Double bond formation based on nitroaldol reaction and radical elimination: a prototype segment connection method for the total synthesis of nigricanoside A dimethyl ester

Takayuki Tsunoda, Kenshu Fujiwara, Satoshi Okamoto, Yoshihiko Kondo, Uichi Akiba, Yusuke Ishigaki, Ryo Katoono, Takanori Suzuki

PII: S0040-4039(18)30428-3
DOI: https://doi.org/10.1016/j.tetlet.2018.03.091
Reference: TETL 49860

To appear in: *Tetrahedron Letters*

Received Date: 1 March 2018
Revised Date: 24 March 2018
Accepted Date: 30 March 2018

Please cite this article as: Tsunoda, T., Fujiwara, K., Okamoto, S., Kondo, Y., Akiba, U., Ishigaki, Y., Katoono, R., Suzuki, T., Double bond formation based on nitroaldol reaction and radical elimination: a prototype segment connection method for the total synthesis of nigricanoside A dimethyl ester, *Tetrahedron Letters* (2018), doi: https://doi.org/10.1016/j.tetlet.2018.03.091

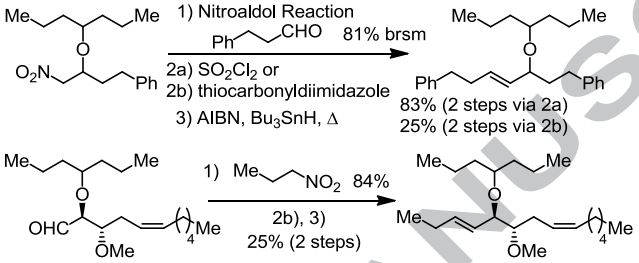
Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

Double bond formation based on nitroaldol reaction and radical elimination: a prototype segment connection method for the total synthesis of nigricanoside A dimethyl ester

Leave this area blank for abstract info.

Takayuki Tsunoda, Kenshu Fujiwara,* Satoshi Okamoto, Yoshihiko Kondo, Uichi Akiba, Yusuke Ishigaki, Ryo Katoono, Takanori Suzuki



Tetrahedron Letters
journal homepage: www.elsevier.com

Double bond formation based on nitroaldol reaction and radical elimination: a prototype segment connection method for the total synthesis of nigricanoside A dimethyl ester

Takayuki Tsunoda [a], Kenshu Fujiwara [b,*], Satoshi Okamoto [a], Yoshihiko Kondo [b], Uichi Akiba [b], Yusuke Ishigaki [a], Ryo Katoono [a] and Takanori Suzuki [a]

[a]*Department of Chemistry, Faculty of Science, Hokkaido University, Sapporo 060-0810, Japan*
[b]*Department of Life Science, Graduate School of Engineering Science, Akita University, Akita 010-8502, Japan*

ARTICLE INFO

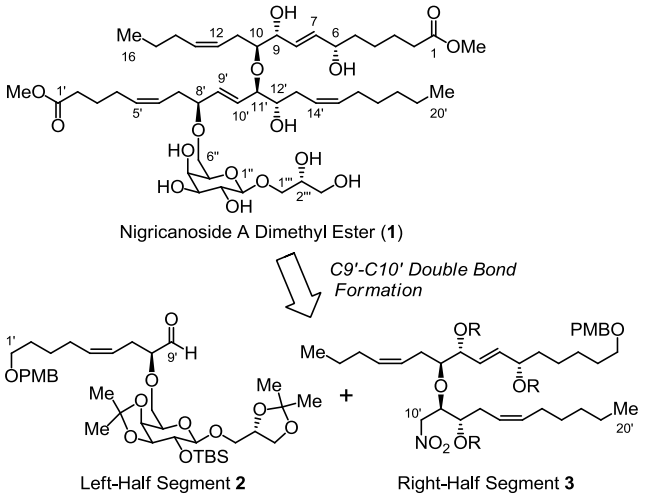
Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Natural product synthesis
Nitroaldol reaction
Radical elimination
Double bond formation
β-chloronitroalkane

ABSTRACT

During the course of our studies toward the total synthesis of nigricanoside A dimethyl ester, a prototype method for the connection of the left- and right-half segments at the C9'-C10' double bond was developed using a model system. The method was based on a simple three-step process including: (i) a nitroaldol reaction, (ii) chlorination or thionocarbonylation, and (iii) radical elimination.

Nigricanoside A dimethyl ester (**1**) (Scheme 1), isolated from the green alga *Avrainvillea nigricans* by Andersen in 2007, is a unique monogalactosyl diacyl glycerol skeleton featuring ether bonds that connect two oxygenated fatty acids and a galactose moiety.[1] Although the stereochemistry of **1** was not completely determined in the first isolation report, its novel structure and a possible strong cytotoxicity against cancer cells, suggested in the report, attracted significant attention from synthetic chemists. Therefore, several research groups,[2,3] including ours,[4] have studied the total synthesis of **1** aimed at the determination of the absolute configuration and demonstration of the cytotoxicity. In our study, a stereoselective method for the construction of the C8'-O-C6" ether of **1** was developed based on the chirality transferring Ireland-Claisen rearrangement.[4] In 2015, MacMillan and Ready achieved the stereochemical assignment of the natural product by stereoselective total synthesis and demonstrated the absence of cytotoxicity.[2] Since then, our interest in the synthesis of **1** shifted toward the development of a new efficient construction process for the novel structure. Thus, we have explored a convergent strategy to construct **1** from the left-half segment **2** and the right-half segment **3** by the union at the C9'-C10' double bond, which has ether groups at both allylic positions (C8' and C11'), a rare structure in acyclic natural products (Scheme 1). Here, we describe the development of a prototype method for the segment connection at the C9'-C10' double bond of **1** based on a nitroaldol reaction and radical elimination.

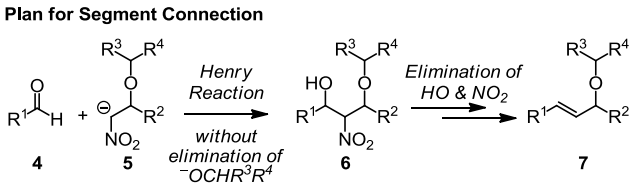


Scheme 1. Plan for the convergent synthesis of nigricanoside A dimethyl ester (**1**).

The segment connection at the C9'-C10' double bond of **1** presents some difficult challenges due to the presence of ether groups at C8' and C11' in addition to other internal double bonds.

* Corresponding author. e-mail: fjwkn@gipc.akita-u.ac.jp

Cross-metathesis is a well-known method for the formation of simple ether-group-adjacent double bonds.[5] However, the C9'-C10' double bond is predicted to react with other internal double bonds at C14'-C15', C7-C8, and C12-C13 by ring-closing olefin metathesis as a side reaction under the cross-metathesis conditions.[6] Therefore, cross-metathesis is inappropriate for the segment connection. Olefination, such as the Julia-Kocienski reaction,[7] includes an addition reaction of a carbanion stabilized by an electron withdrawing group to an aldehyde in the first step. In the application of olefination to the formation of the C9'-C10' double bond, the stabilized carbanion possesses a bulky alkoxy group (C1-C16 chain or the galactose moiety) at the β-position. Since the alkoxy group is a potential leaving group, unfavorable β-elimination is predicted when the carbanion is less stable than the eliminating alkoxide ion. In fact, when a β-alkoxyalkyl 1-phenyl-1H-tetrazol-5-yl sulfone was used in a Julia-Kocienski olefination in our preliminary study, the β-elimination of the alkoxide group predominated to produce a vinyl sulfone as a byproduct.[8] Accordingly, careful selection of the electron withdrawing group to appropriately stabilize the adjacent carbanion is important for the successful segment connection by olefination.



Scheme 2. A plan for segment connection at the double bond adjacent to an ether group.

From the above consideration, we initially planned to connect segments **4** (corresponding to **2**) and **5** (corresponding to **3**) by a process including Henry (nitroaldol) reaction[9] to give a nitroaldol (**6**), followed by elimination of the hydroxy and nitro groups to afford an allyl ether (**7**) (Scheme 2). Since nitroalkanes generally have smaller p*K*a values than alcohols, β-alkoxynitroalkanes are expected to generate stable β-alkoxy-α-nitrocarbanions (**5**), which would react with aldehydes (**4**) without elimination of the β-alkoxy group to give nitroaldols (**6**). The eliminative alkenylation of nitroaldols (**6**) would be achievable based on the high radical reactivity of the nitro group. In this study, simple model compound **8** and advanced model compounds **9a-c** (Figure 1), in which the hept-4-yloxy group at the β-position of the nitro group was modeled on the C1-C16 chain of **1**, were employed to demonstrate the segment connection process.[10]

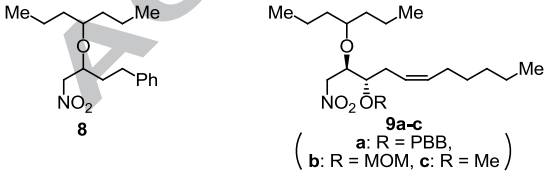
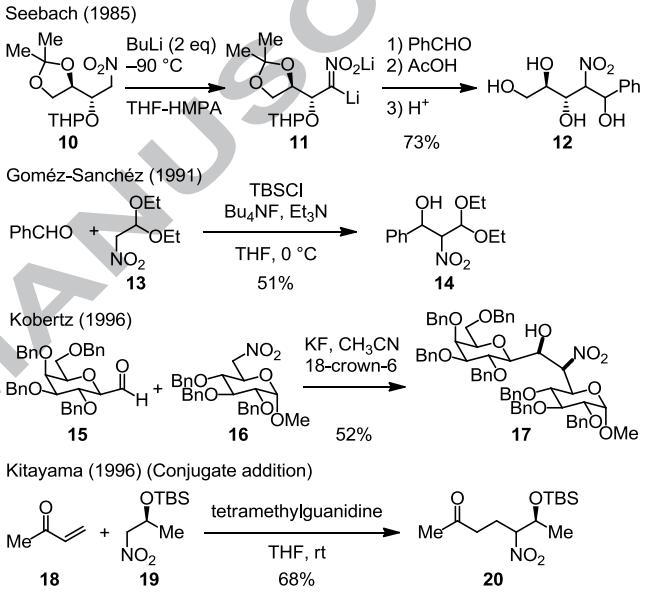


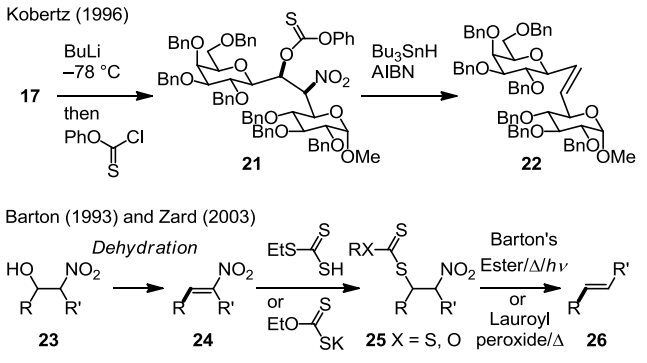
Figure 1. Model compounds **8** and **9a-c**. PBB: *p*-bromobenzyl; MOM: methoxymethyl.

So far, several successful examples have been reported for nitroaldol reactions of β-alkoxynitroalkanes (Scheme 3). Seebach connected dianion **11**, generated from β-alkoxynitro compound **10**, with benzaldehyde to give nitropolyol **12** in high yield after hydrolysis.[11] Fluoride ion-promoted nitroaldol reactions using β-alkoxynitro compounds **13** and **16**, reported by Goméz-Sanchéz[12] and Kobertz,[13] produced nitroaldols **14** and **17**, respectively, in good yields. The anion generated by β-silyloxynitropropane **19** and tetramethylguanidine also reacted with enone **18** without elimination of the β-silyloxy group.[14]

There are only a few examples of the eliminative alkenylation of nitroaldols under radical conditions (Scheme 4). However, Kobertz[13] reported a successful application of Robins' procedure[15] to nitroaldol **17**, which was subjected to thionocarbonylation under basic conditions followed by radical elimination using AIBN and Bu_3SnH, to produce alkene **22** having a 1,4-dialkoxybut-2-ene unit closely related to the C8'-C11' part of **1**. For an alternative method, a three-step sequence including dehydration of a nitroaldol to a nitroalkene, conjugate addition of a trithiocarbonic acid or a xanthate to the nitroalkene, and radical elimination to form an alkene was reported by Barton[16] and Zard.[17] Thus, encouraged by these successful reports, we set out to find suitable conditions for the segment connection process using model compounds **8** and **9a-c**.



Scheme 3. Previous examples for nitroaldol and conjugate addition reactions of β-alkoxynitro compounds. THP: tetrahydropyran-1-yl; TBS: *tert*-butyldimethylsilyl; THF: tetrahydrofuran.

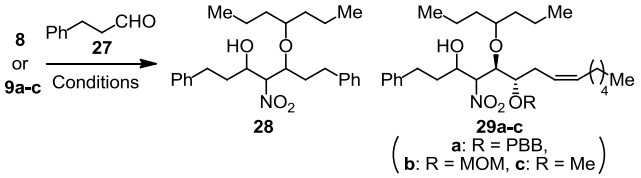


Scheme 4. Previous examples for double bond formation from nitroaldol compounds. AIBN: 2,2'-azodiisobutyronitrile.

First, we examined the nitroaldol reaction of the model compounds **8** and **9a-c** with 3-phenylpropanal (**27**). Selected results are shown in Table 1. When **8** was reacted with **27** in the presence of KF and 18-crown-6 in MeCN according to the Kobertz procedure,[13] a complex mixture of unknown products was obtained (entry 1). Under the Goméz-Sanchéz conditions,[12] model **8** was treated with $Bu_4NF\cdot 3H_2O$, **27**, Et_3N, and TBSCl in

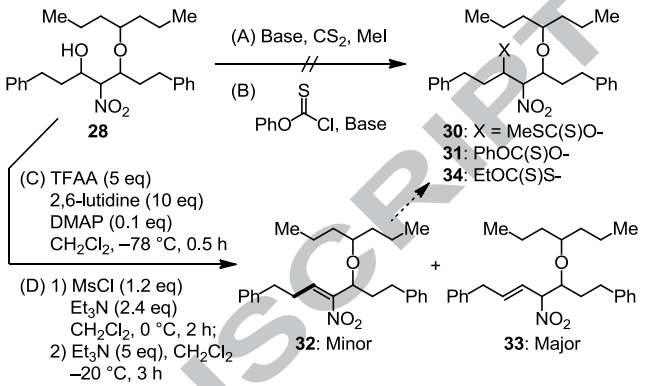
that order in THF to produce nitroaldol **28** (a mixture of four diastereomers) in 55% yield (entry 2). However, the Goméz-Sanchéz conditions were ineffective in the reaction of advanced model **9a** (entry 3). The reaction of **8** with **27** in the presence of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN)[18] in DMF afforded **28** in 53% yield (entry 4). In the reaction, unreacted **8** and **27** were almost completely recovered, and, therefore, the reaction marked a high yield (81%) based on recovered starting material (BRSM). DBN also mediated the nitroaldol reaction of advanced model **9a** with **27** to give **29a** in 59% yield and 88% BRSM yield (entry 5). Advanced models **9b,c** also produced the corresponding products **29b,c** with high BRSM yields (93% and 86%, respectively) and good reproducibility under the same conditions (entries 6 and 7). Besides the conditions in Table 1, we also examined the reaction of the dianion from **8** according to the Seebach procedure;[11] however, it gave a complex mixture of unknown products. Thus, these model studies suggested the suitability of a DBN-mediated nitroaldol reaction between **2** and **3**.

Table 1. Nitroaldol reaction of model compounds **8** and **9a-c**. DBN: 1,5-diazabicyclo[4.3.0]non-5-ene; DMF: *N*,*N*-dimethylformamide.



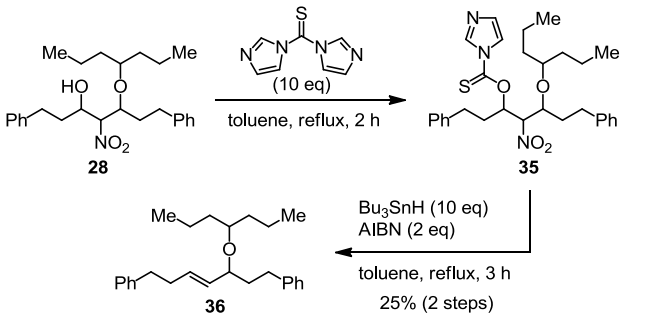
Entry	Conditions	Product Yield
1	**8** (1 eq), **27** (1 eq), KF (cat.), 18-crown-6 (cat.), MeCN, 21 °C, 26 h.	complex mixture
2	**8** (1 eq), $Bu_4NF{\cdot}3H_2O$ (0.25 eq), **27** (0.67 eq), Et_3N (0.67 eq), TBSCl (1 eq), THF, 0 → 23 °C, 0.5 h.	**28**: 55% (from **27**)
3	**9a** (1 eq), $Bu_4NF{\cdot}3H_2O$ (0.25 eq), **27** (0.67 eq), Et_3N (0.67 eq), TBSCl (1 eq), THF, 0 → 23 °C, 0.5 h.	no reaction
4	**8** (1 eq), **27** (1 eq), DBN (3 eq), DMF, 22 °C, 1 h.	**28**: 53% (brsm 81%)
5	**9a** (1 eq), **27** (1 eq), DBN (3 eq), DMF, 22 °C, 2 h.	**29a**: 59% (brsm 88%)
6	**9b** (1 eq), **27** (1 eq), DBN (3 eq), DMF, 22 °C, 2 h.	**29b**: 52% (brsm 93%)
7	**9c** (1 eq), **27** (1 eq), DBN (3 eq), DMF, 22 °C, 2 h.	**29c**: 54% (brsm 86%)

Next, conversion of γ-alkoxy-β-nitroalkanol **28** to xanthate **30**, thionocarbonate **31**, and xanthate **34**, which would be transformed to an alkene under radical elimination (Barton-McCombie) conditions,[19] was attempted (Scheme 5). Although several bases were used, standard conditions for xanthate formation resulted in decomposition of **28** due to the retro-nitroaldol reaction under strong basic conditions (A). When nitroaldol **28** was treated with phenyl chlorothionoformate in the presence of DMAP according to the Robins procedure,[15] no thionocarbonate **31** was produced (B). Next, formation of nitroalkene **32**, which would be an ideal precursor for xanthate **34**, was attempted.[16,17] While treatment of **28** with TFAA in the presence of 2,6-lutidine and DMAP at –78 °C promoted dehydration, undesired migration of the double bond took place under the reaction conditions to give **33**[20] as a major product (C). After several attempts, the mesylate ester of **28** was found to form under standard conditions without elimination. Although elimination of the mesylate with Et_3N at lower temperature was found to show a decreased ratio of double bond migration, migrated alkene **33**[20] was still a major product (D).[21] Thus, no thionocarbonate derivatives **30**, **31**, and **34** were obtained due to instability of the nitroaldol **28** and nitroalkene **32** under basic conditions, which induced the retro-nitroaldol reaction of **28** and migration of the double bond of **32**.



Scheme 5. Attempts of the formation of thionocarbonate derivatives **30**, **31**, and **34** from nitroaldol **28**.

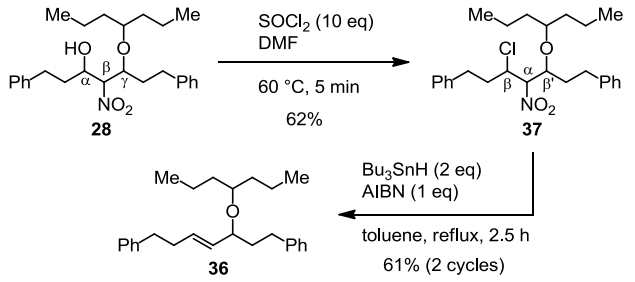
Therefore, we examined the formation of a thionocarbonate derivative from **28** under neutral conditions. After several attempts, it was found that the treatment of **28** with thiocarbonyldiimidazole in refluxing toluene gave imidazolylthionocarbonate **35** (Scheme 6). Due to its lability, the resulting **35** was immediately treated with Bu_3SnH (10 eq) and AIBN (2 eq) in refluxing toluene to produce *E*-alkene **36** in 25% yield. Although we also attempted a tandem one-pot operation for the thionocarbonylation/radical elimination reactions, no alkene **36** was obtained. For the successful formation of alkene **36**, the removal of thiocarbonyldiimidazole and imidazole by extraction was required in the thionocarbonylation step. Thus, although the reaction proceeded in low yield, an easy access of alkene **36** from nitroaldol **28** was realized by a simple two-step reaction method.



Scheme 6. Formation of alkene **36** from **28** by a thionocarbonylation/radical elimination sequence.

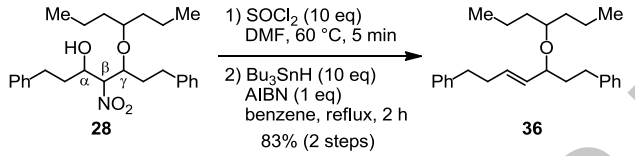
During exploration of the reaction conditions for the conversion of **28** to **32**, we also found that the treatment of **28** (a mixture of diasteromers) with thionyl chloride in DMF at 60 °C for 5 min produced β-chloronitroalkane **37** in good yield (62% after purification) without formation of **32** (Scheme 7). While reaction conditions are known for the conversion of simple nitroaldols to β-chloronitroalkanes,[22] the above reaction is a rare preparation of a β-chloro-β'-alkoxynitroalkane from a γ-alkoxy-β-nitroalkanol. Next, the transformation of **37** to **36** was examined under radical elimination conditions. The treatment of **37** with Bu_3SnH and AIBN in refluxing toluene for 2.5 h

produced *E*-alkene **36** stereoselectively along with unreacted **37**. The mixture of **36** and **37** was subjected again to the same reaction conditions to complete the transformation to **36** (61%).



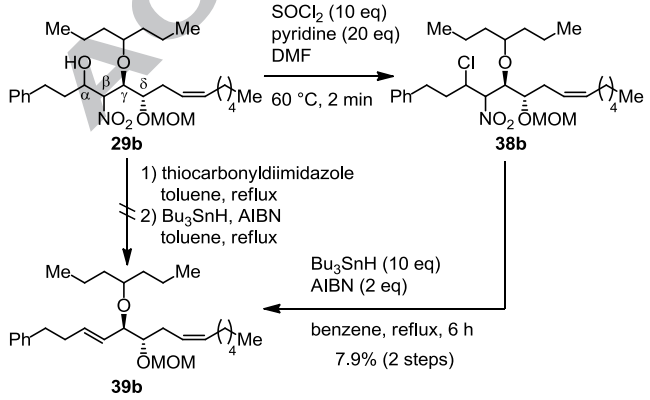
Scheme 7. Double bond formation from nitroaldol **28** via chloride **37**.

Diastereomers of **37** exhibited different stabilities. During silica gel chromatography, one of them decomposed, but the rest were fairly stable. Therefore, the β-chloro-β'-alkoxynitroalkanes were used without purification. When chlorination of **28** and radical elimination were performed sequentially without isolation of **37**, the two-step yield of *E*-alkene **36** was markedly improved (83%) as expected (Scheme 8). Thus, a new method for the conversion of a γ-alkoxy-β-nitroalkanol to a 3-alkoxy-1-alkene has been developed by chlorination followed by radical elimination.



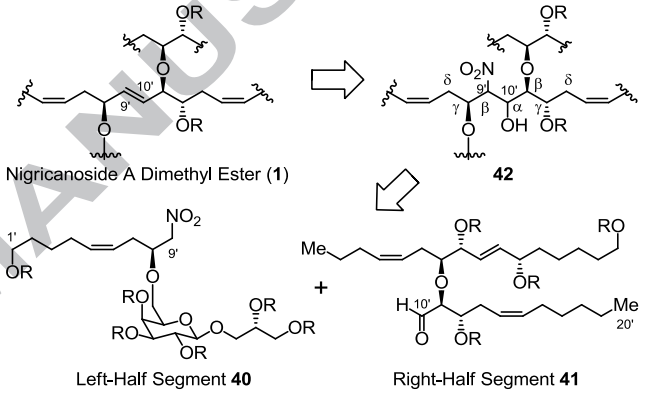
Scheme 8. Sequential two-step double bond formation from nitroaldol **28**.

Double bond formation from the advanced models was examined next. The stepwise treatment of nitroaldol **29b** with thiocarbonyldiimidazole and subsequently with Bu_3SnH and AIBN gave a complex mixture of byproducts and no desired alkene **39b** was detected (Scheme 9). This disappointing result might be attributable to the steric effect of the protected hydroxy group at the δ-position of the thionocarbonate intermediate, by which the disturbance of radical elimination might enhance undesired radical side reactions or the reverse reaction from the labile thionocarbonate intermediate to afford degradation products.

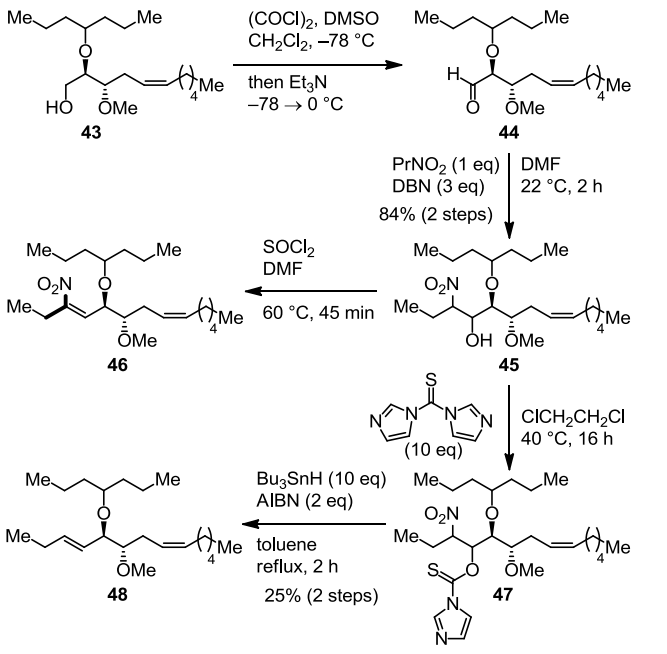


Scheme 9. Double bond formation from nitroaldol **29b**.

The alkene formation by chlorination/radical elimination sequence was then applied to **29a-c**. The reaction of **29a** with thionyl chloride in DMF gave the corresponding chloride in relatively good yield, which was confirmed by NMR analysis on the crude mixture. Although the reduction of the PBB group to a Bn group was anticipated at the stage of radical elimination, the PBB group of the chloride intermediate was, in fact, unexpectedly damaged and removed under the radical conditions to give a complex mixture of byproducts, which had no PBB or Bn groups. Nitroaldols **29b** and **29c** were decomposed in the chlorination step, in which the MOM ether of **29b** and even the methyl ether of **29c** were removed. The addition of pyridine slightly inhibited removal of the MOM group to afford **38b** as a minor component (Scheme 9). Chloride **38b** was reacted with Bu_3SnH and AIBN to produce alkene **39b**[23] in 7.9% total yield. The small production of **39b** was attributable to the low yield of the chlorination step. The radical elimination of **38b** itself proceeded smoothly. Therefore, for the efficient conversion of a γ,δ-dialkoxy-β-nitroalkanol (**29**) to a 3,4-dialkoxy-1-alkene (**39**) via the chlorination/radical elimination sequence, the suppression of the removal of the protecting group of the oxygen atom at the δ-position of the nitroalkanol is required in the chlorination step.



Scheme 10. An alternative plan for the total synthesis of **1**.



Scheme 11. Double bond formation from nitroaldol **45**.

Finally, we designed an alternative plan for the union at the C9'-C10' double bond of **1** (Scheme 10). This plan involved the installation of a nitro group to the left-half segment (**40**) and an

aldehyde to the right-half segment (**41**), thereby avoiding the presence of a problematic alkoxy group at the δ-position in the β-nitro alcohol intermediate (**42**). The plan was demonstrated by use of model aldehyde **44** corresponding to **41** and nitropropane corresponding to **40** (Scheme 11). Aldehyde **44** was prepared from alcohol **43** by Swern oxidation. The reaction of **44** with nitropropane in the presence of DBN in DMF produced nitroaldol **45** as a mixture of diastereomers in 84% yield from **43**. Upon treatment with thionyl chloride in DMF, nitroaldol **45** was only dehydrated to give nitroalkene **46**,[24] while the methyl ether remained intact. On the other hand, reaction of **45** with thiocarbonyldiimidazole in 1,2-dichloroethane at 40 °C followed by treatment with Bu_3SnH and AIBN in refluxing toluene furnished alkene **48**[23] in 25% yield. Thus, although further optimization is required, the three-step process including a nitroaldol reaction, thionocarbonylation, and radical elimination shows promise for the union at the C9'-C10' double bond of **1**.

In conclusion, during the course of our studies toward the total synthesis of nigricanoside A dimethyl ester (**1**), a prototype method for the connection of the left- and right-half segments (**2** and **3** / **40** and **41**) at the C9'-C10' double bond of **1** was developed using a model system. The method was based on a simple three-step process including nitroaldol reaction, chlorination or thionocarbonylation, and radical elimination. Further studies toward the total synthesis of **1** are currently underway in our laboratory.

Acknowledgments

We thank Dr. Eri Fukushi and Mr. Yusuke Takata (GC-MS and NMR Laboratory, Faculty of Agriculture, Hokkaido University) for the measurements of mass spectra. We are also grateful to Prof. Mitsutoshi Jikei and Prof. Kazuya Matsumoto (Department of Materials Science, Graduate School of Engineering Science, Akita University) for the measurements of NMR spectra and to Prof. Tetsuo Tokiwano (Faculty of Bioresource Sciences, Akita Prefectural University) for the measurements of optical rotation. This work was supported by JSPS KAKENHI Grant Number JP15K01794.

Supplementary data

Outline of the synthesis of compounds **8** and **9a-c**, selected spectral data of compounds **8**, **9a-c**, **28**, **29a-c**, **36**, **39b**, **45**, and **48**, and synthetic procedures for **36** and **48**. Supplementary data associated with this article can be found, in the online version, at https://doi.org/##.####/j.tetlet.####.##.###

References and notes

1. Williams, D. E.; Sturgeon, C. M.; Roberge, M.; Andersen, R. J. *J. Am. Chem. Soc.* **2007**, *129*, 5822.
2. For total synthesis, see: Chen, J.; Koswatta, P.; DeBergh, J. R.; Fu, P.; Pan, E.; MacMillan, J. B.; Ready, J. M. *Chem. Sci.* **2015**, *6*, 2932.
3. For other synthetic studies on nigricanosides, see: (a) Kurashina, Y.; Kuwahara, S. *Biosci. Biotechnol. Biochem.* **2012**, *76*, 605. See, also: (b) Espindola, A. P. D. M.; Crouch, R.; DeBergh, J. R.; Ready, J. M.; MacMillan, J. B. *J. Am. Chem. Soc.* **2009**, *131*, 15994. (c) Tortosa, M. *Angew. Chem. Int. Ed.* **2011**, *50*, 3950.
4. Kinashi, N., Fujiwara, K.; Tsunoda, T.; Katoono, R.; Kawai, H.; Suzuki, T. *Tetrahedron Lett.* **2013**, *54*, 4564.
5. For a review, see: Chatterjee, A. K. In *Handbook of Metathesis*; Grubbs, R. H., Ed.; Wiley-VCH: Weinheim, 2003; Vol. 2, pp 246–295.
6. For an example of the coincidence of cross, ring-opening, and ring-closing olefin metathesis reactions, see: Oguri, H.; Sasaki, S.; Oishi, T.; Hirama, M. *Tetrahedron Lett.* **1999**, *40*, 5405.
7. Blakemore, P. R.; Cole, W. J.; Kocienski, P. J.; Morley, A. *Synlett* **1998**, *9*, 26.
8. Kinashi, N.; Fujiwara, K.; Suzuki, T. unpublished result.
9. (a) Henry, L. *Compt. Rend.* **1895**, *120*, 1265. (b) Henry, L. *Bull. Soc. Chim. France* **1895**, *13*, 999.
10. Model **8** was prepared as a racemate. Each advanced model was a single (2*R*,3*S*)-form. The synthesis of compounds **8**, **9a**, **9b**, and **9c** is outlined in Supplementary data.
11. Eyer, M.; Seebach, D. *J. Am. Chem. Soc.* **1985**, *107*, 3601.
12. Fernández, R.; Gasch, C.; Gómez-Sánchez, A.; Vílchez, J. E. *Tetrahedron Lett.* **1991**, *32*, 3225.
13. Kobertz, W. R.; Bertozzi, C. R.; Bednarski, M. D. *J. Org. Chem.* **1996**, *61*, 1894.
14. Kitayama, T. *Tetrahedron* **1996**, *52*, 6139.
15. Robins, M. J.; Wilson, J. S. *J. Am. Chem. Soc.* **1981**, *103*, 932.
16. Barton, D. H. R.; Dorchak, J.; Jaszberényi, J. C. *Tetrahedron Lett.* **1993**, *34*, 8051.
17. Ouvry, G.; Quiclet-Sire, B.; Zard, S. Z. *Org. Lett.* **2003**, *5*, 2907.
18. (a) Ono, N.; Katayama, H.; Nisyiyama, S.; Ogawa, T. *J. Heterocycl. Chem.* **1994**, *31*, 707. (b) Kutovaya, I. V.; Shmatova, O. I.; Tkachuk, V. M.; Melnichenko, N. V.; Vovk M. V.; Nenajdenko, V. G. *Eur. J. Org. Chem.*, **2015**, *30*, 6749.
19. Barton, D. H. R.; McCombie S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.
20. Compound **33** was obtained as a 1:1 mixture of diastereomers, both of which had an *E*-double bond.
21. Compound **32** was produced as a single isomer. The stereochemistry of the trisubstituted double bond of **32** was not determined.
22. (a) Fourneau, J. P. *Bull. Soc. Chim. France* **1940**, *7*, 603. (b) Novikov, S. S.; Belikov, V. M.; Epishina, L. V. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* (Engl. Transl.) **1962**, *11*, 1042. (c) Fukunaga, K.; Okamoto, A.; Kimura, M. *Nippon Kagaku Kaishi* **1983**, 542.
23. The stereochemistry of the newly formed double bond was *E*.
24. Compound **46** was observed as a single isomer. The stereochemistry of the nitro-substituted double bond was not determined.

Highlights

A prototype segment connection method for the synthesis of nigricanoside A dimethyl ester
Olefination to give a double bond, which has an ether group at an allylic position
Olefination by nitroaldol reaction, chlorination or thionocarbonylation, and radical elimination.