Evolution, Development and Personal Experience In Studies of the Allyl Cyanate-to-Isocyanate Rearrangement

In the memory of Prof. Toshio Goto

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Biographical Sketch.

Yoshiyasu Ichikawa was born in Gamagori, Aichi prefecture Japan on 16 March, 1958. He completed his undergraduate studies and PhD work in the Faculty of Agricultural Sciences at Nagoya University. After postdoctoral studies in the Dyson Perrins Laborarory at Oxford, UK, he joined the faculty of Education in Mie University where he pursued his research interests in the synthesis of marine natural products based upon sigmatropic rearrangement and biomimetic approaches. In 1992, he returned to the Nagoya University and then emigrated from Tokai region in central Honshu to the island of Shikoku to join the Faculty of Science at Kochi University in 2004. His research interests remain focused on the total synthesis of natural products and carbohydrate chemistry.

Background

The allyl thiocyanate-to-isothiocyanate rearrangement is an old, well known method for the synthesis of allyl amines (Scheme 1). In 1925, Billeter first discussed the mechanism of this isomerization reaction and proposed that the process proceeds via a cyclic transition state.[1] Systematic investigations focusing on the reaction mechanism were carried out by Smith and Emerson, who observed that the rearrangement of allyl thiocyanate (**1**→**2**) obeys first-order kinetics over a temperature range from 57.8 to 86.4 °C. The kinetic parameters and, in particular the negative activation entropy ($\Delta S^{\neq}$ = –9.4 eu) confirmed that the isomerization proceeds via a highly ordered cyclic transition state.[2] Hydrolysis of the allyl isothiocyanate product **2** with mineral acid completes the good preparative synthetic method for the allyl amine **3**.[3]
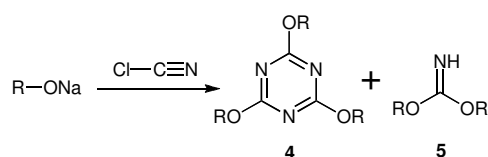
Scheme 1

E_a = 23.8 kcal mol^{-1}, ΔS° = –9.4 eu
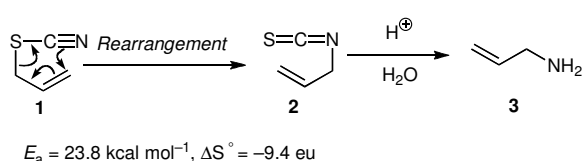
In contrast to studies of the allyl thiocyanate-to-isothiocyanate rearrangement, no reports existed describing the oxygen-counterpart, allyl cyanate-to-isocyanate rearrangement. The long-standing lack of interest in this process by the synthetic community may have been caused by difficulties associated with the synthesis of esters of cyanic acid (H–OCN), in which the aryl or alkyl group is bonded to oxygen (R–OCN).

The preparation and isolation of R–OCN is a tough problem that remained unsolved for a long period. The first reported preparation of R–OCN dates back as far as 1857 when Cloez described the reaction of sodium alkoxides with cyanogen chloride (Scheme 2).[4] However, subsequent investigations showed that the actual products obtained by Cloez are mixtures containing mainly the trimeric trialkyl cyanurates **4** together with dialkyl imidocarbonates **5**. Many unsuccessful attempts to synthesize R–OCN continued for more than 100 years.   As a result, the existence of esters of cyanic acid has been questioned for a long time.[5]
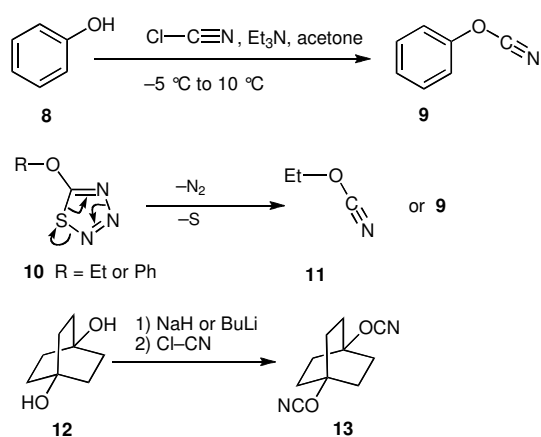
Scheme 2

In 1960, the first successful synthesis of an aryl cyanate by reaction of the sterically hindered phenol **6** with cyanogen chloride was reported by Stroh and Gerber (Scheme 3).[6] Bulky *ortho*-substituents in the phenyl ring apparently prevent the initially formed aryl cyanate **7** from undergoing further reactions.   In addition, the high energy cost associated with the formation of the phenyl cation intermediate blocks the solvolysis and isomerization reactions of **7**.

Scheme 3
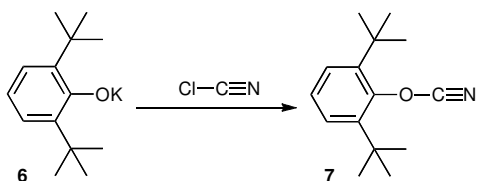
In 1964, four papers describing the synthesis of aryl and alkyl cyanates were published simultaneously (Scheme 4). In one, the German chemists Grigat and Pütter, reported the reaction of phenol **8** with cyanogen chloride in the presence of triethylamine to afford the phenyl cyanate **9**.[7] Holm in Copenhagen[8] and Martin in Berlin[9] independently described the cheletropic reaction of ethoxy and phenoxy 1,2,3,4-thiatriazole to form ethyl and phenyl cyanates (**10**→ **11** or **9**) together with nitrogen and sulfur. Lastly, Kauer in the United States also accomplished the preparation of tertiary alkyl cyanate **13** by employing the reaction of bridgehead alkoxide **12** with cyanogen chloride.[10]

Scheme 4

In 1970, Holm attempted to synthesize the allyl cyanate **16** by using cheletropic reaction of allyl thiatriazole **14** at room temperature (Scheme 5).[11] Contrary to his expectation, only allyl isocyanate **15** was generated as a product of this process. To explain these anomalous experimental results, Holm suggested two possible reaction mechanisms, one (**A**) involving a cheletropic reaction of **14** followed by rearrangement of the formed allyl cyanate (**16** →**15**) and the other (**B**) involving rearrangement of **14** to generate **17** and cheletropic reaction of **17** to afford **15**.   To the best of our knowledge, the hypothesis of the allyl cyanate-to-isocyanate rearrangement put forward by Holm received scant attention from the synthetic community except for one report by Larry E. Overman (see below).

Scheme 5
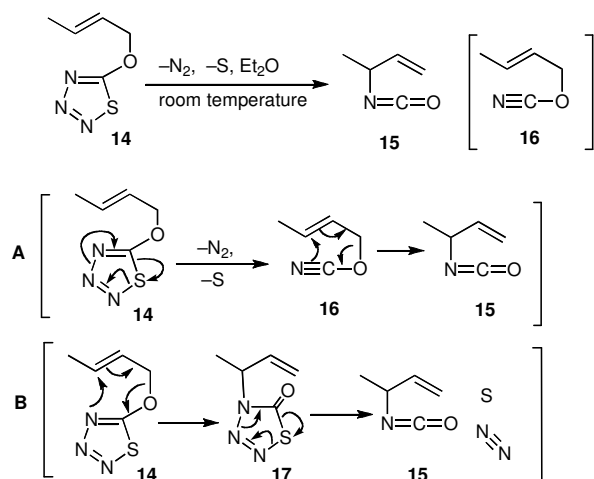
Evolution of the allyl cyanate-to-isocyanate rearrangement. A personal history.

During the period from 1979 to 1986 as a member of the Laboratory of Organic Chemistry (LOC) in the Faculty of Agricultural Sciences at Nagoya University, I became acquainted with the marvelous scientific world of natural products chemistry. As a doctoral student under the direction of Minoru Isobe, I carried out research work aimed at the total synthesis of okadaic acid. During the early days of my scientific career I hoped to be able to carry out future research work in the field of nitrogen-containing natural product synthesis. This taste was partially due to the influence of Toshio Goto, a group leader of LOC, who was interested in the nitrogen-containing and highly oxygenated natural products.

One day, a review article by Isao Kitagawa brought to my attention the aminobisabolenes **18** and **19**, two interesting nitrogen-containing sesquiterpenes that are isolated from marine organisms.[12] Aminobisabolene **18** derives from an Okinawan marine sponge of *Theonella* sp. collected on the coral reef of Hatoma–jima, Okinawa.[13a] Faulkner also reported the isolation of **18** from *Hallicondria* sp. collected on the fringing reef at Ponape, Marshall Islands,[13b] and Scheuer reported the isolation of **19** from *Ciocalypta* sp. collected on PupuKea, O'ahu.[13c]

(6*R*,7*S*)-Aminobisabolene (**18**)   (6*R*,7*R*)-Aminobisabolene (**19**)
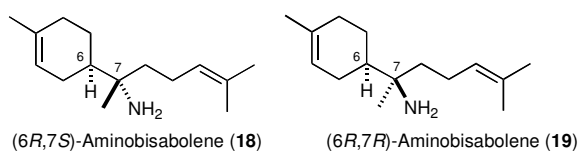
Members of the aminobisabolene family contain challenging structural features, in particular a quaternary carbon center bearing an amino group. As part of a strategy designed for the synthesis of these natural products, I planned to investigate the allyl thiocyanate-to-isothiocyanate rearrangement in the context of natural product synthesis. Although the mechanism of this rearrangement reaction had been established, there were only a few reports of its synthetic applications.

In 1987, when I launched my academic career in the Faculty of Education at Mie University, I started on the synthetic studies of the aminobisabolene based on the allyl thiocyanate-to-isothiocyanate rearrangement. In initial work using model compounds, geranyl thiocyanate **21** was prepared by the reaction of allyl bromide **20** with sodium thiocyanate in aqueous ethanol (Scheme 6). ^{1}H NMR analysis (60 MHz) showed that the products obtained in this process are an equilibrium mixture of thiocyanate **21** and isothiocyanate **22**. Since the rearrangement reaction interconverting **21** and **22** has a relatively small equilibrium constant, the reaction mixture was treated with benzylamine to drive the equilibrium to the right and produce the thiourea **23**. Although a quaternary carbon bearing nitrogen atom is successfully constructed by using this methodology, further functional group manipulations were hampered by the robust nature of the thiourea moiety in **23**.

Scheme 6
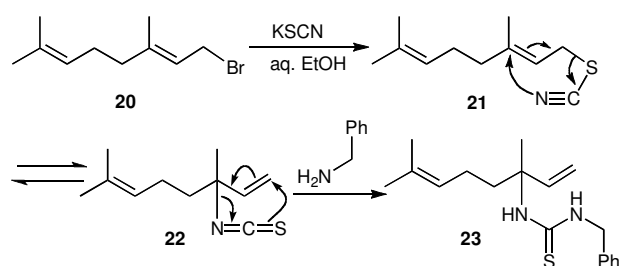
By browsing the chemical literature related to the rearrangement of allyl xanthates,[14) I encountered a gold mine of suggestions reported by Holm (Scheme 5). After reading about the unexpected results documented by Holm, I immediately believed that the hypothesis of an allyl cyanate-to-isocyanate rearrangement is true. It was particularly remarkable for me that this rearrangement appears to occur below room temperature, which is in sharp contrast to the related Overman rearrangement (Scheme 7). Allyl imidate **24** undergoes [3.3] sigmatropic rearrangement to form allyl trichloroacetamide **25** in refluxing xylene (140 °C). As a result of these thoughts, I outlined an ambitious project aimed at developing the allyl cyanate rearrangement as a new synthetic method in the context of the synthesis of the aminobisabolens.
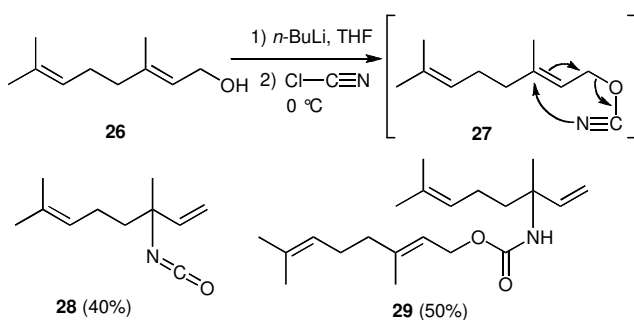
Scheme 7
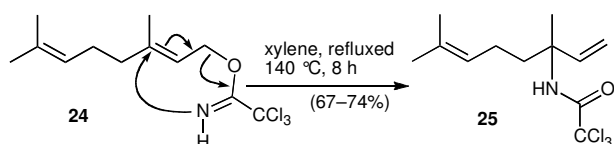
After one year of study without any appreciable success, I recognized that the synthesis of allyl cyanates is a difficult problem and became aware of the earlier (regrettably, no Sci-finder was available at that time) and important contribution to the chemistry of allyl cyanate-to-isocyanate rearrangement made by Overman[16) (Scheme 8). Overman reported that treatment of geraniol **26** with *n*-butyllithium, followed by the reaction of the resultant alkoxide with cyanogen chloride (Cloez method, Scheme 2)

affords a mixture of linalyl isocyanate **28** and the dimeric carbamate **29**. All attempts to optimize formation of the isocyanate **28** were unsuccessful and the competitive reaction of the reactive isocyanate **28** with the starting alkoxide remained as a serious complication. At this point, I decided to discontinue work on the allyl cyanate project and turned my attention to a new approach to the synthesis of aminobisabolenes based upon the Overman Hetero-Claisen rearrangement of an allyl imidates.[17]
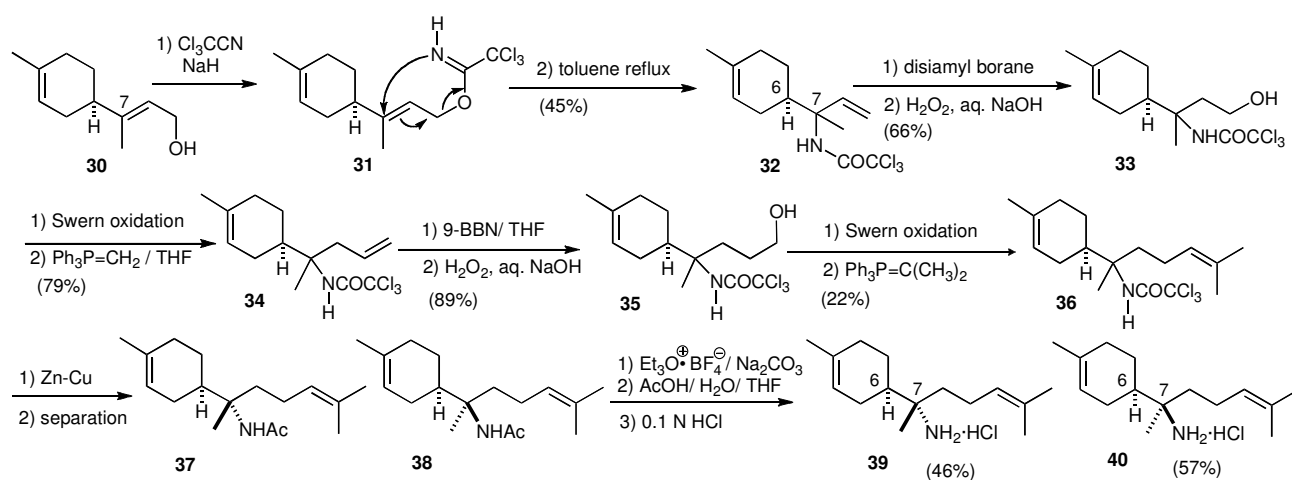
Scheme 8

Our synthesis of aminobisabolenes began with the installation of quaternary carbon atom at C-7 (Scheme 9). Allyl alcohol **30** was transformed into the allyl imidate **31**, which was heated in toluene at reflux for 5 h to provide an 1:1 mixture of the inseparable C-7 diastereoisomers **32** in 45% yield. Repeated hydroboration-oxidation Wittig-olefination sequences (**32** →**33** →**34** and **34** →**35** →**36**) gave rise to the *N*-trichloroacetyl aminobisabolenes **36**. Reduction of trichloromethyl moiety in **36** with zinc copper couple and careful separation of the resultant *N*-acetyl aminobisabolenes furnished **37** and **38** in pure form. Independent reactions of **37** and **38** with Meerwein's

reagent gave the corresponding imino ethers, which were treated with acetic acid in aqueous tetrahydrofuran and 0.1 N hydrogen chloride to provide the aminobisabolene hydrochloride salts **39** and **40** in 46% and 57% yield, respectively.

Scheme 9

After completion of this rather lengthy synthetic scheme, a new approach for the synthesis of the *N*-acetyl aminobisabolene derivatives evolved that was patterned after the hypothetical biogenetic pathway for these natural products (Scheme 10). Specifically, we performed a one-pot process involving acid-catalyzed cyclization of nerolidol **41** in the presence of acetonitrile.[18] It is interesting to compare the yield of the one pot process (4.4%) shown in Scheme 10 to that of 12 step route starting from **30** (1.5%) given in Scheme 9.

Scheme 10
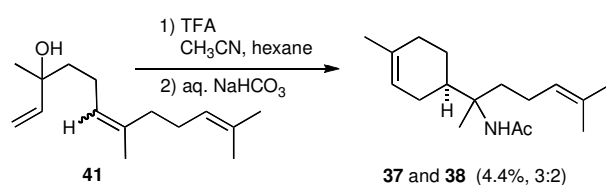
After my studies on the synthesis of aminobisabolenes were finished, I visited the LOC and enjoyed a stimulating discussion of the chemistry with T. Goto. On being told about the difficulties I had with the synthesis of allyl cyanates, Goto stated that it should be an easy problem to solve by using the *dehydration reaction of carbamates*. In the introductory course of organic chemistry, students learned that the dehydration reaction of amides serves a synthetic method for preparing nitriles. Accordingly, the idea of dehydration of carbamates to make cyanates should evolve by analogy (Scheme 11). I guess I had no imagination at this point in my career, even though Professor Goto was the person who taught the undergraduate organic chemistry lecture course I took as a student. In fact, Goto's revelation was the silver lining for a troubled student (Y. I.).
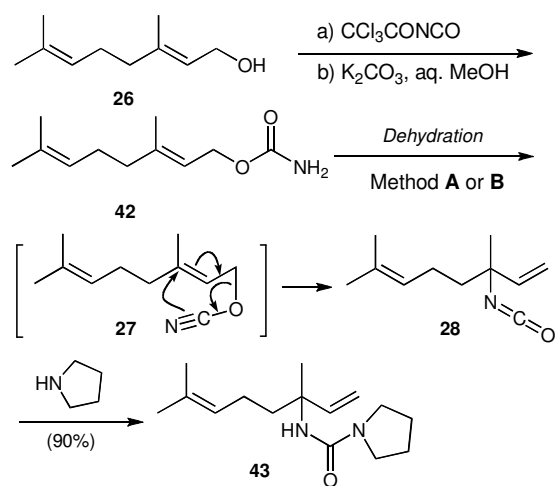
Scheme 11
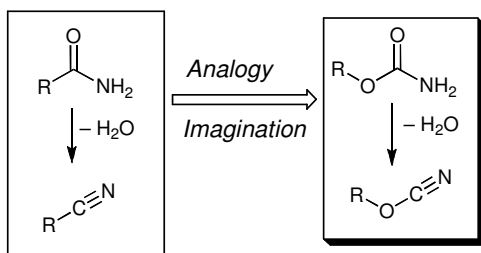
Following the return to my laboratory at Mie University, I searched the literature for the synthesis of carbamates and explored for possible dehydration reagents among those used to form nitriles and isonitriles from amides and formamides. After some experimentation, on October 17 1990 I have found it (eureka !). The long-awaited reactions are exemplified in Scheme 12.[19] Reaction of geraniol **26** with trichloroacetyl

isocyanate followed by hydrolysis with potassium carbonate in aqueous methanol provides the allyl carbamate **42**. Treatment of **42** with trifluoromethanesulfonic anhydride (Tf$_2$O) and diisopropylethylamine in CH$_2$Cl$_2$ at –78 °C for 20 min (Method A) gave a low polarity product (TLC analysis: R$_f$ = 0.8; SiO$_2$ plates; hexane). This dehydration condition was used earlier for the synthesis of isonitriles from formamides by Baldwin, my postdoctoral mentor.[20] Frankly speaking, I had no experience to prepare the isocyanates until this time and did not know that theses highly reactive substances are easily hydrolyzed during workup and purification. In spite of my ignorance about the chemistry of isocyanates, I was fortunate enough to isolate the isocyanate **28** using aqueous workup and silica-gel chromatography. Later, I realized that compounds containing isocyanate groups located at sterically congested positions are relatively stable and isolable using aqueous workup. On the same day of the initial discovery, I also found another dehydration condition (CCl$_4$, PPh$_3$, Et$_3$N, ClCH$_2$Cl$_2$Cl, 60 °C, 100 min), reported by Appel as a synthetic method for the preparation of nitriles from amides,[21] that also can be used to transform **42** to **28**. This protocol was later improved by using the modified Appel's condition (Method B: CBr$_4$, PPh$_3$, Et$_3$N, CH$_2$Cl$_2$, –20 °C), which was initially reported for the preparation of isonitriles from formamides.[22] To confirm its structure, the linalyl isocyanate **28** was transformed into the known urea **43** by reaction with pyrrolidine. Further work established that **42** could be converted to the urea **43** in a one-pot process without the need for isolation of the isocyanate **28** in excellent overall yield (90% from geraniol **26** by employing Method A).

The much faster rate of allyl cyanate-to-isocyanate rearrangement as compared to that of its sulfur counterpart may be a consequence of the strong driving force associated

with formation of a carbonyl vs. thiocarbonyl group and the shorter C–O compared to the

C–S bond distance leading to a more compact six-membered transition state.

Scheme 12

The most impressive example demonstrating the superiority of the allyl cyanate-to-isocyanate rearrrangement is found in the case of the phenylallyl system (Scheme 13). In contrast to the isomerization that takes place with refluxing 3-phenylallyl thiocyanate **44** to give 3-phenylallyl isothiocyanate **45** via an ionization mechanisms,[23] dehydration of the carbamate **46** followed by the allyl cyanate rearrangement and trapping the isocyanate with pyrrolidine produces the urea **47** in 83% yield.

Scheme 13
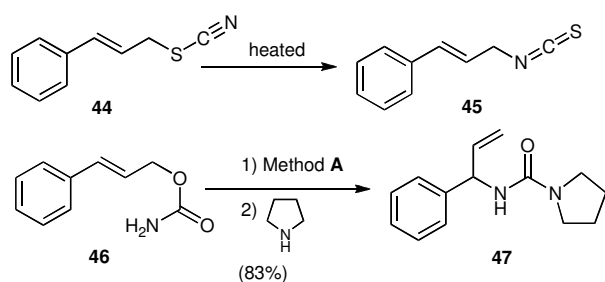
I must admit that at that time I was a bit anxious about a scientific coincidence: others might be engaged in similar research work on the allyl cyanate-to-isocyanate rearrangement. As is often the case, this suspicion proved to be correct as evidenced by the report of Klaus Banert in 1992, which will be described later. One month after the first successful experiments realizing the synthesis of allyl cyanates by using dehydration of allyl carbamates, I submitted a manuscript to *Tetrahedron Letters*, a famous international journal in the field of organic chemistry, but it was rejected. Although deeply disappointed, I recovered and submitted the same manuscript to the, at that time, new journal *Synlett* in

1991 (the first issue of *Synlett* was published in 1989).   I vividly remember when the editor, Hisashi Yamamoto, contacted me by telephone (it was a good time then without e-mail) to read out the decision that my manuscript had been accepted with some minor revisions.

Since rearrangement reactions of allyl cyanates represented an unexplored field at that time, promising and rich plains were opened for cultivation. Key topics in this area that will be discussed below include the stereochemistry of the process and its applications to the synthesis of natural products containing nitrogen-substituted quaternary carbons.

The stereochemistry and mechanism of the allyl cyanate-to-isocyanate rearrangement

Although my initial studies established the allyl cyanate-to-isocyanate rearrangement as a new synthetic method, there was no information about the stereochemistry or mechanism of the process. I was particularly concerned about the possibility that the reaction takes place via an ionization-recombination pathway, which is the predominant route observed in alkyl cyanate-to-isocyante isomerization reactions (Scheme 14).[24] Studies of the kinetics of the isomerization reaction of ethyl cyanate **48** to form ethyl isocyanate **50** in a variety of solvents revealed that the rearrangement could occur by way of a solvent separated ion pair, such as **49**, and subsequent reaction of the recombination product **50** could result in the formation of triethylisocyanurate **51**.   In a related study, Lewis acid-catalyzed rearrangement of alkyl cyanate **13** was reported to form the sterically hindered alkyl isocyanate **52**.[10]

Scheme 14
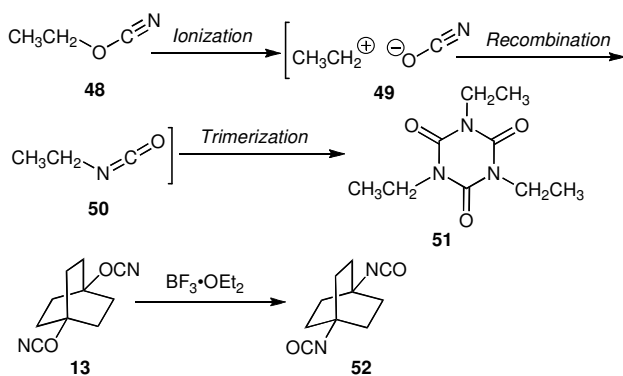
In order to answer the question whether an ionic or concerted mechanism is responsible for this process, we prepared the chiral allyl carbamate **54** from ethyl (*S*)-(−)-lactate **53** (Scheme 15).[25] Dehydration of **54** using PPh$_3$, CBr$_4$, and Et$_3$N occurred smoothly at −20 °C to provide the allyl isocyanate **56**, which was then treated with trimethylaluminum (Me$_3$Al) to furnish the acetamide **57** in 93% yield.

Rearrangement of allyl cyanate **55** proceeds with a high degree of stereochemical control. ^{1}H NMR analysis showed that only the (*E*)-isomer of the product **57** was formed. In addition, the enantiomeric purity of **57** was determined to be 98% by analysis of the corresponding MTPA esters **58**. The absolute stereochemistry of the formed stereogenic center in **57** was determined by analysis of the MTPA amides **59** by using Kusumi's method for elucidation of the absolute configuration of primary amines.[26] The mechanistic investigations demonstrated that the allyl cyanate-to-isocyanate rearrangement is a concerted [3.3] sigmatropic process involving highly selective [1,3]-chirality transfer to the newly formed asymmetric, nitrogen-bearing center. Moreover, the results showed that the rearrangement is a new methodology for the asymmetric synthesis of allyl amines starting from chiral allyl alcohols.

Scheme 15
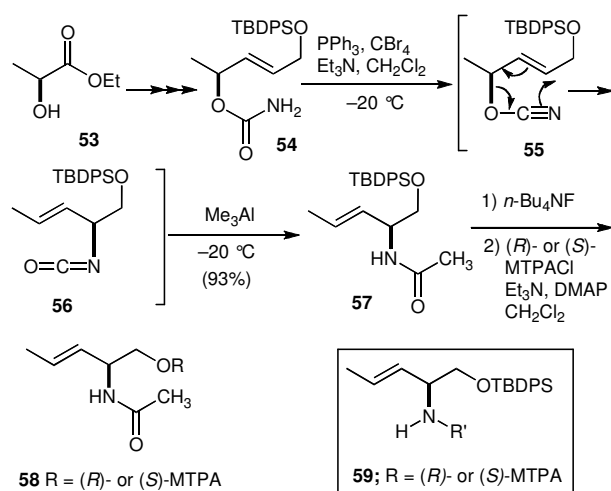
Further examination of the stereochemistry of the allyl cyanate-to-isocyanate rearrangement focused on processes that lead to the construction of nitrogen-substituted quaternary stereogenic centers. This effort was driven by the fact that stereoselective introduction of nitrogen-substituted quaternary carbons is one of the most challenging problems in organic synthesis and that many natural products possess these types of stereocenters.

In order to gain information about the level of [1,3]-chirality transfer taking place from the allyl cyanate to the quaternary asymmetric carbon in the product, we explored the synthesis of (*R*)-α-methylphenylalanine (Scheme 16).[27] The synthesis started with allyl alcohol **61**, which was prepared by enantioselective addition of diethylzinc to the α,β-unsaturated aldehyde **60** in cyclohexane using the method reported by Soai.[28] This reaction proceeded smoothly in the presence of a catalytic amount of

(*S*)-diphenyl(1-methylpyrrolidin-2-yl)methanol (DPMPM, 6 mol%) to provide allyl

alcohol **61** in 83% yield and 80% ee.   Although **61** was obtained with only a modest %

ee, the enantiomeric purity of the corresponding carbamate **62** could be increased to 90%

ee by repeated recrystallization. It should be noted that the highly crystalline nature of

intermediate carbamates is one of the merits of our protocol.   Dehydration of

enantiomerically enriched allyl carbamate **62** was carried out by using

triphenylphosphine, carbon tetrabromide, and triethylamine at 0 °C.   The resulting allyl

cyanate **63** immediately underwent [3.3] sigmatropic rearrangement to afford allyl

isocyanate **64**, which was treated *in situ* with tributyltin methoxide in methanol.

Methyl carbamate **65** was isolated after workup and chromatographic purification in

85% yield.   Transformation of **65** into MTPA ester **66** revealed that excellent chirality

transfer had occurred to the newly formed quaternary stereogenic center in the product.

Scheme 16
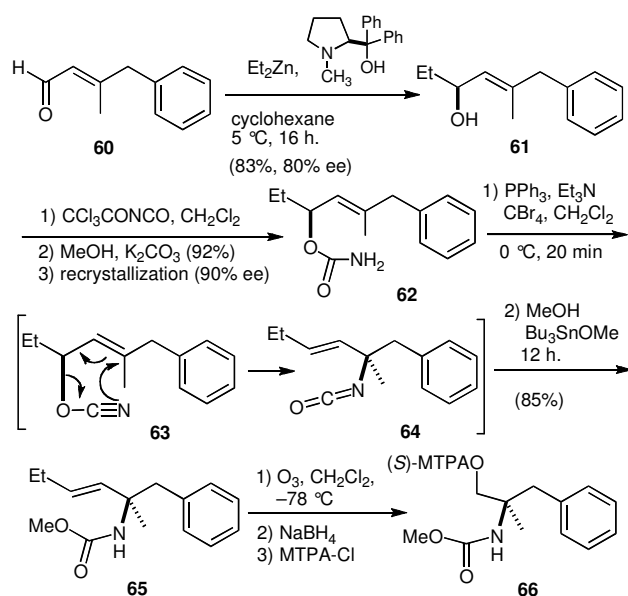
The absolute stereochemistry of the nitrogen-substituted quaternary carbon center was determined by transforming **65** into (*R*)-α-methylphenylalanine (**68**) by way of oxidative cleavage of the double bond and hydrolysis of the carbamate moiety with 6 N hydrogen chloride (Scheme 17). The results of the synthesis of (*R*)-α-methylphenylalanine demonstrated the versatility of this allyl cyanate rearrangement-based approach to the stereoselective installation of an amino group on the quaternary carbon stereocenter.
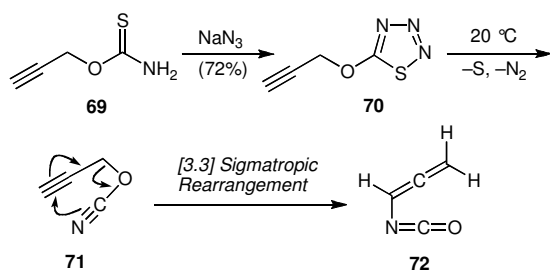
Scheme 17
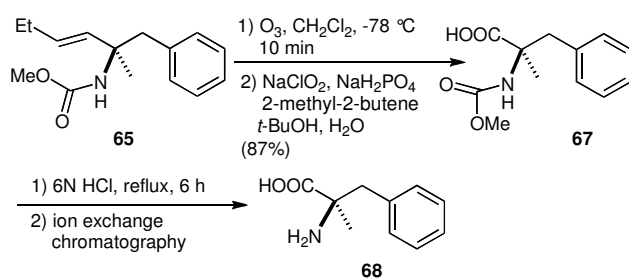
Our stereochemical investigations enabled us to propose that the rearrangement reactions (**55**→**56** and **63**→**64**) take place via a concerted suprafacial pathway involving a puckered cyclohexane like transition state (Figure 1), in which the alkyl group R³ occupies a pseudo-equatorial position (transition state A). This proposal explains the preference for formation of both the (*E*)-stereochemistry at the newly formed double bond and the absolute configuration at the new stereogenic center bearing nitrogen. In contrast, transition state B, in which R³ occupies a pseudo-axial position is unfavorable.

Figure 1
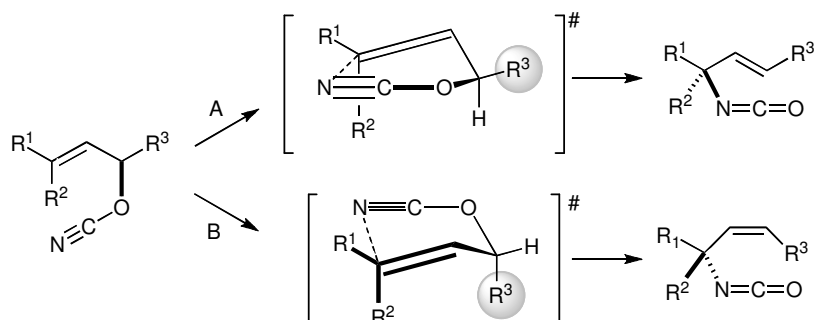
Although our mechanistic investigations confirmed the stereochemistry of the allyl cyanate-to-isocyanate rearrangement, it did not lead to the isolation or NMR detection of allyl cyanates which serve as short-lived intermediates. My friendly competitor, K. Banert was able to isolate propargyl thiatriazole **70** as colorless, explosive crystals, which decomposed in solution even at room temperature to produce allenylisocyanate **72** quantitatively (Scheme 18).[29] In this effort, the conversion of **70**→**72** was followed by using NMR spectroscopy. Importantly, ^{1}H NMR signals of the intermediate **71** was detected, and the maximum proportion of the short-lived quasi-stationary intermediate **71** in the reaction mixture was found to be only 5%.

Scheme 18

In an attempt to synthesize a stable allyl cyanate (Scheme 19), Banert explored the reaction of **73** with cyanogen chloride in the presence of triethylamine (Cloez method). This process generated **74** as a stable yellowish crystalline substance.[30] The isomerization reaction (**74→ 75**) was monitored by employing ^{1}H NMR spectroscopy in the temperature range of 70 – 120 °C. The results enabled the determination of activation parameters for the first-order process. In particular, the large negative activation entropy ($\Delta S_{298}^{\neq} = -126.5 \pm 11$ J mol^{-1}K^{-1}) is characteristic of a reaction taking place by a mechanism involving a cyclic and highly ordered transition state.
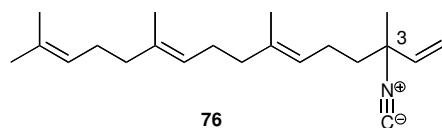
Scheme 19
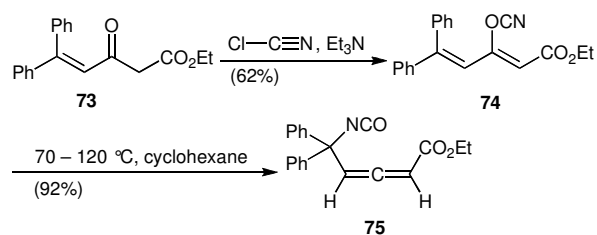
Synthesis of natural products containing nitrogen-substituted quaternary carbon centers

My love for natural products that contain quaternary carbons led to the design and execution of the synthesis of the isonitrile analogue of diterpenoid geranyllinalool **76**, which was isolated by Scheuer during a screening program for bioactive constituents from marine sponges *Halichondria* sp. This natural product, which possesses a unique isonitrile-containing quaternary carbon at C-3, was found to be active against *Staphylococcus aureus*.[31]


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Transformation of geranyl geraniol **77** to the allyl acetamide **79** was accomplished employing similar conditions to those described in Scheme 12 except that, in this case, *in situ* transformation of isocyanate **78** into the acetamide **79** was performed by reaction with Me_3Al in 59 % overall yield (Scheme 20).   Transformation of the acetamide in **79** into isonitrile functionality was straightforward.   Thus, reaction of **79** with Meerwein's reagent followed by treatment with acetic acid in aqueous THF provided the corresponding amine, which was reacted with acetic formic anhydride to form the formamide **80** in 84% overall yield from **79**.   Finally, the formamide **80** was smoothly dehydrated to generate (±)-**76** in 82% yield using the modified Appel's protocol (PPh_3, CBr_4 and iPr_2NEt –20 $^\circ$C, 30 min).[32]
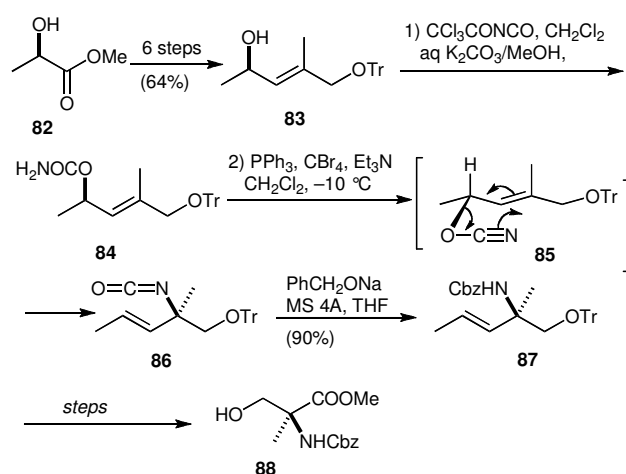
Scheme 20
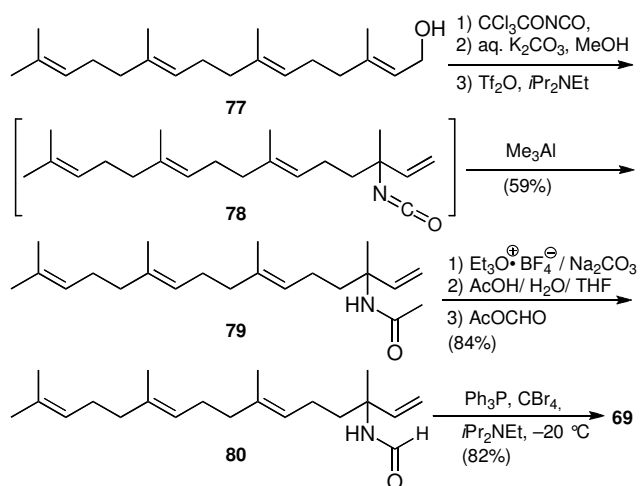
Conagenin (**81**) is a unique, biologically important, secondary metabolite isolated from the culture broths of *Streptomyces roseosporus* by Ishizuka and co-workers.[33] This antibiotic stimulates activated T cells as a low molecular weight immunomodulatory. The unique structure of conagenin is comprised of a right fragment consisting of a α-methylserine, containing quaternary asymmetric center attached to nitrogen and left segment composed of a substituted pentanoic acid with three contiguous stereocenters.
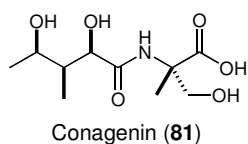
Conagenin (**81**)

The nitrogen-substituted quaternary stereocenter in the right α-methylserine moiety of conagenin was stereoselectively constructed by using [3.3] sigmatropic rearrangement

of an allyl cyanate (Scheme 21).[34)] Starting with D-lactic acid methyl ester (**82**), allyl

alcohol **83** was prepared in 64% overall yield over six steps. Alcohol **83** was then

transformed into allyl carbamate **84**, the dehydration of which was carried out by using the

modified Appel's conditions (PPh$_3$, CBr$_4$, Et$_3$N, CH$_2$Cl$_2$, −10 °C) to generate allyl cyanate

85, which immediately underwent [3.3] sigmatropic rearrangement at −10 °C to afford

allyl isocyanate **86**. After careful work-up, **86** was treated with sodium benzyl alkoxide

in THF to produce the benzyl carbamate **87** in 90% overall yield from **86**.

Transformation of the double bond in **87** into the methoxycarbonyl group was

accomplished by using a four-step sequence, and removal of triphenylmethyl protecting

group with trifluoroacetic acid gave the α-methylserine **88**.

Scheme 21

27

The pentanoic acid **89** and α-methylserine **88** fragments were joined by employing an intramolecular ester-to-amide exchange reaction (Scheme 22). Thus, esterification of **89** with **88,** removal of the Cbz group in **90** by hydrogenolysis and subsequent treatment of the resultant ester **91** with aqueous sodium bicarbonate gave rise to the amide **92** in 90% yield over three steps. Finally, deprotection of the acetyl and methyl ester protecting groups in **92** completed the synthesis of (+)-conagenin (**81**).
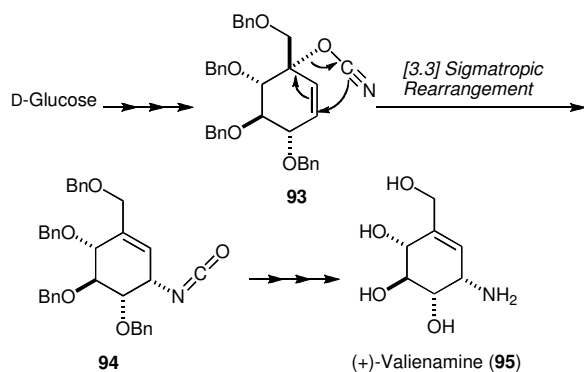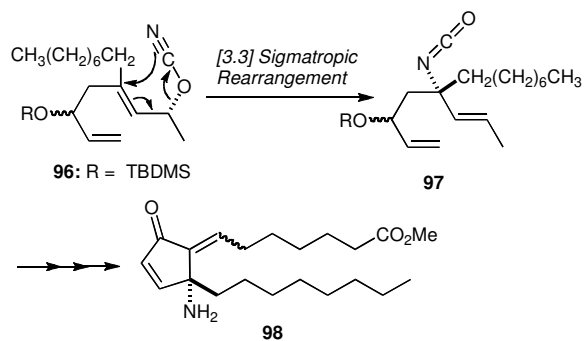
Scheme 22
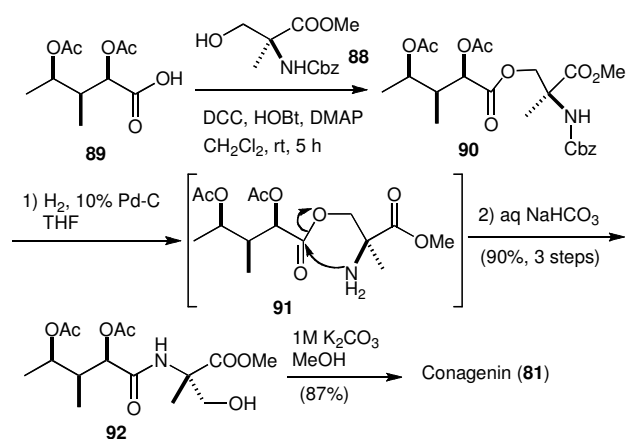
Coda

It is rewarding to see that many synthetic chemists have subsequently enjoyed the allyl cyanate-to-isocyanate rearrangement reaction in their work. For example, Vasella reported the synthesis of carbasaccharide (+)-valienamine (**95**) from D-glucose (Scheme 23) which employs this process in a key step.[35] Specifically, the allyl amine moiety in **95** was successfully constructed by way of a [3.3] sigmatropic rearrangement of allyl cyanate (**93**→**94**).
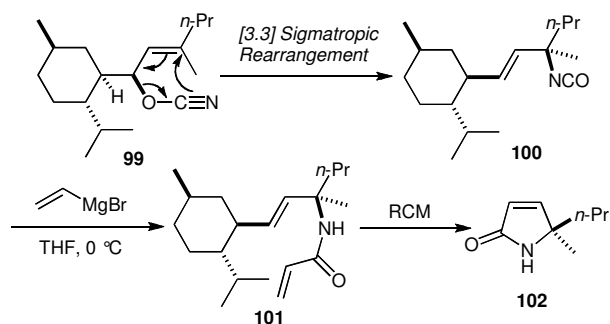
Scheme 23

A synthesis of the novel 12-amino alkylidenecyclopentenone prostaglandin **98,** reported by Florent (Scheme 24), involved use of a [3.3] bond reorganization process of allyl cyanate **96** to from **97** as a crucial step for the construction of the nitrogen-substituted quaternary stereocenter.[36]

Scheme 24

96: R = TBDMS   **97**

98

Using *p*-menthane-3-carboxaldehyde as a chiral auxiliary, Spino prepared chiral allyl isocyanate **99** to access *N*-heterocycles bearing a quaternary chiral carbon (Scheme 25). Treatment of isocyanate **100** with vinylmagnesium bromide gave the acrylamide **101**, which was subjected to ring-closing metathesis (RCM) to form pyrrolone **102**.[37]

Scheme 25

References

1. (a) Billeter, O. *Helv. Chim. Acta*. **1925**, *8*, 337. (b) For a comprehensive discussion of the rearrangement of allyl thiocyanates, Giles, D. E. In *The Chemistry of Cyanates and Their Thio Derivatives Part 1*, Chapter 12, p. 381; Patai, S., Ed.; Wiley-Interscience: New York, **1977.**

2. Smith, P. A. S.; Emerson, D. W. *J. Am. Chem. Soc*. **1960**, *82*, 3076.

3. Leffler, M. T. *Org. Synth., Coll. Vol. 2* **1943**, p. 24.

4. Cloez, R. *C. R. Acad. Sci. Paris* **1857**, *44*, 482.

5. (a) Jensen, K. A.; Holm, A. In *The Chemistry of Cyanates and Their Thio Derivatives Part 1*, Chapter 16, p. 569; Patai, S., Ed.; Wiley-Interscience: New York, **1977**. (b) Grigat, E.; Pütter, R. *Angew. Chem., Int. Ed. Engl.* **1967**, *6*, 206. (c) Grigat, E. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 949. (d) Grashey, R. In *Comprehensive Organic Synthesis*, Vol. 6, p. 225; Trost, B. M.; Fleming, I., Eds.; Pergamon: Oxford, **1991**.

6. Stroh, R.; Gerber, H. *Angew. Chem.* **1960**, *72*, 1000.

7. (a) Grigat, E.; Pütter, R. *Chem. Ber.* **1964**, *97*, 3012. (b) Martin, D. *Org. Synth., Coll. Vol. 7* **1943**, p. 435.

8. Jensen, K. A.; Holm, A. *Acta Chem. Scand.* **1964**, *18*, 826.

9. (a) Martin, D. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 311. (b) Martin, D. *Chem. Ber.* **1964**, *97*, 2689.

10. Kauer, J. C.; Henderson, W. W. *J. Am. Chem. Soc*. **1964**, *86*, 4732.

11. Christophersen, C.; Holm, A. *Acta Chem. Scand.* **1970**, *24*, 1512.

12. Kitagawa, I.; *Kagaku-Zoukan*, **1987**, *111*, p. 133.

13. (a) Kitagawa, I.; Yoshioka, N.; Kamba, C.; Yoshikawa, M.; Hamamoto, Y. *Chem. Pharm. Bull.* **1987**, *35(2)*, 928. (b) Sullivan, B. W.; Faulkner, D. J.; Okamoto, K. T.; Chen, M. H. M.; Clardy, J. *J. Org. Chem.* **1986**, *51*, 5143. (c) Gulavita, N. K.; deSilva, E. D.; Hagadone, M. R.; Karuso, P.; Scheuer, P. J.; VanDuyne, G. D.; Clardy. J. *J. Org. Chem.* **1986**, *51*, 5136.

14. In a study paralleling our exploration of the synthesis of aminobisabolenes, we probed the synthesis of the sulfur-containing natural product agelasidine A using an allyl xanthate-to-dithiocarbonate rearrangement. See, Ichikawa, Y. *Tetrahedron Lett.* **1988**, *29*, 4957.

15. (a) Overman, L. E. *J. Am. Chem. Soc.* **1974**, *96*, 597.   (b) Overman, L. E. *J. Am. Chem. Soc.* **1974**, *98*, 2901. (c) Clizbe, L. A.; Overman, L. E. In *Org. Synth.*, *Coll. Vol. 6* **1988**, p. 507.

16. Overman, L. E.; Kakimoto, M. *J. Org. Chem.* **1978**, *43*, 4564.

17. Ichikawa, Y. *Chem. Lett.* **1990**, 1347.

18. A solution of commercially available nerolidol **41** (a 3:2 mixture of *Z*- and *E*-isomers, 5.01 g) in hexane cooled to 0 °C was added acetonitrile (14 ml) and TFA (8.0 ml). The resulting biphasic mixture was vigorously stirred at 0 °C for 24 h, and then poured into aq. $NaHCO_3$. Usual workup followed by silica-gel chromatography (hexane $\rightarrow$ ether/hexane 1:2) gave the recovered starting material (1.23 g) and crude products,

which were purified by recrystallization (ether and hexane) to furnish aminobisabolenes (a 2:1 mixture of **37** and **38**, 195 mg, 4.4% yield based upon the consumed starting materials).

19.   Ichikawa, Y. *Synlett* **1991**, 238.   To the best of our knowledge, this protocol is the first example of the synthesis of cyanates from carbamates by dehydration. Later, I found a report of an unsuccessful synthesis of cyanates by dehydration of carbamates using P_2O_5 and DCC.   See, Jensen, K. A..; Holm, A. *Acta Chem. Scand.* **1964**, *18*, 2417.

20. Baldwin, J. E.; O'Neil, I. A. *Synlett* **1990**, 603.

21. Appel, R.; Kleinstuck, R.; Ziehn, K. *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 132.

22. Ichikawa, Y. *J. Chem. Soc. Perkin Trans. 1* **1992**, 2135. (b) O'Neil, I. A.   In *Comprehensive Organic Functional Group Transformations*, Vol. 3, p. 696; Katritzky, A.; Meth-Cohn, O.; Ress, C. W., Eds.; Pergamon: Oxford, **1995**.

23. Bergmann, E.   *J. Chem. Soc.* **1935**, 1361.

24. Martin, D.; Niclas, H-J.; Habisch, D.   *Liebigs Ann. Chem.* **1969**, *727*, 10.

25. Ichikawa, Y.; Tsuboi, K.; Isobe, M.   *J. Chem. Soc., Perkin Trans. 1* **1994**, 2791.

26. T. Kusumi, T. Fukushima, I. Ohtani and H. Kakisawa, *Tetrahedron Lett.* **1991**, *32*, 2939.

27.   Ichikawa, Y.; Yamauchi, E.; Isobe, M.   *Biosci. Biotech. Biochem.* **2005**, *69 (5),* 939.

28. Soai, K., Ookawa, A., Kaba, T., and Ogawa, K., *J. Am. Chem. Soc.* **1987**, *109*, 7111.

29.   Banert, K.; Groth, S.   *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 866.

30. Banert, K.; Melzer, A. *Tetrahedron Lett.* **2001**, *42*, 6133.

31. (a) Burreson, B. J.; Scheuer, P. J. *J. C. S. Chem. Commun.* **1974**, 1035.   (b) Burreson, B. J.; Christophersen, C.; Scheuer, P. J. *Tetrahedron* **1975**, *31,* 2015.

32. Ichikawa, Y.; Yamazaki, M.; Isobe, M.   *J. Chem. Soc., Perkin Trans. 1* **1993**, 2429.

33.   (a) Yamashita, T.; Iijima, M.; Nakamura, H.; Isshiki, K.; Naganawa, H.; Hattori, S.; Hamada, M; Ishizuka, M.; Takeuchi, T.; Iitaka, Y. *J. Antibiot.* **1991**, *44*, 557. (b) Hamada, M.; Yamamoto, S.; Moriguchi, S.; Kishino, Y. *J. Antibiot.* **2001**, *54*, 349

34. Matsukawa, Y.; Isobe. M.; Kotsuki. H.; Ichikawa, Y. *J. Org. Chem.* **2005**, *70*, 5339.

35. Kapferer, P.; Sarabia, F.; Vasella, A. *Helv. Chim. Acta.* **1999**, *82*, 645.

36. Roulland, E.; Monneret, C.; Florent, J-C.; Bennejean, C.; Renard, P.; Leonce, S. *J. Org. Chem.* **2002**, *67*, 4399.

37. Roy, S.; Spino, C. *Org. Lett.* **2006**, *8*, 939.