Organic & Biomolecular Chemistry

Diastereoselective synthesis of (Z)-fluoroalkene dipeptide isosteres utilizing chiral auxiliaries

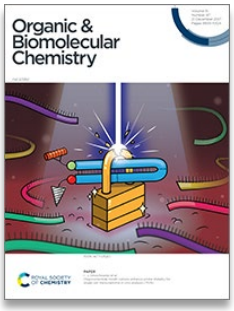
Journal:	*Organic & Biomolecular Chemistry*
Manuscript ID	OB-COM-02-2025-000189
Article Type:	Communication
Date Submitted by the Author:	30-Dec-2024

Complete List of Authors:	Kobayakawa, Takuya; Institute of Science Tokyo Institute of Integrated Research Laboratory for Biomaterials and Bioengineering, Department of Medicinal Chemistry Arioka, Marisa; Institute of Science Tokyo Institute of Integrated Research Laboratory for Biomaterials and Bioengineering, Department of Medicinal Chemistry Yamamoto, Kenichi; Institute of Science Tokyo Institute of Integrated Research Laboratory for Biomaterials and Bioengineering, Department of Medicinal Chemistry Tsuji, Kohei; Institute of Science Tokyo Institute of Integrated Research Laboratory for Biomaterials and Bioengineering, Department of Medicinal Chemistry Tamamura, Hirokazu; Institute of Science Tokyo Institute of Integrated Research Laboratory for Biomaterials and Bioengineering, Department of Medicinal Chemistry

Organic & Biomolecular Chemistry

Guidelines for Reviewers

Thank you very much for agreeing to review this manuscript for *Organic & Biomolecular Chemistry* (*OBC*).



OBC publishes original and high impact research and reviews in organic chemistry. We welcome research that shows new or significantly improved protocols or methodologies in total synthesis, synthetic methodology or physical and theoretical organic chemistry as well as research that shows a significant advance in the organic chemistry or molecular design aspects of chemical biology, catalysis, supramolecular and macromolecular chemistry, theoretical chemistry, mechanism-oriented physical organic chemistry, medicinal chemistry or natural products.

OBC's Impact Factor is **2.9** (2023 Journal Citation Reports®)

The following manuscript has been submitted for consideration as a

COMMUNICATION

OBC is one of the fastest organic chemistry journals in the field, with an average receipt to first decision time of just 14.1 days for Communications.* We would appreciate you assisting us in providing this service by submitting your review by the deadline in the invitation message.

OBC Communications should report **urgent new work** that makes a **highly-significant impact** in the field. Research findings should be presented in a succinct and informative way, emphasising the importance and potential impact of the research. Specific guidance on this is on the next page. In your report, **please comment on the novelty and likely impact of the work**.

We ask reviewers to examine manuscripts very carefully, and recommend rejection of articles that do not meet our high novelty, quality and impact expectations. When making your recommendation please take into account:

- That articles should be scientifically sound with the conclusions supported by the experimental data in line with our **characterisation guidelines** found here: **rsc.li/2KKSE0H**
- That **routine or incremental work**, however competently researched and reported, should not be recommended for publication if it does not meet our expectations of novelty and impact.
- If you feel that this work is **significant but not urgent** enough for publication as a Communication, please comment on whether it would be **suitable as an *OBC* full paper** (either in its current form or with additional work).

Best regards,

Professor Anthony Davis
Editorial Board Chair
University of Bristol

Dr Katie Lim
Executive Editor
Royal Society of Chemistry

Contact us

Please visit our reviewer hub for further details of our processes, policies and reviewer responsibilities as well as guidance on how to review, or click the links below.

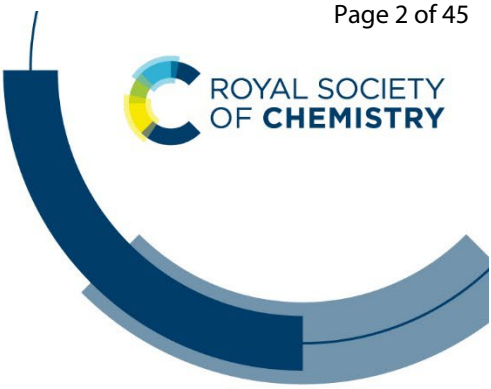
What to do when you review

Reviewer responsibilities

Process & policies

** Based on the average time from receipt to first decision for Communications submitted in 2023.*

Organic & Biomolecular Chemistry



Scope and standards

Details about some key areas of our scope are below. In all cases authors should include in their article clear rationale for why their research has been carried out.

Organic synthesis: We welcome important research in all areas of organic synthesis, including studies on small organic molecules and biomolecules, and studies that report purely synthetic work without biological data. Total or multistep syntheses should report new or improved strategies or methods, or a more efficient route to the target compound. Methodology studies should show a significant improvement on known methods. Research that extends known methodology to a different class of compounds is generally not suitable, unless that class is significantly different in scope to previously reported methodology.

Physical and theoretical organic chemistry: We welcome studies that report new models of reactivity, selectivity, bonding or structure, or new computational methods and have relevance for the design of subsequent experiments. That relevance should be clearly justified in the paper. Relevance is perhaps most clearly demonstrated by the description of testable predictions derived from the results of the reported theoretical work; the tests of these predictions could be contained in the same paper in which the predictions are described. Computational research that merely reproduces experimental data is not suitable for *OBC.*

Chemical biology: We welcome articles that report new or improved methodologies in the chemical aspects of chemical biology, including design, development and use of chemical tools, chemical studies of biomolecules such as carbohydrates, proteins and nucleic acids or biological processes such as protein-protein interactions and epigenetics, and chemical methods such as imaging and labelling techniques.

Catalysis: We welcome studies on catalysis, including metal catalysis, organocatalysis and biocatalysis, which present a significant organic chemistry advance. The application of a new catalyst to a known reaction must present a significant methodological advance. However, studies showcasing routine modification in the catalyst structure for a known reaction or the preparation of a compound library by a known catalytic reaction followed by routine photophysical or biological studies are typically not suitable. Theoretical studies that provide significant new mechanistic insights into synthetic or biological catalysts are welcome. Routine biochemistry studies of catalytic mechanisms, for instance routine studies using tools such as site-directed mutagenesis, are not typically suitable.

Supramolecular, macromolecular and organic materials: We welcome studies that report important new work in the molecular design of supramolecular or macromolecular compounds or organic materials either with a strong component in organic synthesis or with novel organic structural features. You may wish to consider our materials journals for articles outside this scope.

Sensors: We publish articles describing sensors for ions and/or molecules provided that: (a) they address targets and situations of practical relevance; and (b) they represent significant and demonstrable improvements on previous methodology. In particular, sensors for species in artificial surroundings (for example, hydrophilic ions in organic solvents) will not typically be acceptable for publication.

Medicinal chemistry: We welcome studies that report significant synthetic or bioorganic research that is directed towards medicinal chemistry applications. Studies that show routine syntheses accompanied by biological testing are generally not suitable for *OBC*. Our companion journal, *RSC Medicinal Chemistry*, is more suitable for articles that report significant research in core medicinal chemistry disciplines.

Natural products: We welcome articles that report new and interesting syntheses of natural products (see Organic Synthesis guidelines above) or chemical studies of biosynthetic pathways. Isolation or identification studies are welcome when the compound being reported:
1) Has a novel structural class with unreported carbon skeleton, unusual functional groups or unusual modifications and/or
2) Displays a potent or unexpected biological activity or an unexpected mechanism of action. Routine isolation studies are not suitable for *OBC*.

Hirokazu Tamamura, Ph. D.
Phone: +81-3-5280-8036
Fax: +81-3-5280-8039
e-mail: tamamura.mr@tmd.ac.jp

Institute of SCIENCE TOKYO

Dept. Medicinal Chemistry
Lab. Biomaterials and Bioengineering
Inst. Int. Res.
Inst. Science Tokyo
Chiyoda-ku, Tokyo 101-0062, JAPAN

Feb 2/2025

Organic & Biomolecular Chemistry Editorial Office

Ms: transferred from ChemComm - CC-COM-12-2024-006767
Title: "Diastereoselective synthesis of (Z)-fluoroalkene dipeptide isosteres utilizing chiral auxiliaries"
Author(s): Takuya Kobayakawa, Marisa Arioka, Kenichi Yamamoto, Kohei Tsuji and Hirokazu Tamamura

---

Dear Editor,

We are very grateful for your e-mailed letter dated on Jan 28, 2025, which contains to the transfer of our manuscript to Organic & Biomolecular Chemistry from ChemComm (CC-COM-12-2024-006767).
We have made all necessary changes and corrections to comments provided by the reviewers as follows.
We believe that our manuscript is improved and became suitable to the quality for publication in ***Organic & Biomolecular Chemistry***.

Correspondences to Reviewer #1:
Thank you for the reviewer's positive comments.
 # In Abstract: In dipeptide isostere, no N-terminal and C-terminal residues are present.

> We do agree with Reviewer #1's comment. Thank you for pointing this out. The following additions and corrections have been made.
"…Ellman's imine for corresponding to the *N*-terminal amino acid residues and Oppolzer's sultam for corresponding to the *C*-terminal amino acid residues, …"

 # Why is Zn enolate effective but Li-enolate is not in the reaction of Ellman's imine with difluroacetate anions? This depends on the thermal stability of the anions?

> Thank you for pointing this out. Zn-enolate is effective but Li-enolate is not in the reaction of Ellman's imine with difluroacetate anions. Li-enolate did not produce the target compound and might cause beta-lactam formation.

Correspondences to Reviewer #2:
Thank you for the reviewer's comments.
1. Fig. 1c: The general structure includes "Xaa" without any discussion of amino acid substitution on the substrate. Replace "Xaa" with "R" or add a substrate bearing an amino acid to justify its inclusion.

> Thank you for pointing this out. "Xaa" at Fig. 1c has been replaced with a specific amino acid substrate.

2. Configuration in Table 1: In the paragraph below Table 1, replace "(L,L)-configuration" with "(L,D)-

configuration" and vice versa. Alternatively, since the authors use R/S notation elsewhere in the manuscript, they should consider using R/S consistently.

> We do agree with Reviewer #2's comment. Thank you very much. The "(L,L)-configuration" was replaced with "(*S*,*R*)-configuration" and "(L,D)-configuration" was replaced by "(*S*,*S*)-configuration". Fixed.

3. Scheme 1: Consider deleting Scheme 1, as Ellman's imine synthesis is well-known and does not require further elaboration.

> Thank you very much for pointing this out. We do agree with Reviewer #2's opinion "Ellman's imine synthesis is very famous," but in the synthesis of FADI, Ellman's imine is a key compound. So, we would like to keep Scheme 1.

4. Paragraph 2, Line 4: Change "this approach" to "these approaches"

> Thank you very much for pointing this out. We changed "this approach" to "these approaches".

5. *Page 2, Line 4: Remove "an enolate 4"*

> Thank you very much for pointing this out. The "to generate an enolate 4" has been removed.

6. Above Scheme 4: Change "caused" to "resulted in"

> Thank you very much for pointing this out. The "caused" has been rewritten to "resulted in".

7. Yields: Replace "sufficient yield" with "satisfactory yield"

> We do agree with Reviewer #2's comment. Thank you very much. Changed.

8. Below Table 1, Line 2: Change "obtained" to "provided" for better flow.

> Thank you very much. Changed.

9. Page 3, Line 6: Remove "that match"

> We do agree with Reviewer #2's comment. Thank you very much. The "that match" was removed.

Correspondences to Reviewer #3:

Thank you for the reviewer's comments.

1. Configurations (L,L) and (L,D) mentioned on page 2 and 3 would be much better denoted using standard CIP stereodescriptors.

> We do agree with Reviewer #3's comment. Thank you very much. All configurations to (L,L) and (L,D) have been rewritten as (*S*,*R*) and (*S*,*S*).

2. A brief note about how absolute configuration was determined will be helpful in the manuscript.

> We do agree with Reviewer #3's comment. Thank you very much. A note was added to #26 of "Notes and references."

3. In Table 1, in the formula for cuprate "2" before LiBr should not be subscript. In this scheme also, it would be good to add reaction times.

> We do agree with Reviewer #3's comment. Thank you very much. The indicated items were corrected.

In closing, we greatly appreciate the reviewers' comments concerning ways to improve this manuscript, and we feel that the revised manuscript is of great improvements over the original. We earnestly hope the revised version will meet the usual high standards set for ***Organic & Biomolecular Chemistry***.

Sincerely,

Hirokazu Tamamura, Ph. D. (Professor)
Lab. Biomaterials and Bioengineering
Inst. Int. Res.
Inst. Science Tokyo

Correspondences to Reviewer #1:
Thank you for the reviewer's positive comments.
 # In Abstract: In dipeptide isostere, no N-terminal and C-terminal residues are present.

> We do agree with Reviewer #1's comment. Thank you for pointing this out. The following additions and corrections have been made.
"…Ellman's imine for corresponding to the *N*-terminal amino acid residues and Oppolzer's sultam for corresponding to the *C*-terminal amino acid residues, …"

 # Why is Zn enolate effective but Li-enolate is not in the reaction of Ellman's imine with difluroacetate anions? This depends on the thermal stability of the anions?

> Thank you for pointing this out. Zn-enolate is effective but Li-enolate is not in the reaction of Ellman's imine with difluroacetate anions. Li-enolate did not produce the target compound and might cause beta-lactam formation.

Correspondences to Reviewer #2:
Thank you for the reviewer's comments.
1. Fig. 1c: The general structure includes "Xaa" without any discussion of amino acid substitution on the substrate. Replace "Xaa" with "R" or add a substrate bearing an amino acid to justify its inclusion.

> Thank you for pointing this out. "Xaa" at Fig. 1c has been replaced with a specific amino acid substrate.

2. Configuration in Table 1: In the paragraph below Table 1, replace "(L,L)-configuration" with "(L,D)-configuration" and vice versa. Alternatively, since the authors use R/S notation elsewhere in the manuscript, they should consider using R/S consistently.

> We do agree with Reviewer #2's comment. Thank you very much. The "(L,L)-configuration" was replaced with "(*S*,*R*)-configuration" and "(L,D)-configuration" was replaced by "(*S*,*S*)-configuration". Fixed.

3. Scheme 1: Consider deleting Scheme 1, as Ellman's imine synthesis is well-known and does not require further elaboration.

> Thank you very much for pointing this out. We do agree with Reviewer #2's opinion "Ellman's imine synthesis is very famous," but in the synthesis of FADI, Ellman's imine is a key compound. So, we would like to keep Scheme 1.

4. Paragraph 2, Line 4: Change "this approach" to "these approaches"

> Thank you very much for pointing this out. We changed "this approach" to "these approaches".

5. *Page 2, Line 4: Remove "an enolate 4"*

> Thank you very much for pointing this out. The "to generate an enolate 4" has been removed.

6. Above Scheme 4: Change "caused" to "resulted in"

> Thank you very much for pointing this out. The "caused" has been rewritten to "resulted in".

7. Yields: Replace "sufficient yield" with "satisfactory yield"

> We do agree with Reviewer #2's comment. Thank you very much. Changed.

8. Below Table 1, Line 2: Change "obtained" to "provided" for better flow.

> Thank you very much. Changed.

9. Page 3, Line 6: Remove "that match"

> We do agree with Reviewer #2's comment. Thank you very much. The "that match" was removed.

Correspondences to Reviewer #3:

Thank you for the reviewer's comments.

1. Configurations (L,L) and (L,D) mentioned on page 2 and 3 would be much better denoted using standard CIP stereodescriptors.

> We do agree with Reviewer #3's comment. Thank you very much. All configurations to (L,L) and (L,D) have been rewritten as (*S*,*R*) and (*S*,*S*).

2. A brief note about how absolute configuration was determined will be helpful in the manuscript.

> We do agree with Reviewer #3's comment. Thank you very much. A note was added to #26 of "Notes and references."

3. In Table 1, in the formula for cuprate "2" before LiBr should not be subscript. In this scheme also, it would be good to add reaction times.

> We do agree with Reviewer #3's comment. Thank you very much. The indicated items were corrected.

Organic & Biomolecular Chemistry

ARTICLE

Diastereoselective synthesis of (Z)-fluoroalkene dipeptide isosteres utilizing chiral auxiliaries

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

Takuya Kobayakawa, ‡,a Marisa Arioka, ‡,a Kenichi Yamamoto, ‡,a Kohei Tsuji and Hirokazu Tamamura*,a

An efficient method for diastereo-controlled synthesis of (*Z*)-fluoroalkene dipeptide isosteres (FADIs) was developed. Two chiral centers were constructed by applying our synthetic methodology for chloroalkene dipeptide isosteres (CADIs) using Ellman's imine for corresponding to the *N*-terminal amino acid residues and Oppolzer's sultam for corresponding to the *C*-terminal amino acid residues, affording dipeptidomimetic in a stereocontrolled manner with high diastereoselectivity.

In drug discovery research, biological equivalents are currently being developed to enhance the activity of bioactive molecules and improve their stability *in vivo*.[1] In peptide drug discovery, (*E*)-alkene dipeptide isosteres (EADIs) are being developed as dipeptidomimetics, which mimic the ground state of amide structures.[2] EADIs are expected to serve as chemical equivalents of amide bonds due to their structural homology to natural dipeptides. However, they have lower dipole moments and poorer spatial control effect compared to natural peptide bonds, which might reduce their efficacy as dipeptide equivalents.

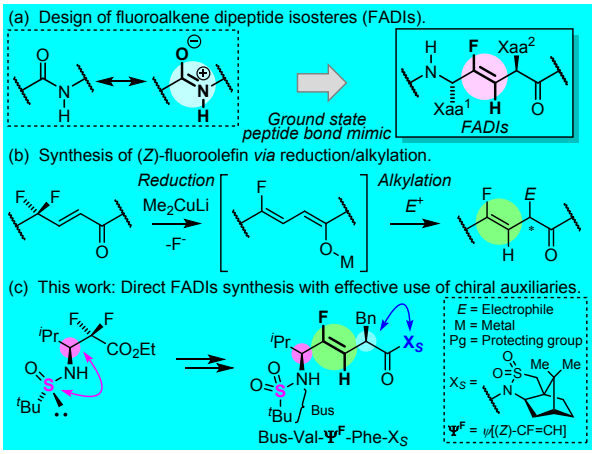


Fig. 1 Concept of FADIs and their syntheses.

Previously, syntheses of FADIs using classical olefination reactions, such as the Peterson reaction,[6,7] aldol condensation,[8] and Horner-Wadsworth-Emmons reaction,[9] were reported. However, these approaches cannot provide high *E*/*Z* selectivity of the olefin. In this situation, Otaka, Narumi et al. reported that treatment of γ,γ-difluoro-unsaturated esters with organocopper reagents causes reductive defluorination *via* a single electron transfer mechanism that proceeds in a (*Z*)-selective manner (Fig 1-(b)).[10,11] They discovered that alkylation reactions proceed by capturing the dienoate intermediate with the corresponding electrophile.[11,12] This method might solve the problem of low *E*/*Z* selectivity. On the other hand, it faces challenges including many operational steps in application of FADIs to solid-phase peptide synthesis (SPPS).

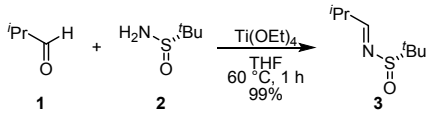
Recently, our group has successfully developed an efficient method employing chiral *tert*-butylsulfinamide[13] in the synthesis of chloroalkene dipeptide isosteres (CADIs), in consideration of their application to the SPPS.[14-19] In the structure of CADIs, the fluorine atom of FADIs is replaced with a chlorine atom in the olefinic unit. These CADIs serve as effective peptide bond mimetics because both the van der Waals radius and electronegative properties of the chlorine atom match those of the oxygen atom in natural amide bonds.[3-5] When these CADIs were incorporated into bioactive peptides, the resulting peptidomimetics exhibited superior pharmacological activities compared to their parent peptides. Here, we report a novel method for the synthesis of FADIs, which combines the synthetic method for CADIs[14-18] and the method reported by Otaka, Narumi et al.[10-12] (Fig 1-(c)). We found that FADIs with two chiral centers can be constructed facilely and stereoselectively by utilizing chiral *tert*-butylsulfinamide[13] and camphorsultam.[20]

[a] *Laboratory for Biomaterials and Bioengineering, Institute of Integrated Research, Institute of Science Tokyo, 2-3-10 Kandasurugadai, Chiyoda-ku, Tokyo 101-0062, Japan. E-mail: tamamura.mr@tmd.ac.jp.*

‡ These authors contributed equally to this work.

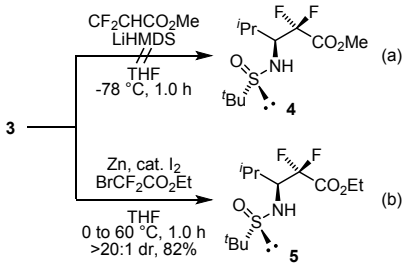
† Electronic supplementary information (ESI) available: Experimental procedures, ^{1}H NMR, ^{13}C NMR charts and additional data. See DOI: 10.1039/x0xx00000x

To prepare the precursor corresponding to the *N*-terminal amino acid, the chiral imine **3** was obtained by the reaction of the chiral *tert*-butylsulfinamide **2** with the aldehyde **1** corresponding to the side chain of the *N*-terminal amino acid (Scheme 1).[13]



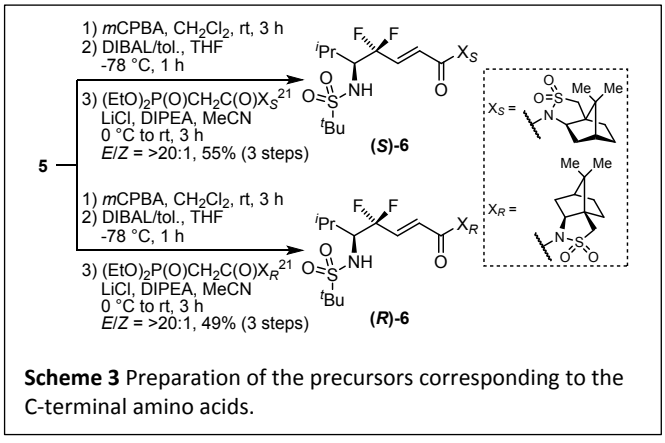
Scheme 1 Preparation of the precursor corresponding to the *N*-terminal amino acid.

When the Mannich reaction was performed by using LiHMDS and the obtained imine **3**, the desired product was not obtained (Scheme 2-(a)). On the other hand, the Mannich reaction with an organozinc reagent afforded the desired ester **5** with a chiral center corresponding to the *N*-terminal amino acid in high diastereoselectivity and an excellent yield (Scheme 2-(b)).[21]



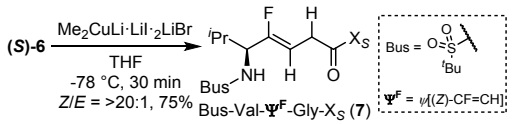
Scheme 2 Diastereoselective synthesis of the chiral center corresponding to the N-terminal amino acid.

The N^{α}-*tert*-butylsulfinyl group of the obtained ester **5** was converted to the *tert*-butylsulfonyl (Bus) group[20] by *m*CPBA oxidation followed by DIBAL reduction and the subsequent Horner-Wadsworth-Emmons reaction using phosphate esters containing camphorsultams,[22] which resulted in the synthesis of both (*S*)- and (*R*)-sultams **6** (Scheme 3).



Scheme 3 Preparation of the precursors corresponding to the C-terminal amino acids.

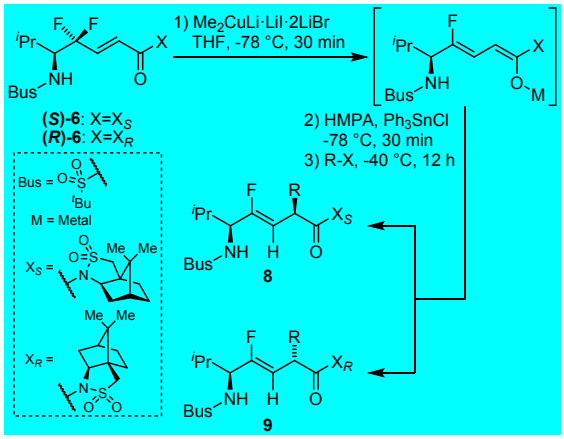
Since the chiral center corresponding to the *N*-terminal amino acid was constructed, construction of the fluoroalkene structure and the chiral center corresponding to the *C*-terminal amino acid was explored including asymmetric alkylation. Treatment of sultam **(*S*)-6** with a Gilman cuprate[23] resulted in a reductive defluorination reaction and afforded a Val-Gly type FADI **7** in high *Z*-selectivity and a satisfactory yield.



Scheme 4 Reductive defluorination reaction utilizing a Gilman cuprate.

Gilman cuprate conduct reductive defluorination followed by transmetalation on the produced dienolate intermediate.[11,12,24,25] Subsequently, the asymmetric alkylation using an electrophile was performed (Table 1).

Table 1 Diastereoselective synthesis of (*Z*)-fluoroalkene dipeptide isosteres by reduction/transmetalation/alkylation.



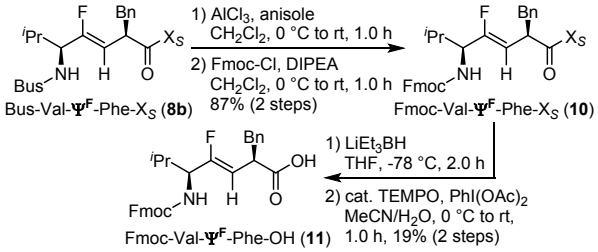
entry	substrate	R-X	product (%, at 3 steps)[b]	dr[c]
1	**(*S*)-6**	Me-I	**8a**, 56	>20:1
2	**(*S*)-6**	Bn-Br	**8b**, 65	>20:1
3	**(*S*)-6**	^{t}BuOC(O)CH$_2$-Br	**8c**, 50	>20:1
4	**(*R*)-6**	Me-I	**9a**, 58	>20:1
5	**(*R*)-6**	Bn-Br	**9b**, 66	>20:1
6	**(*R*)-6**	^{t}BuOC(O)CH$_2$-Br	**9c**, 50	>20:1

[a] All reactions were carried out on a 0.3 mmol scale with 4 equiv. of organocuprates, 16 equiv. of HMPA, 2 equiv. of Ph_3SnCl, and 8 equiv. of alkyl halide. [b] Yields are for the isolated products. [c] Determined by ^{1}H NMR of unpurified reaction mixtures.

In the case of using (*S*)-sultam **(*S*)-6** as the substrate, the asymmetric alkylation with methyl iodide provided the corresponding Val-Ala type FADI with the (*S*,*R*)-configuration in high diastereoselectivity and sufficient yield (Table 1, entry 1).

This reaction was applicable with benzyl bromide and *tert*-butyl 2-bromoacetate (Table 1, entries 2 and 3). In addition, the reaction proceeded similarly for (*R*)-sultam **(*R*)-6** having the opposite configuration, which afforded the corresponding FADIs with (*S*,*S*)-configuration (Table 1, entries 4-6). The stereo-configuration was determined by deriving FADI **8b** to the known compounds[12] and confirmed by ^{1}H NMR, ^{13}C NMR, and optical rotations (see the Supplementary Information for details).[26]

Since the synthetic methods for various (*S*,*R*)- or (*S*,*S*)-type FADIs have been established, the conversion reactions for application to peptide synthesis were investigated (Scheme 5).



Scheme 5 Synthesis of Fmoc-Val-ψ[(*Z*)-CF=CH]-Phe-OH (**11**).

Deprotection of the Bus group of **8b** with $AlCl_3$ and anisole[27] followed by Fmoc-protection produced the Fmoc-protected compound **10**. Finally, the obtained product **10** was reduced to the corresponding aldehyde followed by the oxidation[28] to provide the desired Fmoc-protected carboxylic acid (Fmoc-Val-ψ[(*Z*)-CF=CH]-Phe-OH) **11** in moderate overall yield from **8b** without significant epimerization or olefin isomerization.

In this study, we have successfully synthesized peptidomimetics with FADI containing two chiral centers by effectively utilizing chiral *tert*-butylsulfinamide and camphorsultam. Compared to previous FADI synthetic methods, the present strategy can provide FADIs via a more concise route under mild reaction conditions. Furthermore, this strategy would be provided for facile application of FADIs to peptide synthesis.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this study are available within the published article and its Electronic supplementary information (ESI).

Acknowledgements

This work was supported in part by the grant for JSPS KAKENHI Grant Number 24K02144 (H.T.) and 23K14318 (T.K.); Japan Agency for Medical Research and Development (AMED) JP24ama121043 (Research Support Project for Life Science and Drug Discovery, BINDS) (H.T.); and JST SPRING, Grant Number JPMJSP2180 (K.Y.). This research is based on the Cooperative Research Project of Research Center for Biomedical Engineering.

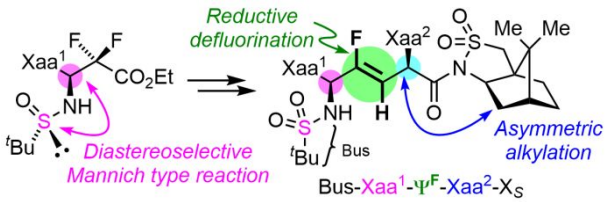
Notes and references

1. N. Ohashi and H. Tamamura, in *Amino Acids, Peptides and Proteins, Vol. 41, Chap. 1*, ed. M. Ryadnov and F. Hudecz, The Royal Society of Chemistry, Cambridge, 2017, pp. 1-29.
2. H. Tamamura, T. Kobayakawa and N. Ohashi, *Mid-size drugs based on peptides and peptidomimetics: A New Drug Category*, Springer Briefs in Pharmaceutical Science & Drug Development, Singapore, 2018.
3. R.J. Abraham, S.L.R. Ellison, P. Schonholzer and W.A. Thomas, *Tetrahedron*, 1986, **42**, 2101-2110.
4. P. Wipf, T.C. Henninger and S.J. Geib, *J. Org. Chem.*, 1998, **63**, 6088-6089.
5. A. Bondi, *J. Phys. Chem.*, 1964, **68**, 441-451.
6. L.G. Boros, B. De Corte, R.H. Gimi, J.T. Welch, Y. Wu and R.E. Handschumacher, *Tetrahedron Lett.*, 1994, **35**, 6033-6036.
7. J.T. Welch and J. Lin, *Tetrahedron*, 1996, **52**, 291-304.
8. P.A. Bartlett and A. Otake, *J. Org. Chem.*, 1995, **60**, 3107-3111.
9. P. Van der Veken, K. Senten, I. Kertèsz, I.D. Meester, A.-M. Lambeir, M.-B. Maes, S. Scharpé, A. Haemers and K. Augustyns, *J. Med. Chem.*, 2005, **48**, 1768-1780.
10. A. Otaka, E. Mitsuyama, H. Watanabe, S. Oishi, H. Tamamura and N. Fujii, *Chem. Commun*. 2000, 1081-1082.
11. T. Narumi, A. Niida, K. Tomita, S. Oishi, A. Otaka, H. Ohno, N. Fujii, *Chem. Commun*. 2006, 4720-4722.
12. T. Narumi, K. Tomita, E. Inokuchi, K. Kobayashi, S. Oishi, H. Ohno and N. Fujii, *Tetrahedron*, 2008, **64**, 4332-4346.
13. M. T. Robak, M. A. Herbage and J. A. Ellman. *Chem Rev.*, 2010, **110**, 3600-3740.
14. T. Narumi, T. Kobayakawa, H. Aikawa, S. Seike and H. Tamamura, *Org. Lett.*, 2012, **14**, 4490-4493.
15. T. Kobayakawa, T. Narumi and H. Tamamura, *Org. Lett.*, 2015, **17**, 2302-2305.
16. T. Kobayakawa and H. Tamamura, *Tetrahedron*, 2016, **72**, 4968-4971.
17. T. Kobayakawa and H. Tamamura, *Tetrahedron*, 2017, **73**, 4464-4471.
18. T. Kobayakawa, Y. Matsuzaki, K. Hozumi, W. Nomura, M. Nomizu and H. Tamamura, *ACS Med. Chem. Lett.*, 2018, **9**, 6-10.
19. T. Kobayakawa, C. Azuma, Y. Watanabe, S. Sawamura, A. Taniguchi, Y. Hayashi, K. Tsuji and H. Tamamura, *J. Org. Chem.*, 2021, **86**, 5091-5101.
20. P. Sun and S. M. Weinreb, *J. Org. Chem.*, 1997, **62**, 8604-8608.
21. D. D. Staas, K. L. Savage, C. F. Homnick, N. N. Tsou and R. G. Ball, *J. Org. Chem.*, 2002, **67**, 8276-8279.
22. W. Oppolzer, D. Dupuis, G. Poli, T. M. Raynham and G. Bernardinelli, *Tetrahedron Lett.*, 1988, **29**, 5885-5888.
23. H. Gilman, R. G. Jones, L. A. Woods, *J. Org. Chem.*, 1952, **17**, 1630-1634.
24. M. Suzuki, A. Yanagisawa, and R. Noyori, *J. Am. Chem. Soc.*, 1985, **107**, 3348-3349.
25. M. Suzuki, A. Yanagisawa and R. Noyori, *J. Am. Chem. Soc.*, 1988, **110**, 4718-4726.
26. see the Electronic supplementary information.
27. T. Mita, Y. Higuchi and Y. Sato, *Chem-Eur J.*, 2013, **19**, 1123-1128.
28. Y. Zhu, A. Loudet and K. Burgess, *Org. Lett.*, 2010, **12**, 4392-4395.

Data availability

The data supporting this study are available within the published article and its Electronic supplementary information (ESI).

A graphical and textual abstract for the Table of contents entry



Diastereo-controlled synthesis of FADIs: A diastereo-controlled synthetic method for (Z)-fluoroalkene dipeptide isosteres (FADIs) was developed. Two chiral centers were constructed by applying our synthetic methodology for chloroalkene dipeptide isosteres (CADIs).

Electronic supplementary information (ESI)

Diastereoselective synthesis of (*Z*)-fluoroalkene dipeptide isosteres utilizing chiral auxiliaries

Takuya Kobayakawa,‡ Marisa Arioka,‡ Kenichi Yamamoto,‡ Kohei Tsuji and Hirokazu Tamamura*

Laboratory for Biomaterials and Bioengineering, Institute of Integrated Research, Institute of Science Tokyo, 2-3-10 Kandasurugadai, Chiyoda-ku, Tokyo 101-0062, Japan. E-mail: tamamura.mr@tmd.ac.jp

Table of contents

I. General information S2
I-I. General methods S2
I-II. Characterization Data S2
II. Experimental procedures S3
III. Determination of steric configuration S14
III-I. Derivation to the known compound: Boc-Val-ψ[(*Z*)-CF=CH]-Phe-OMe (S7) S14
III-II. Derivation to the compound: Boc-Val-ψ[(*Z*)-CF=CH]-D-Phe-OMe (S8) S15
III-III. Comparison of Spectroscopic Methodology S16
IV. ^{1}H NMR and ^{13}C NMR charts S17

I. General information

I-I. General methods

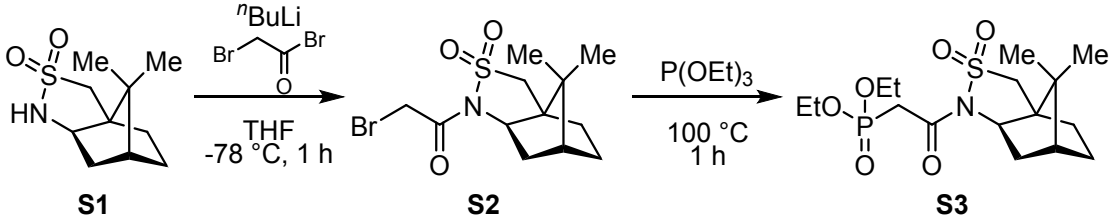
All reactions were performed using commercially supplied reagents and solvents in dried glassware under an atmosphere of nitrogen unless otherwise noted. Thin-layer chromatography (TLC) was performed on Merck $60F_{254}$ precoated silica gel plates and was visualized by fluorescence quenching under UV light and by staining with phosphomolybdic acid, *p*-anisaldehyde, or ninhydrin, respectively. Flash column chromatography was carried out with silica gel 60 N (Kanto Chemical Co., Inc.). Flash column chromatography was carried out with ‘‘Biotage Isolera One’’ equipped with ‘‘Sfar Silica HC Duo Cartridge’’.

All reactions utilizing air- or moisture-sensitive reagents were performed in dried glassware under an atmosphere of nitrogen or Ar, using commercially supplied solvents and reagents purchased from FUJIFILM Wako Pure Chemical Corporation, Kanto Chemical Co., Inc., Merck, Nacalai Tesque, Inc., Tokyo Chemical Industry Co., Ltd. (TCI), and Absolute Chiral without further purification unless otherwise noted. Thin-layer chromatography (TLC) was performed on Merck $60F_{254}$ precoated silica gel plates and was visualized by fluorescence quenching under UV light and by staining with phosphomolybdic acid, *p*-anisaldehyde, or ninhydrin, respectively. Flash column chromatography was carried out with silica gel 60 N (Kanto Chemical Co., Inc.) or automatic silica gel flash column chromatography system (Isolera One (Biotage, Sweden) and Pure C-815 (Buchi, Switzerland)).

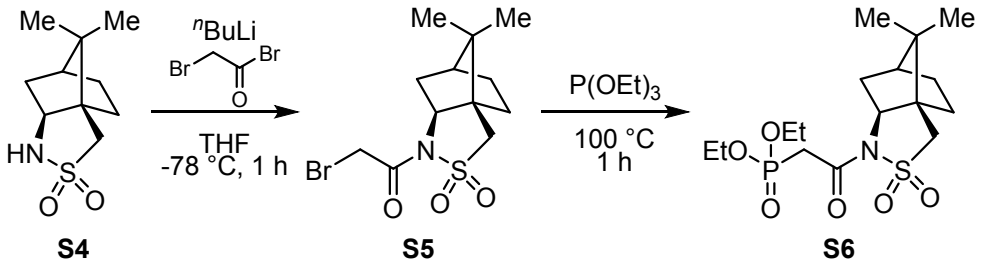
I-II. Characterization Data

^{1}H NMR (400 MHz or 500 MHz) and ^{13}C NMR (100 MHz or 125 MHz) spectra were recorded using a Bruker AVANCE III 400 spectrometer, Bruker AVANCE 500 spectrometer (Bruker, USA), and JNM-ECA500 (JEOL, Japan). Coupling constants are reported in Hertz, and peak shifts are reported in d (ppm) relative to $CDCl_3$ (^{1}H 7.26 ppm, ^{13}C 77.16 ppm). Low- and high-resolution mass spectra were recorded on a Bruker Daltonics micrOTOF focus in the positive and negative detection mode.

II. Experimental procedures

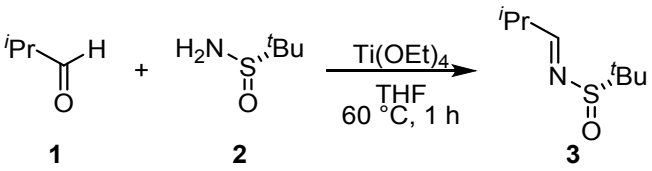


Diethyl (2-((3a*S*,6*R*,7a*R*)-8,8-dimethyl-2,2-dioxidotetrahydro-3*H*-3a,6-methanobenzo[*c*]isothiazol-1(4*H*)-yl)-2-oxoethyl)phosphonate (**S3**): To a solution of (1*S*)-(−)-2,10-camphorsultam **S1** (4.31 g, 20.0 mmol) in THF (80.0 mL) was slowly added ^{n}BuLi (1.60 M, 15.0 mL, 24.0 mmol) at -78 °C under argon, and the mixture was stirred for 15 min. Bromoacetyl bromide (1.92 mL, 22.0 mmol) was added dropwise to the solution, the mixture was stirred for 1 h. The reaction mixture was quenched by the addition of silica gel (25.0 g), and the solvent was removed under reduced pressure. The mixture was eluted directly with Et_2O, and the solvent was removed under reduced pressure to obtain the bromoacetyl-(*S*)-camphor-10,2-sultam **S2**, which was used immediately in the next step without purification. A solution containing bromoacetyl-(*S*)-camphor-10,2-sultam **S2** in triethyl phosphite (6.86 mL, 40.0 mmol) was heated for 1 h under argon, and the triethyl phosphite was removed under reduced pressure. The crude product (still containing some triethyl phosphite) was purified using flash column chromatography over silica gel with ^{n}hexane/EtOAc (1:1) to obtain the title compound **S3** as a colorless oil (7.40 g, 18.8 mmol, 94% in 2 steps): $[\alpha]_D^{27}$ = -51.3 (c 1.03, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.23-4.14 (m, 4H), 3.89 (dd, *J* = 7.8, 5.0 Hz, 1H), 3.61-3.43 (m, 3H), 3.21 (dd, *J* = 22, 15 Hz,1H), 2.19-2.14 (m, 1H), 2.07 (dd, *J* = 14, 7.8 Hz, 1H), 1.96-1.86 (m, 3H), 1.44-1.31 (m, 8H), 1.18 (s, 3H), 0.971 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 163.8 (d, *J* = 7.1 Hz), 65.4, 63.0 (d, *J* = 6.2 Hz), 62.7 (d, *J* = 6.3 Hz), 53.0, 48.5, 48.0, 44.8, 38.3, 35.1 (d, *J* = 138 Hz), 32.9, 26.6, 20.9, 20.0, 16.5 (d, *J* = 6.3 Hz), 16.4 (d, *J* = 6.3 Hz); HRMS (ESI), *m/z* calcd for $C_{16}H_{28}NNaO_6PS$ $[M+H]^+$ 416.1267, found 416.1262.



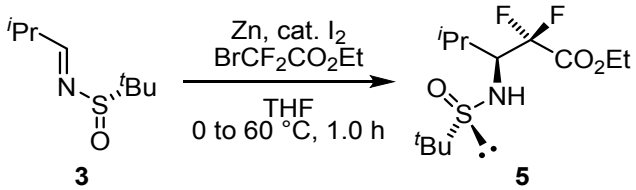
Diethyl (2-((3a*R*,6*S*,7a*S*)-8,8-dimethyl-2,2-dioxidotetrahydro-3*H*-3a,6-methanobenzo[*c*]isothiazol-1(4*H*)-yl)-2-oxoethyl)phosphonate (**S6**): To a solution of (1*R*)-(+)-2,10-camphorsultam **S4**(4.32 g, 20.0 mmol) in THF (80.0 mL) was slowly added ^{n}BuLi (1.60 M, 15.0 mL, 24.0 mmol) at -78 °C under argon, and the mixture was stirred for 15 min. Bromoacetyl bromide (1.92 mL, 22.0 mmol) was added dropwise to the solution, the mixture was stirred for 1 h. The reaction mixture was quenched by the addition of silica gel (25.0 g), and the solvent was removed under reduced pressure. The mixture was eluted directly with Et_2O, and the solvent was

removed under reduced pressure to obtain the bromoacetyl-(*R*)-camphor-10,2-sultam **S5**, which was used immediately in the next step without purification. A solution containing bromoacetyl-(*S*)-camphor-10,2-sultam **S5** in triethyl phosphite (6.86 mL, 40.0 mmol) was heated for 1 h under argon, and the triethyl phosphite was removed under reduced pressure. The crude product (still containing some triethyl phosphite) was purified using flash column chromatography over silica gel with *n*hexane/EtOAc (1:1) to obtain the title compound **S6** as a colorless oil (7.78 g, 19.8 mmol, 99% in 2 steps): $[\alpha]_D^{27}$ = 36.1 (c 1.10, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 4.20-4.08 (m, 4H), 3.87-3.84 (m, 1H), 3.53 (dd, *J* = 20, 15 Hz, 1H), 3.45 (dd, *J* = 29, 14 Hz, 2H), 3.17 (dd, *J* = 22, 15 Hz, 1H), 2.15-2.08 (m, 2H), 1.94-1.85 (m, 3H), 1.35-1.27 (m, 8H), 1.14 (s, 3H), 0.937 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$) δ 163.6 (d, *J* = 6.7 Hz), 65.3, 62.9 (d, *J* = 6.1 Hz), 62.8 (d, *J* = 6.2 Hz) , 53.0, 48.4, 47.9, 44.7, 38.3, 35.0 (d, *J* = 137 Hz), 32.8, 26.5, 20.8, 20.0, 16.4 (d, *J* = 3.5 Hz) 16.3 (d, *J* = 6.0 Hz); HRMS (ESI), *m/z* calcd for $C_{16}H_{29}NO_6PS$ $[M+H]^+$ 394.1448, found 394.1444.



1 **2** **3**

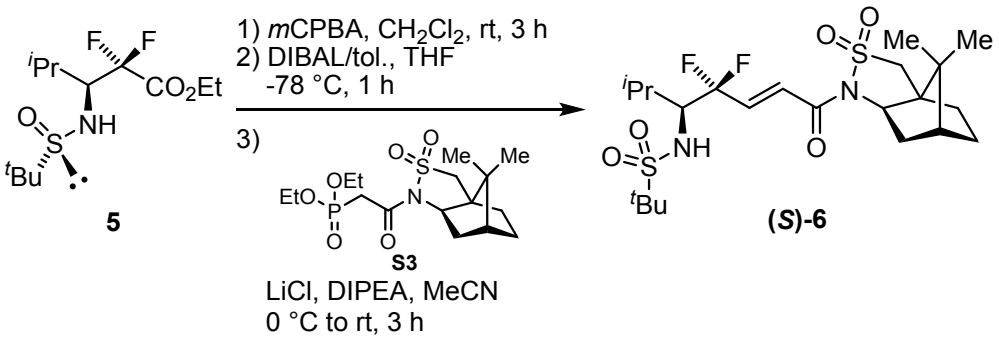
(*S*,*E*)-2-Methyl-*N*-(2-methylpropylidene)propane-2-sulfinamide (**3**): To a solution of (*S*)-(-)-*tert*-butylsulfinamide **2** (1.21 g, 10.0 mmol) in THF (20.0mL) was added isobuthylaldehyde **1** (913 μL, 10.0 mmol) and $Ti(OEt)_4$ (3.15 mL, 15.0 mmol) under argon, and the reaction mixture was stirred at 60 °C for 1 h. After cooling to 0 °C, the reaction was quenched with crashed ice. The resulting suspension was filtrated through a plug of celite, and filter cake was washed with EtOAc. The mixture was extracted with EtOAc, and the extract was dried over $MgSO_4$. The organic layer was concentration under reduced pressure followed by flash chromatography over silica gel *n*hexane/EtOAc (9:1) to obtain the title compound **3** as a colorless oil (1.74g, 9.93 mmol, 99%): $[\alpha]_D^{22}$ = 48.2 (c 1.07, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, *J* = 4.4 Hz, 1H), 2.75-2.69 (m, 1H), 1.19 (s, 9H), 1.18 (d, *J* = 2.6 Hz, 3H), 1.16 (d, *J* = 2.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 173.7, 56.6, 35.0, 22.4 (3C), 19.1 (2C); HRMS (ESI), *m/z* calcd for $C_8H_{18}NOS$ $[M+H]^+$ 176.1104, found 176.1107.



3 **5**

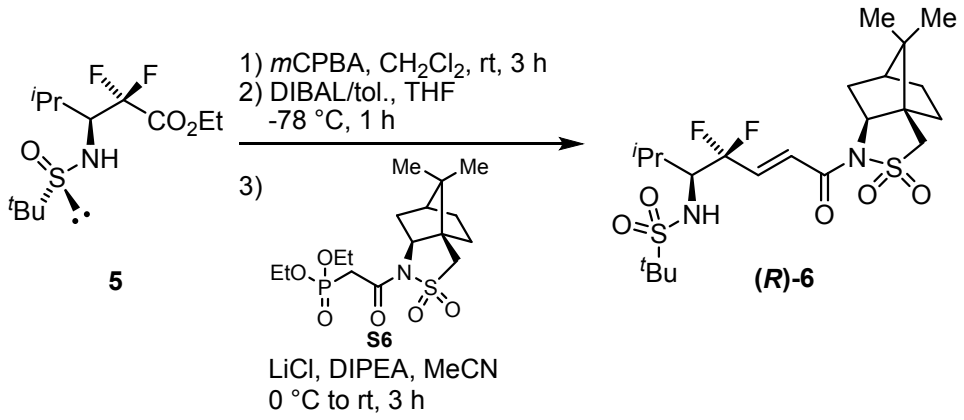
Ethyl (*S*)-3-(((*S*)-*tert*-butylsulfinyl)amino)-2,2-difluoro-4-methylpentanoate (**5**): To a solution of zinc (1.96 g, 30.0 mmol) in THF (35.0 mL) was added iodine (634 mg, 2.50 mmol) and ethyl bromodifluoroacetate (2.56 mL, 20.0 mmol) under argon at 0 °C, and the reaction mixture was stirred at 60 °C for 30 min. After cooling to 0 °C, a solution of imine **3** (1.75 mg, 10.0 mmol) in THF (5.00 mL) under argon was added to the reaction

mixture, and the mixture was stirred at 60 °C for 1 h. After cooling to 0 °C, the reaction was quenched with saturated aqueous NH_4Cl and saturated aqueous $Na_2S_2O_3$. The reaction mixture was extracted with EtOAc, and the extract was dried over $MgSO_4$. The organic layer was concentration under reduced pressure followed by flash chromatography over silica gel ^{n}hexane/EtOAc (3:1) to obtain the title compound **5** as a colorless oil (2.46 g, 8.21 mmol, 82%, >20:1 dr): $[\alpha]_D^{23}$ = 18.9 (c 1.06, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.39 (q, *J* = 7.2 Hz, 2H), 3.80-3.72 (m, 1H), 3.59 (d, *J* = 9.9 Hz, 1H), 2.18 (dq, *J* = 9.1, 4.1 Hz, 1H), 1.37 (t, *J* = 7.2 Hz, 3H), 1.26 (s, 9H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.946 (d, *J* = 6.8 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 163.4 (t, *J* = 32 Hz), 115.3 (t, *J* = 257 Hz), 63.6, 62.8 (dt, *J* = 25, 22 Hz), 57.3, 27.9, 23.0 (3C), 21.1, 16.5, 14.0; HRMS (ESI), *m/z* calcd for $C_{12}H_{24}F_2NO_3S$ $[M+H]^+$ 300.1439, found 300.1438.



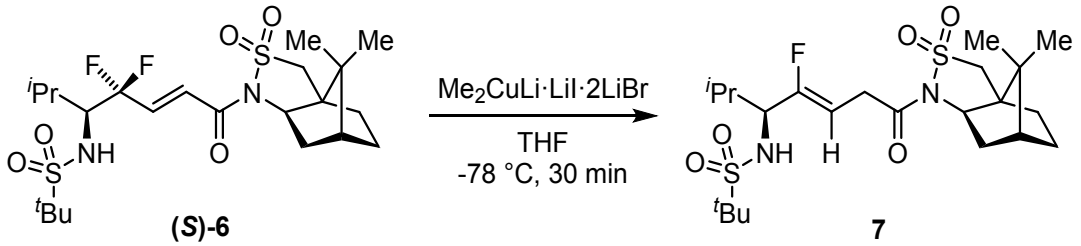
***N*-((*S*,*E*)-7-((3a*S*,6*R*,7a*R*)-8,8-dimethyl-2,2-dioxidotetrahydro-3*H*-3a,6-methanobenzo[*c*]isothiazol-1(4*H*)-yl)-4,4-difluoro-2-methyl-7-oxohept-5-en-3-yl)-2-methylpropane-2-sulfonamide** (**(*S*)-6**): To a solution of *N*-sulfinyl ethyl ester **5** (1.50 g, 5.00 mmol) in CH_2Cl_2 (15.0 mL) was added *m*CPBA (≤77% purity, 2.24 g, 10.0 mmol) in CH_2Cl_2 (5.00 mL) at 0 °C, and the mixture was stirred at room temperature for 3 h. After cooling to 0 °C, the reaction was quenched with saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$. The reaction mixture was extracted with EtOAc, and the extract was dried over $MgSO_4$. The organic layer was concentration under reduced pressure to obtain the *N*-sulfonyl ethyl ester, which was used immediately in next step without purification. To a solution of *N*-sulfonyl ethyl ester in THF (25.0 mL) was added dropwise a solution of DIBAL-H in toluene (1.00 M, 10.0 mL, 10.0 mmol) at -78 ºC under argon, and the mixture was stirred at -78 ºC for 1 h. The reaction was quenched by saturated aqueous Rochelle salt. The reaction mixture was extracted with diethyl ether and dried over $MgSO_4$. The organic layer was concentration under reduced pressure to obtain the aldehyde, which was used immediately in next step without purification. To a stirred solution of diethylphosphonylacetyl-(*S*)-camphor-10,2-sultam **S3** (2.36 g, 6.00 mmol) in MeCN (20.0 mL) was added LiCl (509 mg, 12.0 mmol) and DIPEA (1.05 mL, 6.00 mmol) at 0 ºC under argon. After stirred for 10 min, a solution of the aldehyde in MeCN (5.00 mL) under argon was added to the mixture, and the mixture was stirred for 3 h at room temperature. The reaction mixture was quenched by saturated aqueous NH_4Cl and extracted with EtOAc, and the extract was dried over $MgSO_4$. The organic layer was concentration under reduced pressure followed by flash chromatography over silica gel with ^{n}hexane/EtOAc (3:1) to obtain the title compound **(*S*)-6** as a semisolid (1.41 g, 2.76 mmol, 55 % in 3 steps, *E*/*Z* = >20:1): $[\alpha]_D^{23}$ = -41.6 (c 1.11, $CHCl_3$);

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.04 (d, *J* = 16 Hz, 1H), 6.85 (dt, *J* = 15, 9.5 Hz, 1H), 4.01 (d, *J* = 10 Hz, 1H), 3.96-3.93 (m, 1H), 3.84-3.77 (m, 1H), 3.55 (d, *J* = 14 Hz, 1H), 3.46 (d, *J* = 14 Hz, 1H), 3.12 (dd, *J* = 20, 14 Hz, 1H), 2.17-2.03 (m, 3H), 1.99-1.85 (m, 5H), 1.44 (s, 9H), 1.18 (s, 3H), 1.13-1.09 (m, 3H), 0.993 (s, 3H), 0.964-0.939 (m, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 162.5, 137.7 (t, *J* = 27 Hz), 126.0 (t, *J* = 7.9 Hz), 120.0 (t, *J* = 246 Hz), 65.3, 62.8 (dd. *J* = 26, 23 Hz), 61.0, 54.2 (d, *J* = 254 Hz), 50.5, 48.5 (d, *J* = 115 Hz), 44.9, 38.4 (d, *J* = 271 Hz), 32.5 (d, *J* = 129 Hz), 28.0 (d, *J* = 254 Hz), 26.6, 24.6 (3C), 21.1 (d, *J* = 10 Hz), 20.6 (d, *J* = 8.3 Hz), 20.5 (d, *J* = 128 Hz), 17.0; HRMS (ESI), *m/z* calcd for $C_{22}H_{37}F_2N_2O_5S_2$ $[M+H]^+$ 511.2106, found 511.2104.

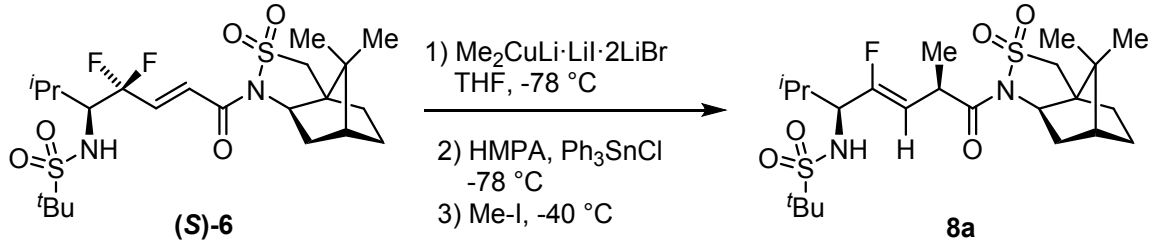


***N*-((*S*,*E*)-7-((3a*R*,6*S*,7a*S*)-8,8-dimethyl-2,2-dioxidotetrahydro-3*H*-3a,6-methanobenzo[*c*]isothiazol-1(4*H*)-yl)-4,4-difluoro-2-methyl-7-oxohept-5-en-3-yl)-2-methylpropane-2-sulfonamide** (**(*R*)-6**): To a solution of *N*-sulfinyl ethyl ester **5** (2.47 g, 8.25 mmol) in CH_2Cl_2 (28.0 mL) was added *m*CPBA (≤77% purity, 2.77 g, 12.4 mmol) in CH_2Cl_2 (5.00 mL) at 0 °C, and the mixture was stirred at room temperature for 3 h. After cooling to 0 °C, the reaction was quenched with saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$. The reaction mixture was extracted with EtOAc, and the extract was dried over $MgSO_4$. The organic layer was concentration under reduced pressure to obtain the *N*-sulfonyl ethyl ester, which was used immediately in next step without purification. To a solution of *N*-sulfonyl ethyl ester in THF (33.0 mL) was added dropwise a solution of DIBAL-H in toluene (1.00 M, 16.5 mL, 16.5 mmol) at -78 ºC under argon, and the mixture was stirred at -78 ºC for 1 h. The reaction was quenched by saturated aqueous Rochelle salt. The reaction mixture was extracted with diethyl ether and dried over $MgSO_4$. The organic layer was concentration under reduced pressure to obtain the aldehyde, which was used immediately in next step without purification. To a stirred solution of diethylphosphonylacetyl-(*R*)-camphor-10,2-sultam **S6** (3.89 g, 9.90 mmol) in MeCN (28.0 mL) was added LiCl (839 mg, 19.8 mmol) and DIPEA (1.72 mL, 9.90 mmol) at 0 ºC under argon. After stirred for 10 min, a solution of the aldehyde in MeCN (5.00 mL) under argon was added to the mixture, and the mixture was stirred for 3 h at room temperature. The reaction mixture was quenched by saturated aqueous NH_4Cl and extracted with EtOAc, and the extract was dried over $MgSO_4$. The organic layer was concentration under reduced pressure followed by flash chromatography over silica gel with ^{n}hexane/EtOAc (3:1 to 2:1) to obtain the title compound **(*R*)-6** as a semisolid (2.07 g, 4.04 mmol, 49 % in 3 steps, *E*/*Z* = >20:1): $[\alpha]_D^{23}$ = 43.4 (c 1.07, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05-7.01 (m, 1H), 6.91-6.81 (m, 1H), 3.97-3.93 (m, 2H), 3.86-3.76 (m,

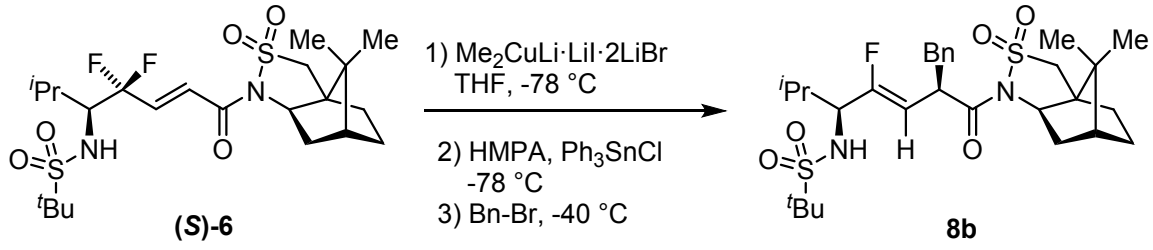
1H), 3.56-3.40 (m, 3H), 3.15-3.07 (m, 1H), 2.16-2.07 (m, 3H), 1.96-1.84 (m, 5H), 1.43 (s, 9H), 1.16 (s, 3H), 1.10 (d, J = 6.9 Hz, 3H), 0.962 (d, J = 6.8 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 162.5, 138.0 (t, J = 25 Hz), 125.8 (t, J = 8.4 Hz), 120.0 (t, J = 245 Hz), 65.3, 62.7 (t. J = 24 Hz), 61.0, 54.2 (d, J = 258 Hz), 50.5, 48.5 (d, J = 113 Hz), 44.8, 37.3 (d, J = 280 Hz), 32.5 (d, J = 129 Hz), 28.9, 26.8 (d, J =50 Hz), 24.6 (3C), 21.0 (d, J = 11 Hz), 20.8 (d, J = 48 Hz), 20.5 (d, J = 125 Hz), 17.0; HRMS (ESI), *m/z* calcd for $C_{22}H_{37}F_2N_2O_5S_2$ $[M+H]^+$ 511.2106, found 511.2108.



***N*-((*S*,*Z*)-7-((3a*S*,6*R*,7a*R*)-8,8-Dimethyl-2,2-dioxidotetrahydro-3*H*-3a,6-methanobenzo[*c*]isothiazol-1(4*H*)-yl)-4-fluoro-2-methyl-7-oxohept-4-en-3-yl)-2-methylpropane-2-sulfonamide** (**7**): To a suspension of CuI (152 mg, 800 μmol) in THF (7.00 mL) was added dropwise a solution of MeLi·LiBr complex in Et_2O (1.50 M, 1.07 mL, 1.60 mmol) at -78 ºC under argon, and the mixture was stirred at 0 ºC for 10 min. To the solution of the organocuprate was added dropwise a solution of the *N*-enoyl sultam **(*S*)-6** (102 mg, 200 μmol) in THF (1.00 mL) at -78 ºC. After stirred at -78 ºC for 30 min, the reaction was quenched by addition of a 3:2 saturated aqueous NH_4Cl-28% NH_3 aqueous solution with additional stirring at room temperature for 30 min. The mixture was extracted with diethyl ether, and the extract was dried over $MgSO_4$. The organic layer was concentration under reduced pressure followed by flash chromatography over silica gel with ^{n}hexane/EtOAc (2:1) to obtain the title compound **7** as colorless oil (74.3 mg, 151 μmol, 97%, Z/E = >20:1): $[\alpha]_D^{23}$ = -35.0 (c 1.14, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.02 (dt, J = 36, 6.9 Hz, 1H), 3.78-3.61 (m, 3H), 3.54-3.39 (m, 3H), 3.10 (d, J = 4.0 Hz, 2H), 2.14-2.06 (m, 1H), 1.92-1.84 (m, 3H), 1.47-1.43 (m, 2H), 1.36 (s, 9H), 1.12 (s, 3H), 1.04-0.961 (m, 6H), 0.921 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 168.7, 159.0 (d, J = 261 Hz), 99.8 (d, J = 13 Hz), 77.4, 65.4, 63.0, 61.4 (d, J = 26 Hz), 60.0, 55.1, 53.0, 50.9, 50.5, 47.7 (d, J = 31 Hz), 44.8, 36.2, 32.9, 32.0, 26.7 (d, J = 38 Hz), 24.4 (d, J = 20 Hz), 20.6 (d, J = 4.4 Hz), 20.5 (d, J = 97 Hz), 19.2 (d, J = 38 Hz); HRMS (ESI), *m/z* calcd for $C_{22}H_{38}FN_2O_5S_2$ $[M+H]^+$ 493.2201, found 493.2196.

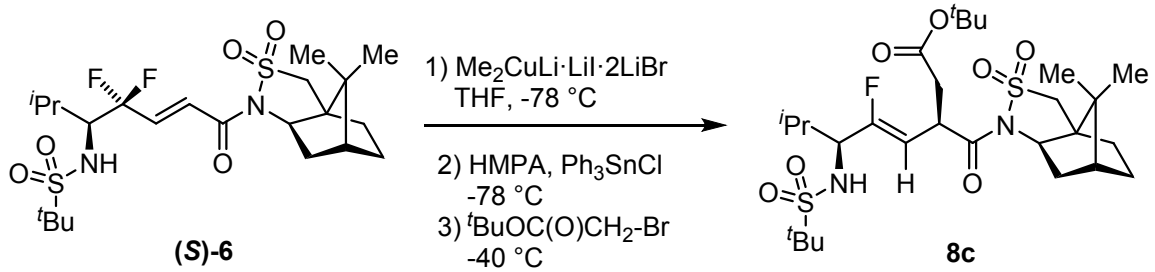


***N*-((3*S*,6*R*,*Z*)-7-((3a*S*,6*R*,7a*R*)-8,8-Dimethyl-2,2-dioxidotetrahydro-3*H*-3a,6-methanobenzo[*c*]isothiazol-1(4*H*)-yl)-4-fluoro-2,6-dimethyl-7-oxohept-4-en-3-yl)-2-methylpropane-2-sulfonamide** (**8a**): To a suspension of CuI (229 mg, 1.20 mmol) in THF (4100 mL) was added dropwise a solution of MeLi·LiBr complex in Et_2O (1.5 M, 1.60 mL, 2.40 mmol) at -78 ºC under argon, and the mixture was stirred at 0 ºC for 10 min. To the solution of the organocuprate was added dropwise a solution of the *N*-enoyl sultam **(*S*)-6** (153 mg, 300 μmol) in THF (1.00 mL) at -78 ºC. The mixture was stirred at -78 ºC for 30 min and HMPA (835 μL, 4.80 mmol) was added dropwise to the mixture. After stirring at -78 ºC for 30 min, a solution of triphenyltin chloride (231 mg, 600 μmol) in THF (1.00 mL) was added dropwise, and the mixture was then stirred at -40 ºC for 30 min and methyl iodide (149 μL, 2.40 mmol) was added dropwise. The mixture was stirred at -40 ºC for 12 h. The reaction was quenched by addition of a 3:2 saturated NH_4Cl-28% NH_3 aqueous solution with additional stirring at room temperature for 30 min. The mixture was extracted with Et_2O and the extract was washed with brine and dried over $MgSO_4$. The organic layer was concentration under reduced pressure followed by flash chromatography over silica gel with ^{n}hexane/EtOAc (2:1) to obtain the title compound **8a** (85.5 mg, 1.69 mmol, 56% yield, *Z*/*E* = >20:1, >20:1 dr) as a white solid: $[\alpha]_D^{24}$ = -46.8 (c 1.24, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 5.01 (dd, *J* = 37, 8.8 Hz, 1H), 4.24 (d, *J* = 9.3 Hz, 2H), 4.20-4.16 (m, 1H), 3.88-3.85 (m, 1H), 3.72-3.61 (m, 1H), 3.47 (q, *J* = 14 Hz, 2H), 3.43-3.38 (m, 1H), 1.90-1.85 (m, 8H), 1.36 (s, 9 H), 1.14 (s, 3H), 1.11 (s, 3H), 1.02 (d, *J* = 6.8 Hz, 3H), 0.942 (d, *J* = 6.8 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 173.5, 156.9 (d, *J* = 261 Hz), 106.9 (d, *J* = 12 Hz), 65.0, 62.8, 61.4 (d, *J* = 26 Hz), 60.4, 59.8, 50.3, 48.1 (d, *J* = 68 Hz), 46.0 (d, *J* = 290 Hz), 44.7, 38.3, 36.1, 35.8 (d, *J* = 3.7 Hz), 32.3 (d, *J* = 96 Hz), 31.9, 26.6 (d, *J* = 38 Hz), 24.2, 20.6 (d, *J* = 35Hz), 20.2 (d, *J* = 65 Hz), 19.6, 19.2 (d, *J* = 26 Hz); HRMS (ESI), *m/z* calcd for $C_{23}H_{40}FN_2O_5S_2$ $[M+H]^+$ 507.2357, found 507.2353.



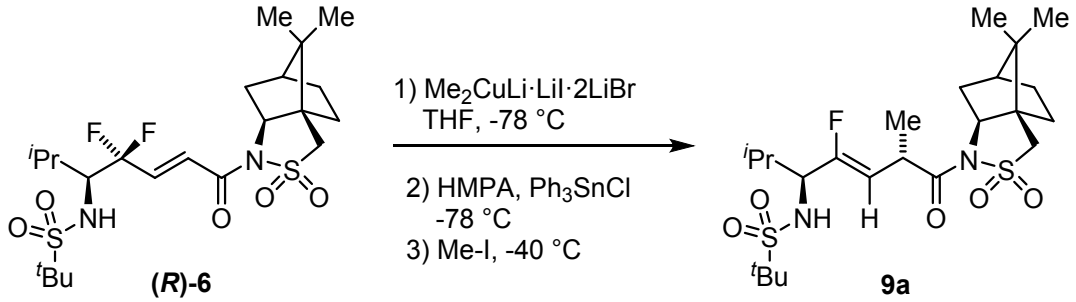
***N*-((3*S*,6*R*,*Z*)-6-Benzyl-7-((3a*S*,6*R*,7a*R*)-8,8-dimethyl-2,2-dioxidotetrahydro-3*H*-3a,6-methanobenzo[*c*]isothiazol-1(4*H*)-yl)-4-fluoro-2-methyl-7-oxohept-4-en-3-yl)-2-methylpropane-2-sulfonamide** (**8b**): To a suspension of CuI (229 mg, 1.20 mmol) in THF (10.0 mL) was added dropwise a solution of MeLi·LiBr complex in Et_2O (1.5 M, 1.60 mL, 2.40 mmol) at -78 ºC under argon, and the mixture was stirred at 0 ºC for 10 min. To the solution of the organocuprate was added dropwise a solution of the *N*-enoyl sultam **(*S*)-6** (153 mg, 300 μmol) in THF (1.0 mL) at -78 ºC. The mixture was stirred at -78 ºC for 30 min and HMPA (835 μL, 4.80 mmol) was added dropwise to the mixture. After stirring at -78 ºC for 30 min, a solution of triphenyltin chloride (231 mg, 600 μmol) in THF (1.0 mL) was added dropwise, and the mixture was then stirred at -40 ºC for 30 min and benzyl bromide (285 μL, 2.40 mmol) was added dropwise. The mixture

was stirred at -40 ºC for 12 h. The reaction was quenched by addition of a 3:2 saturated NH_4Cl-28% NH_3 aqueous solution with additional stirring at room temperature for 30 min. The mixture was extracted with Et_2O and the extract was washed with brine and dried over $MgSO_4$. The organic layer was concentration under reduced pressure followed by flash chromatography over silica gel with ^{n}hexane/EtOAc (4:1) to obtain the title compound **8b** (114 mg, 195 μmol, 65% yield, *Z*/*E* = >20:1, >20:1 dr) as a white solid: $[\alpha]_D^{24}$ = -38.8 (c 1.09, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24-7.14 (m, 5H), 4.92 (dd, *J* = 36, 9.2 Hz, 1H), 4.54 (q, *J* = 8.1 Hz, 1H), 4.04 (d, *J* = 9.6 Hz, 1H), 3.79 (s, 1H), 3.70-3.62 (m, 1H), 3.45-3.36 (m, 2H), 3.15-3.08 (m, 2H), 2.81 (dd, *J* = 13, 7.3 Hz, 1H), 2.00-1.83 (m, 7H), 1.30 (s, 9H), 1.13 (s, 3H), 0.985 (d, *J* = 6.8 Hz, 3H), 0.945 (d, *J* = 6.8 Hz, 3H), 0.879 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 172.3, 157.9 (d, *J* = 262 Hz), 137.3, 129.5 (2C), 128.5 (2C),126.9, 105.6 (d, *J* = 12 Hz), 65.1, 63.0, 61.5 (d, *J* = 25 Hz), 61.4 (d, *J* = 394 Hz), 54.2 (d, *J* = 210 Hz), 49.4 (d, *J* = 272 Hz), 46.3 (d, *J* = 365 Hz), 46.2 (d, *J* = 369 Hz), 42.9, 39.3 (d, *J* = 249 Hz), 36.2, 32.9, 32.1 (d, *J* = 32 Hz), 26.9 (d, *J* = 49 Hz), 24.3 (3C), 20.6 (d, *J* = 3.2 Hz), 19.9 (d, *J* = 192 Hz), 19.5 (d, *J* = 93 Hz); HRMS (ESI), *m/z* calcd for $C_{29}H_{44}FN_2O_5S_2$ $[M+H]^+$ 583.2670, found 583.2672.

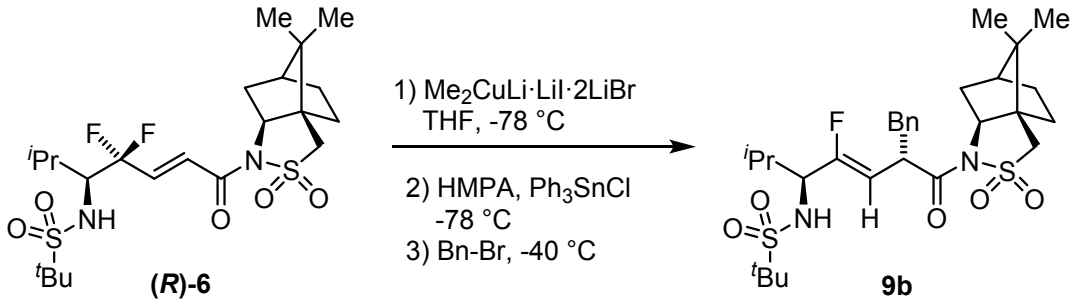


***tert*-Butyl (3*R*,6*S*,*Z*)-3-((3a*S*,6*R*,7a*R*)-8,8-dimethyl-2,2-dioxidohexahydro-3*H*-3a,6-methanobenzo[*c*]isothiazole-1-carbonyl)-6-((1,1-dimethylethyl)sulfonamido)-5-fluoro-7-methyloct-4-enoate** (**8c**): To a suspension of CuI (229 mg, 300 μmol) in THF (10.0 mL) was added dropwise a solution of MeLi·LiBr complex in Et_2O (1.5 M, 1.60 mL, 2.40 mmol) at -78 ºC under argon, and the mixture was stirred at 0 ºC for 10 min. To the solution of the organocuprate was added dropwise a solution of the *N*-enoyl sultam **(*S*)-6** (153 mg, 300 μmol) in THF (1.00 mL) at -78 ºC. The mixture was stirred at -78 ºC for 30 min and HMPA (835 μL, 4.80 mmol) was added dropwise to the mixture. After stirring at -78 ºC for 30 min, a solution of triphenyltin chloride (231 mg, 600 μmol) in THF (1.00 mL) was added dropwise, and the mixture was then stirred at -40 ºC for 30 min and *tert*-butyl bromoacetate (352 μL, 2.40 mmol) was added dropwise. The mixture was stirred at -40 ºC for 12 h. The reaction was quenched by addition of a 3:2 saturated NH_4Cl-28% NH_3 aqueous solution with additional stirring at room temperature for 30 min. The mixture was extracted with Et_2O and the extract was washed with brine and dried over $MgSO_4$. The organic layer was concentration under reduced pressure followed by flash chromatography over silica gel with ^{n}hexane/EtOAc (2:1) to obtain the title compound **8c** (91.0 mg, 150 μmol, 50% yield, *Z*/*E* = >20:1, >20:1 dr) as a white solid: $[\alpha]_D^{24}$ = -40.8 (c 1.13, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.88 (dd, *J* = 36, 9.2 Hz, 1H), 4.41-4.35 (m, 1H), 4.14-4.11 (m 1H), 3.90-3.87 (m, 1H), 3.73-3.63 (m, 1H), 3.50-3.39 (m, 2H), 2.78 (dd, *J* = 16, 8.5 Hz, 1H), 2.52 (dd, *J* = 16, 5.4 Hz, 1H), 1.93-1.82 (m, 7H), 1.40 (s, 9H), 1.36 (s, 9H), 1.20 (s, 3H), 1.01 (d, *J* = 6.8 Hz, 3H), 0.971 (d, *J* = 6.8

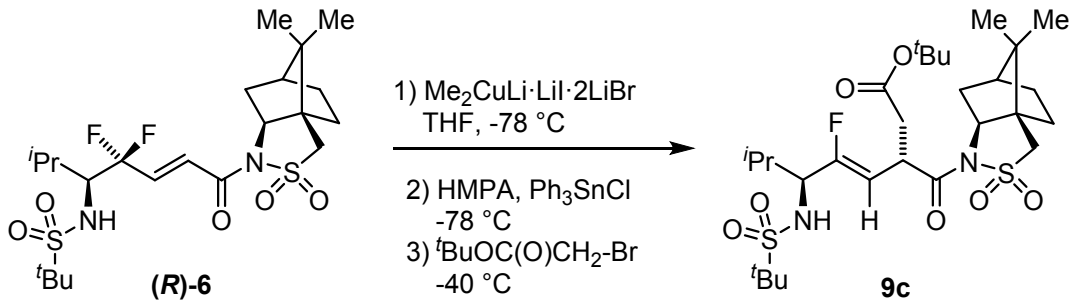
Hz, 3H), 0.952 (s, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 171.7 169.8, 158.2 (d, J = 263 Hz), 104.7 (d, J = 12 Hz), 81.2, 67.4, 65.3, 63.0, 61.4 (d, J = 26 Hz), 60.0, 55.1 53.1, 50.3 (d, J = 34 Hz), 48.3 (d, J = 73 Hz), 44.7, 38.5 (d, J = 102 Hz), 37.9 (d, J = 3.2 Hz), 35.2 (d, J = 191 Hz), 32.5 (d, J = 81 Hz), 28.1 (3C), 25.6 (d, J = 210 Hz), 24.3 (3C), 20.4 (d, J = 55 Hz), 19.1 (d, J = 22 Hz); HRMS (ESI), *m/z* calcd for $C_{28}H_{48}FN_2O_7S_2$ $[M+H]^+$ 607.2881, found 607.2880.



***N*-((3*S*,6*S*,*Z*)-7-((3a*R*,6*S*,7a*S*)-8,8-Dimethyl-2,2-dioxidotetrahydro-3*H*-3a,6-methanobenzo[*c*]isothiazol-1(4*H*)-yl)-4-fluoro-2,6-dimethyl-7-oxohept-4-en-3-yl)-2-methylpropane-2-sulfonamide** (**9a**): To a suspension of CuI (229 mg, 1.20 mmol) in THF (10.0 mL) was added dropwise a solution of MeLi·LiBr complex in Et_2O (1.5 M, 1.60 mL, 2.40 mmol) at -78 ºC under argon, and the mixture was stirred at 0 ºC for 10 min. To the solution of the organocuprate was added dropwise a solution of the *N*-enoyl sultam **(*R*)-6** (153 mg, 300 μmmol) in THF (1.00 mL) at -78 ºC. The mixture was stirred at -78 ºC for 30 min and HMPA (835 μL, 4.80 mmol) was added dropwise to the mixture. After stirring at -78 ºC for 30 min, a solution of triphenyltin chloride (231 mg, 600 μmol) in THF (1.00 mL) was added dropwise, and the mixture was then stirred at -40 ºC for 30 min and methyl iodide (149 μL, 2.40 mmol) was added dropwise. The mixture was stirred at -40 ºC for 12 h. The reaction was quenched by addition of a 3:2 saturated NH_4Cl-28% NH_3 aqueous solution with additional stirring at room temperature for 30 min. The mixture was extracted with Et_2O and the extract was washed with brine and dried over $MgSO_4$. The organic layer was concentration under reduced pressure followed by flash chromatography over silica gel with ^{n}hexane/EtOAc (2:1) to obtain the title compound **9a** (88.2 mg, 174 μmol, 58% yield, *Z*/*E* = >20:1, >20:1 dr) as a white solid: $[\alpha]_D^{26}$ = 37.7 (c 1.06, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$) δ 5.07 (dd, J = 37, 8.6 Hz, 1H), 4.22-4.15 (m, 1H), 4.12-4.11 (m, 2H), 3.87-3.84 (m, 1H), 3.76-3.66 (m, 1H), 3.53-3.39 (m, 3H), 1.93-1.85 (m, 8H), 1.35 (s, 9H), 1.15 (s, 3H), 1.12 (s, 3H), 1.02 (d, J = 6.8 Hz, 3H), 0.970 (d, J = 6.4 Hz, 3H); $^{13}C\{^{1}H\}$ NMR (100 MHz, $CDCl_3$) δ 173.6, 157.2 (d, J = 261 Hz), 107.0 (d, J = 12 Hz), 65.1, 63.0, 61.2 (d, J = 27 Hz), 60.0, 54.2, 50.4, 48.6, 47.8 (d, J = 31 Hz), 46.6 (d, J = 366 Hz), 44.8, 38.4, 36.2, 32.9, 32.0, 26.9, 26.6, 24.3, 20.7 (d, J = 33 Hz), 20.3 (d, J = 65 Hz), 19.1 (d, J = 51 Hz); HRMS (ESI), *m/z* calcd for $C_{23}H_{40}FN_2O_5S_2$ $[M+H]^+$ 507.2357, found 507.2354.

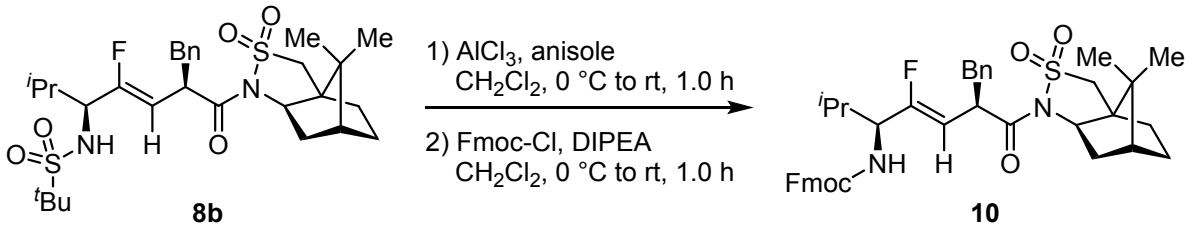


***N*-((3*S*,6*S*,*Z*)-6-benzyl-7-((3a*R*,6*S*,7a*S*)-8,8-dimethyl-2,2-dioxidotetrahydro-3*H*-3a,6-methanobenzo[*c*]isothiazol-1(4*H*)-yl)-4-fluoro-2-methyl-7-oxohept-4-en-3-yl)-2-methylpropane-2-sulfonamide** (**9b**): To a suspension of CuI (229 mg, 1.2 mmol) in THF (10.0 mL) was added dropwise a solution of MeLi·LiBr complex in Et_2O (1.5 M, 1.60 mL, 2.40 mmol) at -78 ºC under argon, and the mixture was stirred at 0 ºC for 10 min. To the solution of the organocuprate was added dropwise a solution of the *N*-enoyl sultam **(*R*)-6** (153 mg, 300 μmol) in THF (1.00 mL) at -78 ºC. The mixture was stirred at -78 ºC for 30 min and HMPA (835 μL, 2.40 mmol) was added dropwise to the mixture. After stirring at -78 ºC for 30 min, a solution of triphenyltin chloride (231 mg, 600 μmol) in THF (1.00 mL) was added dropwise, and the mixture was then stirred at -40 ºC for 30 min and benzyl bromide (285 μL, 2.40 mmol) was added dropwise. The mixture was stirred at -40 ºC for 12 h. The reaction was quenched by addition of a 3:2 saturated NH_4Cl-28% NH_3 aqueous solution with additional stirring at room temperature for 30 min. The mixture was extracted with Et_2O and the extract was washed with brine and dried over $MgSO_4$. The organic layer was concentration under reduced pressure followed by flash chromatography over silica gel with ^{n}hexane/EtOAc (2:1) to obtain the title compound **9b** (115 mg, 198 μmol, 66% yield, *Z*/*E* = >20:1, >20:1 dr) as a white solid: $[\alpha]_D^{28}$ = 28.6 (c 1.01, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22-7.13 (m, 5H), 4.92 (dd, *J* = 36, 9.2 Hz, 1H), 4.54-4.48 (m, 1H), 3.77 (s, 1H), 3.71-3.61 (m, 1H), 3.42-3.39 (m, 2H), 3.18-3.10 (m, 2H), 2.76 (dd, *J* = 13, 8.1 Hz, 1H), 1.91-1.80 (m, 7H), 1.32 (s, 9H), 1.12 (s, 3H), 0.925-0.890 (m, 6H), 0.770-0.754 (m, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 172.3, 158.0 (d, *J* = 263 Hz), 137.4, 129.5 (2C), 128.5 (2C), 126.9, 105.2 (d, *J* = 12 Hz), 65.1, 63.0, 61.5 (d, *J* = 301 Hz), 55.1, 53.1, 50.5, 48.1 (d, *J* = 60 Hz), 47.6, 44.7 (d, *J* = 17 Hz), 41.7 (d, *J* = 31 Hz), 40.3, 38.3, 36.2, 32.5 (d, *J* = 82 Hz), 32.0. 26.7 (d, *J* = 38 Hz), 24.5, 24.3, 20.3 (d, *J* = 70 Hz), 18.9 (d, *J* = 38 Hz); HRMS (ESI), *m/z* calcd for $C_{29}H_{43}FN_2NaO_5S_2$ $[M+Na]^+$ 605.2490, found 605.2493.



***tert*-Butyl (3*S*,6*S*,*Z*)-3-((3a*R*,6*S*,7a*S*)-8,8-dimethyl-2,2-dioxidohexahydro-3*H*-3a,6-methanobenzo[*c*]isothiazole-1-carbonyl)-6-((1,1-dimethylethyl)sulfonamido)-5-fluoro-7-methyloct-4-**

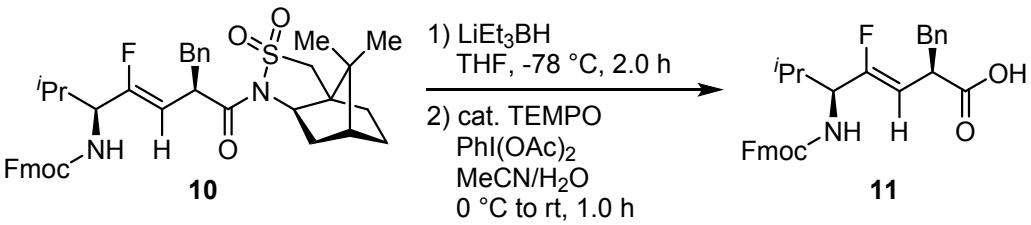
enoate (**9c**): To a suspension of CuI (229 mg, 1.20 mmol) in THF (10.0 mL) was added dropwise a solution of MeLi·LiBr complex in Et_2O (1.5 M, 1.60 mL, 2.40 mmol) at -78 ºC under argon, and the mixture was stirred at 0 ºC for 10 min. To the solution of the organocuprate was added dropwise a solution of the *N*-enoyl sultam **(*R*)-6** (153 mg, 300 μmol) in THF (1.00 mL) at -78 ºC. The mixture was stirred at -78 ºC for 30 min and HMPA (835 μL, 4.80 mmol) was added dropwise to the mixture. After stirring at -78 ºC for 30 min, a solution of triphenyltin chloride (231 mg, 600 μmol) in THF (1.00 mL) was added dropwise, and the mixture was then stirred at -40 ºC for 30 min and *tert*-butyl bromoacetate (352 μL, 2.40 mmol) was added dropwise. The mixture was stirred at -40 ºC for 12 h. The reaction was quenched by addition of a 3:2 saturated NH_4Cl-28% NH_3 aqueous solution with additional stirring at room temperature for 30 min. The mixture was extracted with Et_2O and the extract was washed with brine and dried over $MgSO_4$. The organic layer was concentration under reduced pressure followed by flash chromatography over silica gel with *n*hexane/EtOAc (2:1) to obtain the title compound **9c** (91.0 mg, 150 μmol, 50% yield, *Z*/*E* = >20:1, >20:1 dr) as a white solid: $[\alpha]_D^{27}$ = 30.5 (c 0.990, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.94 (dd, *J* = 36, 9.1 Hz, 1H), 4.39-4.34 (m, 1H), 4.15-4.13 (m 1H), 3.90-3.86 (m, 1H), 3.75-3.65 (m, 1H), 3.50-3.39 (m, 2H), 2.79 (dd, *J* = 16, 7.9 Hz, 1H), 2.54 (dd, *J* = 16, 5.8 Hz, 1H), 2.03-1.86 (m, 7H), 1.40 (s, 9H), 1.35 (s, 9H), 1.19 (s, 3H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.971-0.955 (m, 6H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 171.6, 169.7, 158.2 (d, *J* = 263 Hz), 104.6 (d, *J* = 12 Hz), 81.3, 65.2, 61.2 (d, *J* = 27 Hz), 60.1, 55.1, 53.1, 47.9, 46.7 (d, *J* = 399 Hz), 38.6 (d, *J* = 133 Hz), 38.1, 37.1 (d, *J* = 174 Hz), 32.5 (d, *J* = 90 Hz), 28.1 (3C), 28.0, 26.6, 24.5, 24.3 (3C), 20.7, 20.4 (d, *J* = 63 Hz), 19.1 (d, *J* = 55 Hz); HRMS (ESI), *m/z* calcd for $C_{28}H_{47}FN_2NaO_7S_2$ $[M+Na]^+$ 629.2701, found 629.2706.



8b **10**

(9*H*-Fluoren-9-yl)methyl ((3*S*,6*R*,*Z*)-6-benzyl-7-((3a*S*,6*R*,7a*R*)-8,8-dimethyl-2,2-dioxidotetrahydro-3*H*-3a,6-methanobenzo[*c*]isothiazol-1(4*H*)-yl)-4-fluoro-2-methyl-7-oxohept-4-en-3-yl)carbamate (**10**): To a solution of the ester **8b** (117 mg, 200 μmol) in CH_2Cl_2 (2.00 mL) was added anisole (65.2 μL, 600 μmol) and $AlCl_3$ (99.9 mg, 750 μmol) under argon. After stirring for 1.0 h at room temperature, the reaction was quenched with saturated aqueous Rochelle salt solution, NH_3 aqueous, and extracted with CH_2Cl_2. The extract was washed dried over $MgSO_4$. The reaction mixture was concentrated under reduced pressure to obtain the deprotected amine, which was used immediately in the next step without purification. To a solution of the amine in CH_2Cl_2 (2.00 mL) was added Fmoc-Cl (56.9 mg, 220 μmol) and DIPEA (40.1 μL, 230 μmol) under argon. After stirring for 1.0 h at room temperature, the reaction was quenched with saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2. The extract was washed with brine and dried over $MgSO_4$. The organic layer was concentration under reduced pressure followed by flash chromatography over silica gel with *n*hexane/EtOAc (3:1 to 2:1) to obtain the title compound **10** as a white solid (119 mg, 174 μmol, 87%): $[\alpha]_D^{27}$ = -37.2 (c 1.22, $CHCl_3$); ^{1}H NMR

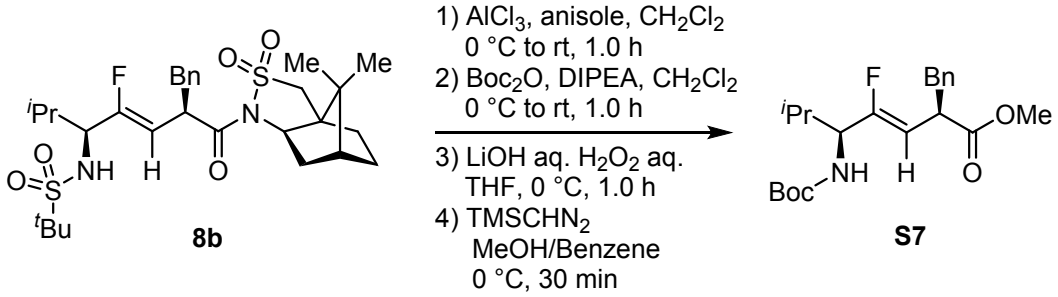
(500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.4 Hz, 2H), 7.60 (d, *J* = 7.4 Hz, 2H), 7.40 (t, *J* = 7.4 Hz, 2H), 7.33 (t, *J* = 7.4 Hz, 2H), 7.23-7.07 (m, 5H), 5.00 (dd, *J* = 36, 9.3 Hz, 1H), 4.88 (d, *J* = 9.6 Hz, 1H), 4.55-4.35 (m, 3H), 4.23 (t, *J* = 6.8 Hz, 1H) 3.94 (dt, *J* = 24, 9.0 Hz, 1H), 3.78 (s, 1H), 3.42-3.35 (m, 2H), 3.14-3.07 (m, 1H), 2.77 (dd, *J* = 14, 7.5 Hz, 1H), 1.98-1.74 (m, 8H), 0.964 (dd, *J* = 20, 6.8 Hz, 6H), 0.879 (s, 3H), 0.735 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 172.3, 157.9 (d, *J* = 262 Hz), 155.8, 144.0, 141.4, 137.5, 129.6, 129.0 (d, *J* = 123 Hz), 128.3 (2C), 127.8, 127.2, 126.7, 125.2 (d, *J* = 8.6 Hz), 120.1 (2C), 105.6 (d, *J* = 13 Hz), 104.9 (d, *J* = 12 Hz), 66.0 (d, *J* = 221 Hz), 61.5 (d, *J* = 25 Hz), 61.4 (d, *J* = 394 Hz), 59.8, 58.4 (d, *J* = 26 Hz), 55.2, 53.1, 49.0 (d, *J* = 360 Hz), 48.3, 47.7, 47.4, 46.0 (d, *J* = 338 Hz), 41.8 (d, *J* = 336 Hz), 38.4, 36.2, 32.9, 32.0, 30.4, 26.5, 24.3, 20.3 (d, *J* = 89 Hz), 19.0 (d, *J* = 71 Hz); HRMS (ESI), *m/z* calcd for $C_{40}H_{46}FN_2O_5S$ $[M+H]^+$ 685.3106, found 685.3103.



(2*R*,5*S*,*Z*)-5-((((9*H*-Fluoren-9-yl)methoxy)carbonyl)amino)-2-benzyl-4-fluoro-6-methylhept-3-enoic acid (**11**): To a solution of **10** (171 mg, 250 μmol) in THF (2.50 mL) was added $LiEt_3BH$ in THF (1.00 M, 750 μL, 750 μmol) at -78 ºC under argon, and the mixture was stirred for 2.0 h at -78 ºC. The reaction was quenched with MeOH and extracted with Et_2O. The extract was washed with brine and dried over $MgSO_4$. The reaction mixture was concentration under reduced pressure to obtain the aldehyde, which was used immediately in the next step without purification. To solution of TEMPO (11.7 mg, 80 μmol) and $PhI(OAc)_2$ (11.7 mg, 80 μmol) in MeCN (1.00 mL) and H_2O (250 μL) was added the alcohol in MeCN (1.00 mL). After stirring for 1.0 h at room temperature, the reaction was quenched with saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$ solution. The mixture was extracted with EtOAc, and the extract was dried over $MgSO_4$. The organic layer was concentration under reduced pressure followed by flash chromatography over silica gel with ^{n}hexane/EtOAc (1:1) to obtain the title compound **11** as a white solid (23.3 mg, 47.5 μmol, 19%): $[\alpha]_D^{27}$ = -44.5 (c 1.17, $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, *J* = 7.5 Hz, 2H), 7.59 (d, *J* = 5.0 Hz, 2H), 7.41 (t, *J* = 7.2 Hz, 2H), 7.32 (t, *J* = 7.2 Hz, 2H), 7.20-7.10 (m, 5H), 4.89 (dd, *J* = 36, 9.8 Hz, 1H), 4.80 (d, *J* = 9.5 Hz, 1H), 4.52-4.49 (m, 2H), 4.40-4.36 (m, 1H), 4.22 (t, *J* = 6.8 Hz, 1H), 3.94 (dt, *J* = 22, 8.8 Hz, 1H), 3.77-3.70 (m, 1H), 3.12 (dd, *J* = 14, 6.3 Hz, 1H), 2.80 (dd, *J* = 13, 8.5 Hz, 1H), 1.85-1.78 (m, 1H), 0.857 (dd, *J* = 14, 6.6 Hz, 6H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 178.0, 158.6 (d, *J* = 260 Hz), 155.8, 144.0 (2C), 141.5 (2C), 138.0, 129.2 (2C), 128.4 (2C), 127.9 (2C), 127.2 (2C), 126.7 (2C), 125.1, 120.2 (2C), 104.7 (d, *J* = 12 Hz), 67.0, 58.2 (d, *J* = 27 Hz), 47.4, 42.5, 38.5, 30.2, 19.4, 18.6; HRMS (ESI), *m/z* calcd for $C_{30}H_{31}FNO_4$ $[M+H]^+$ 488.2232, found 488.2229.

III. Determination of steric configuration

III-I. Derivation to the known compound: Boc-Val-ψ[(*Z*)-CF=CH]-Phe-OMe (S7)



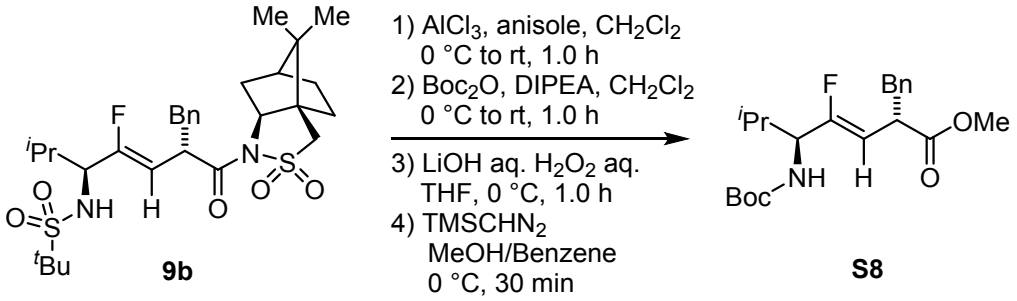
Methyl (2*R*,5*S*,*Z*)-2-benzyl-5-((*tert*-butoxycarbonyl)amino)-4-fluoro-6-methylhept-3-enoate (**S7**): To a solution of the ester **8b** (190 mg, 326 μmol) in CH_2Cl_2 (3.00 mL) was added anisole (53.1 μL, 489 μmol) and $AlCl_3$ (130 mg, 978 μmol) under argon. After stirring for 1.0 h at room temperature, the reaction was quenched with saturated aqueous Rochelle salt solution, NH_3 aqueous, and extracted with CH_2Cl_2. The extract was washed dried over $MgSO_4$. The organic layer was concentrated under reduced pressure to obtain the deprotected amine, which was used immediately in the next step without purification.

To a solution of the amine in CH_2Cl_2 (3.00 mL) was added Boc_2O (85.4 mg, 391 μmol) and DIPEA (85.2 μL, 489 μmol) under argon. After stirring for 1.0 h at room temperature, the reaction was quenched with saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2. The extract was dried over $MgSO_4$. The organic layer was concentrated under reduced pressure to obtain the protected amine, which was used immediately in the next step without purification.

To a solution of the protected amine in THF (3.00 mL) was added the aqueous H_2O_2 (166.5 μL, 1.63 mmol) and the aqueous LiOH (1.00 M, 652 μL, 652 μmol) at 0 °C, and the reaction mixture was stirred for 1.0 h at room temperature. The reaction was quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc. The extract was washed with brine and dried over $MgSO_4$. The mixture was concentration under reduced pressure to obtain the carboxylic acid, which was used immediately in the next step without purification

To a solution of the carboxylic acid in toluene/MeOH (1:1, 6.00 mL) was added $TMSCHN_2$ in ^{n}hexane (0.6 M, 538 μL, 323 μmol) at 0 ºC under argon, and the mixture was stirred for 2 h at 0 ºC. The reaction mixture was concentration under reduced pressure followed by flash chromatography over silica gel with ^{n}hexane/EtOAc (3:1 to 2:1) to obtain the title compound **S7** as a white solid (65.8 mg, 173 μmol, 53%): $[\alpha]_D^{20}$ = -75.2 (c 0.990, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27-7.14 (m, 5H), 4.88 (dd, *J* = 36, 9.7 Hz, 1H), 4.59 (d, *J* = 9.4 Hz, 1H), 3.96-3.88 (m, 1H), 3.78-3.72 (m, 1H), 3.63 (s, 3H), 3.08 (dd, *J* = 14, 7.0 Hz, 3H), 2.81 (dd, *J* = 14, 7.9 Hz, 3H), 1.83-1.77 (m, 1H), 1.45 (s, 9H), 0.868 (d, *J* = 6.7 Hz, 1H), 0.833 (d, *J* = 6.7 Hz, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 173.5, 158.8 (d, *J* = 260 Hz), 155.1, 138.2, 129.0 (2C), 128.3 (2C), 126.5, 104.5 (d, *J* = 13 Hz), 79.7, 57.3 (d, *J* = 27 Hz), 51.9, 42.5, 38.7, 30.1, 28.3 (3C), 19.2, 18.1; HRMS (ESI), *m/z* calcd for $C_{21}H_{31}FNO_4$ $[M+H]^+$ 380.2232, found 380.2330.

III-II. Derivation to the compound: Boc-Val-*ψ*[(*Z*)-CF=CH]-D-Phe-OMe (S8)



Methyl (2*S*,5*S*,*Z*)-2-benzyl-5-((*tert*-butoxycarbonyl)amino)-4-fluoro-6-methylhept-3-enoate (S8): To a solution of the ester **9b** (74.3 mg, 127 μmol) in CH_2Cl_2 (2.00 mL) was added anisole (20.7 μL, 191 μmol) and $AlCl_3$ (50.8 mg, 381 μmol) under argon. After stirring for 1.0 h at room temperature, the reaction was quenched with saturated aqueous Rochelle salt solution, NH_3 aqueous, and extracted with CH_2Cl_2. The extract was washed dried over $MgSO_4$. The organic layer was concentrated under reduced pressure to obtain the deprotected amine, which was used immediately in the next step without purification.

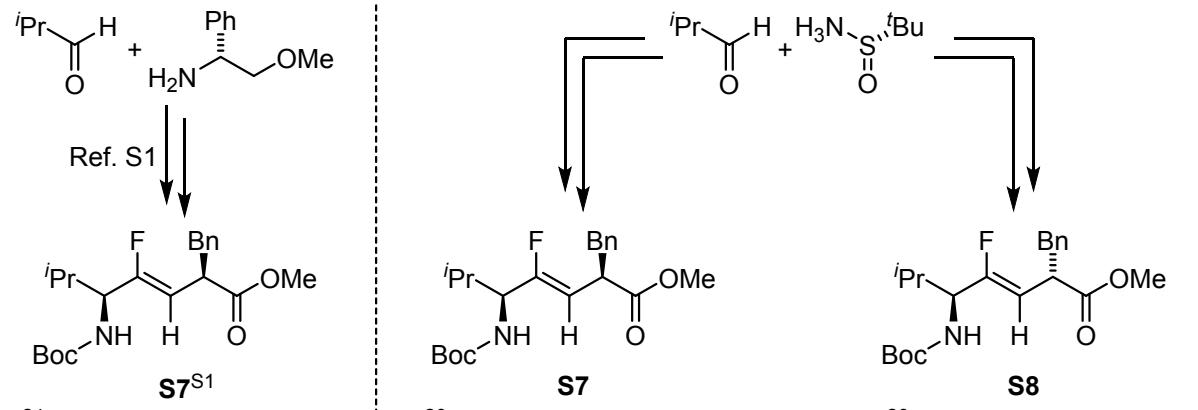
To a solution of the amine in CH_2Cl_2 (2.00 mL) was added Boc_2O (33.3 mg, 152 μmol) and DIPEA (33.2 μL, 191 μmol) under argon. After stirring for 1.0 h at room temperature, the reaction was quenched with saturated aqueous NH_4Cl solution and extracted with CH_2Cl_2. The extract was dried over $MgSO_4$. The organic layer was concentrated under reduced pressure to obtain the protected amine, which was used immediately in the next step without purification.

To a solution of the protected amine in THF (2.00 mL) was added the aqueous H_2O_2 (64.9 μL, 640 μmol) and the aqueous LiOH (1.00 M, 254 μL, 254 μmol) at 0 °C, and the reaction mixture was stirred for 1.0 h at room temperature. The reaction was quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc. The extract was washed with brine and dried over $MgSO_4$. The mixture was concentration under reduced pressure to obtain the carboxylic acid, which was used immediately in the next step without purification

To a solution of the carboxylic acid in toluene/MeOH (1:1, 3.00 mL) was added $TMSCHN_2$ in ^{n}hexane (0.6 M, 265 μL, 159 μmol) at 0 ºC under argon, and the mixture was stirred for 2 h at 0 ºC. The reaction mixture was concentration under reduced pressure followed by flash chromatography over silica gel with ^{n}hexane/EtOAc (3:1 to 2:1) to obtain the title compound **S8** as a white solid (21.8 mg, 57.0 μmol, 45%): $[\alpha]_D^{20}$ = 17.8 (c 1.09, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.13 (m, 5H), 4.85 (dd, *J* = 36, 9.9 Hz, 1H), 4.65 (d, *J* = 9.4 Hz, 1H), 3.95-3.86 (m, 1H), 3.81-3.74 (m, 1H), 3.63 (s, 3H), 3.08 (dd, *J* = 14, 6.9 Hz, 1H), 2.81 (dd, *J* = 14, 8.1 Hz, 1H), 1.80-1.75 (m, 1H), 1.44 (s, 9H), 0.822 (d, *J* = 6.8 Hz, 3H), 0.733 (d, *J* = 6.6 Hz, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 173.4, 158.7 (d, *J* = 260 Hz), 155.1, 138.2, 129.0 (2C), 128.4 (2C), 126.5, 104.6 (d, *J* = 13 Hz), 79.7, 57.1 (d, *J* = 27 Hz), 51.9, 42.5, 38.7, 30.2, 28.3 (3C), 19.0, 18.0; HRMS (ESI), *m/z* calcd for $C_{21}H_{31}FNO_4$ $[M+H]^+$ 380.2232, found 380.2232.

III-III. Comparison of Spectroscopic Methodology

The spectroscopic data of compound **S7**, which was synthesized by the present method, were compatible with those of the previous research[S1] in analyses of ^{1}H NMR, ^{13}C NMR, and optical rotation. Furthermore, the optical rotation of the (L,L) isomer **S7** was negative, whereas that of the epimer, the (L,D) isomer **S8**, was positive.



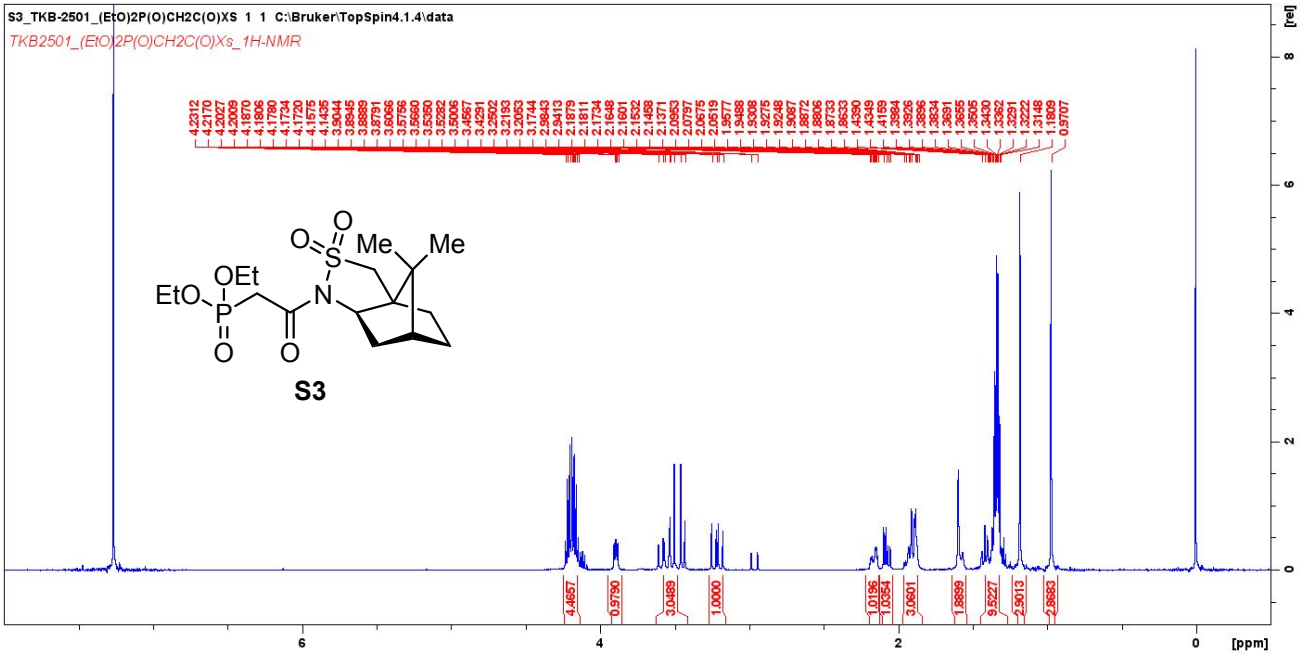
S7[S1] $[\alpha]^{24}_{D}$ = -76.8 (c 0.660, $CHCl_3$)

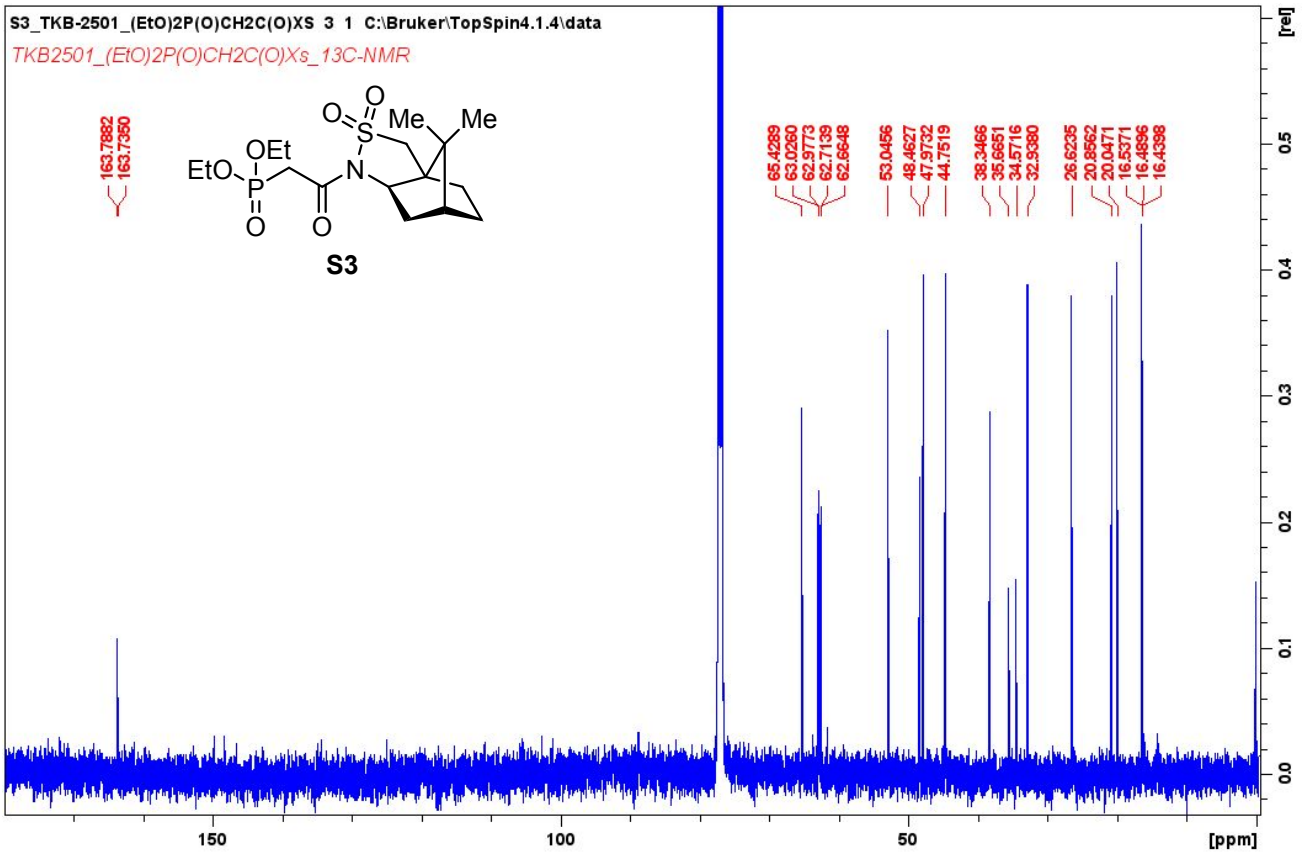
S7 $[\alpha]^{20}_{D}$ = -75.2 (c 0.990, $CHCl_3$)

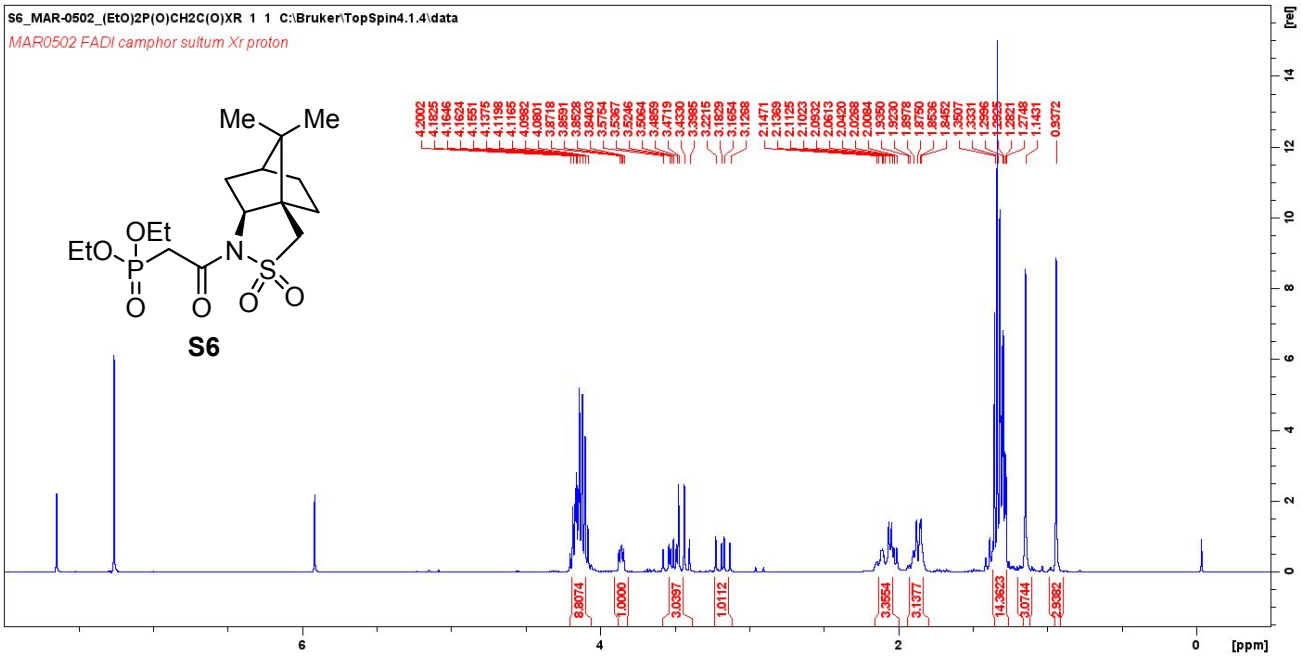
S8 $[\alpha]^{20}_{D}$ = 17.8 (c 1.09, $CHCl_3$)

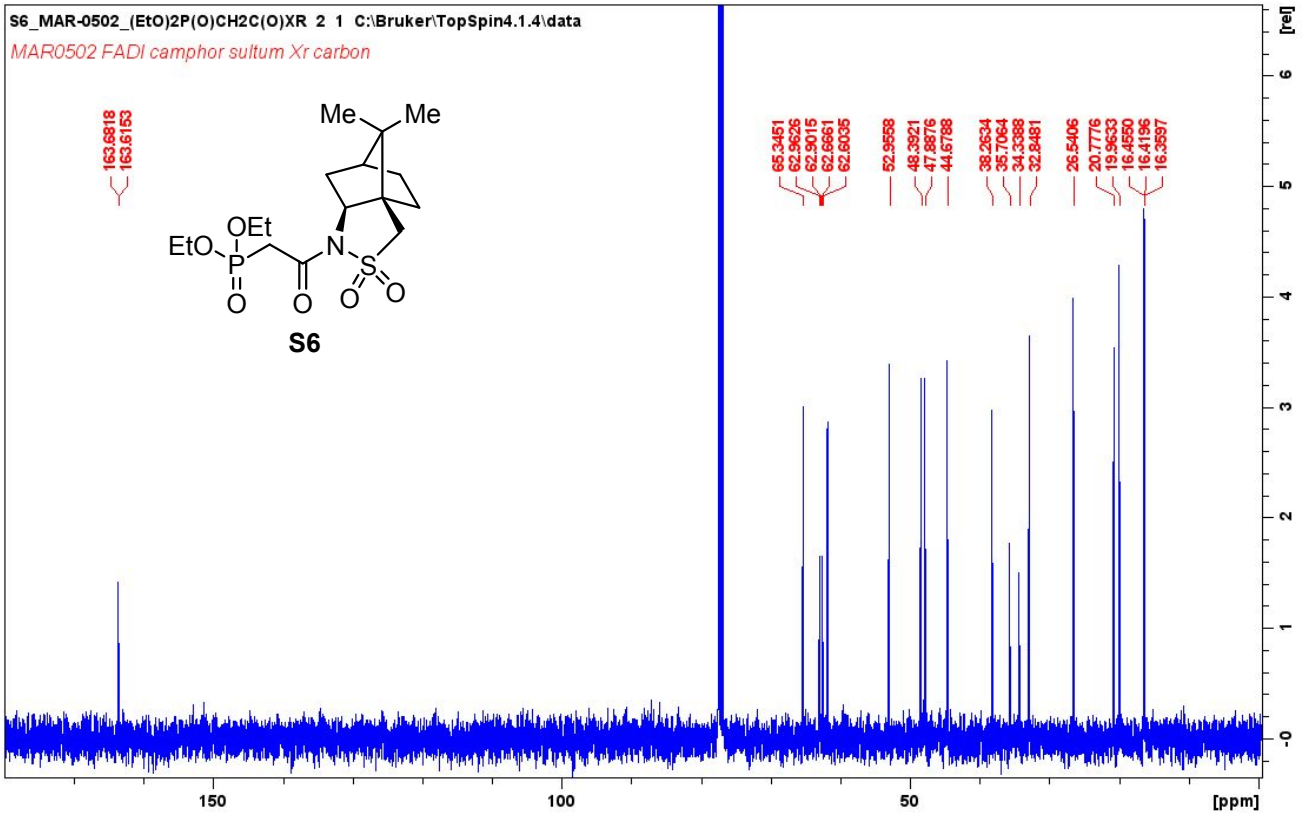
S1) Narumi, T.; Tomita, K.; Inokuchi, E.; Kobayashi, K.; Oishi, S.; Ohno, H.; Fujii, N. *Tetrahedron* **2008**, *64*, 4332-4346.

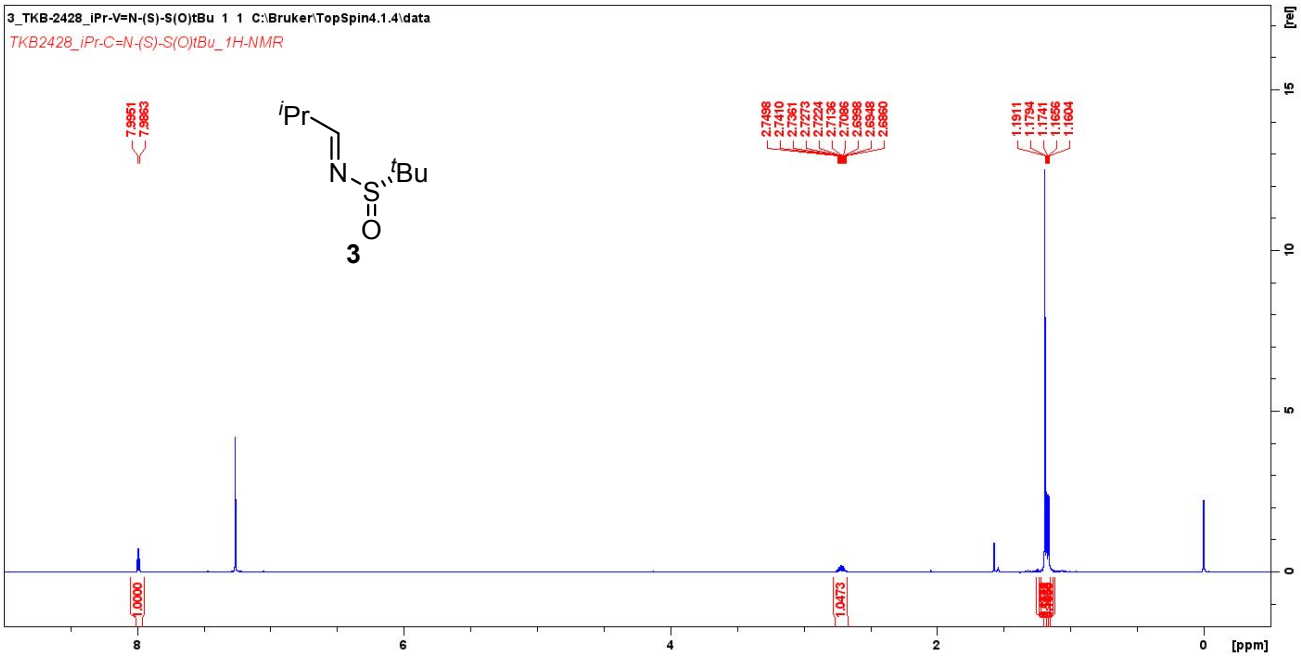
IV. ^{1}H NMR and ^{13}C NMR charts

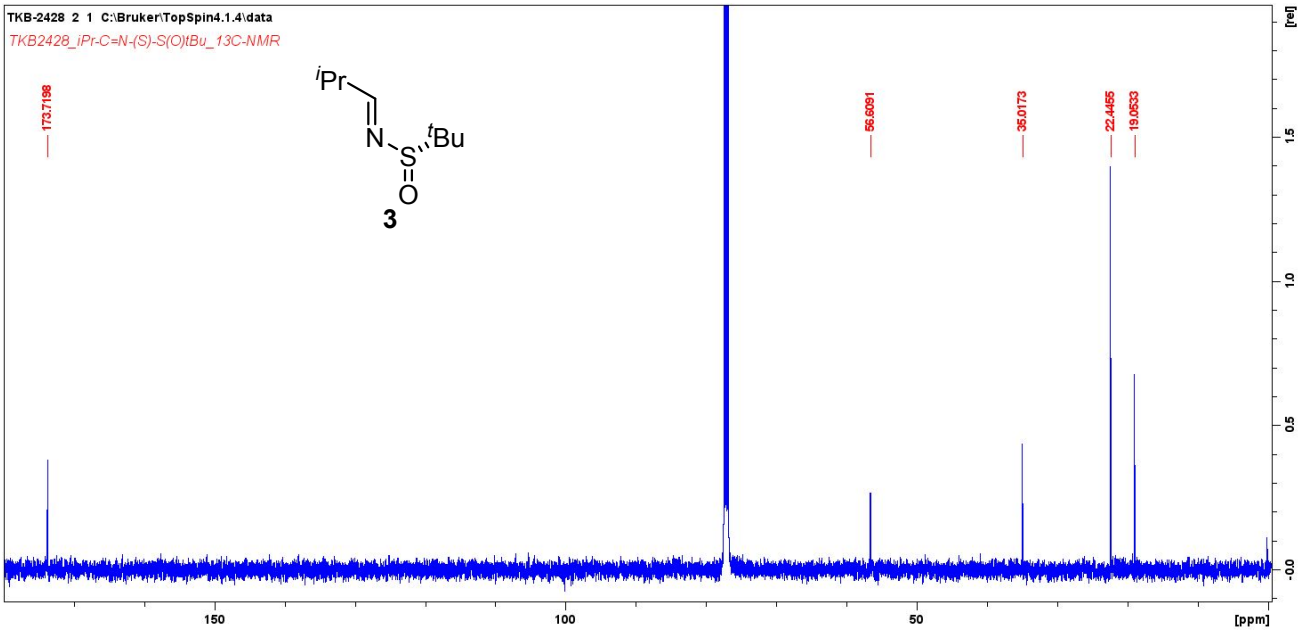


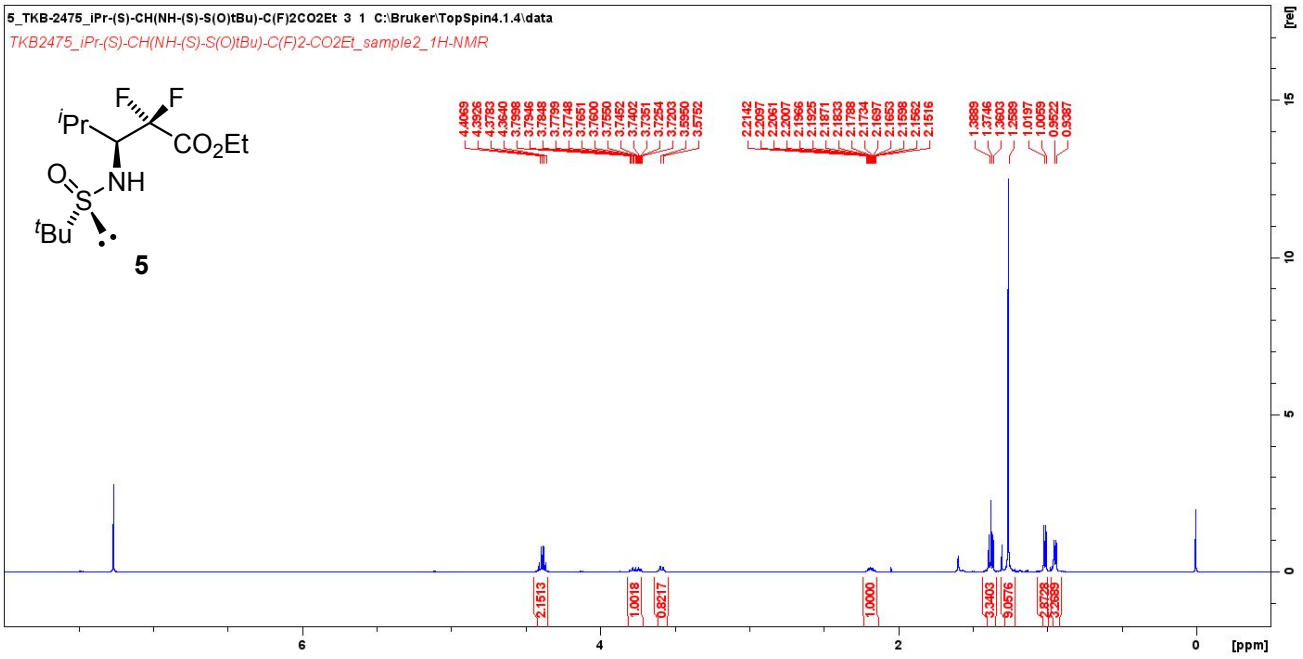


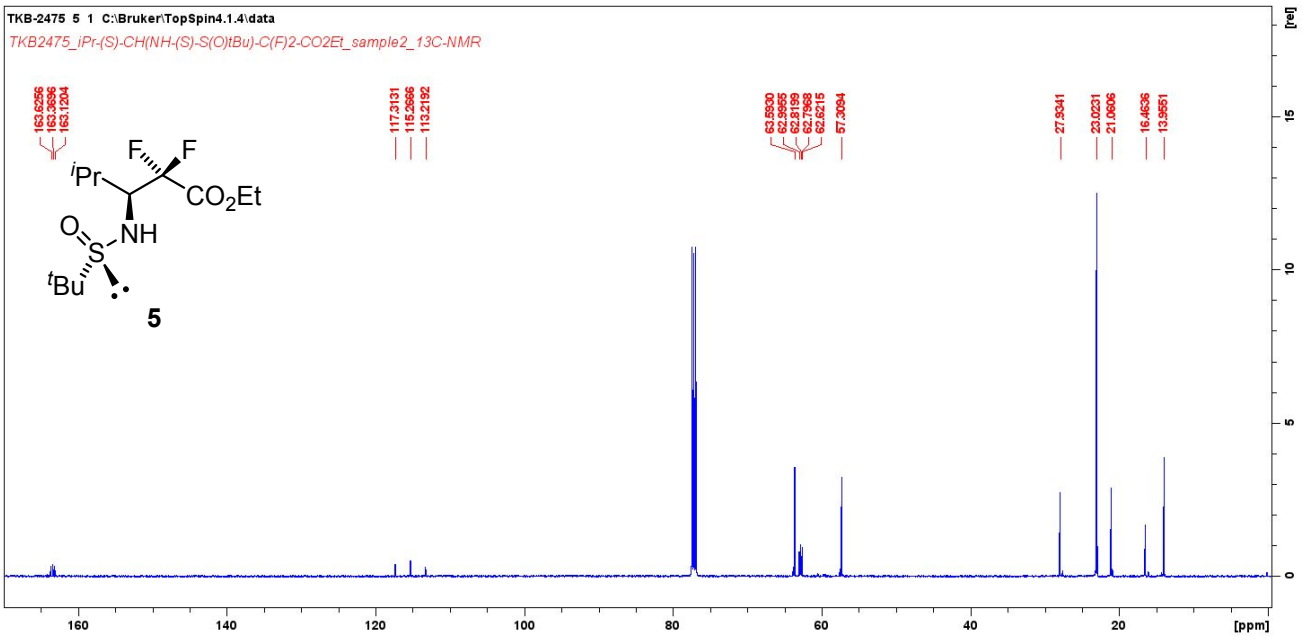

S6_MAR-0502_(EtO)2P(O)CH2C(O)XR 1 1 C:\Bruker\TopSpin4.1.4\data
MAR0502 FADI camphor sultum Xr proton
Me
Me
EtO
OEt
P
N
S
O
S6
[rel]
[ppm]

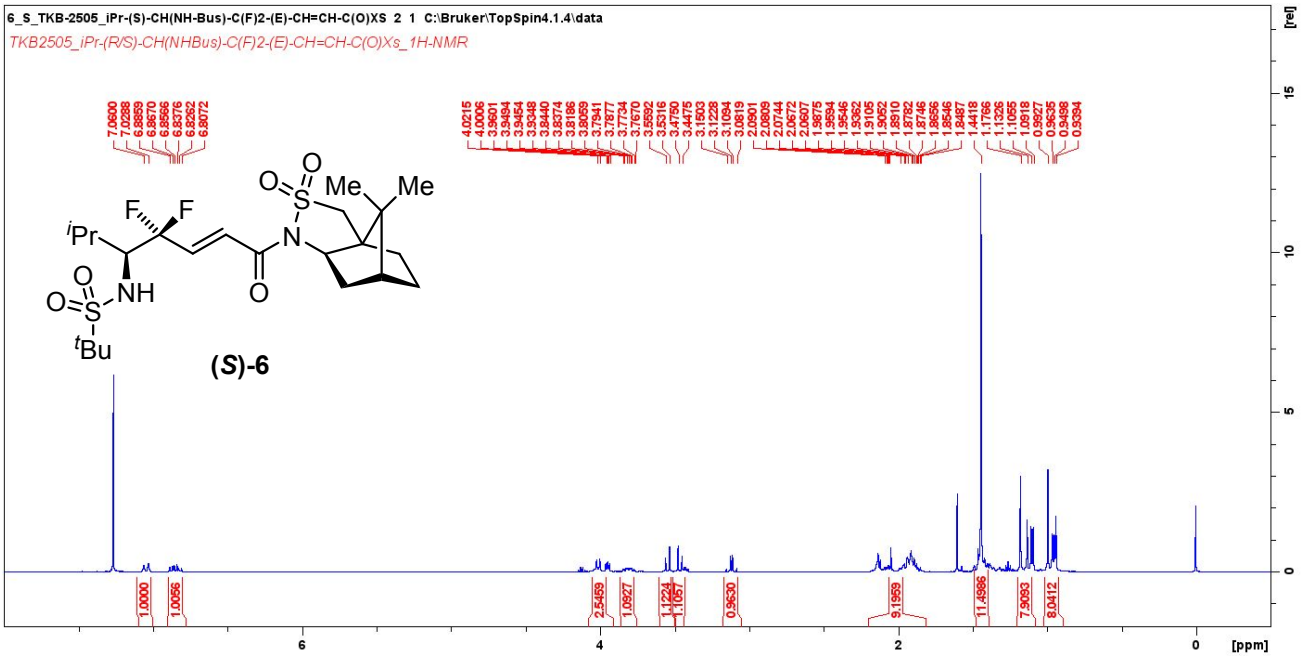

S6_MAR-0502_(EtO)2P(O)CH2C(O)XR 2 1 C:\Bruker\TopSpin4.1.4\data
MAR0502 FADI camphor sultum Xr carbon
Me
Me
EtO
OEt
P
N
S
O
S6
[rel]
[ppm]

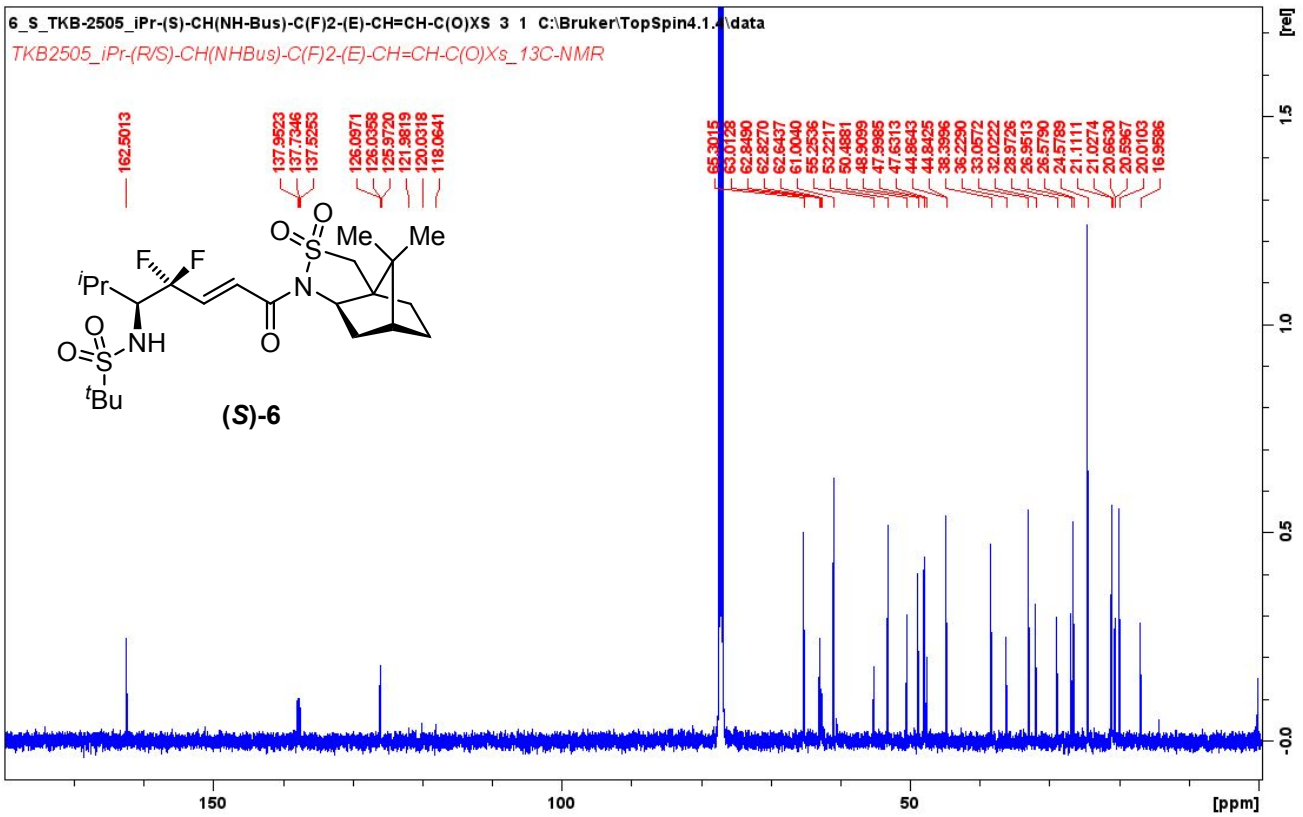

3_TKB-2428_iPr-V=N-(S)-S(O)tBu 1 1 C:\Bruker\TopSpin4.1.4\data
TKB2428_iPr-C=N-(S)-S(O)tBu_1H-NMR
7.9951
7.9863
2.7498
2.7410
2.7361
2.7273
2.7224
2.7136
2.7086
2.6998
2.6948
2.6860
1.1911
1.1794
1.1741
1.1656
1.1604
iPr
N
S
O
tBu
3
1.0000
1.0473
8
6
4
2
0
[ppm]
[rel]

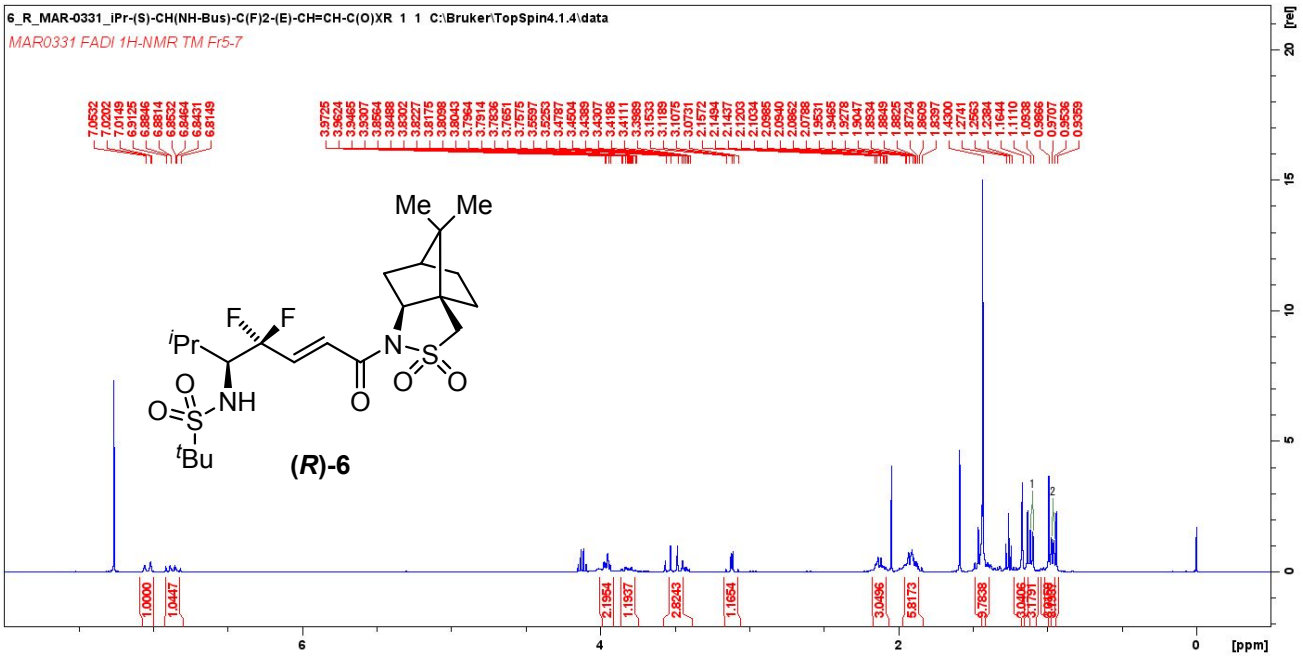

TKB-2428 2 1 C:\Bruker\TopSpin4.1.4\data
TKB2428_iPr-C=N-(S)-S(O)tBu_13C-NMR
173.7198
56.6091
35.0173
22.4455
19.0533
iPr
N
S
O
tBu
3
150
100
50
[ppm]
[rel]

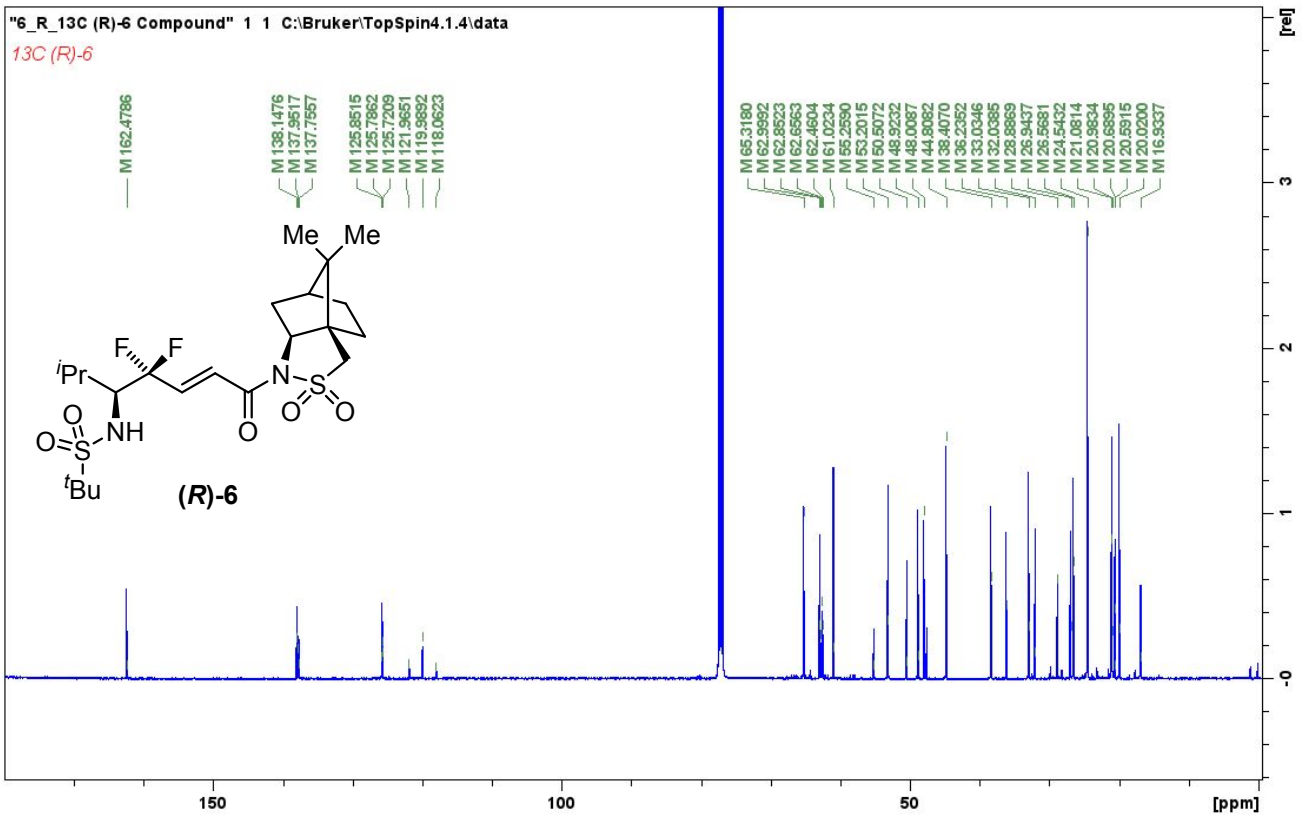

5_TKB-2475_iPr-(S)-CH(NH-(S)-S(O)tBu)-C(F)2CO2Et 3 1 C:\Bruker\TopSpin4.1.4\data
TKB2475_iPr-(S)-CH(NH-(S)-S(O)tBu)-C(F)2-CO2Et_sample2_1H-NMR
5
[ppm]

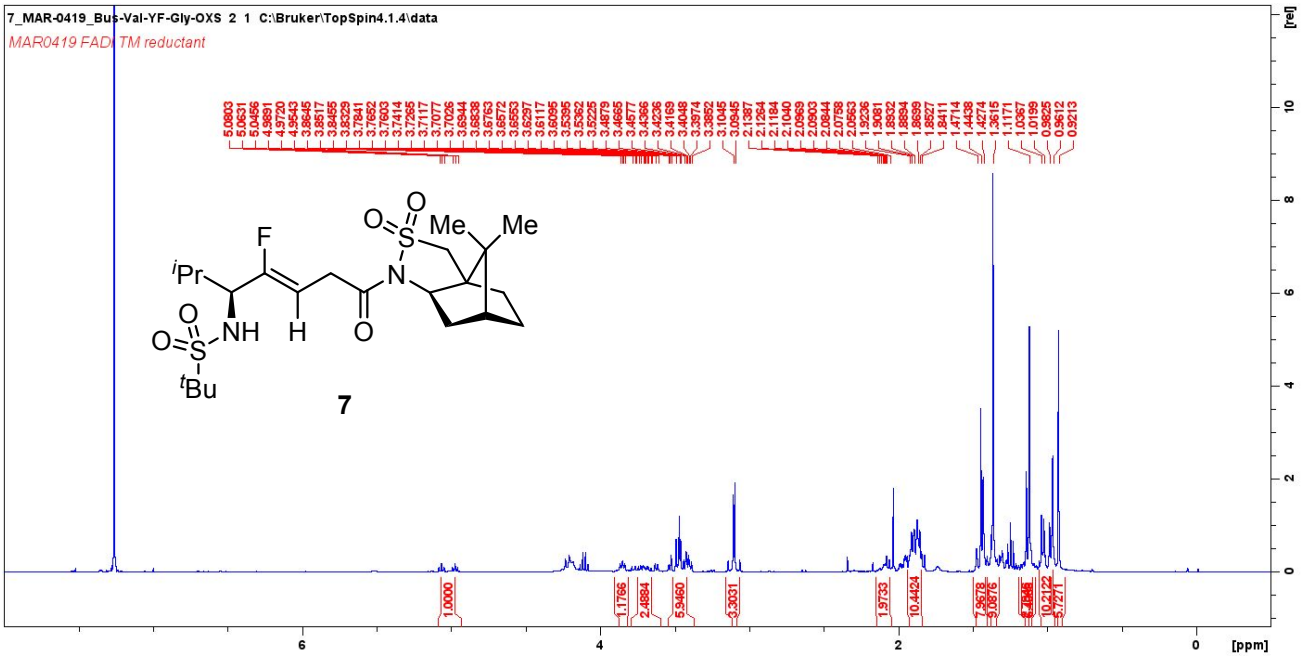

TKB-2475 5 1 C:\Bruker\TopSpin4.1.4\data
TKB2475_iPr-(S)-CH(NH-(S)-S(O)tBu)-C(F)2-CO2Et_sample2_13C-NMR
5
[ppm]

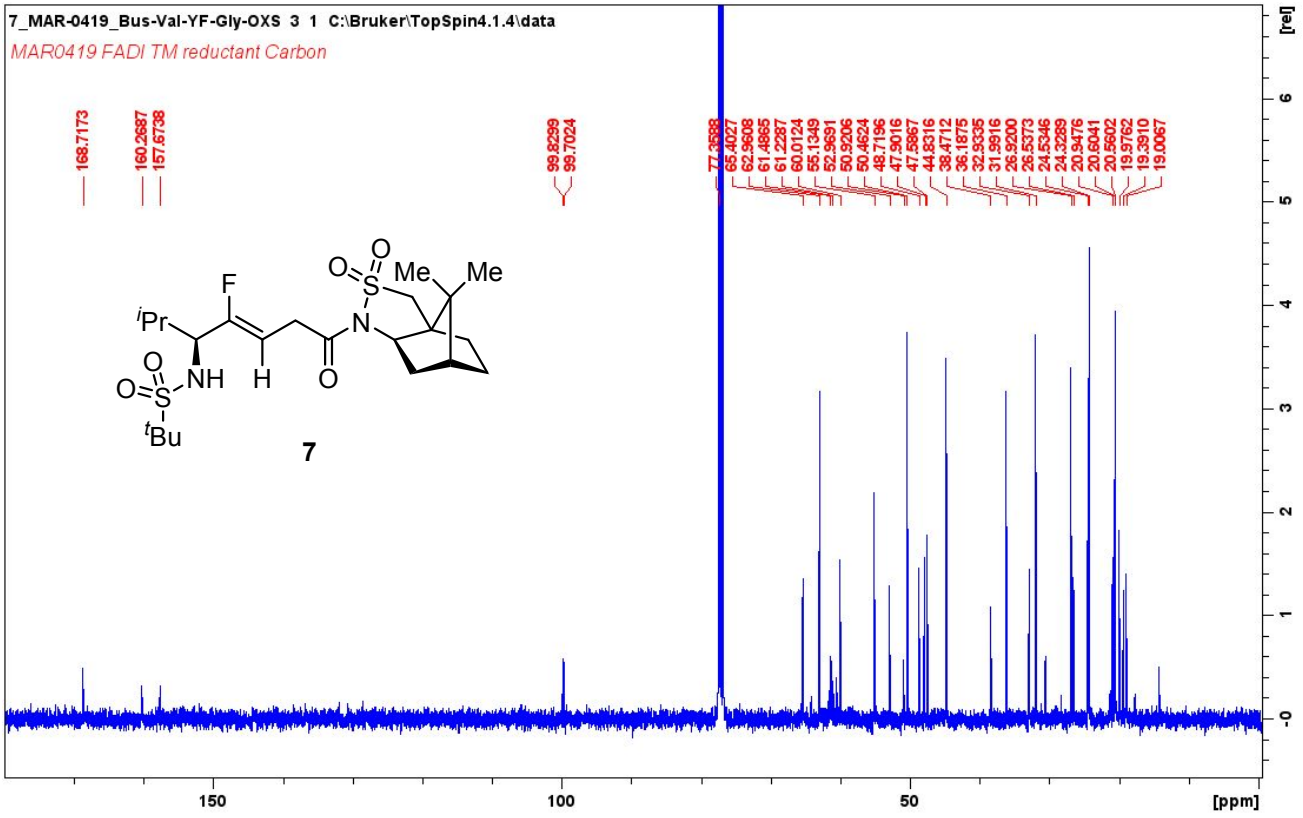

6_S_TKB-2505_iPr-(S)-CH(NH-Bus)-C(F)2-(E)-CH=CH-C(O)XS 2 1 C:\Bruker\TopSpin4.1.4\data
TKB2505_iPr-(R/S)-CH(NHBus)-C(F)2-(E)-CH=CH-C(O)Xs_1H-NMR
(S)-6
[ppm]
[rel]

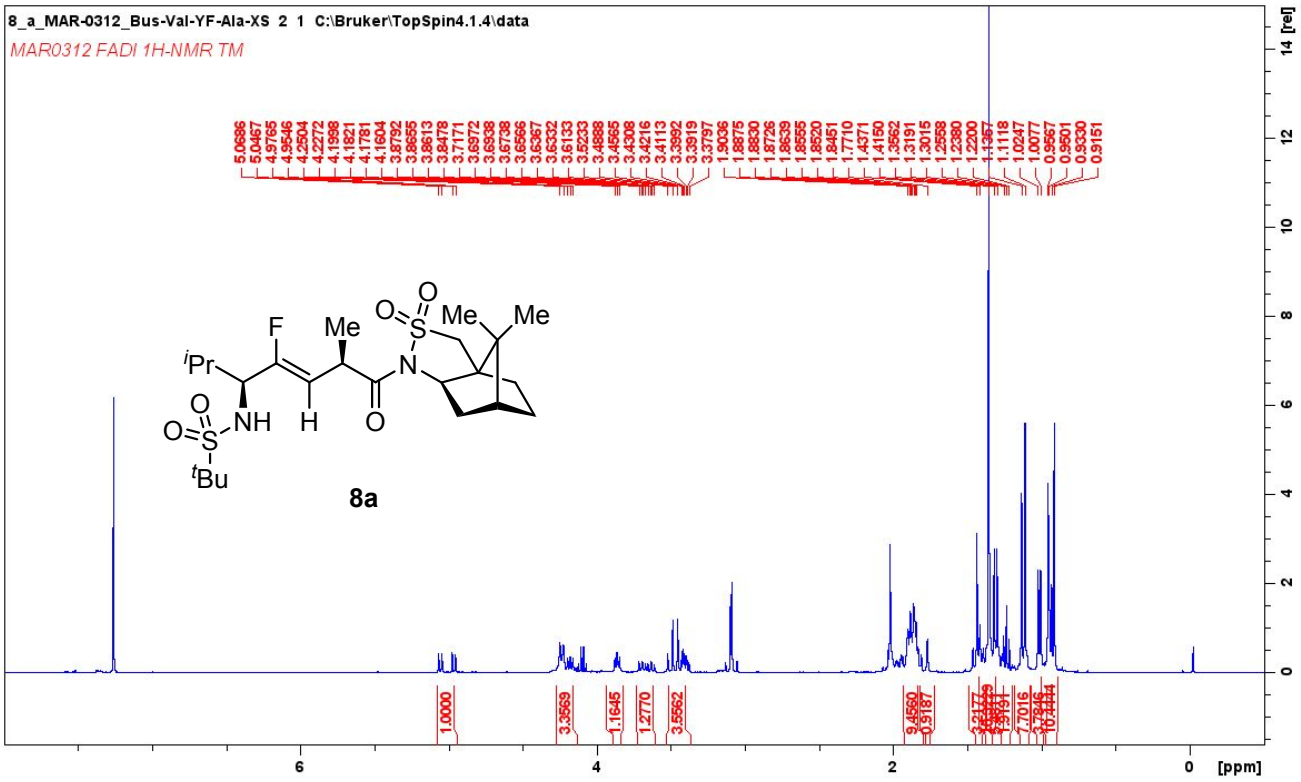

6_S_TKB-2505_iPr-(S)-CH(NH-Bus)-C(F)2-(E)-CH=CH-C(O)XS 3 1 C:\Bruker\TopSpin4.1.4\data
TKB2505_iPr-(R/S)-CH(NHBus)-C(F)2-(E)-CH=CH-C(O)Xs_13C-NMR
(S)-6
[ppm]
[rel]

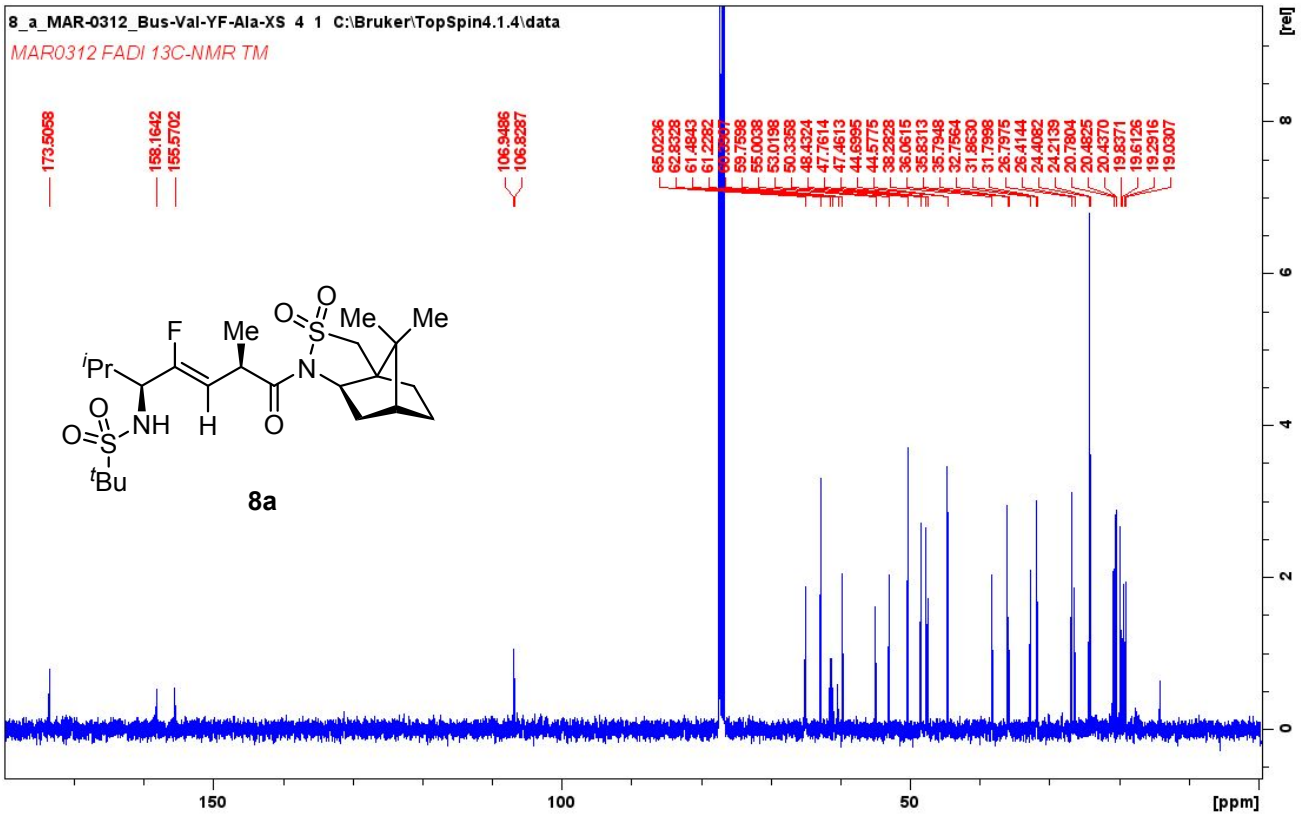

6_R_MAR-0331_iPr-(S)-CH(NH-Bus)-C(F)2-(E)-CH=CH-C(O)XR 1 1 C:\Bruker\TopSpin4.1.4\data
MAR0331 FADI 1H-NMR TM Fr5-7
(R)-6
[ppm]
[rel]

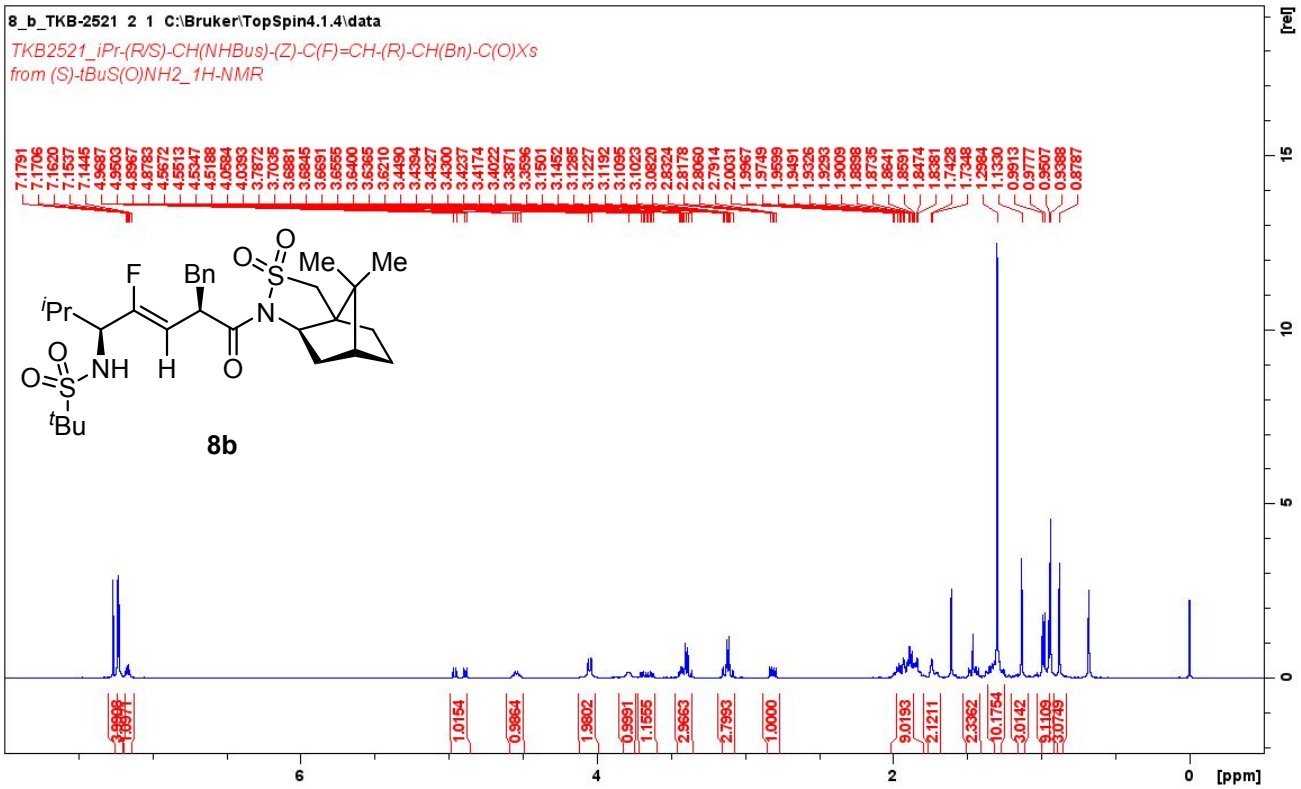

"6_R_13C (R)-6 Compound" 1 1 C:\Bruker\TopSpin4.1.4\data
13C (R)-6
(R)-6
[ppm]
[rel]

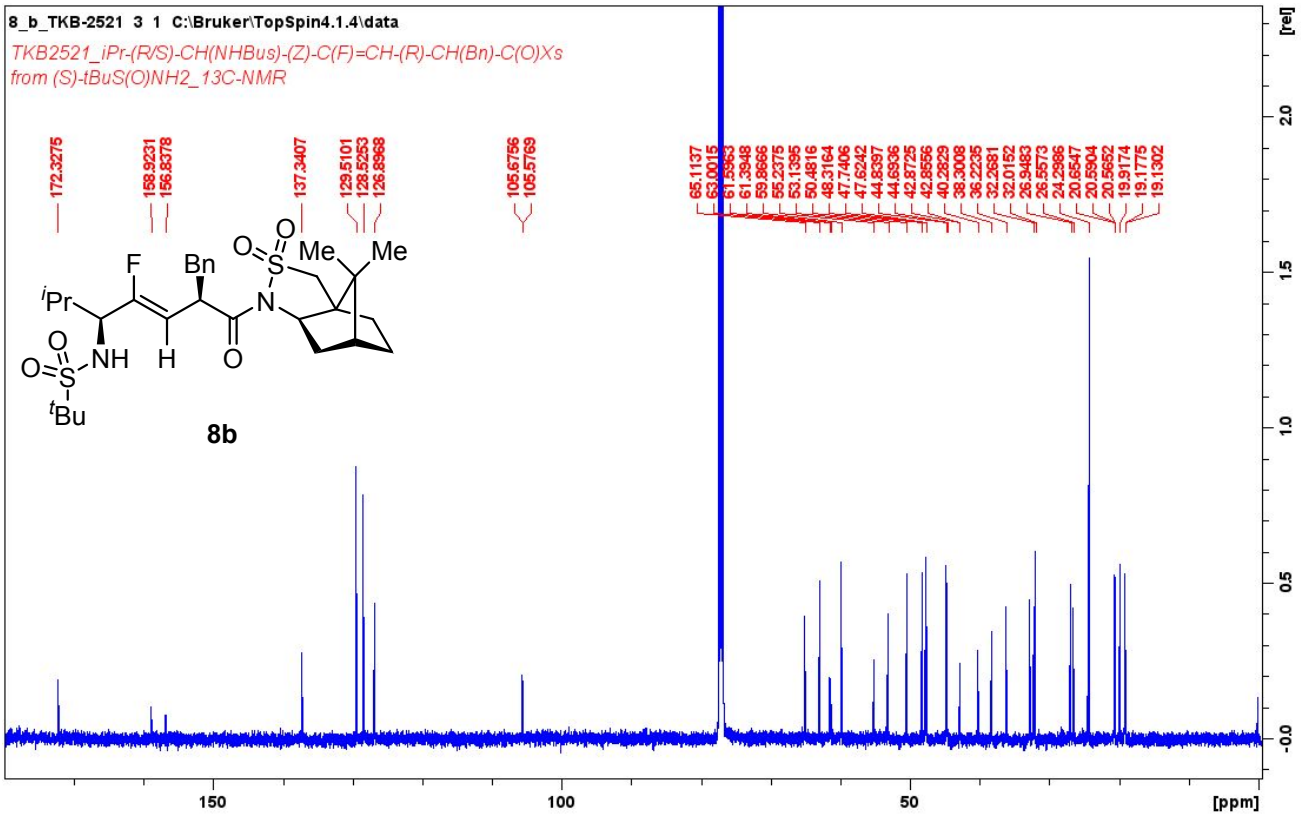

7_MAR-0419_Bus-Val-YF-Gly-OXS 2 1 C:\Bruker\TopSpin4.1.4\data
MAR0419 FADI TM reductant
7
[ppm]
[rel]

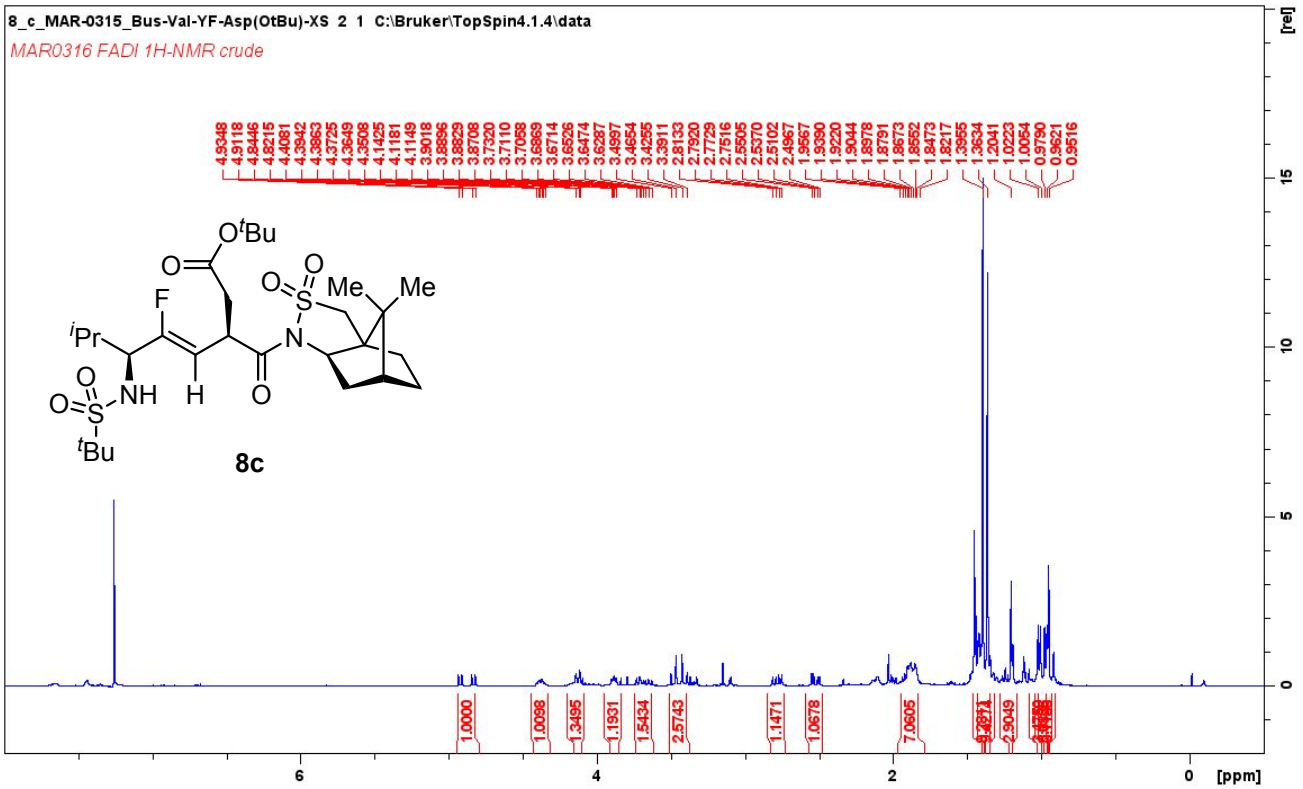

7_MAR-0419_Bus-Val-YF-Gly-OXS 3 1 C:\Bruker\TopSpin4.1.4\data
MAR0419 FADI TM reductant Carbon
7
[ppm]
[rel]

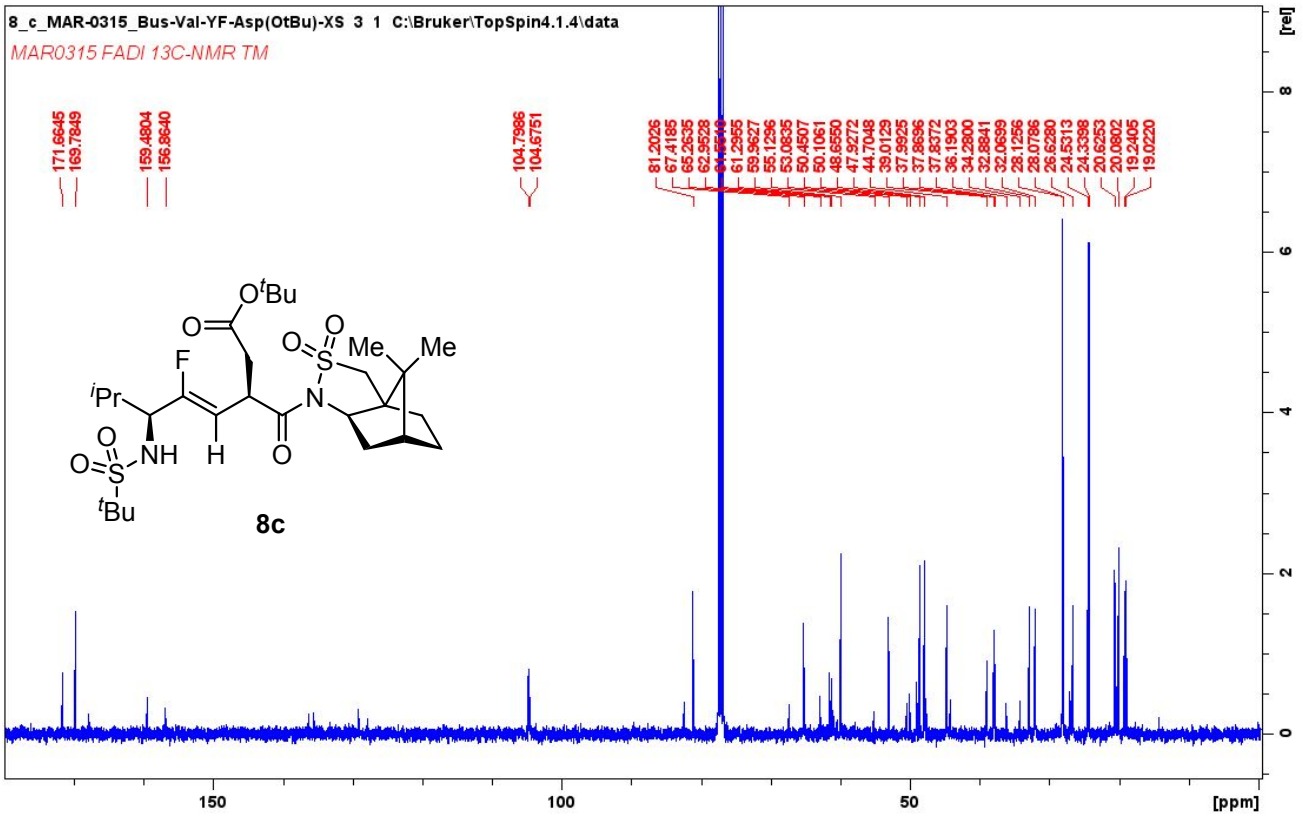

8_a_MAR-0312_Bus-Val-YF-Ala-XS 2 1 C:\Bruker\TopSpin4.1.4\data
MAR0312 FADI 1H-NMR TM
8a
[ppm]

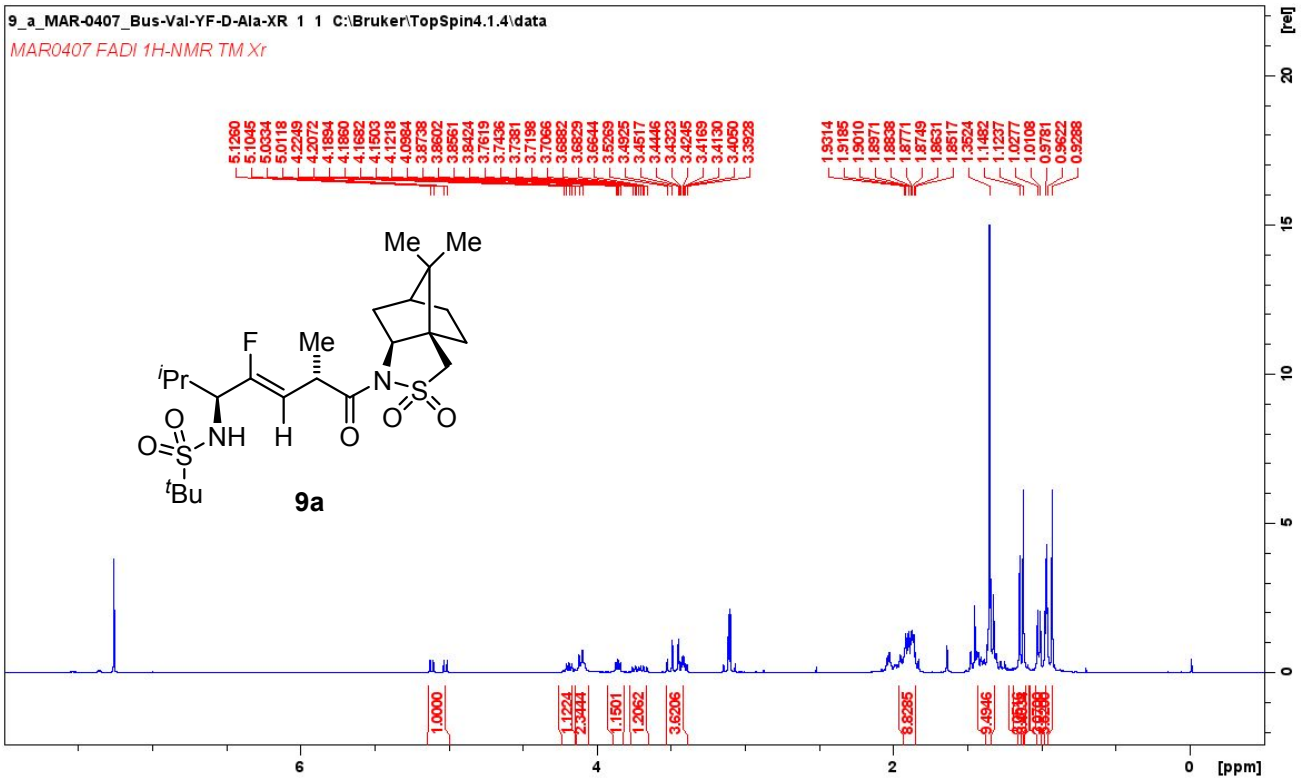

8_a_MAR-0312_Bus-Val-YF-Ala-XS 4 1 C:\Bruker\TopSpin4.1.4\data
MAR0312 FADI 13C-NMR TM
8a
[ppm]

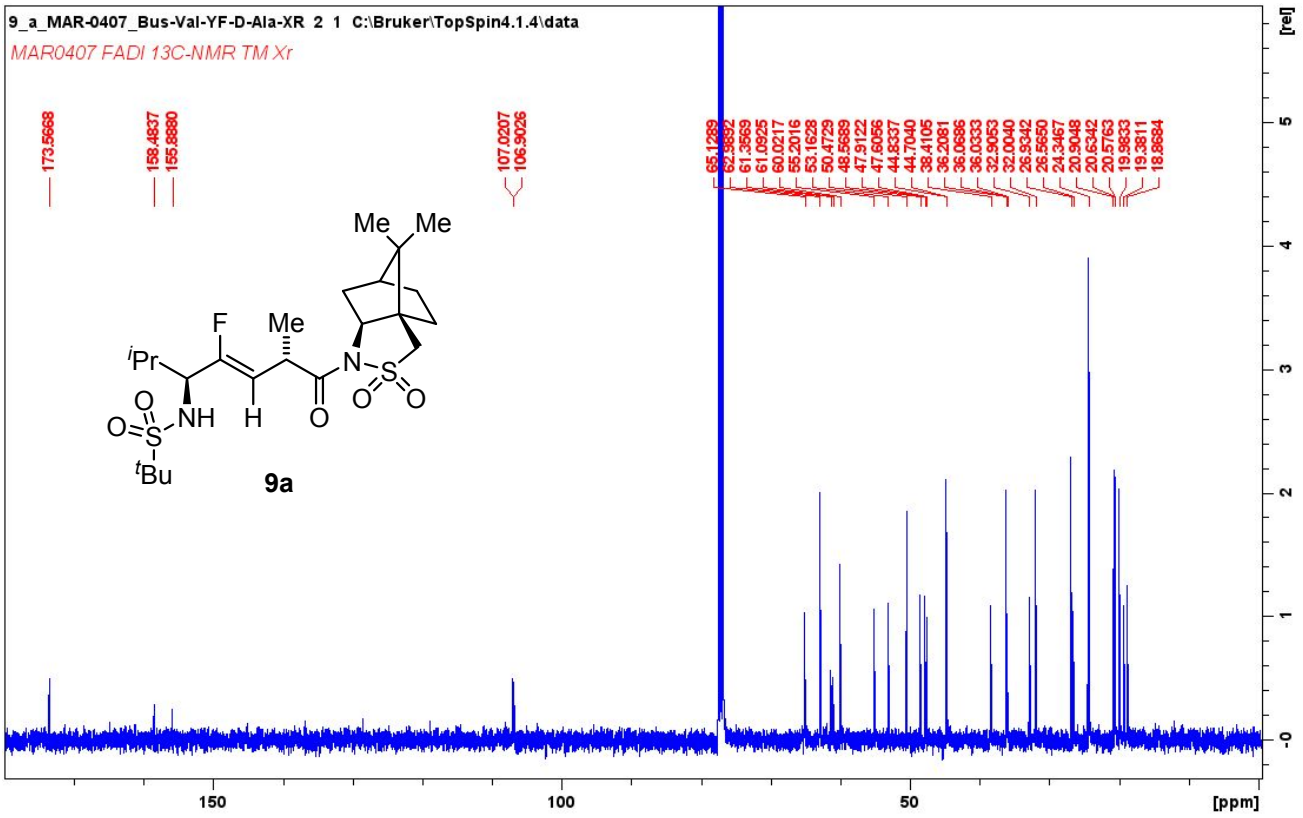

8_b_TKB-2521 2 1 C:\Bruker\TopSpin4.1.4\data
TKB2521_iPr-(R/S)-CH(NHBus)-(Z)-C(F)=CH-(R)-CH(Bn)-C(O)Xs
from (S)-tBuS(O)NH2_1H-NMR
8b
[ppm]
[rel]

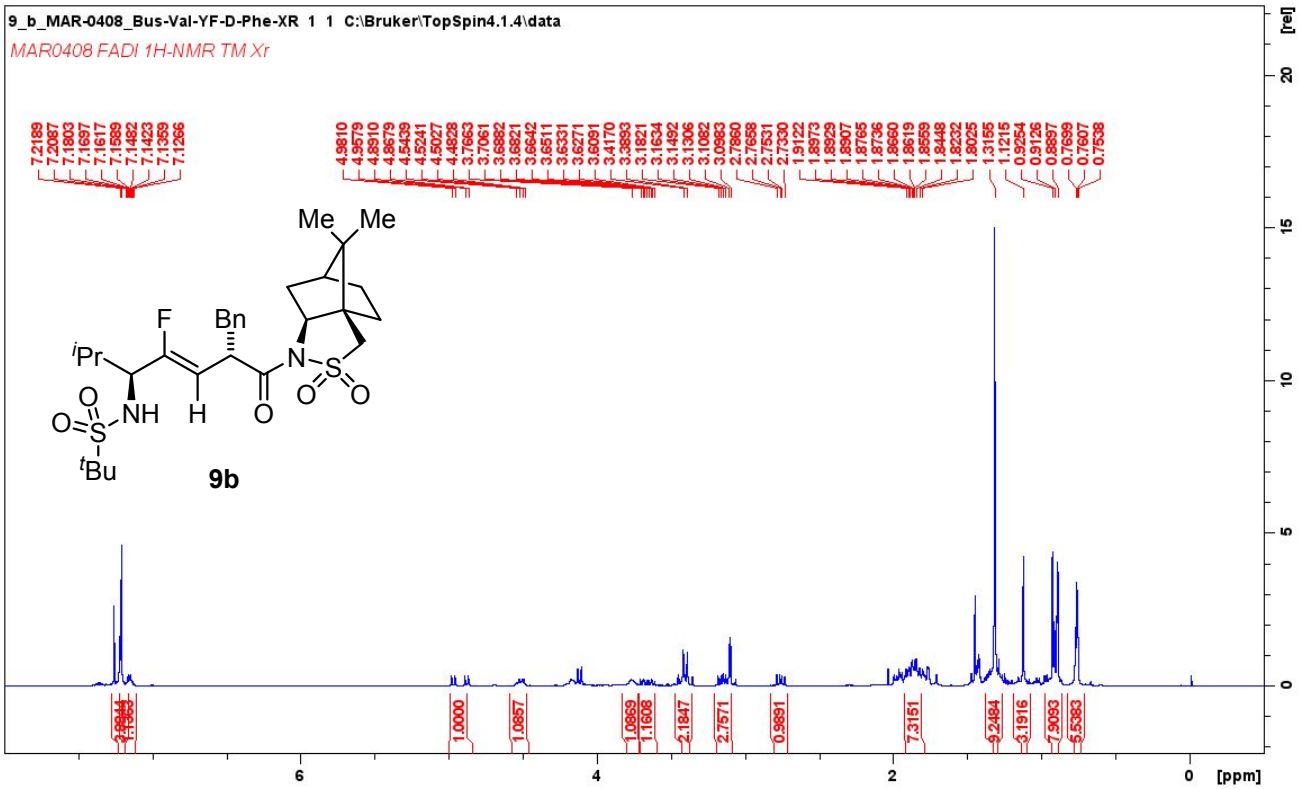

8_b_TKB-2521 3 1 C:\Bruker\TopSpin4.1.4\data
TKB2521_iPr-(R/S)-CH(NHBus)-(Z)-C(F)=CH-(R)-CH(Bn)-C(O)Xs
from (S)-tBuS(O)NH2_13C-NMR
8b
[ppm]
[rel]

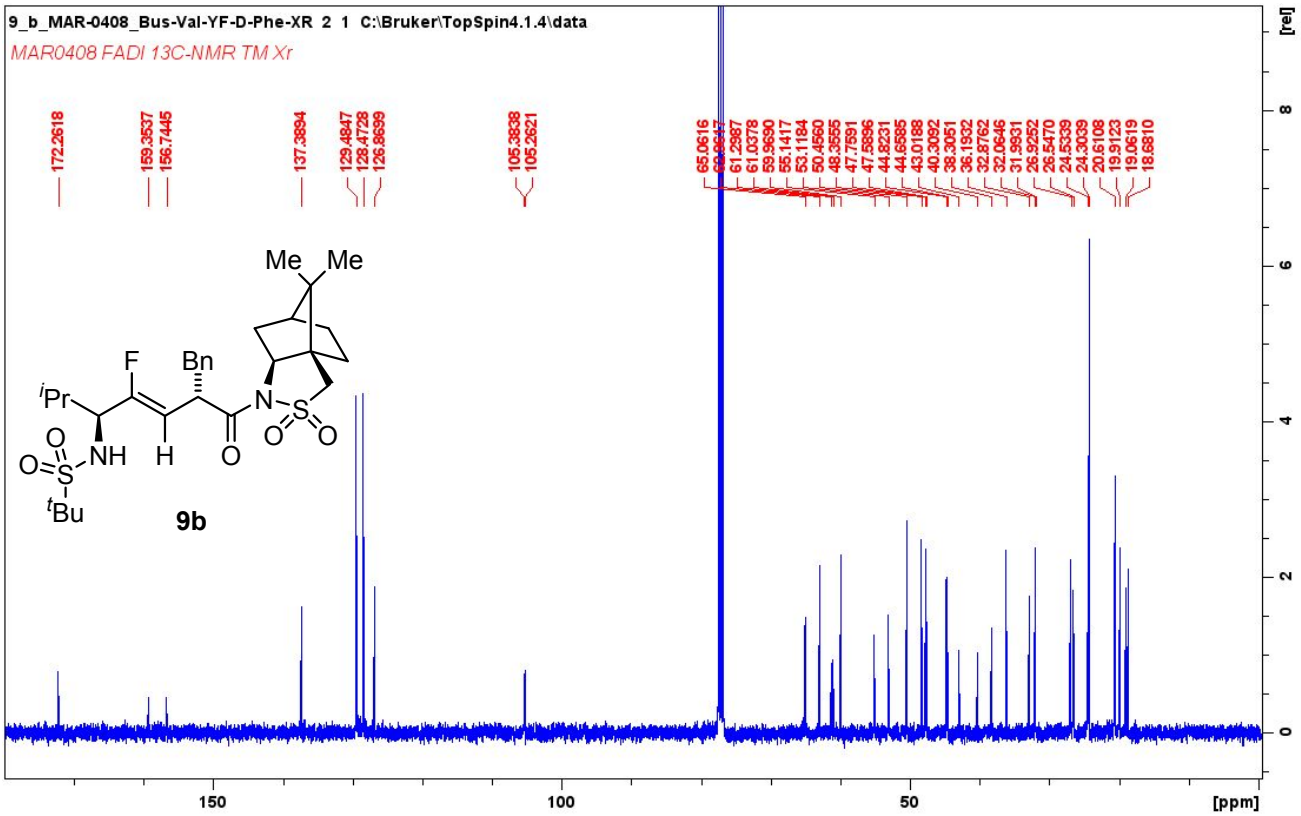

8_c_MAR-0315_Bus-Val-YF-Asp(OtBu)-XS 2 1 C:\Bruker\TopSpin4.1.4\data
MAR0316 FADI 1H-NMR crude
8c
[ppm]
[rel]

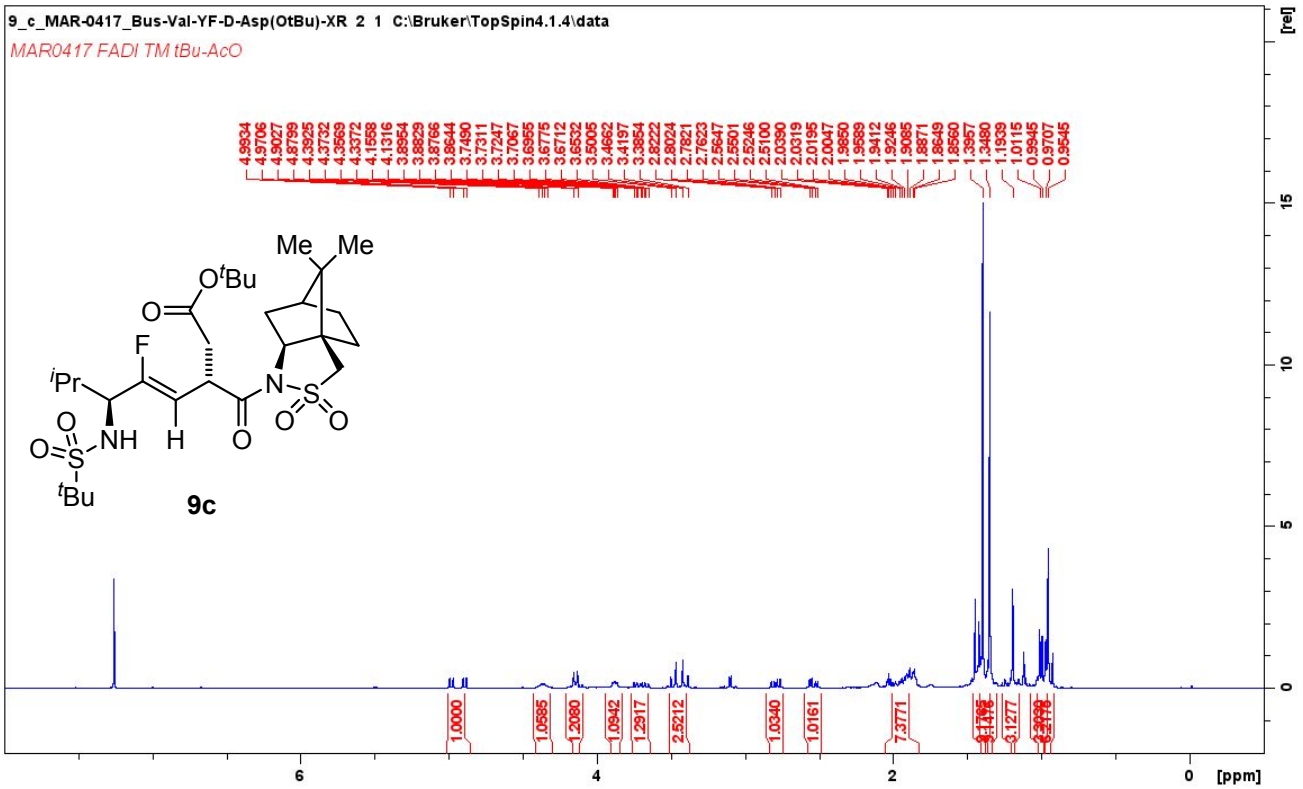

8_c_MAR-0315_Bus-Val-YF-Asp(OtBu)-XS 3 1 C:\Bruker\TopSpin4.1.4\data
MAR0315 FADI 13C-NMR TM
8c
[ppm]
[rel]

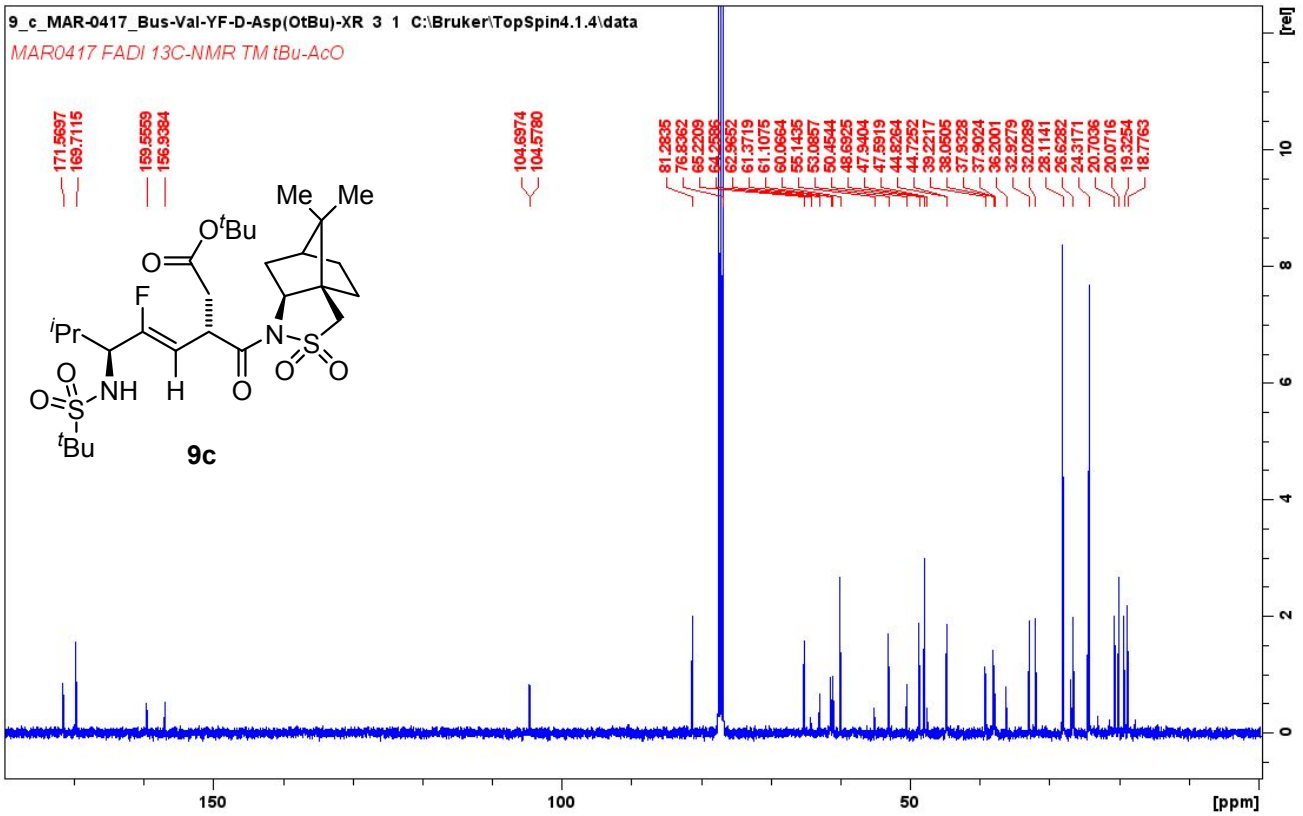

9_a_MAR-0407_Bus-Val-YF-D-Ala-XR 1 1 C:\Bruker\TopSpin4.1.4\data
MAR0407 FADI 1H-NMR TM Xr
9a
[ppm]
[rel]

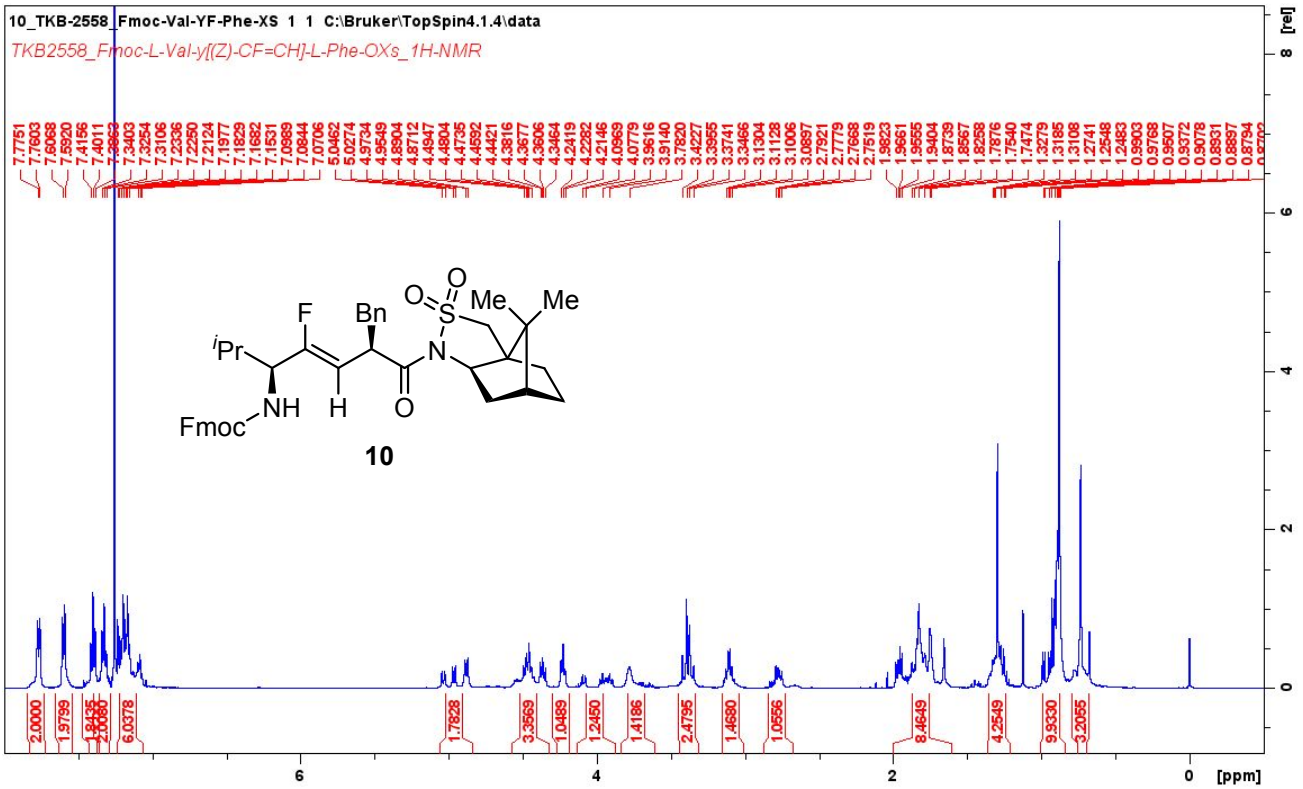

9_a_MAR-0407_Bus-Val-YF-D-Ala-XR 2 1 C:\Bruker\TopSpin4.1.4\data
MAR0407 FADI 13C-NMR TM Xr
9a
[ppm]
[rel]

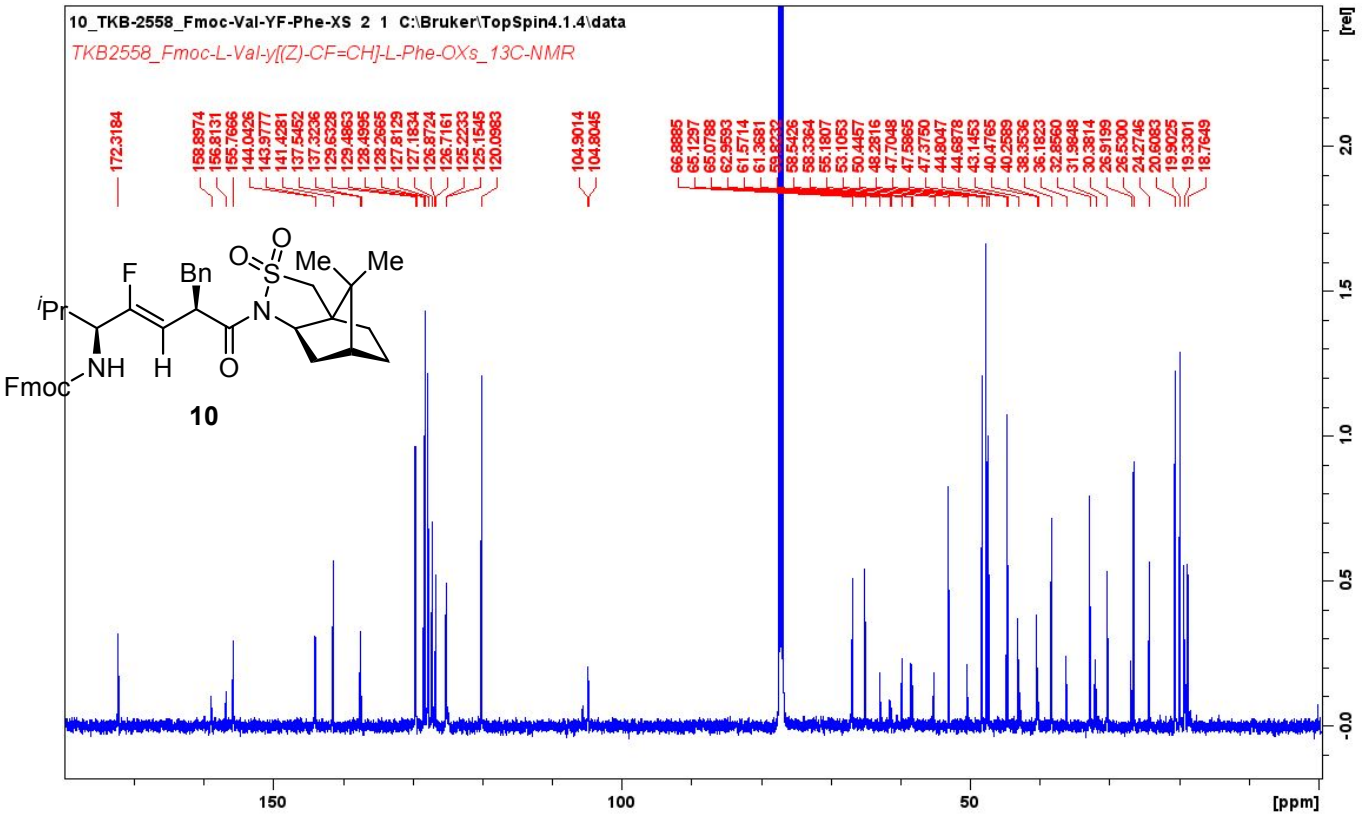

9_b_MAR-0408_Bus-Val-YF-D-Phe-XR 1 1 C:\Bruker\TopSpin4.1.4\data
MAR0408 FADI 1H-NMR TM Xr
9b
[ppm]
[rel]

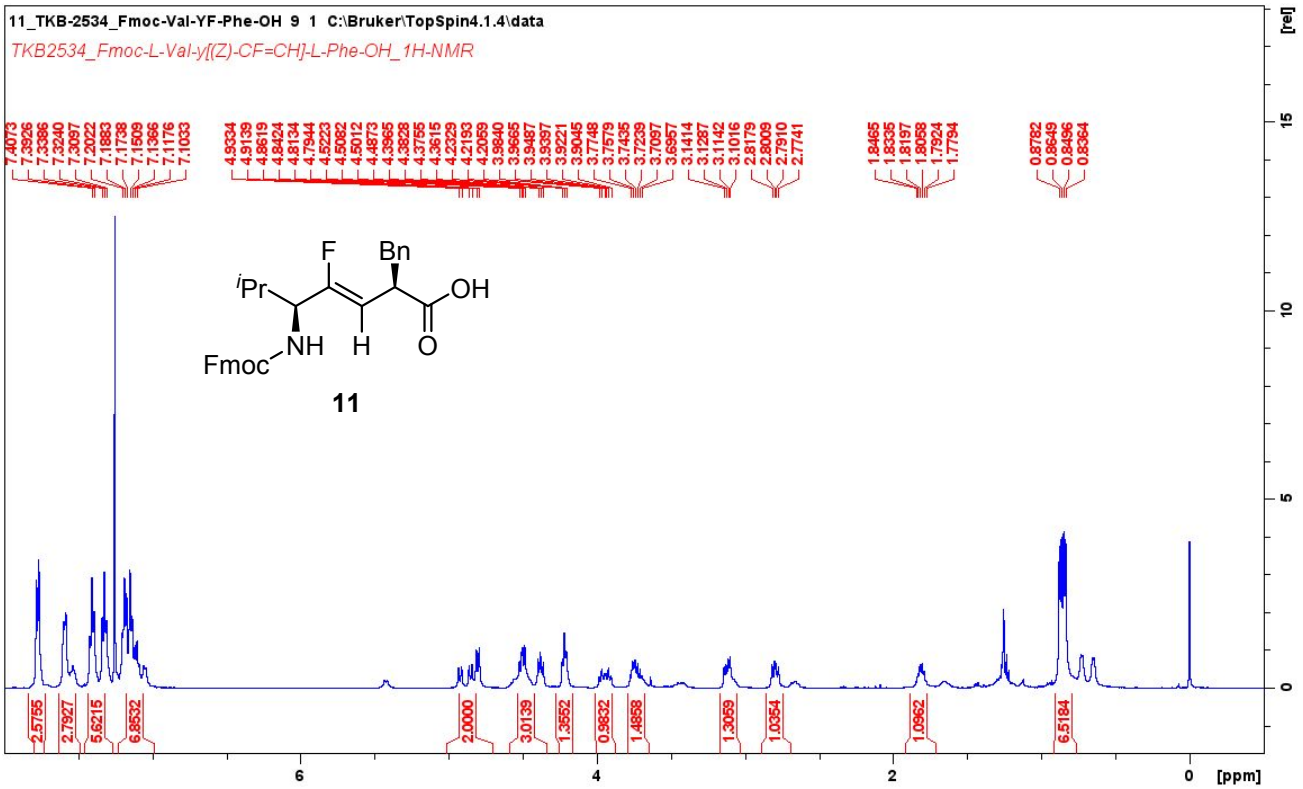

9_b_MAR-0408_Bus-Val-YF-D-Phe-XR 2 1 C:\Bruker\TopSpin4.1.4\data
MAR0408 FADI 13C-NMR TM Xr
9b
[ppm]
[rel]

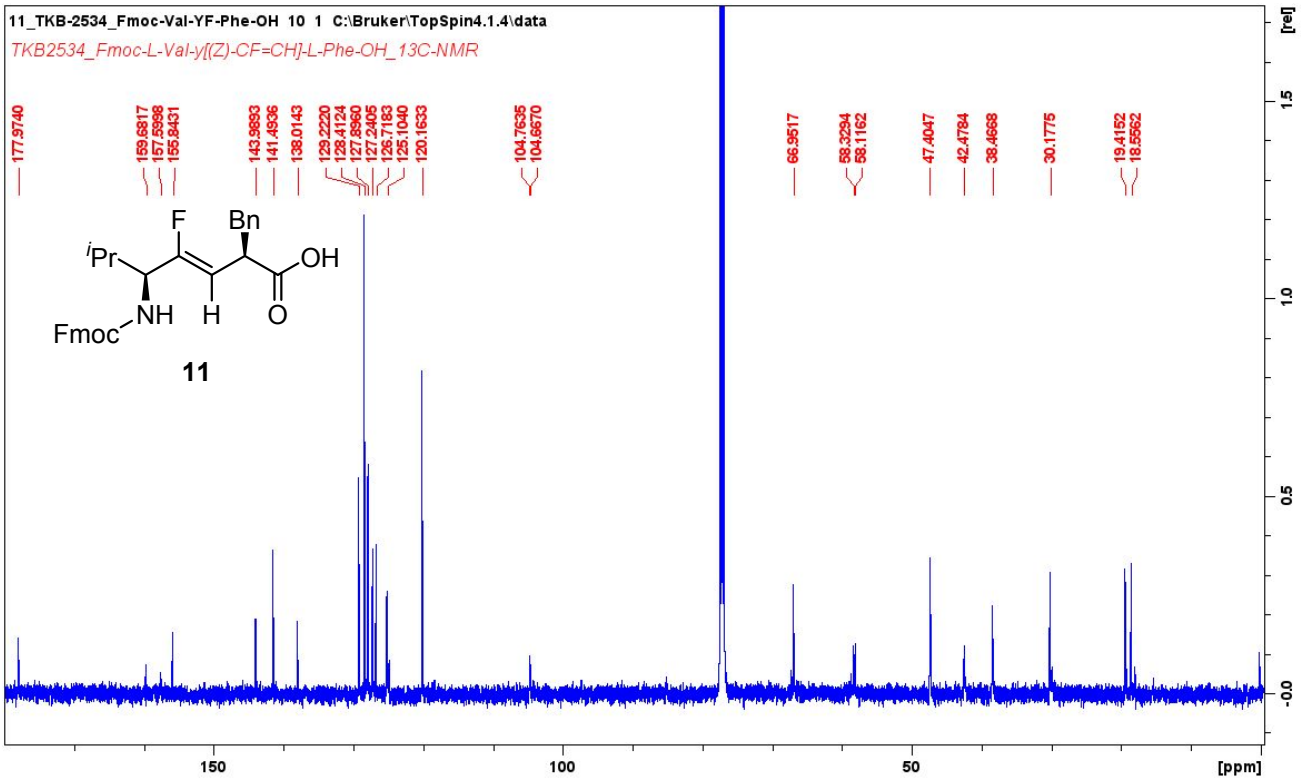

9_c_MAR-0417_Bus-Val-YF-D-Asp(OtBu)-XR 2 1 C:\Bruker\TopSpin4.1.4\data
MAR0417 FADI TM tBu-AcO
9c
[ppm]
[rel]

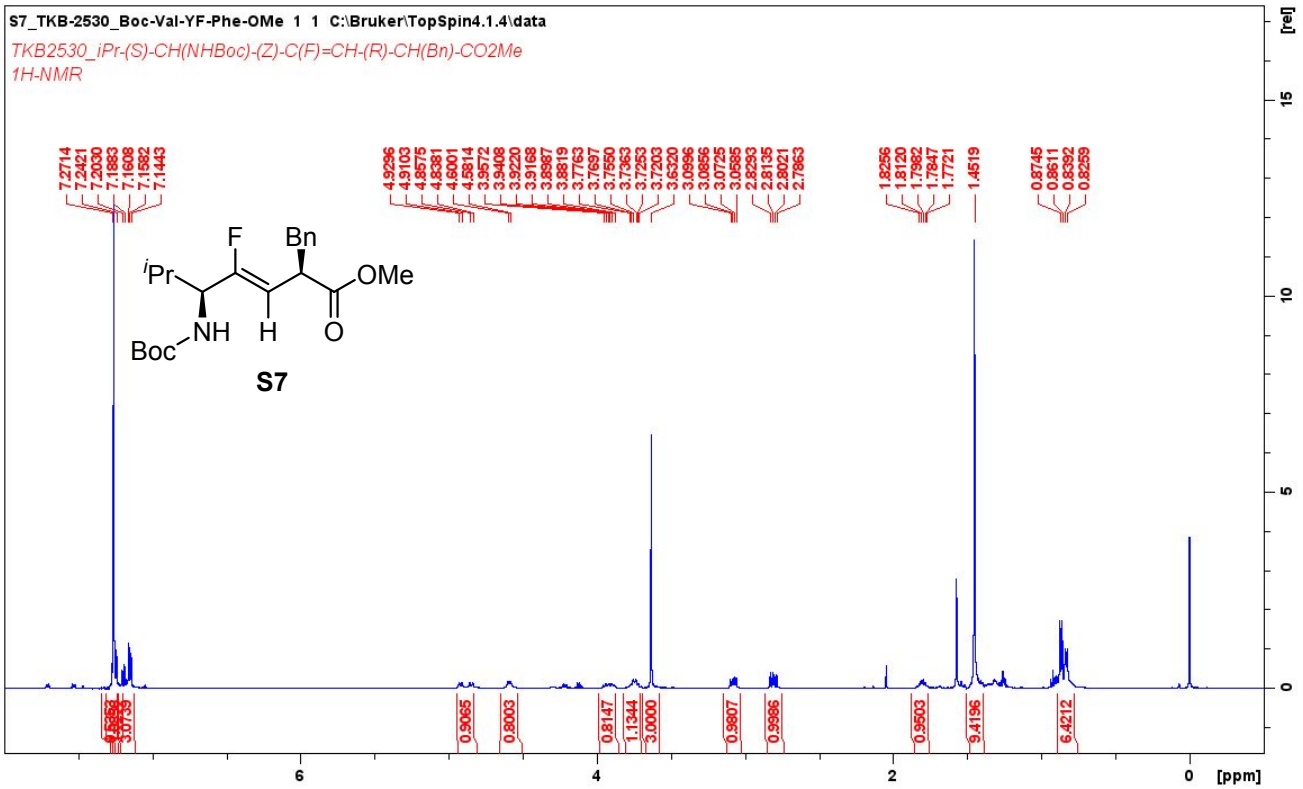

9_c_MAR-0417_Bus-Val-YF-D-Asp(OtBu)-XR 3 1 C:\Bruker\TopSpin4.1.4\data
MAR0417 FADI 13C-NMR TM tBu-AcO
9c
[ppm]
[rel]

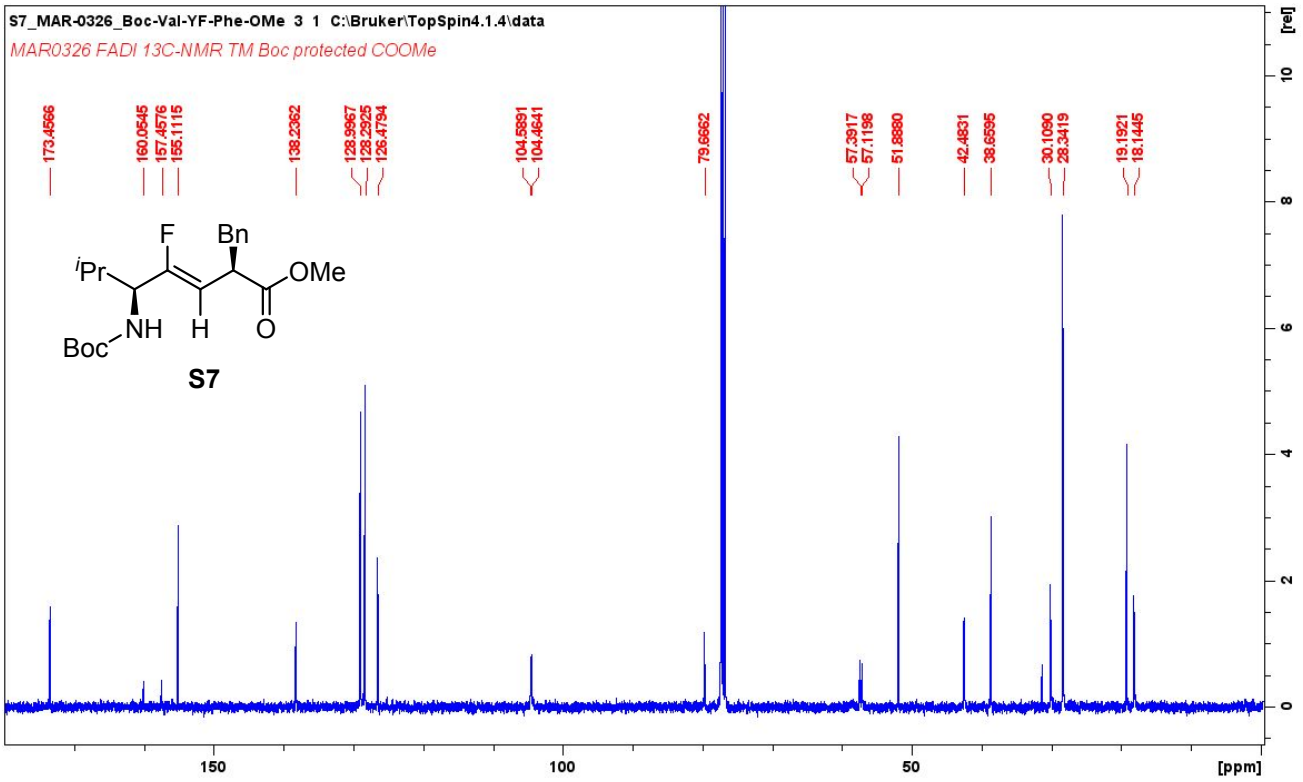

10_TKB-2558_Fmoc-Val-YF-Phe-XS 1 1 C:\Bruker\TopSpin4.1.4\data
TKB2558_Fmoc-L-Val-y[(Z)-CF=CH]-L-Phe-OXs_1H-NMR
F
Bn
Me
Me
iPr
NH
H
O
Fmoc
10
[ppm]
[rel]

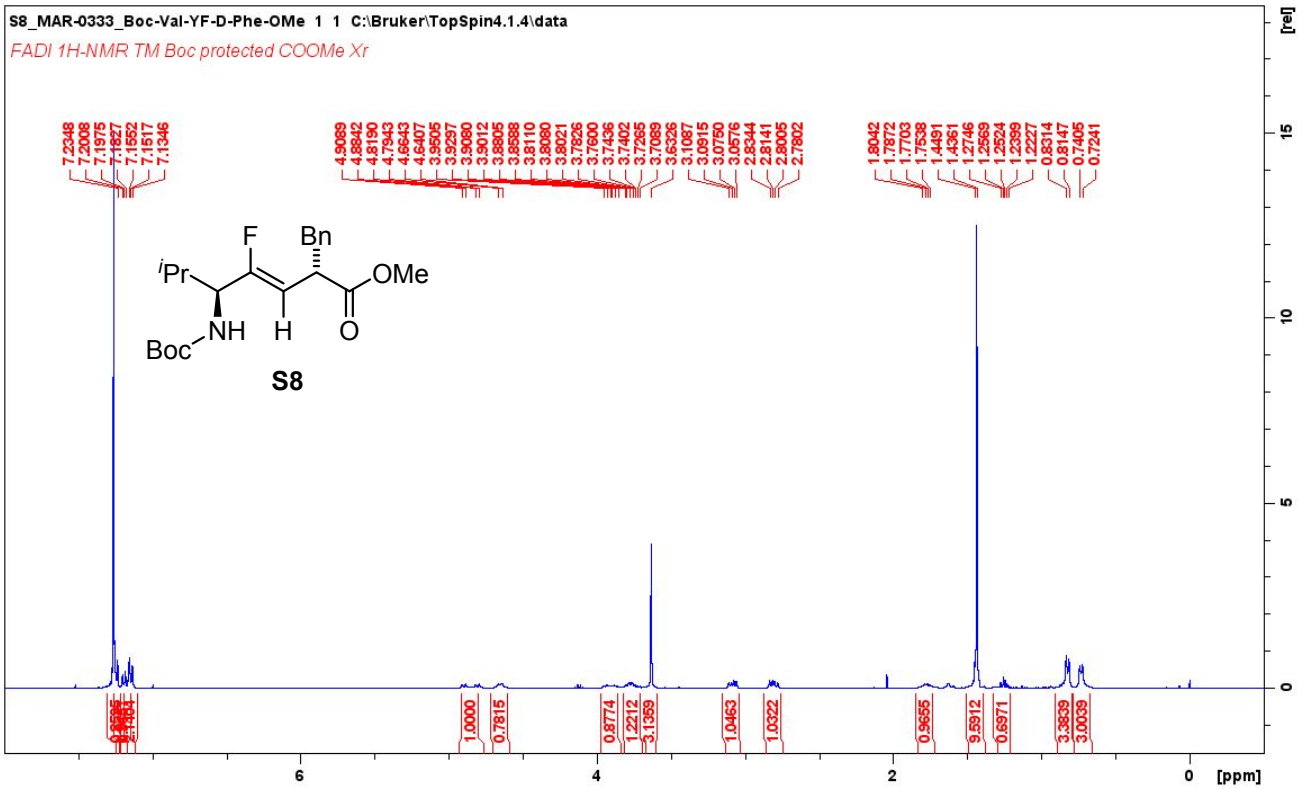

10_TKB-2558_Fmoc-Val-YF-Phe-XS 2 1 C:\Bruker\TopSpin4.1.4\data
TKB2558_Fmoc-L-Val-y[(Z)-CF=CH]-L-Phe-OXs_13C-NMR
F
Bn
Me
Me
iPr
NH
H
O
Fmoc
10
[ppm]
[rel]

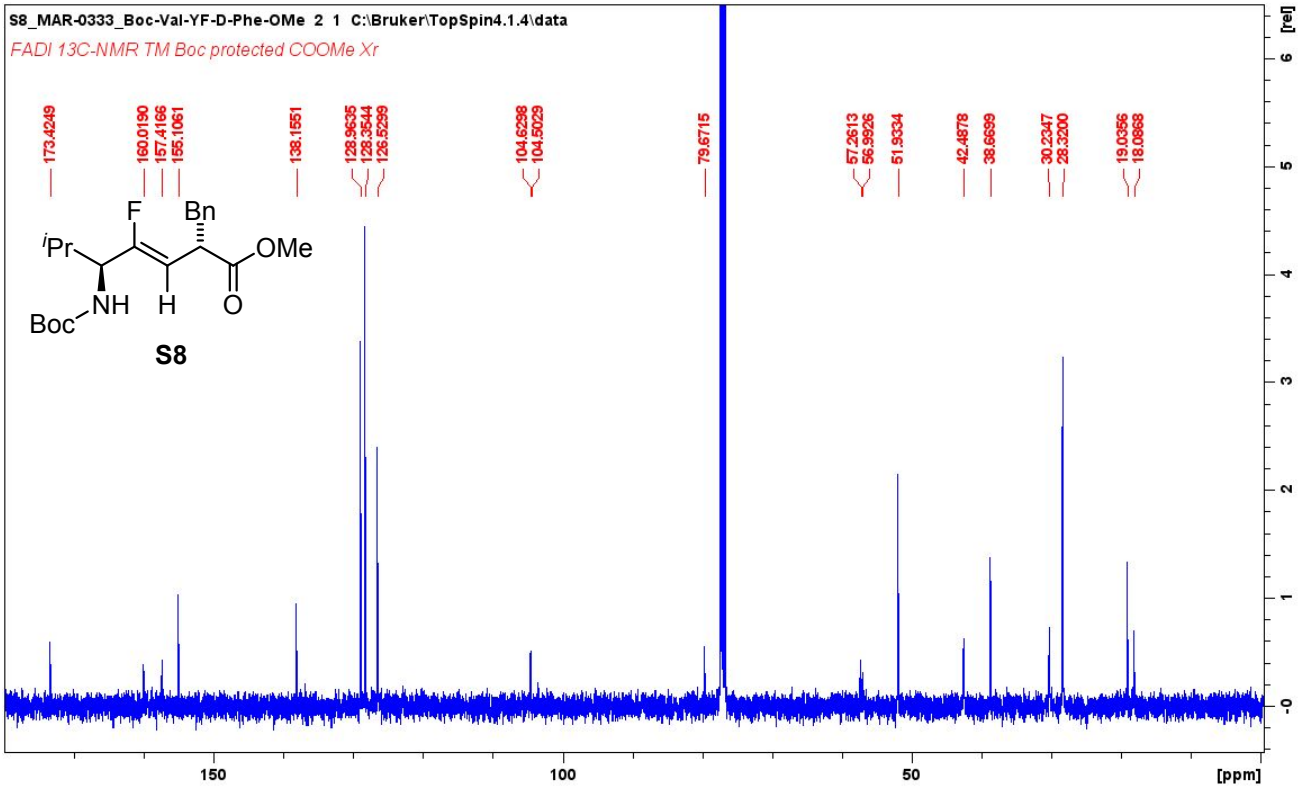

11_TKB-2534_Fmoc-Val-YF-Phe-OH 9 1 C:\Bruker\TopSpin4.1.4\data
TKB2534_Fmoc-L-Val-y[(Z)-CF=CH]-L-Phe-OH_1H-NMR
F
Bn
iPr
OH
NH
H
O
Fmoc
11
[rel]
[ppm]


11_TKB-2534_Fmoc-Val-YF-Phe-OH 10 1 C:\Bruker\TopSpin4.1.4\data
TKB2534_Fmoc-L-Val-y[(Z)-CF=CH]-L-Phe-OH_13C-NMR
F
Bn
iPr
OH
NH
H
O
Fmoc
11
[rel]
[ppm]


S7_TKB-2530_Boc-Val-YF-Phe-OMe 1 1 C:\Bruker\TopSpin4.1.4\data
TKB2530_iPr-(S)-CH(NHBoc)-(Z)-C(F)=CH-(R)-CH(Bn)-CO2Me
1H-NMR
F
Bn
iPr
OMe
NH
H
O
Boc
S7
[ppm]
[rel]


S7_MAR-0326_Boc-Val-YF-Phe-OMe 3 1 C:\Bruker\TopSpin4.1.4\data
MAR0326 FADI 13C-NMR TM Boc protected COOMe
F
Bn
iPr
OMe
NH
H
O
Boc
S7
[ppm]
[rel]


S8_MAR-0333_Boc-Val-YF-D-Phe-OMe 1 1 C:\Bruker\TopSpin4.1.4\data
FADI 1H-NMR TM Boc protected COOMe Xr
F
Bn
iPr
OMe
NH
H
O
Boc
S8
[ppm]
[rel]


S8_MAR-0333_Boc-Val-YF-D-Phe-OMe 2 1 C:\Bruker\TopSpin4.1.4\data
FADI 13C-NMR TM Boc protected COOMe Xr
F
Bn
iPr
OMe
NH
H
O
Boc
S8
[ppm]
[rel]