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STEREOCONTROLLED SYNTHESIS OF NITROGEN-SUBSTITUTED QUATERNARY STEREOGENIC CENTERS: LESSONS FROM A SYNTHETIC ROUTE TO THE CORE STRUCTURE OF SPHINGOFUNGIN E

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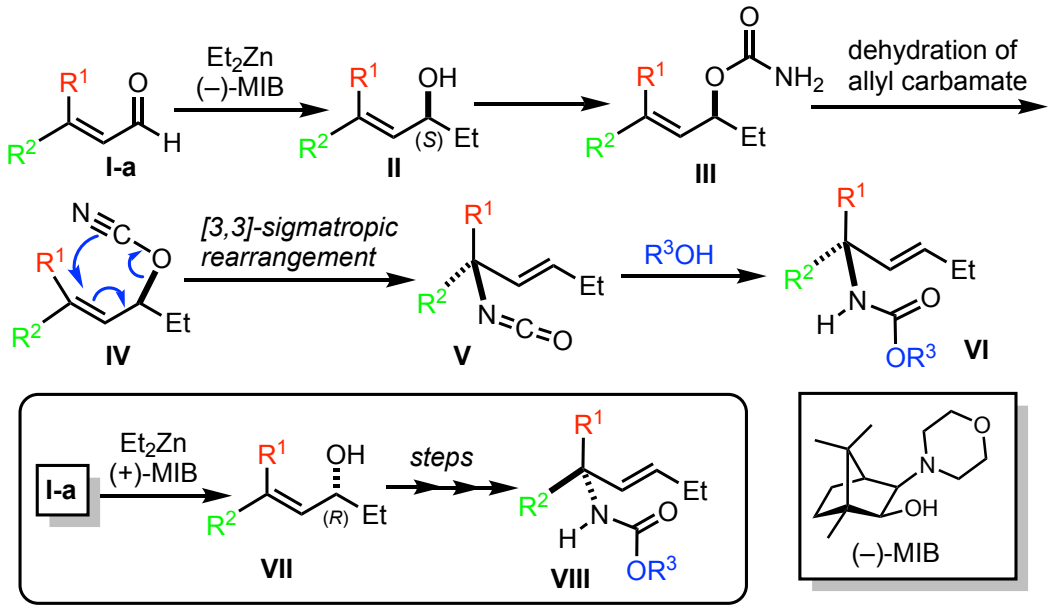
Abstract – A strategy has been developed for stereocontrolled synthesis of nitrogen-substituted quaternary stereogenic centers that utilizes enantioselective addition of diethylzinc to α,β-unsaturated aldehydes and allyl cyanate-to-isocyanate rearrangement as key steps. The power and flexibility of this approach was demonstrated by its use in a stereocontrolled synthesis of the core structure of sphingofungin E and its epimer.

INTRODUCTION

Stereoselective synthesis of quaternary stereogenic centers is among the most challenging problems in synthetic organic chemistry.[1] Our research group has had longstanding interest in developing strategies to address this challenge, especially when stereogenic centers contain nitrogen substituents which exist as an architectural element in a variety of nitrogen-containing natural products.[2] In order to confront this challenge, we designed a unique strategy that is based on the allyl cyanate-to-isocyanate rearrangement[3] (Scheme 1). The proposed approach to generate nitrogen-substituted quaternary stereogenic centers begins with (–)-3-*exo*-morpholinoisoborneol (MIB) catalyzed enantioselective addition of diethylzinc (Et_2Zn) to a β,β-disubstituted-α,β-unsaturated aldehyde **I-a** to produce (*S*)-allyl alcohol **II** in a predictable enantioselective manner.[4] Transformation of alcohol **II** to allyl carbamate **III** followed by dehydration should form the allyl cyanate intermediate **IV**, which is expected to immediately undergo concerted [3,3]-sigmatropic rearrangement to yield allyl isocyanate **V** with a high degree of [1,3]-chirality transfer.[5]

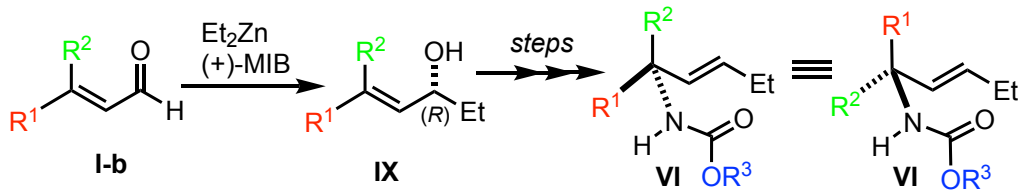
Treatment of the resultant allyl isocyanate **V** with an alcohol would then form carbamate **VI** which possesses the target nitrogen-substituted quaternary stereogenic center.[6]



Scheme 1. Strategy for stereoselective installation of nitrogen-substituted quaternary stereogenic centers

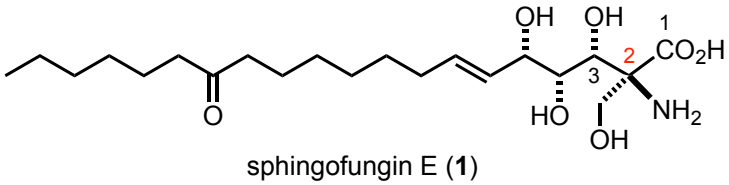
We recognized that the success of this approach depends on several potentially critical issues. Firstly, when the R^1 and R^2 groups in **I-a** contain stereogenic centers, a matched-mismatched problem could potentially complicate enantioselectivity of Et_2Zn addition to the aldehyde (**I-a**→**II**), because the stereochemical outcome of asymmetric synthesis would often be dependent to some extent on the relationship between the absolute configuration of the chiral ligand and that of the substrate.[7] Although worry of consideration, this problem might not be important in the proposed process because addition of Et_2Zn occurs at the aldehyde that is remote from stereogenic centers in the R^1 and R^2 substituents. Moreover, because the stereochemistry of the allyl cyanate-to-isocyanate rearrangement (**IV**→**V**) is tightly governed by steric factors in the six-membered transition state of the concerted [3,3]-pericyclic process, we anticipated that the absolute configuration at the new formed stereogenic center would be more strongly controlled by the preexisting stereogenic center in the cyanate **IV** rather than those in the R^1 and R^2 groups. Secondly, because addition of Et_2Zn to an aldehyde would occur under mild conditions, it should have a high compatibility with functional groups in R^1 and R^2. Thirdly, by choosing an appropriate alcohol in the step (**V** → **VI**), it should be possible to generate the carbamate moiety in **VI** with a readily removable protecting group. Fourthly, the stereospecific nature of allyl cyanate-to-isocyanate rearrangement would enable the absolute configuration of the product to be inverted by altering the stereochemistry of starting allyl alcohols. Namely, use of the enantiomeric chiral ligand (+)-MIB in the step (Scheme 1, **I-a**→ **VII**) and [1,3]-chirality transfer of the resulting

(*R*)-allyl alcohol **VII** by sigmatropic rearrangement would offer the stereoselective synthesis of the product **VIII** with inverted absolute configuration. Finally, this approach has the flexibility of dealing with the issues of olefin geometry control during the synthesis of β,β-disubstituted-α,β-unsaturated aldehyde **I-a**. For example, the geometric isomer **I-b** (Scheme 2) would often generate during the synthesis of **I-a**. This problem would be circumvented by altering the absolute configuration of the allyl alcohol. Specifically, by utilizing (+)-MIB, geometric isomer **I-b** can be transformed to (*R*)-allyl alcohol **IX**, which upon sigmatropic rearrangement would form **VI**.[8] Recent endeavors aimed at developing the preparative utility of the procedures (Schemes 1 and 2) led us to explore a synthetic route to the core structure of sphingofungin E.



Scheme 2. Transformation of a stereoisomeric β,β-disubstituted-α,β-unsaturated aldehyde **I-b**

Sphingofungin E (**1**), a member of the sphingofungin family, was isolated from the fermentation broth of *Paecilomyces variotii* by a group at Merck (Figure 1).[9] Sphingofungin E and its A–D relatives were found to block the biosynthesis of sphingolipids in both yeast and mammalian cells. This effect is a consequence of the potent inhibitory activities against serine palmitoyltransferase, an enzyme involved in the first step of sphingosine biosynthetic pathway. Among congeners in this family, sphingofungin E is the most highly oxygenated and it contains a unique C-2 quaternary stereogenic center bearing nitrogen, both of which make its synthesis challenging. Owing to its close similarity in structure to the immunosuppressive agent myriocin, sphingofungin E and its analogues have attracted significant attention from the synthetic community.[10] To date, several groups have described interesting approaches to the synthesis of sphingofungin E.[11] Among these studies, two groups focused on the use of sigmatropic rearrangement to secure the C-2 quaternary stereogenic center, one developed by Chida utilizing the Overman rearrangement[11d,11e] and the other by Martinková using the allyl isothiocyanate rearrangement.[11h]



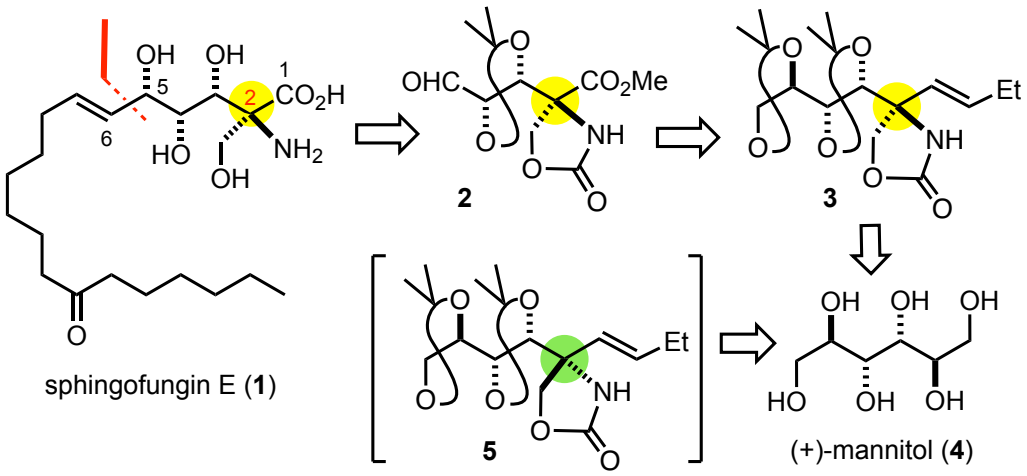
sphingofungin E (**1**)

Figure 1. Structure of sphingofungin E possessing a nitrogen-substituted C-2 quaternary stereogenic center

Reported here is a synthesis of the core structure of sphingofungin E that takes advantage of the new strategy for unambiguous stereocontrolled creation of the C-2 quaternary center, which involves a pathway that relies on enantioselective addition of Et_2Zn and the allyl cyanate-to-isocyanate rearrangement as key steps.

RESULTS AND DISCUSSION

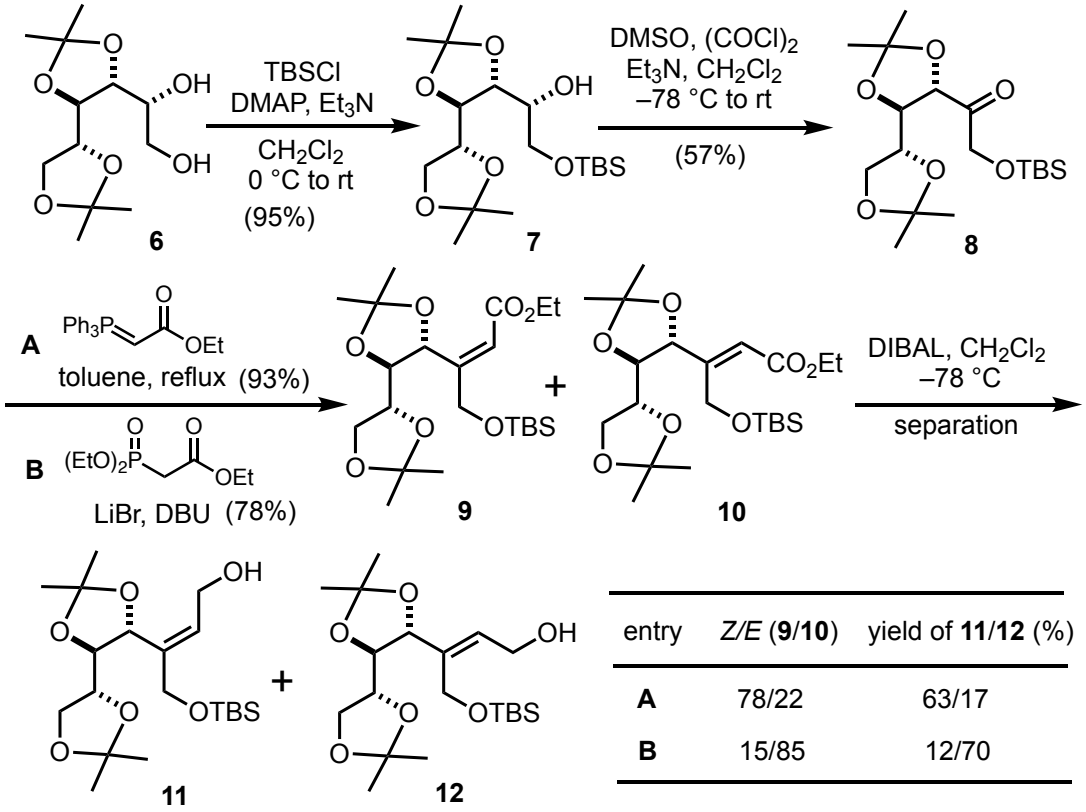
Our retrosynthetic analysis of sphingofungin E dissects the molecule at the C–C bond between C-5 and C-6 (Scheme 3). This approach leads to the aldehyde **2**, which contains three chiral stereogenic centers and properly protected forms of the critical functional groups in the target.[12] Further analysis shows that **2** could arise by proper manipulation of the olefin moiety in **3**, a core structure of sphingofungin E. We envisioned that this key building block **3** could be constructed by using the strategy depicted in Schemes 1 and 2. Further retrosynthesis of **3** realized C2-symmetric and commercially available sweetener (+)-mannitol (**4**) as the starting material. Moreover, to evaluate the potential utility of our stereocontrol approach, we plan to pursue the synthesis of the epimer **5**, which could serve as a precursor for the synthesis of a C-2 epimer of sphingofungin E.



Scheme 3. Retrosynthesis of sphingofungin E and its C-2 epimer

The synthetic pathway arising from this analysis began by protecting the primary hydroxyl group in mannitol derivative **6**[13] by treatment with *tert*-butyldimethylsilyl (TBS) chloride and triethylamine in the presence of a catalytic amount of 4-dimethylaminopyridine (DMAP) (Scheme 4). This process produced TBS ether **7** in 95% yield,[14] which was then subjected to Swern oxidation to generate ketone **8** in 57% yield. Wittig olefination of **8** using ethyl 2-(triphenylphosphoranylidene)acetate in toluene at reflux provided an inseparable 78:22 mixture of **9** and **10** in 93% yield (Scheme 4, entry **A**). DIBAL reduction of this mixture followed by chromatographic separation furnished (*Z*)-allyl alcohol **11** in a 63% yield,

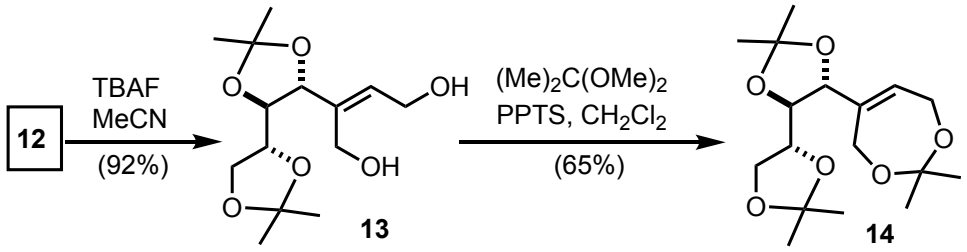
accompanied by a 17% yield of (*E*)-allyl alcohol **12**. We envisioned that the problem associated with generation of considerable amounts of the undesired **12** would be readily remedied using the method depicted in Scheme 2, and, as a result, both **11** and **12** could be transformed to the central core of sphingophangin E. In contrast to Wittig olefination, Horner-Wadsworth-Emmons condensation of ketone **8** with triethyl phosphonoacetate employing lithium bromide and DBU[15] took place with reversed selectivity to generate a 15:85 mixture of **9** and **10** in 78% yield (Scheme 4, entry **B**).[16] Subsequent DIBAL reduction of this mixture gave rise to **11** and **12** in 12 and 70% respective yields.



entry	*Z*/*E* (**9**/**10**)	yield of **11**/**12** (%)
A	78/22	63/17
B	15/85	12/70

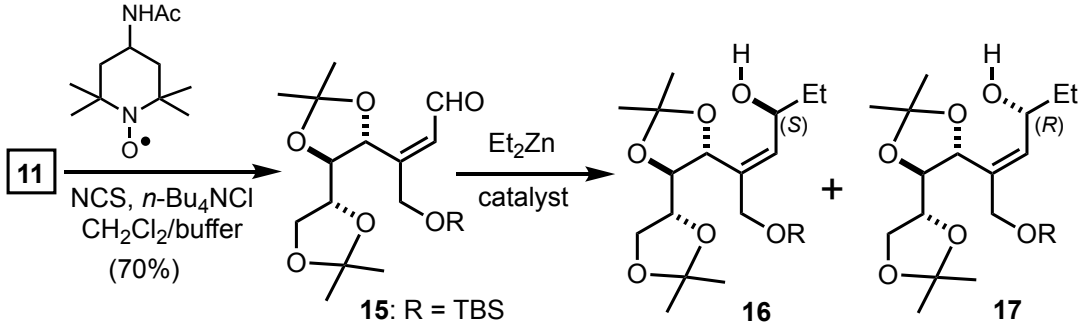
Scheme 4. Synthesis of allyl alcohols **11** and **12** from a mannitol derivative **6**

The structure of (*E*)-olefin geometry in allyl alcohol **12** was confirmed by its ability to be transformed to the corresponding acetonide **14** (Scheme 5). Specifically, removal of TBS group in **12** with tetra-*n*-butylammonium fluoride (TBAF) gave the diol **13**. Upon treatment of **13** with 2,2-dimethoxypropane and pyridinium *p*-toluenesulfonate (PPTS), the cyclic seven-membered ketal **14** was obtained in 65% yield. In contrast, similar treatment of the diol prepared from (*Z*)-allyl alcohol **11** did not react and was recovered unchanged.



Scheme 5. Confirmation of the (*E*)-olefin geometry of **12** by its transformation to the cyclic ketal **14**

Attention next turned to the preparation of the (*Z*)-α,β-unsaturated aldehyde **15** and its MIB-catalyzed enantioselective addition of Et_2Zn (Scheme 6). For this purpose, 4-acetamido-TEMPO catalyzed oxidation of the (*Z*)-allyl alcohol **11** using *N*-chlorosuccinimide (NCS) as a primary oxidant in a two-phase (CH_2Cl_2–H_2O) system produced aldehyde **15** in 70% yield.[17] We did not use TEMPO in this process, because TLC mobility of TEMPO is close to that of the product **15**. A three-gram scale reaction of the (*Z*)-α,β-unsaturated aldehyde **15** with Et_2Zn in the presence of a catalytic amount of (–)-MIB (10 mol%) in a mixture of toluene and hexane (8:1) at 0 °C for 16 h formed (*S,Z*)-allyl alcohol **16** with excellent face selectivity (Scheme 6, entry **A**, **16**:**17** = >98:2) in 88% yield.[18] In a similar manner, enantioselective addition of Et_2Zn to aldehyde **15** using 10 mol% of (+)-MIB as catalyst proceeded smoothly to produce the (*R,Z*)-allyl alcohol **17** predominantly (Scheme 6, entry **B**, **16**:**17** = 5:95) in 78% yield.[19] Because a complete reversal of diastereoselectivity in a pair of processes (Scheme 6, entries **A** and **B**) is observed, it is evident that no matched-mismatched issues exist.[7]

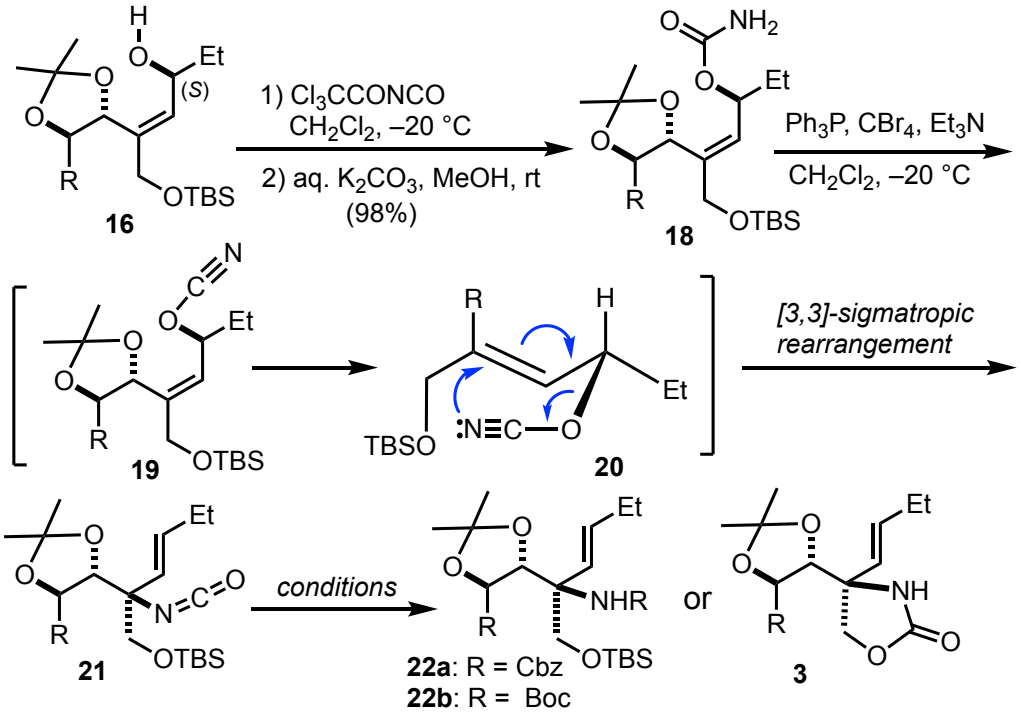


entry	catalyst[a]	yield (%)	dr (**16**:**17**)
A	(–)-MIB	88[b]	>98:2
B	(+)-MIB	78[b]	5:95

[a]10 mo% catalyst was used.
[b]An isolated yield of the major isomer after separation by chromatography.

Scheme 6. MIB-catalyzed enantioselective addition of diethylzinc to (*Z*)-β,β-disubstituted-α,β-unsaturated aldehyde **15**

With allyl alcohols in hand, we next explored [1,3]-chirality transfer through exploitation of the allyl cyanate-to-isocyanate rearrangement (Scheme 7). To this end, (*S,Z*)-allyl alcohol **16** was treated with trichloroacetyl isocyanate followed by hydrolysis with potassium carbonate in aqueous methanol. Chromatographic purification led to isolation of carbamate **18** (98% yield), which was then subjected to dehydration using triphenylphosphine, carbon tetrabromide and triethylamine at –20 °C. The in situ generated allyl cyanate **19** underwent spontaneous [3,3]-sigmatropic rearrangement to form allyl isocyanate **21**. In order to avoid hydrolysis of the isocyanate function in **21**, a careful aqueous work up procedure was employed to isolate crude **21**, which was immediately dissolved in THF and treated with lithium benzyl alkoxide[20] or *tert*-butoxide[3c, 21] to produce the respective Cbz- or Boc-carbamate **22a** or **22b** albeit in low yields (Scheme 7, entries **A**: 28% and **B**: 17%). It is likely that the highly congested quaternary carbon linked to the isocyanate group in **21** creates severe steric obstruction to the addition of alkoxide. We next explored an intramolecular trapping reaction of the isocyanate group in **21**. To our delight, treatment of **21** with TBAF in acetonitrile produced cyclic carbamate **3** in an improved 67% yield (Scheme 7, entry **C**). Encouraged by this result, various fluoride reagents and solvents were tested and



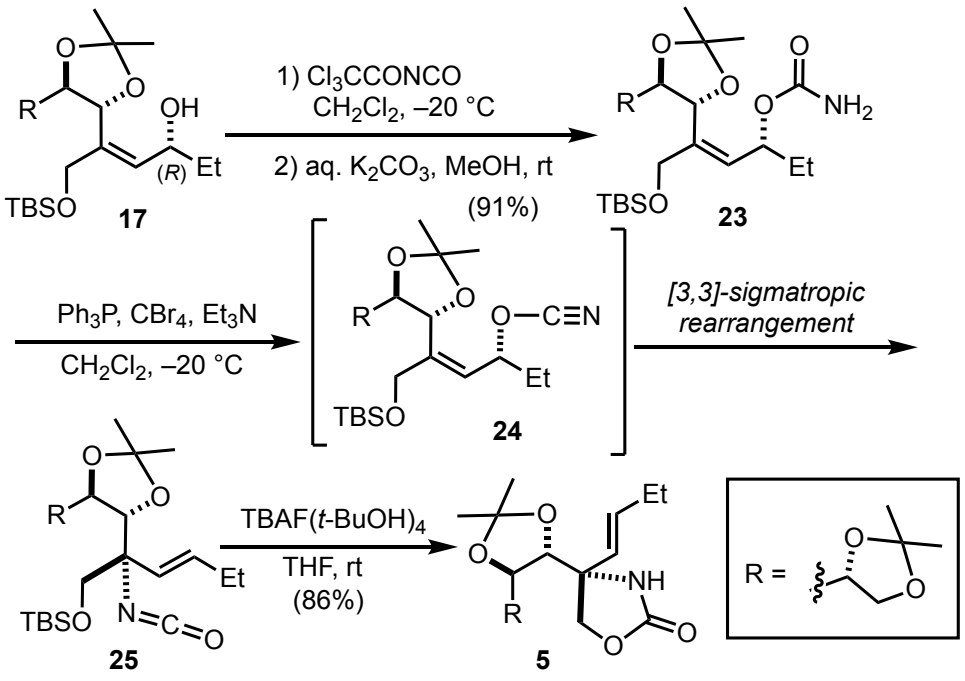
entry	conditions	product	yield (%)
A	$PhCH_2OLi$, THF	**22a**	28
B	*tert*-BuOLi, THF	**22b**	17
C	TBAF, MeCN	**3**	67
D	TBAF(*t*-BuOH)$_4$, THF	**3**	84

R =

Scheme 7. Allyl cyanate-to-isocyanate rearrangement of (*S,Z*)-β,β-disubstituted allyl alcohol **16**

we finally found that use of tetrabutylammonium tetra(*tert*-butyl alcohol)-coordinated fluoride {TBAF(*t*-BuOH)$_4$}[22] in THF generated the central core of sphingofungin E **3** exclusively in 84% yield (entry **D**).[23] The stereochemistry of the newly introduced stereogenic center was assigned as represented in the structure of **3** owing to the fact that the rearrangement proceeds through the six-membered transition state **20** having a pseudo-equatorially oriented ethyl group, which permits a smooth and predictable C–O to C–N transfer of chirality across the allyl system. This stereochemical assignment of the nitrogen-substituted quaternary stereogenic center in **3** was unequivocally established by using X-ray crystallographic analysis of a derivative (see below).

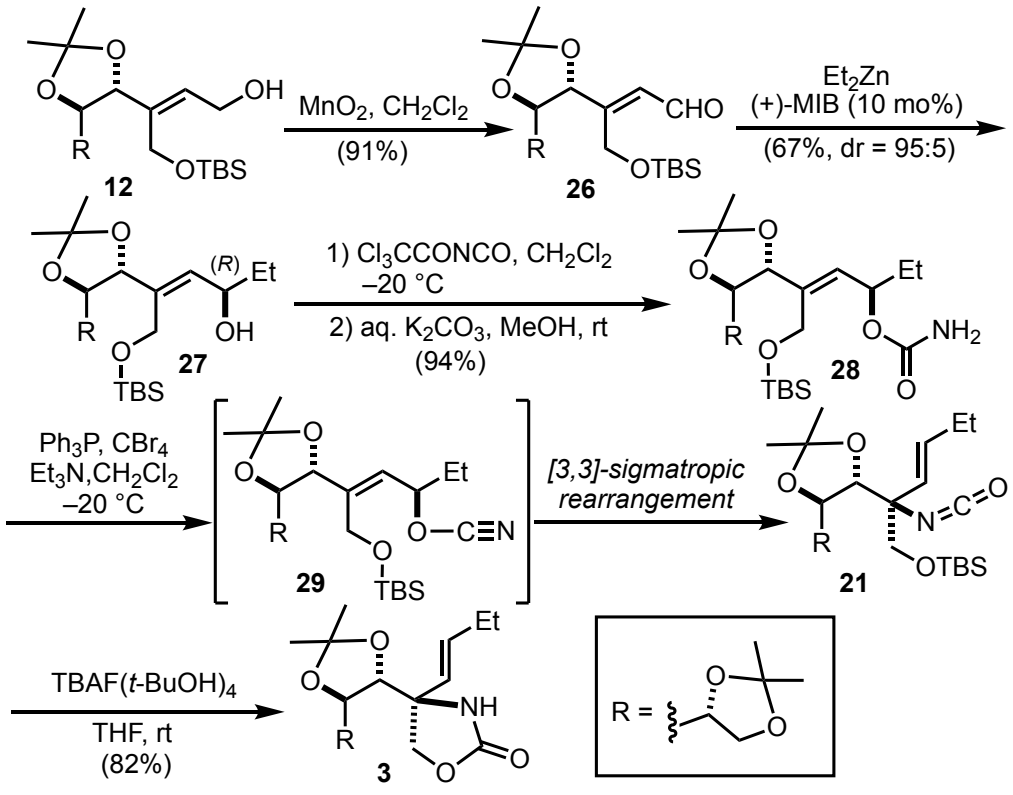
We next investigated [3,3]-sigmatropic rearrangement of the (*R,Z*)-allyl alcohol **17** to generate the product **5**, which would serve as an intermediate in the synthesis of an unnatural C-2 diastereomer of sphingofungin E (Scheme 8). Using similar conditions to those given in Scheme 7, carbamoylation of **17** and dehydration of the carbamate **23** produced allyl cyanate **24**, which underwent spontaneous [3,3]-pericyclic rearrangement to produce allyl isocyanate **25**. Removal of the TBS group in **25** by treatment with {TBAF(*t*-BuOH)$_4$} and ensuing intramolecular trapping of the isocyanate group by the neighboring hydroxyl moiety led to formation of oxazolidinone **5** in 78% overall yield from **17**.[23]



Scheme 8. Synthesis of **5**, a C-2 epimer of the central core of sphingofungin E

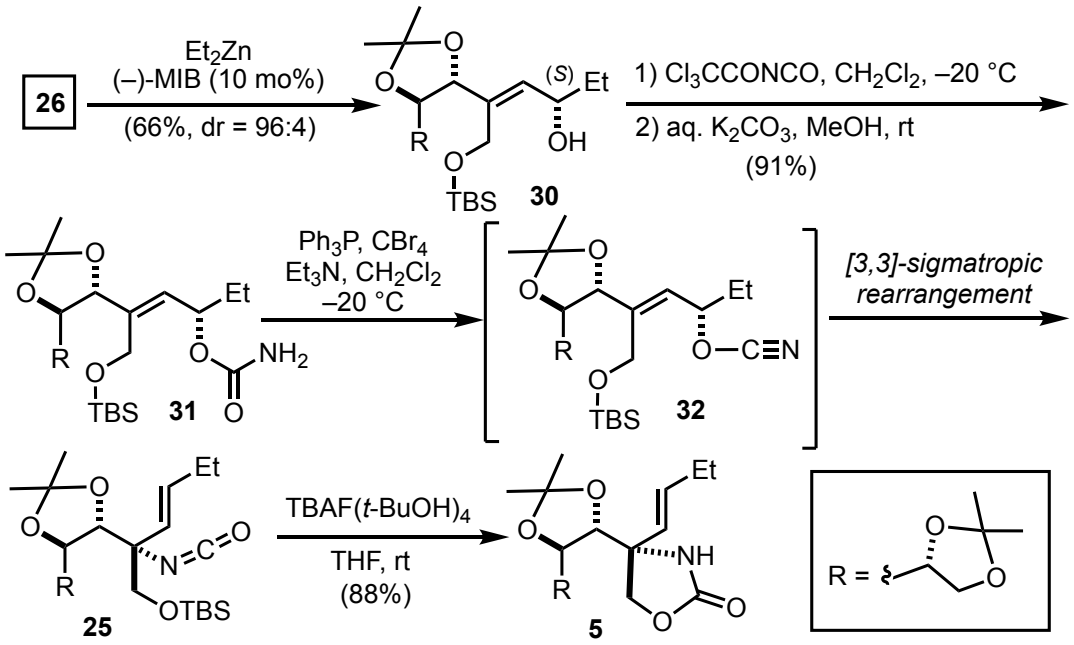
The results described above (Schemes 7 and 8) verified the utility of our strategy (Scheme 1), which enables the synthesis of both diastereomers with respect to the nitrogen-substituted quaternary stereogenic centers by switching chiral catalysts in an enantioselective addition of Et_2Zn followed by [3,3]-sigmatropic rearrangement.

We next turned our attention to the problem associated with formation of significant amounts of (*E*)-allyl alcohol **12** in the Wittig olefination reaction (Scheme 4). Accordingly, a study was carried out to establish that **12** can be transformed into the central core of sphingofungin E **3** by using the strategy described in Scheme 2. For this purpose, we initially examined the oxidation reaction of (*E*)-allyl alcohol **12** (Scheme 9). Unfortunately, TEMPO oxidation of **12** resulted in only a moderate 57% yield of (*E*)-aldehyde **26** along with a considerable amount of formation of the (*Z*)-isomer. In an exploration seeking an alternative oxidant, we found that reaction of **12** with activated manganese oxide (MnO_2) cleanly produced (*E*)-aldehyde **26** in good yield (91%) without formation of the olefin isomer. (+)-MIB-catalyzed enantioselective addition of Et_2Zn to **26**, performed using conditions similar to those depicted in Scheme 6, followed by chromatographic purification afforded (*R*,*E*)-allyl alcohol **27** in 67% yield (dr = 95:5). By using conditions similar to those used to carry out the sequence depicted in Scheme 7, carbamoylation of (*R,E*)-allyl alcohol **27**, subsequent dehydration of the formed carbamate **28** and concomitant rearrangement of the allyl cyanate intermediate **29** generated allyl isocyanate **21**. Finally, removal of TBS group in **21** gave rise to **3** in 77% overall yield from **27**.[23] This finding clearly demonstrates that issues arising from the moderate selectivity of Wittig olefination (Scheme 4) can be resolved by utilizing the strategy described in Scheme 2.



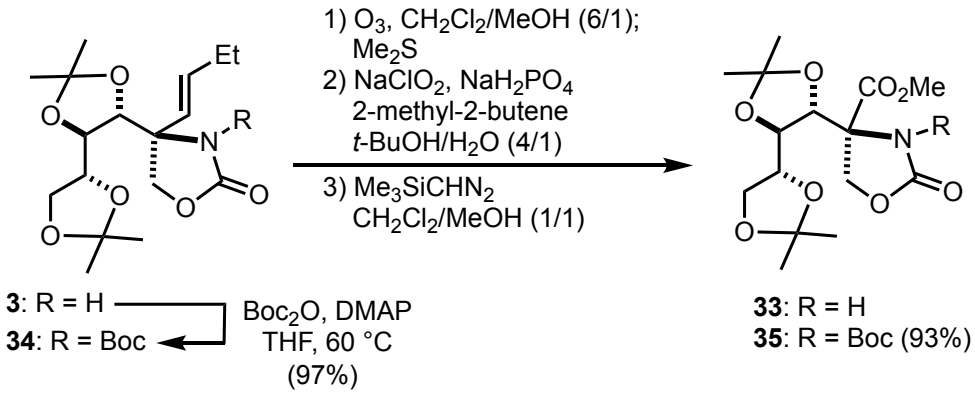
Scheme 9. Transformation of (*E*)-allyl alcohol **12** to the central core of sphingofungin E **3**

Next, a study was conducted to explore the route designed to transform (*E*)-allyl aldehyde **26** to the C-2 epimeric central core of sphingofungin E **5** (Scheme 10). As anticipated, enantioselective addition of Et_2Zn to the aldehyde **26** took place using 10 mol% (–)-MIB to produce (*S,E*)-allyl alcohol **30** in 66% yield (dr = 96:4). Carbamoylation of **30** followed by dehydration of the formed **31** generated allyl cyanate **32**, which underwent spontaneous rearrangement to produce allyl isocyanate **25**. Treatment of a THF solution of **25** with {TBAF(*t*-BuOH)$_4$} promoted TBS group removal and ensuing intramolecular isocyanate trapping to form **5** in 80% overall yield from (*S,E*)-allyl alcohol **30**.[23]



Scheme 10. Transformation of (*E*)-aldehyde **26** to the C-2 epimeric central core of sphingofungin E **5**

In the final phase of our research effort, we assessed a route for conversion of **3** to **35**, an advanced intermediate in the synthesis of sphingofungin E (Scheme 11). To this end, transformation of the olefin moiety in **3** to a methyl ester was performed using a three-step sequence involving i) oxidative cleavage of the double bond in **3** by sequential treatment with ozone and dimethyl sulfide, ii) Pinick oxidation to convert the resulting aldehyde to the corresponding carboxylic acid,[24] and iii) esterification by treatment with trimethylsilyldiazomethane. While this route produced methyl ester **33**, it occurred in a low 33% overall yield. After some experimentation, we found that *N*-protection of oxazolidinone in **3** with *tert*-butoxycarbonyl (Boc) group improved the yields. In fact, treatment of **3** with di-*tert*-butyldicarbonate (Boc_2O) and DMAP in THF at 60 °C formed the imide **34** in a 97% yield. Further subjection of **34** to the three-step sequence descrived above produced methyl ester **35** in 93% yield. Fortunately, methyl ester **35** formed a single crystal suitable for an X-ray crystallography study. Analysis of the crystallographic data enabled unequivocal assignment of the absolute configuration of the C-2 quaternary nitrogen bearing stereogenic center (Figure 2).[25]



Scheme 11. Preparation of an advanced intermediate **35** in the synthesis of sphingofungin E

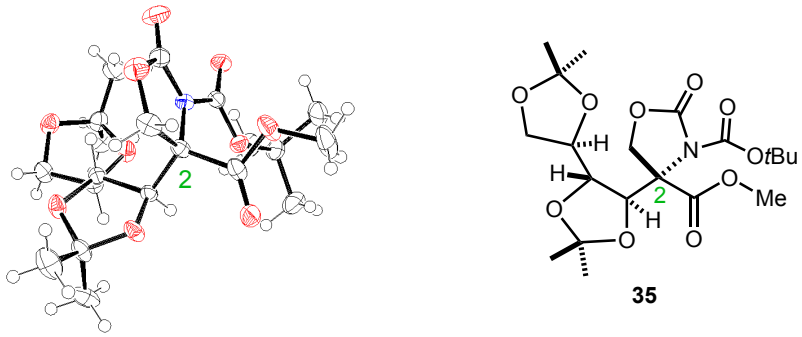


Figure 2. Plot of the X-ray crystallographic data of **35**

CONCLUSIONS

The investigation descrbed above led to developoment of an approach to the synthesis of nitrogen-substituted quaternary stereogenic centers that relies on MIB-catalyzed enantioselective addition of Et_2Zn and [3,3]-sigmatropic rearrangement of allyl cyanate. As demonstrated by its application to the synthesis of the core structure of sphingofungin E **3** an its C-2 epimer **5**, asymmetric centers bearing nitrogen were constructed at the sterically encumbered positons with high levels of stereocontrol. In particular, our procedure provided ready access to not only the core structure of sphingofungin E but also to its C-2 epimer by simple choice of the (+)- and (–)-enantiomers of the catalysts MIB that promote enantioselective addition of Et_2Zn. Futhermore, the approach circumvents issues associated with stereoselective synthesis of β,β-disubstituted-α,β-unsaturated aldehydes. Specifically, the fact that synthesis of **3** can be accomplished starting with both (*Z*)- and (*E*)-allyl alcohols **11** and **12** (Schemes 7 and 9) overcomes the problem of steteocontrolled synthesis of (*Z*)- and (*E*)-β,β-disubstituted-α,β-allyl aldehydes. Lessons learned during this study will likely be utilized in developing methods for stereoselective synthesis of quaternary stereogenic centers bearing nitrogen substituents.

EXPERIMENTAL

MIB-Catalyzed Enantioselective Addition of Et_2Zn; Typical Procedure

(*S*,*Z*)-6-((*tert*-Butyldimethylsilyl)oxy)-5-((4*S*,4'*R*,5*R*)-2,2,2',2'-tetramethyl-[4,4'-bi(1,3-dioxolan)]-5-yl)hex-4-en-3-ol (16). To a solution of (*Z*)-α,β-unsaturated aldehyde **15** (3.05 g, 7.61 mmol) and (–)-MIB (182 mg, 0.76 mmol) in toluene (122 ml) cooled to 0 °C was added a solution of diethylzinc (1.0 M in hexane, 15.2 ml, 15.2 mmol) dropwise over 5 min. The reaction mixture was kept at 0 °C for 16 h, and then quenched with aqueous 1 M $KHSO_4$. The separated aqueous layer was extracted with Et_2O. The combined organic layer was washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated. The resulting crude product was analyzed by ^1H NMR, which determined the diastereoselectivity to be >98:2. Silica gel chromatography of the residue (Et_2O/toluene 1:5) gave (*S,Z*)-allyl alcohol **16** (2.87 g, 88%) as a colorless oil. R_f = 0.66 (eluting with v/v 1:2 AcOEt/hexane). $[\alpha]_D^{25}$ –27.9 (*c* 1.00, $CHCl_3$); IR (NaCl) ν_{max} 3493, 2957, 1693, 1462, 1373 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.08 (s, 6H), 0.91 (s, 9H), 0.94 (t, *J* = 7.0 Hz, 3H), 1.35 (s, 3H), 1.39 (s, 6H), 1.43 (s, 3H), 1.72–1.59 (m, 2H), 4.02–3.92 (m, 2H), 4.22–4.10 (m, 3H), 4.40–4.28 (m, 3H), 4.98 (d, *J* = 8.0 Hz, 1H), 5.78 (d, *J* = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ –5.4, –5.3, 9.7, 18.2, 25.1, 25.8, 26.3, 26.7, 26.8, 29.6, 61.9, 67.1, 67.6, 77.2, 78.7, 109.1, 110.2, 133.5, 136.6; HRMS (ESI): *m/z* calcd for $C_{22}H_{42}O_6NaSi$ $[M+Na]^+$ 453.2648, found 453.2629.

Preparation of Carbamate; Typical Procedure

(*S*,*Z*)-6-((*tert*-Butyldimethylsilyl)oxy)-5-((4*S*,4'*R*,5*R*)-2,2,2',2'-tetramethyl-[4,4'-bi(1,3-dioxolan)]-5-yl)hex-4-en-3-yl carbamate (18). To a solution of (*S,Z*)-allyl alcohol **16** (126 mg, 0.29 mmol) in CH_2Cl_2 (2.0 ml) cooled to –20 °C was added trichloroacetyl isocyanate (0.12 ml, 0.58 mmol). After being stirred at –20 °C for 40 min, the solvent was removed by evaporation under reduced pressure. The resulting residue was dissolved in a mixture of MeOH (0.5 ml) and 2 M aqueous potassium carbonate (2.0 ml), and then was stirred at room temperature for 4.0 h. MeOH was removed by evaporation and the resulting aqueous layer was extracted with Et_2O. The combined organic extracts were washed with brine, dried over anhydrous Na_2SO_4 and then concentrated under reduced pressure. The resulting residue was purified by silica gel chromatography (AcOEt/hexane 1:4) to afford carbamate **18** (136 mg, 98%) as a colorless oil. $[\alpha]_D^{25}$ –14.4 (*c* 1.00, $CHCl_3$); IR (NaCl) ν_{max} 3450, 3361, 2956, 2933, 1727, 1601 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 0.08 (s, 6H), 0.91 (t, *J* = 9.0 Hz, 3H), 0.92 (s, 9H), 1.32 (s, 3H), 1.37 (s, 3H), 1.39 (s, 3H), 1.42 (s, 3H), 1.60 (dq, *J* = 28.0, 21.0 Hz, 1H), 1.75 (dt, *J* = 20.0, 13.5 Hz, 1H), 4.02–3.93 (m, 2H), 4.13 (dt, *J* = 16.0, 12.0 Hz, 2H), 4.25 (s, 2H), 4.65 (s, 2H), 4.70 (d, *J* = 8.0 Hz, 1H), 5.50 (dt, *J* = 9.5, 9.0 Hz, 1H), 5.75 (d, *J* = 10.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ –5.1, –5.0, 9.3, 18.5, 25.3, 26.1, 26.7, 27.0, 27.1, 28.5, 61.7, 66.2, 72.2, 76.1, 76.7, 78.6, 109.4, 109.5, 128.8, 136.7,

156.5; HRMS (ESI): *m/z* calcd for $C_{23}H_{43}NO_7Si$ $[M+H]^+$ 474.2887, found 474.2877.

[3,3]-Sigmatropic Rearrangement of Allyl Cyanate; Typical Procedure

(*S*)-4-((*E*)-But-1-en-1-yl)-4-((4*S*,4'*R*,5*R*)-2,2,2',2'-tetramethyl-[4,4'-bi(1,3-dioxolan)]-5-yl)oxazolidin-2-one (3). To a solution of carbamate **18** (502 mg, 1.06 mmol), triphenylphosphine (980 mg, 3.71 mmol) and triethylamine (0.68 ml, 4.87 mmol) in CH_2Cl_2 (7.0 ml) at –20 °C was added a solution of carbon tetrabromide (1.33 g, 4.02 mmol) in CH_2Cl_2 (3.0 ml). After being stirred at –20 °C for 20 min, the resulting reaction mixture was diluted with hexane (30 ml). After stirring at room temperature for 10 min, aqueous $KHSO_4$ (1 M, 30 ml) was added. The separated aqueous layer was extracted with hexane. The combined organic layer was washed with water, saturated $NaHCO_3$ and brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting crude products containing allyl isocyanate **21** and triphenylphosphine oxide, was diluted with hexane and the precipitated triphenylphosphine oxide was removed by filtration through a pad of Celite. The filter cake was washed with hexane, and the combined filtrate was concentrated under reduced pressure to afford crude **21** (794 mg), which was dissolved in THF (7.0 ml). The resulting solution was cooled to 0 °C and then treated with a solution of tetrabutylammonium tetra(*tert*-butyl alcohol)-coordinated fluoride {$Bu_4NF(t$BuOH$)_4$} (831 mg, 3.18 mmol) in THF (3.0 ml). After stirring at 0 °C for 20 min, the reaction mixture was concentrated under reduced pressure to afford the crude residue, which was purified by silica gel chromatography (AcOEt/hexane 1:4) to afford the core structure of sphingofungin E **3** (304 mg, 84%) as a white solid. Mp 85–86 °C (recrystallized from ether/hexane); $[\alpha]_D^{25}$ +57.9 (*c* 1.00, $CHCl_3$); IR (KBr) ν_{max} 3290, 2990, 1764 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ 1.01 (t, *J* = 7.0 Hz, 3H), 1.35 (s, 3H), 1.36 (s, 3H), 1.39 (s, 3H), 1.41 (s, 3H), 2.13 (dt, *J* = 14.5, 14.0 Hz, 2H), 3.70 (dd, *J* = 9.0, 6.0 Hz, 1H), 3.93 (dd, *J* = 9.0, 5.0 Hz, 1H), 4.06 (dt, *J* = 9.0, 9.0 Hz, 1H), 4.20–4.10 (m, 2H), 4.48 (s, 1H), 5.33 (s, 1H), 5.58 (d, *J* =15.0 Hz, 1H), 5.87 (dt, *J* = 15.5, 13.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 13.1, 25.1, 25.3, 26.4, 27.0, 27.6, 62.1, 67.7, 72.4, 76.8, 84.4, 110.0, 110.6, 127.0, 134.4, 158.6; HRMS (ESI): *m/z* calcd for $C_{17}H_{28}NO_6$ $[M+H]^+$ 342.1917, found 342.1916.

SUPPORTING INFORMATION

Supporting information inculding experimental procedures, compound characterization data, crystallographic data, and ^1H and ^{13}C NMR spectra is available via Internet at https://www.heterocycles.jp/newlibrary/downloads/PDFsi/27874/106/4.

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