.2557. Found: 569.2580.

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