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Asymmetric Synthesis of (+)-Geranyllinaloisocyanide: Assignment of Absolute Stereochemistry

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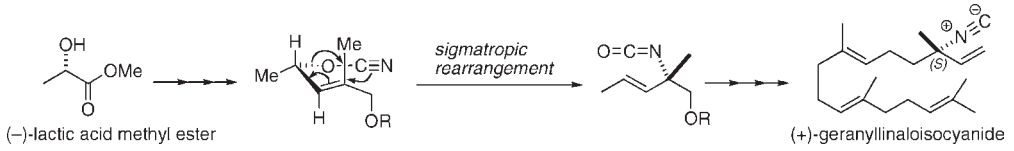
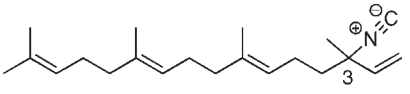
ABSTRACT



The first nonracemic synthesis of (+)-geranyllinaloisocyanide, starting with (−)-lactic acid methyl ester, has been accomplished by exploiting a [3.3] sigmatropic rearrangement of allyl cyanate. The synthesis enables assignment of the *S* configuration of the C(3) isocyano substituted, quaternary stereogenic center in natural geranyllinaloisocyanide.

In 1974, Scheuer and Burreson reported the isolation of geranyllinaloisocyanide (**1**) from the marine sponge *Halichondria sp.*, collected by trawling at 200 m north of Oahu in Hawaii.[1] Spectroscopic analysis and degradation studies led to elucidation of the unique structure of this marine natural product as an isocyanide analogue of the jasmine constituent, geranyllinalool (Figure 1).

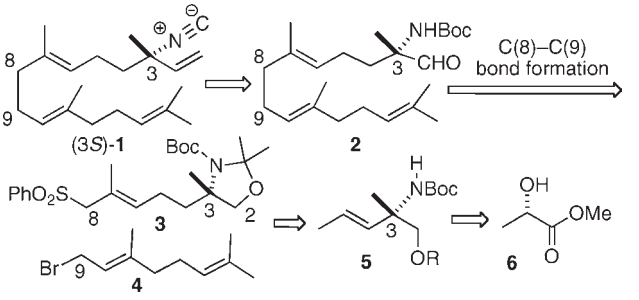


geranyllinaloisocyanide (**1**)

Figure 1. Unknown stereochemistry at C(3) of geranyllinaloisocyanide.

Although geranyllinaloisocyanide is the first example of a diterpene possessing an isocyano group, determination of its absolute stereochemistry at C(3) and asymmetric synthesis have not yet been explored.[2] In this report, we present the first asymmetric synthesis of **1** and assignment of the absolute configuration of the quaternary stereogenic carbon possessing the isocyano group.

Scheme 1. Retrosynthetic Analysis of (3*S*)-Geranyllinaloisocyanide (**1**)



Our retrosynthetic plan for the synthesis of geranyllinaloisocyanide is shown in Scheme 1. Since the absolute configuration at C(3) in **1** had not been defined, we

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

(2) For the synthesis of racemic **1**, see: Ichikawa, Y.; Yamazaki, M.; Isobe, M. *J. Chem. Soc., Perkin Trans. 1* **1993**, 2429.

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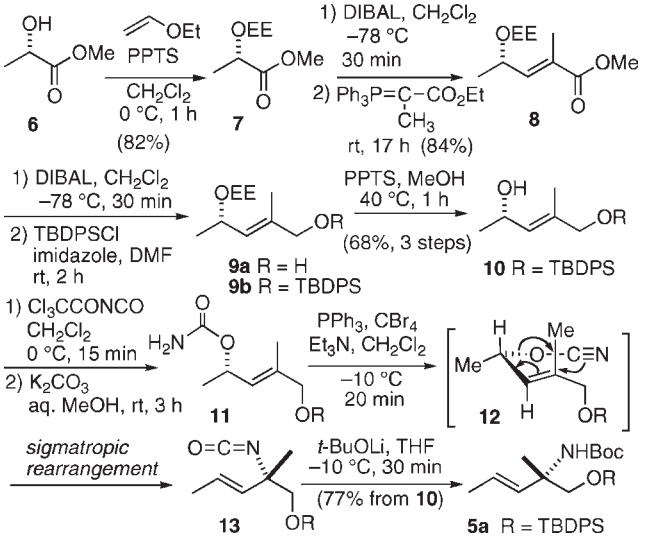
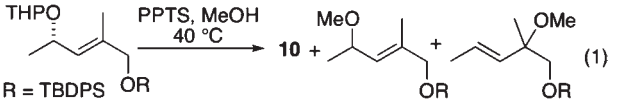
arbitrarily selected (3*S*)-**1** as the target. We envisioned that (3*S*)-**1** could arise from the α,α-dialkyl amino aldehyde **2** via either the Julia–Kocienski or Wittig olefination. Intermediate **2** in turn could be obtained by the coupling reaction of a carbanion generated from the sulfone **3** corresponding to the C(2–8) section of the target, with geranyl bromide **4**. Further disconnection of **3** led to the synthon **5**, whose quaternary stereocenter could be created by using [3.3] sigmatropic rearrangement attended by a transfer of chirality originating from (−)-lactic acid methyl ester (**6**).[3]

Scheme 2. Synthesis of Synthon **5** by Exploiting Sigmatropic Rearrangement

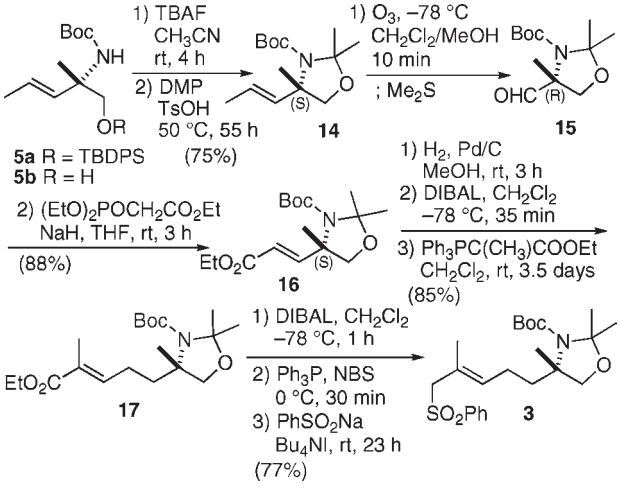


The synthesis of synthon **5** began with protection of the commercially available L-(−)-lactic acid methyl ester (**6**) by treatment with ethyl vinyl ether in the presence of pyridinium *p*-toluenesulfonate (PPTS) to afford the ethoxyethyl ether **7** (Scheme 2). Diisobutylaluminum hydride (DIBAL) reduction of **7** followed by Wittig reaction with ethyl 2-(triphenylphosphoranylidene)propionate provided the α,β-unsaturated ester **8** exclusively in 84% yield after chromatographic purification. DIBAL reduction of the ester moiety in **8** followed by protection of the resulting allyl alcohol **9a** as a *tert*-butyldiphenylsilyl (TBDPS) ether gave rise to **9b**. Careful removal of the ethoxyethyl ether group in **9b** with PPTS in methanol furnished allyl alcohol **10** in 68% overall yield in three steps. It should be noted that an initial route, using THP protection of **6**, was found to be complicated by the formation of the products derived from carbocation intermediates (eq 1).[4]

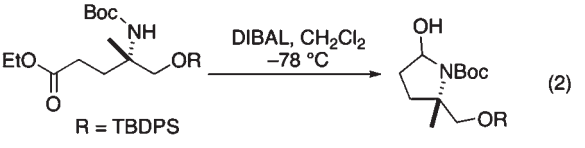


Allyl alcohol **10** was then transformed to the allyl carbamate **11** by treatment with trichloroacetyl isocyanate followed by hydrolysis of the resultant *N*-trichloroacetyl carbamate with potassium carbonate in aq methanol. [1,3]-Chirality transfer to install the nitrogen-substituent quaternary stereogenic center was carried out by using [3,3] sigmatropic rearrangement of the allyl cyanate.[3c] Specifically, dehydration of **11** employing a modified version of Appel's conditions (PPh_3, CBr_4, Et_3N, CH_2Cl_2, −10 °C)[5] generated the allyl cyanate **12** which spontaneously underwent [3.3] sigmatropic rearrangement to afford the corresponding allyl isocyanate **13**. After careful workup, the resultant isocyanate **13** was immediately treated with lithium *tert*-butoxide in THF to furnish **5a** in 77% overall yield from **10**.[6]

Scheme 3. Synthesis of the C(2–8) Sulfone **3**



Synthesis of the C(2–8) sulfone **3** began with protecting group manipulation of **5a**, involving desilylation with TBAF, followed by acetonide formation using 2,2-dimethoxypropane (DMP) to afford **14** in 75% yield (Scheme 3). This protecting group change was necessitated by the fact that DIBAL reduction of the ester shown in eq 2 was quite problematic. The aldehyde proton was not detected by ^1H NMR analysis of the products, whose structures were tentatively assigned to be the cyclized prducts.



(3) (a) Ichikawa, Y. *Synlett* **1991**, 238. (b) Ichikawa, Y. *Synlett* **2007**, 2927. (c) Ichikawa, Y.; Yamauchi, E.; Isobe, M. *Biosci. Biotechnol. Biochem.* **2005**, *69*, 939. (d) Matsukawa, Y.; Isobe, M.; Kotsuki., H.; Ichikawa, Y. *J. Org. Chem.* **2005**, *70*, 5339.

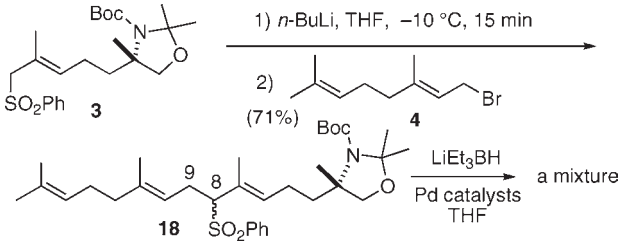
(4) The unusual nature of γ,γ-dialkyl allylic secondary alcohol derivatives has been known to be strongly susceptible to solvolysis reactions. See: Vernon, D. A. *J. Chem. Soc.* **1954**, 423.

(5) Ichikawa, Y. *J. Chem. Soc., Perkin Trans. 1* **1992**, 2135.

(6) (a) Kaiser, E. M.; Woodruff, R. A. *J. Org. Chem.* **1970**, *35*, 1198. (b) Crowther, G. P.; Kaiser, E. M.; Woodruff, R. A.; Hauer, C. R. *Organic Synthesis*, Coll. Vol. 6; John Wiley and Sons: New York; p 259.

Ozonolysis of **14** afforded the protected (*R*)-α-methylserinal **15**,[7] which was immediately subjected to Horner–Wadsworth–Emmons olefination to furnish a 97:3 mixture of (*E*)- and (*Z*)-α,β-unsaturated ester **16** in 88% yield. Catalytic hydrogenation of **16** followed by DIBAL reduction of the ester and Wittig olefination provided (*E*)-α,β-unsaturated ester **17** predominantly in 85% yield over three steps. Transformation of **17** into allyl sulfone **3** was then accomplished in three steps involving DIBAL reduction, mesylation, and displacement reaction with benzenesulfinic acid sodium salt in 77% yield.[8]

Scheme 4. Coupling of Sulfone **3** with Geranyl Bromide **4** To Construct the C(8)–C(9) Bond



Our attempts to build the C(8)–C(9) bond and to remove the sulfone moiety are shown in Scheme 4. C(8)–C(9) bond construction was achieved by treatment of **3** with *n*-butyllithium in THF at −10 °C to generate the corresponding sulfone carbanion, which was then reacted with freshly prepared geranyl bromide **4** (4 equiv) to produce a diastereomeric mixture of the coupling products **18** in 71% yield. Removal of the sulfone from **18** was examined by palladium-catalyzed reduction of allyl sulfone with lithium triethylborohydride ($LiEt_3BH$). In spite of a successful precedent in the literature,[9] this process under several conditions with varying palladium catalysts (dppe, dppp, dppb, dphephos, dppf, and *rac*-BINAP ligands) could not be satisfactorily accomplished, leading always to significant amounts of olefin regio- and stereochemical scrambling. Consequently, an alternative route that switched the sulfone and bromide groups was developed.

In order to examine this new approach, allyl bromide **19** was prepared from **17** (Scheme 5) and sulfone **20** was generated from geraniol.[8] The conversion of **17** to **19** was carried out via a three-step sequence, involving DIBAL reduction, mesylation of the resulting allyl alcohol, and treatment of the allyl mesylate with lithium bromide.

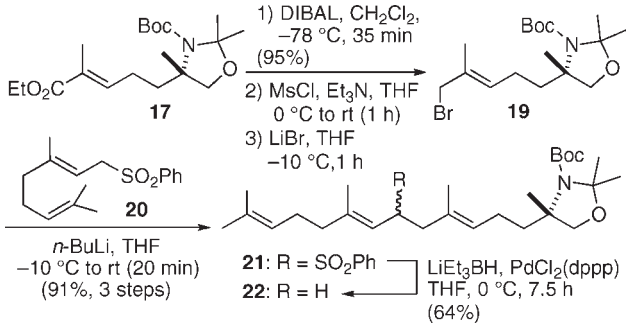
(7) For the syntheses of (*S*)- and (*R*)-*N*-Boc-*N*,*O*-isopropylidene-α-methylserinals, see: (a) Alias, M.; Cativiela, C.; Diaz-de-Villegas, M.; Galvez, J. A.; Lapena, Y. *Tetrahedron* **1988**, *54*, 14693. (b) Avenoza, A.; Cativiela, C.; Corzana, F.; Peregrina, J. M.; Zurbano, M. *J. Org. Chem.* **1999**, *64*, 8220.

(8) Murakami, T.; Furusawa, K. *Synthesis* **2002**, 479.

(9) Min, J.-H.; Lee, J.-S.; Yang, J.-D.; Koo, S. *J. Org. Chem.* **2003**, *68*, 7925.

(10) (a) Kotake, H.; Yamamoto, T.; Kinoshita, H. *Chem. Lett.* **1982**, 1331. (b) Hutchins, R. O.; Learn, K. *J. Org. Chem.* **1982**, *47*, 4380. (c) Trost, B. M.; Machacek, M. R.; Tsui, H. C. *J. Am. Chem. Soc.* **2005**, *127*, 7014.

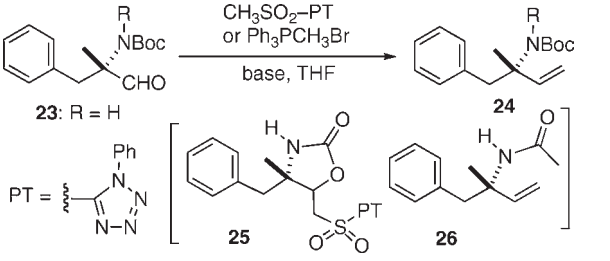
Scheme 5. Successful Coupling of **19** with **20** and Removal of Sufone in **21**



Freshly prepared allyl bromide **19** was quickly reacted with 4 equiv of sulfone carbanion prepared from **20** in THF at −10 °C for 30 min, allowing the coupling product **21** to be isolated in 91% yield. Importantly, running the reduction of allyl sulfone **21** with $LiEt_3BH$ in the presence of $PdCl_2$(dppp) at 0 °C afforded the desulfonylated product **22** in 64% yield with no observable olefin scrambling (^{1}H NMR analysis of the product).[10]

Since olefination of α,α-dialkylaminoaldehydes was expected to be difficult due to the steric environment at the neopentyl position [**2** → (3*S*)-**1**, Scheme 1], we initially investigated this crucial transformation by employing the model aldehyde **23** (Table 1). Through the use of the one-pot Julia–Kocienski olefination[10] with 1-phenyl-1*H*-tetrazol-5-yl (PT) sulfone and LiHMDS (entry A), the olefin **24** was obtained, albeit in a low yield (25%), along with substantial amounts of byproduct tentatively assigned as oxazolidinones **25**. Although switching the base to KHMDS or NaHMDS improved the yields to modest levels (52 and 40%, respectively, entries B and C), we could not suppress the formation of **25**. Surprisingly, the Wittig

Table 1. Model Studies of the Olefination Process



entry	reagents	bases	temp	time (h)	yields of **24**
A	CH_3SO_2–PT	LiHMDS	−20 °C	3	25%
B	CH_3SO_2–PT	NaHMDS	−20 °C	24	52%
C	CH_3SO_2–PT	KHMDS	−20 °C	19	40%
D	Ph_3PCH_3Br	LiHMDS	rt	3	0%
E	Ph_3PCH_3Br	NaHMDS	rt	1	34%
F	Ph_3PCH_3Br	KHMDS	rt	3	93%

reaction of **23** was highly dependent on the countercation of hexamethyldisilazane, which was used as a base to generate the ylide from methyltriphenylphosphonium bromide. In the case of LiHMDS (entry D), none of the desired product **24** was produced, and the major product was amide **26**. Further screening of the bases showed that NaHMDS afforded **24** in low yield (34%, entry E) along with a considerable amount of **26**. However, the use of KHMDS provided **24** predominantly in good yield (93%, entry F). Although no proof exists, we surmised that the metal counterion in the carbamate anion (**23**: R = Li, Na, and K) generated by deprotonation during olefination and/or in the intermediate betaine determined the pathway of the product distributions and yields.

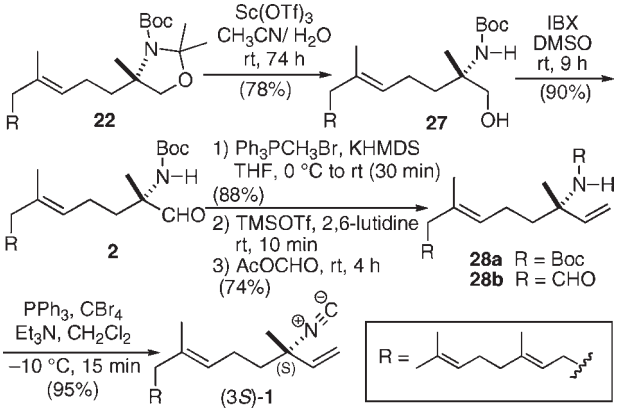
With the key intermediate **22** in hand and conditions for terminal olefin construction established, the final stage for the synthesis of (3*S*)-**1** was investigated (Scheme 6). Cleavage of the acetonide in **22** without hydrolysis of the N-Boc group was carried out using scandium triflate in aq acetonitrile to afford **27** in 78% yield (based on recovered starting material).[7b] Oxidation of the alcohol **27** with IBX in DMSO provided aldehyde **2**, which was immediately subjected to Wittig olefination using the optimal conditions established in Table 1 to furnish **28a** in 88% yield. Although Boc deprotection of **28a** with TFA gave a complex mixture of products, trimethylsilyl triflate in the presence of 2,6-lutidine reported by Ohfune[12] cleanly afforded the amine, which was subsequently treated with acetic formic anhydride to give rise to the formamide **28b** in 74% yield in two steps. Finally, dehydration of formamide **28b** with modification of Appel's conditions[5] completed the synthesis of isocyanide (3*S*)-**1**.

The spectroscopic properties (IR, ^{1}H and ^{13}C NMR) of the synthetic material matched those of the natural product.

(11) (a) Julia, M.; Paris, J.-M. *Tetrahedron Lett.* **1973**, *14*, 4833. (b) Blakemore, P. R.; Cole, W. J.; Kochiensky, P.; Morley, A. *Synlett* **1998**, 26.
(12) Sakaitani, M.; Ohfune, Y. *J. Org. Chem.* **1990**, *55*, 870.

The results of the optical rotation measurements demonstrated that synthetic (3*S*)-**1** is the dextrotatory enantiomer with an $[\alpha]_D^{25}$ value of +27.8 (*c* 2.24 in CCl_4) that is the same sign as that reported for the natural product ($[\alpha]_D^{21}$ +15, *c* 2.8 in CCl_4), thus confirming the absolute configuration of natural geranyllinaloisocyanide as represented in structure (3*S*)-**1**.

Scheme 6. Completion of the Synthesis of (3*S*)-**1**



In conclusion, we succeeded in the first asymmetric synthesis of geranyllinaloisocyanide and assignment of the *S* absolute stereochemistry at the C(3) quaternary center in this natural product.

Acknowledgment. We are grateful for financial support provided by Nagase Science and Technology Foundation.

Supporting Information Available. Experimental procedures and characterization data for all new compounds and copies of NMR spectra. This material is avaibalble free of charge via the Internet at http://pubs.acs.org.