ORGANIC LETTERS

2010
Vol. 12, No. 5
904−907

Total Synthesis of 10-Isocyano-4-cadinene and Determination of Its Absolute Configuration

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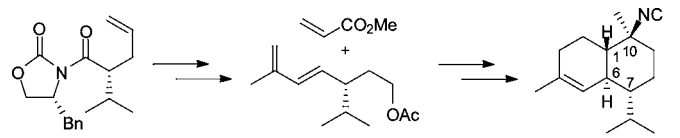
Received November 26, 2009

ABSTRACT



10-Isocyano-4-cadinene

The first enantioselective total synthesis of 10-isocyano-4-cadinene, a marine sesquiterpene isolated from nudibranchs of the family *Phyllidiidae*, was achieved. The cadinene is expected to be a novel nontoxic antifouling agent. In the synthesis, an intermolecular Diels−Alder reaction and a SmI_2-induced Barbier-type reaction were employed as key steps. The absolute configuration of 10-isocyano-4-cadinene was determined to be (1*S*, 6*S*, 7*R*, 10*S*) on the basis of the total synthesis. Antifouling activities against *Balanus amphitrite* with both enantiomers of 10-isocyano-4-cadinene were also evaluated.

10-Isocyano-4-cadinene (**1**), a marine sesquiterpene isolated by Okino et al.[1] from nudibranchs of the family *Phyllidiidae* along with other sesquiterpenes, such as 10-isocyano-4-amorphene (**2**), 2-isocyanotrachyopsane (**3**), and axisonitrile-3 (**4**), exhibits potent antifouling activity[2] against the larvae of the barnacle *Balanus amphitrite* (Figure 1). As a fouling inhibitor, tributyltin (TBT)[3] has been used widely in ships' hulls and fishing nets since the early 1960s. Unfortunately, due to the toxicity of TBT, the marine environment has been seriously compromised. For example, TBT-exposed oysters exhibit abnormal shell development, brittle shells, poor weight gain, and imposex.[4] Thus, cadinene **1** is expected to be a novel lead compound[5] for nontoxic antifouling agents. Structurally, **1** has four continuous stereocenters, including a quaternary carbon center with a biologically important isocyanide group. Although the relative configuration of **1** was assigned as shown in Figure 1

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(1) Okino, T.; Yoshimura, E.; Hirota, H.; Fusetani, N. *Tetrahedron* **1996**, *52*, 9447–9454.
(2) (a) Fusetani, N. *Nat. Prod. Rep.* **2004**, *21*, 94–104. (b) Garson, M. J.; Simpson, J. S. *Nat. Prod. Rep.* **2004**, *21*, 164–179.
(3) Evans, S. M. *Biofouling* **1999**, *14*, 117–129.
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10.1021/ol9027336
Published on Web 02/04/2010

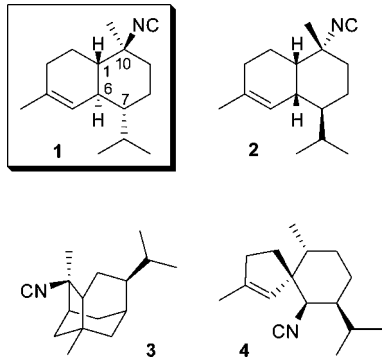
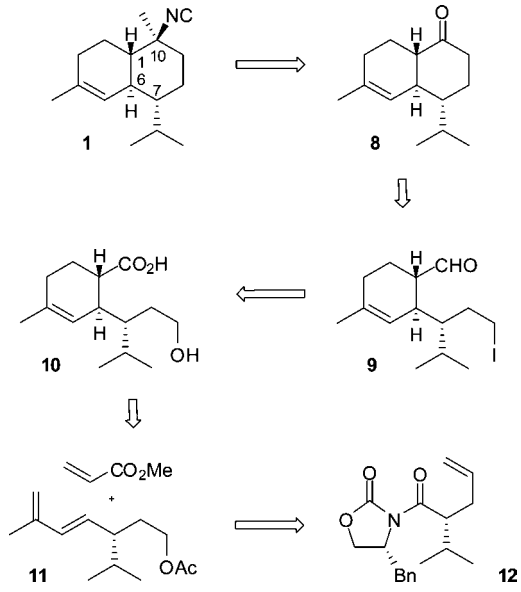


Figure 1. Sesquiterpenes from nudibranchs of the family *Phyllidiidae*.

using 1D and 2D NMR experiments, the absolute configuration has not been determined. Herein, we report the first total synthesis of both enantiomers of **1** and the determination of absolute configuration based on the enantioselective total synthesis.

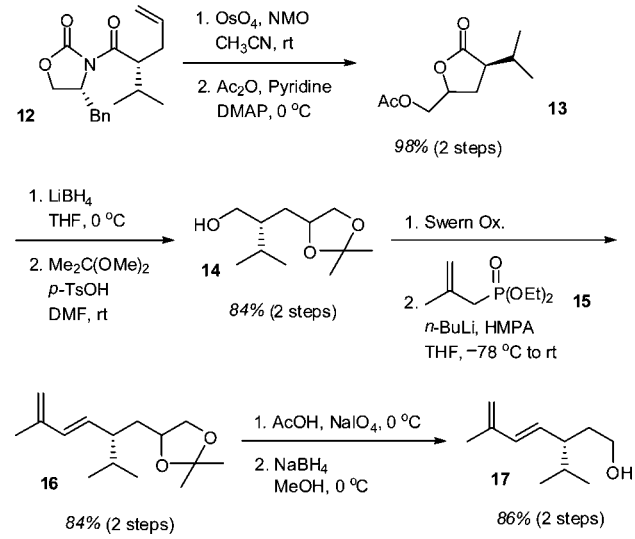
Scheme 1. Retrosynthetic Analysis of 10-Isocyano-4-cadinene



Retrosynthetic analysis of **1** is shown in Scheme 1. We envisioned the construction of the *trans* relationship between C1 and C6 by intermolecular Diels−Alder reaction[6] followed by isomerization under basic conditions because it is known that *cis*-decalin frameworks are selectively formed through the corresponding intramolecular Diels−Alder reaction.[7,8] The functional groups at C10 would be installed with the ketone **8** at a later stage of the synthesis. To construct the cyclohexane ring of **8**, Barbier-type cyclization induced by SmI_2 would be employed with aldehyde **9**, derived from the carboxylic acid **10**. As mentioned above, the *trans* relationship at C1 and C6 in **10** would be constructed by an intermolecular Diels−Alder reaction with methyl acrylate and the diene **11**, followed by isomerization.

The synthesis commenced with the known imide **12**,[9] prepared via Evans alkylation with allyl bromide (Scheme 2). After the OsO_4 oxidation of the olefin moiety followed by spontaneous lactonization of the resultant diol, acetylation of the primary alcohol gave the acetate **13**, and the chiral auxiliary was recovered.[9b] The acetate **13** was converted into the alcohol **14** through $LiBH_4$ reduction and subsequent selective acetonide protection of the 1,2-diol moiety. Swern oxidation of **14** and successive Horner−Wadsworth−Emmons reaction using diethyl (2-methylallyl) phosphonate **15**[7m,10] yielded the *E*-diene **16** as a single geometric isomer. The diene **16** was then transformed to the intermolecular Diels−Alder precursor **11** by the following sequence of transformations: (1) one-pot deprotection of the acetonide group and oxidative treatment with $NaIO_4$, (2) reduction of the resulting aldehyde (Scheme 2), and (3) acetylation (Scheme 3). The intermolecular Diels−Alder reaction of **11** with methyl acylate in the presence of $MeAlCl_2$[11] in xylene[12] afforded cyclohexene **18** as a mixture of four diastereomers

Scheme 2. Synthesis of Diene Alcohol **17**



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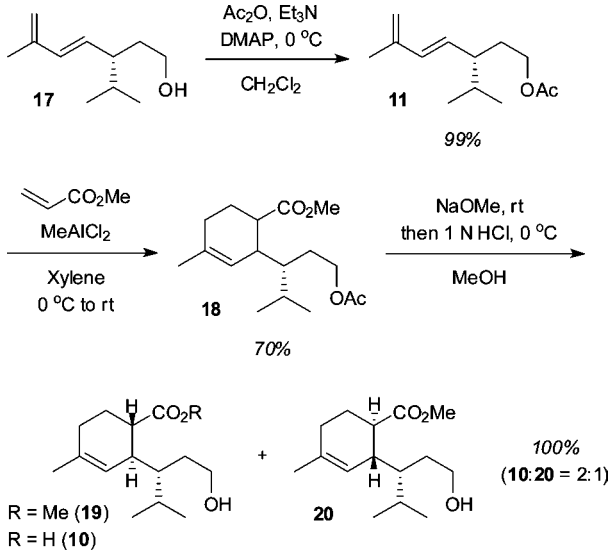
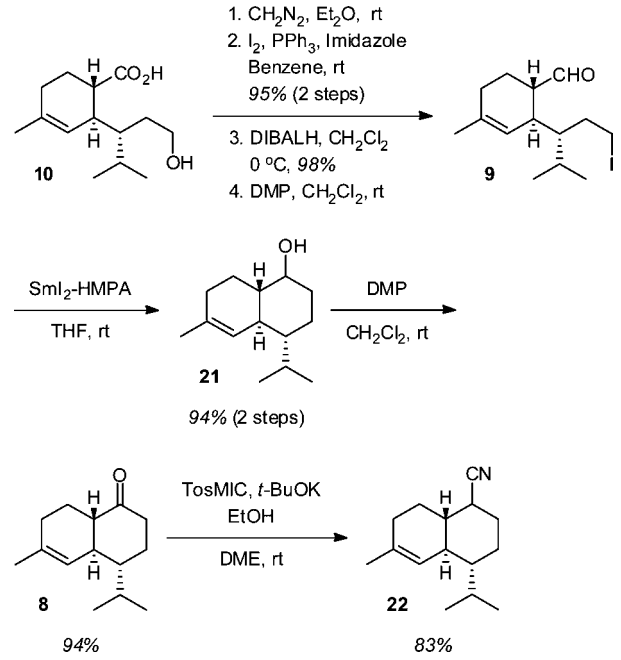
Scheme 3. Diels−Alder Reaction Using the Lewis Acid



in good yield. The mixture was equilibrated with NaOMe in MeOH (0.08 M) to that of the two *trans*-esters **19** and **20**. The desired ester **19** was hydrolyzed with complete selectivity by the slow addition of 1 N HCl to the MeOH solution at 0 °C to provide the easily separable mixture of the desired carboxylic acid **10** and the unhydrolyzed ester **20** (**10**:**20** = 2:1). Separation of these two *trans* diastereomers was essential for the total synthesis. After extensive studies, we found the excellent method mentioned above.[13]

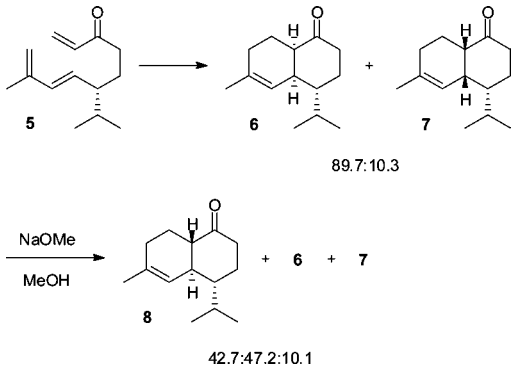
With the cyclohexene in hand, we turned our attention to construction of the right side cyclohexane ring and the quaternary carbon center at C10. The carboxylic acid **10** was transformed to the cyclization precursor **9** in 4 steps (Scheme 4). The SmI_2-induced Barbier-type cyclization[14] of **9** in the

Scheme 4. Synthesis of Nitrile **22**



presence of HMPA occurred cleanly in excellent yield to give the alcohol **21**, which was oxidized with Dess−Martin periodinane (DMP).[15] To construct the quaternary carbon center, the nitrile **22** was derived from ketone **8** with *p*-toluenesulfonylmethyl isocyanide (TosMIC).[7l,16] The nitrile **22** was next reduced to the aldehyde **23** (Scheme 5).[17] The alkylation of **23** with *p*-methoxybenzyl chloromethyl ether **24**[18] successfully afforded the PMB ether,[19,20] which was subjected to Wolff−Kishner conditions[21] to afford the PMB ether **25** as a single diastereomer. The PMB ether **25** was

(8) For a typical example, the intramolecular Diels−Alder reaction of the (±)-trienone **5** afforded a mixture of the (±)-*cis*-decalins **6** and **7** in a ratio of 89.7:10.3. Furthermore, the mixture of **6** and **7** was isomerized by NaOMe in MeOH forming an inseparable mixture of the (±)-*trans*-decalin **8** and **6** and **7** in a ratio of 42.7:47.2:10.1. See ref 7b.



(9) (a) Hodgson, D. M.; Foley, A. M.; Lovell, P. J. *Synlett* **1999**, 744–746. (b) Rüeger, H.; Stutz, S.; Spindler, F.; Maibaum, J. *Tetrahedron Lett.* **2000**, *41*, 10085–10089.

(10) Wang, Y.; West, F. G. *Synthesis* **2002**, 99–103.

(11) (a) Roush, W. R.; Barda, D. A. *J. Am. Chem. Soc.* **1997**, *119*, 7402–7403. (b) Schürer, S. C.; Blechert, S. *Synlett* **1999**, 1879–1882. (c) Roush, W. R.; Limberakis, C.; Kunz, R. K.; Barda, D. A. *Org. Lett.* **2002**, *4*, 1543–1546.

(12) Among the solvents examined (xylene, toluene, benzene, and CH_2Cl_2), xylene was found to be the best for yield.

(13) For example, treatment of **18** (four diastereomers) with NaOMe in dilute MeOH solution (0.02 M) and neutralization with 1 N HCl afforded a mixture of **19** and **20** without hydrolysis of the methyl ester moiety. Attempted separation of **19** and **20** by silica gel chromatography failed.

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(15) (a) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156. (b) Dess, D. B.; Martin, J. C. *J. Am. Chem. Soc.* **1991**, *113*, 7277–7287.

(16) Oldenziel, O. H.; van Leusen, A. M. *Tetrahedron Lett.* **1973**, *14*, 1357–1360.

(17) Alkylation of **22** under various conditions resulted in low yield or a complex mixture. See ref 7l.

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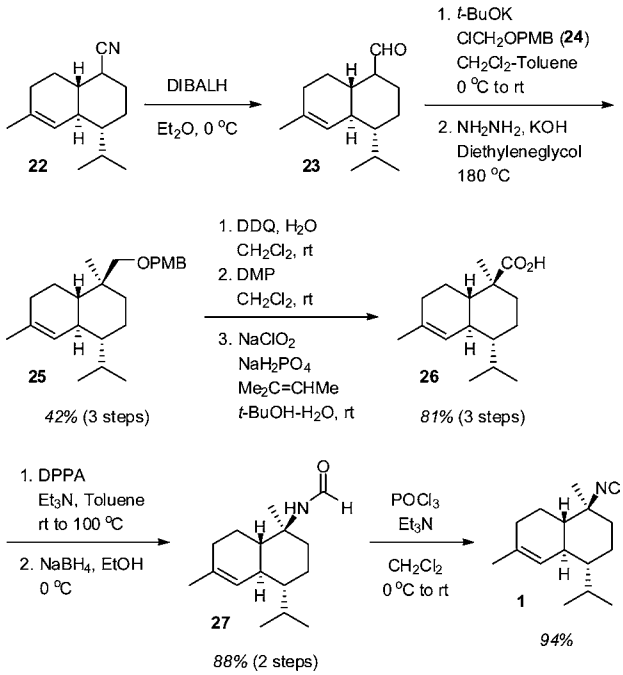
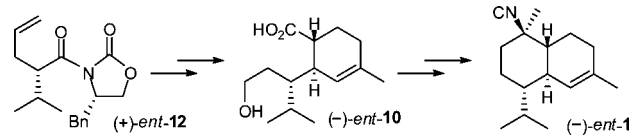
(19) α-Alkylation of **23** took place from an equatorial orientation in a completely stereoselective manner. For similar equatorial alkylations, see: (a) Ireland, R. E.; Mander, L. N. *J. Org. Chem.* **1967**, *32*, 689–696. (b) Ireland, R. E.; Mander, L. N. *J. Org. Chem.* **1969**, *34*, 142–152. (c) Vishnumuthy, K.; Cheung, E.; Scheffer, J. R.; Scott, C. *Org. Lett.* **2002**, *4*, 1071–1074.

(20) It was found that α-alkylation of **23** with MeI and *t*-BuOK and Pinnick oxidation gave the 10-epimer of **26** as a sole stereoisomer, from which 10-*epi*-10-isocyano-4-cadinene was synthesized following the same synthetic scheme.

Scheme 5. Synthesis of (+)-10-Isocyano-4-cadinene (**1**)



Scheme 6. Synthesis of (−)-10-Isocyano-4-cadinene (*ent*-**1**)



Therefore, the absolute configuration of (+)-**1** is unambiguously established as (1*S*, 6*S*, 7*R*, 10*S*).

Antifouling activities were evaluated with both (+)-**1** and (−)-*ent*-**1**. Table 1 shows EC_{50} values (50% effective concentration) against cyprid larvae of the barnacle *Balanus amphitrite* exposed to each compound for 48 h. Interestingly, both compounds showed almost the same EC_{50} values, which correspond to that of the natural sample. These results clearly suggest that the absolute configuration of 10-isocyano-4-cadinene has no effect on the antifouling activity.

Table 1. Bioactivities of Synthetic (+)- and (−)-10-Isocyano-4-cadinene

entry	compound	EC_{50}[a]
1	natural (+)-**1**[b]	0.14 μg/mL
2	synthetic (+)-**1**	0.06 μg/mL
3	synthetic (−)-*ent*-**1**	0.08 μg/mL

[a] EC_{50} (μg/mL): antifouling activities against *Balanus amphitrite*. [b] See ref 1.

converted into the aldehyde by removal of the PMB group with DDQ, followed by Dess-Martin oxidation. Pinnick oxidation led to the carboxylic acid **26**, which was subjected to Curtius rearrangement using diphenylphosphoryl azide (DPPA)[7l,22] to give the isocyanate. The isocyanato group was converted into an isonitrile group in two steps by $NaBH_4$ reduction[22] and dehydration of 10-formamido-4-cadinene (**27**)[23] to achieve the total synthesis of **1**. All spectroscopic data (^1H and ^{13}C NMR, MS, IR) of synthetic **1** are identical to those of natural **1**. The optical rotation of synthetic (+)-**1**, $[\alpha]_D^{23}$ +59.8 (*c* 0.65, $CHCl_3$), is similar to that of the natural product, $[\alpha]_D^{23}$ +63.6 (*c* 0.60, $CHCl_3$).[1] We also synthesized the enantiomer, (−)-10-isocyano-4-cadinene (*ent*-**1**), from the (+)-imide *ent*-**12** via the (−)-carboxylic acid *ent*-**10** by using the same synthetic procedure (Scheme 6). The optical rotation of (−)-*ent*-**1**, $[\alpha]_D^{23}$ −58.2 (*c* 0.68, $CHCl_3$), is opposite in sign to that of the natural product.

In summary, the first total synthesis of (+)- and (−)-10-isocyano-4-cadinene was completed by an intermolecular Diels−Alder reaction and SmI_2-induced Barbier-type reaction to construct the characteristic *trans*-decalin framework. The absolute configuration of natural 10-isocyano-4-cadinene was determined to be (1*S*, 6*S*, 7*R*, 10*S*). Furthermore, it was revealed that both enantiomers have almost the same antifouling activities.

Acknowledgment. We thank the 21st Century COE Research Assistantship for doctoral candidates and the Global COE Research Assistantship for doctoral candidates (to K. N.) and a Global COE Research grant for young scientists (to T. U. and K. N.).

Supporting Information Available: Experimental procedures and copies of ^1H NMR and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL9027336

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(23) 10-Formamido-4-cadinene (**27**), a natural product isolated from the sponge *Acanthella cavernosa*, exhibits antifouling activity against the larvae of the barnacle *Balanus amphitrite* (EC_{50} 0.50 μg/mL). All data (^1H and ^{13}C NMR, MS) of the synthetic **27** were identical with those in the literature. See: Nogata, Y.; Yoshimura, E.; Shinshima, K.; Kitano, Y.; Sakaguchi, I. *Biofouling* **2003**, *19*, 193−196.