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Efficient formal synthesis of (±)-axamide-1 and (±)-axisonitrile-1 via an intramolecular Hosomi–Sakurai reaction

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ABSTRACT

A formal synthesis of (±)-axamide-1 and (±)-axisonitrile-1 was achieved by using an intramolecular Hosomi–Sakurai reaction of the allylsilane derivative, as a key step, in which [(3-but-3-en-1-yl-3-methylcyclohex-1-en-1-yl)methyl](trimethyl)silane was transformed to a bicyclic compound possessing a core carbon framework under the oxidative dihydroxylation reaction conditions, in one step.

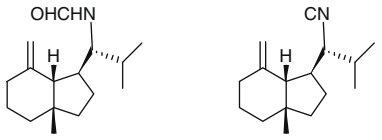
Axamide-1 **1** and axisonitrile-1 **2**, isolated from the marine sponge *Axinella cannabina*, belong to the family of axane sesquiterpenoids. This class of natural products exhibit unusual structural features based on a cis-fused hexahydroindane framework with an *exo*-methylene unit and a functionalized side chain (Fig. 1).[1–7] Some of the compounds exhibit interesting biological properties.[8]

Regarding the synthesis of these sesquiterpenes, there have been three racemic synthesis[9–11] and one chiral synthesis.[12] In these syntheses, ingenious strategies were devised in order to construct the central perhydroindane skeleton with an *exo*-methylene unit. Our interest in axane sesquiterpene chemistry grew out of a desire to develop a new, perhaps practical and general route for the synthesis of this class of natural products.

Recently, we have developed an efficient methodology for the construction of a bicyclo[3.3.1]nonane ring system with an *exo*-methylene moiety by employing an intramolecular Hosomi–Sakurai reaction. We have already successfully applied the methodology to the stereoselective synthesis of (+)-upial[13] and trifarienols.[14]

As a part of our continuing work on the synthesis of functionalized polycyclic carbocyclic systems from readily available starting material, we are interested in establishing an efficient synthetic route to axane sesquiterpenoids having a bicyclo[4.3.0]nonane ring system by employing an intramolecular Hosomi–Sakurai reaction as a key reaction.[15]

The retrosynthetic route to axane sesquiterpenes is depicted in Figure 2, in which we envisaged that the target natural products could be obtained from alcohol **3** according to the literature procedures.[11] Based on the consideration of our previous results, we



1. Axamide-1 **2.** Axisonitrile-1

Figure 1. Structures of axamide-1 and axisonitrile-1.

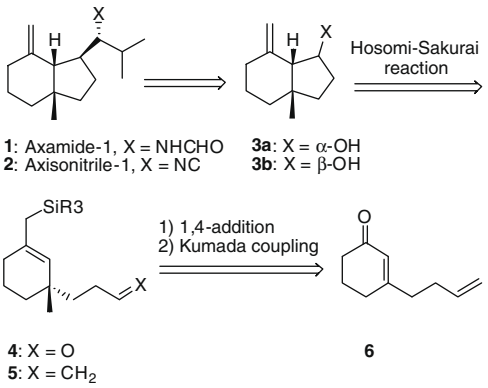


Figure 2. Retrosynthetic route to axane sesquiterpenes.

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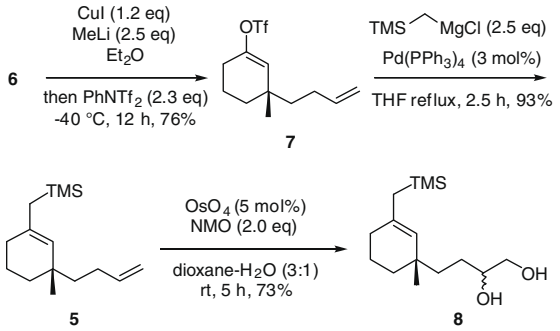


Scheme 1. Preparation of diol **8**.

decided to exploit an intramolecular Hosomi–Sakurai reaction of aldehyde **4** for the synthesis of **3**, since the basic carbon framework and an *exo*-methylene unit of the target compounds could be constructed by this reaction simultaneously. Aldehyde **4** would easily be obtained from the corresponding olefin **5** by oxidation, and olefin **5** might be transformed from the literature-known 3-(but-3-en-1-yl)cyclohex-2-en-1-one **6**[10c] via Michael addition of a methyl group, followed by Kumada coupling of the resulting triflate with trimethylsilylmethylmagnesium chloride in the presence of a palladium catalyst as shown in our previous work.

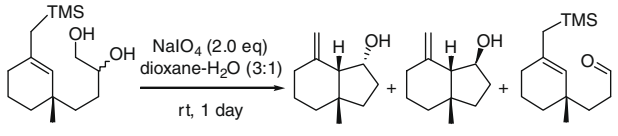
The requisite key compound **5** was prepared as follows.

Treatment of 3-(but-3-en-1-yl)cyclohex-2-en-1-one **6** with methyllithium in the presence of copper(I) iodide in ether at -40 °C for 20 min afforded the addition product, which on further treatment with $PhNTf_2$ at the same temperature for 12 h gave triflate **7** in 76% yield. Coupling reaction of **7** with trimethylsilylmethylmagnesium chloride in the presence of $Pd(PPh_3)_4$ in refluxing THF for 2.5 h gave the desired allylsilane **5**[16] in 93% yield. To obtain aldehyde **4**, dihydroxylation of **5** with a catalytic amount of OsO_4 and NMO was carried out to give diol **8** in 73% yield (Scheme 1).

Oxidative cleavage of **8** with $NaIO_4$ in dioxane–H_2O (3:1) was first attempted at room temperature for 1 day; however, the desired aldehyde **4** was isolated in only 3% yield. Interestingly, the major product in this reaction was identified to be the cyclization compound **3b**[17] (12% yield), where an intramolecular Hosomi–Sakurai reaction probably took place instantaneously via aldehyde **4** by the presence of $NaIO_4$ (entry 1). It is notable that this one-step conversion of **8** to **3** proceeded in a concentration-dependent manner. In fact, when the oxidative cleavage was carried out in 0.01 M or 0.02 M solution, the yield of **3b** was improved to 53% (entries 4 and 5). The results obtained in this study are summarized in Table 1.

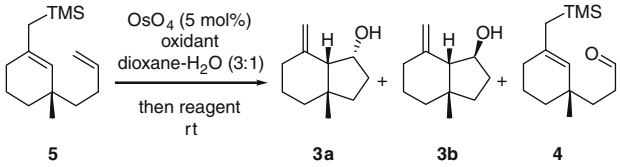
The α-alcohol **3a** obtained as a minor product in this conversion was the key intermediate in Kuo's synthesis of the target compounds, and its spectroscopic data were identical with those reported.[11] Thus, a formal synthesis of axane sesquiterpenes was achieved at this stage; however, some modification is required to improve the reaction sequences.

Table 1
One-pot conversion of **8** to **3** under the oxidative cleavage reaction condition



Entry	Concn	Products		
		3a (%)	**3b** (%)	**4** (%)
1	0.5	—	12	3
2	0.1	—	15	5
3	0.05	5	16	1
4	0.02	15	53	4
5	0.01	16	53	10

Table 2
One-pot conversion of **5** to **3**



Entry	Concn	Oxidant (equiv)	Reagent (equiv)	Products		
				3a (%)	**3b** (%)	**4** (%)
1	0.02	None	$NaIO_4$ (2.0)	None	None	None
2	0.02	None	$NaIO_4$ (4.0)	None	None	None
3	0.1 to 0.02	NMO (2.0)	$NaIO_4$ (2.0)	None	None	59
4	0.1 to 0.02	NMO (2.0)	$NaIO_4$ (4.0)	None	28	25
5	0.1 to 0.02	NMO (2.0)	$NaIO_4$ (8.0)	17	62	None

Since diol **8** could be transformed to **3** in one step, we next investigated one-pot conversion of olefin **5** to **3b** without isolation of diol **8**, hopefully under mild reaction conditions, to prove that the reaction sequence is efficient.

As can be seen in Table 2, the attempted one-pot conversion did not take place in the absence of oxidant NMO (entries 1 and 2). When 2 equiv of NMO and 2 equiv of $NaIO_4$ were employed for this reaction, aldehyde **4** was isolated as the major product in 59% yield (entry 3). The best result was obtained when this reaction was carried out by using 2 equiv of NMO and 8 equiv of $NaIO_4$ in dioxane/H_2O = 3:1 (v/v) at room temperature for 1 day, providing **3b** in 62% yield. The stereoselectivity exhibited in the formation of **3b** as the major product can be rationalized by assuming that this cyclization would proceed via the more favorable dipolar model **TS-A** rather than **TS-B** as depicted in Figure 3.[18]

Since we were able to establish an efficient synthetic route for the core carbon framework having an *exo*-methylene unit of the target compounds in very short steps, further transformation of β-alcohol **3b** to the known intermediate[11] for the synthesis of (±)-axamide-1 and (±)-axisonitrile-1 was then investigated. Although difficulties were initially encountered in the conversion of the hydroxyl group to a cyano group and also in inversion of the secondary hydroxyl group using Mitsunobu reaction under various reaction conditions, Parikh–Doering oxidation[19] of **3b** finally afforded the known ketone **9** in 61% yield (Scheme 2).

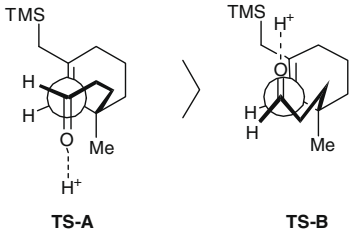
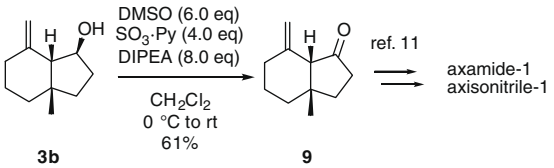


Figure 3. Plausible stereochemical pathway in the Hosomi–Sakurai reaction to give **3b** predominantly.



Scheme 2. Conversion of **3b** to the known ketone **9**.

Since ketone **9** was already transformed into (±)-axamide-1 and (±)-axisonitrile-1 by Kuo et al.,[11] this synthesis constitutes their formal synthesis.

In summary, we were able to establish an efficient formal synthesis of (±)-axamide-1 and (±)-axisonitrile-1 by employing an intramolecular Hosomi–Sakurai reaction as a key step. The synthetic strategy is quite general and the reaction sequence is relatively short with reasonable yields. The strategy developed here provides a further useful example of an intramolecular Hosomi–Sakurai reaction in the synthesis of natural products.

Acknowledgments

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16. *Selected data for compound* **5**: IR ν max 1248 cm^{-1}; ^1H NMR ($CDCl_3$; 400 MHz) δ 5.82 (ddt, J = 6.6, 10.2, 16.8 Hz, 1H), 4.99 (ddt, J = 1.6, 3.6, 16.8 Hz, 1H), 4.93 (s, 1H), 4.90 (ddt, J = 1.6, 2.2, 10.2 Hz, 1H), 2.08–1.95 (m, 2H), 1.89–1.76 (m, 2H), 1.65–1.55 (m, 2H), 1.46–1.26 (m, 4H), 1.38 (s, 2H), 0.93 (s, 3H), 0.00 (s, 9H); ^{13}C NMR ($CDCl_3$; 100 MHz) δ 140.0, 133.9, 128.7, 113.6, 114.5, 42.6, 34.6, 34.5, 31.2, 28.8, 27.9, 19.9, −1.18 (3); MS (EI): 236 (M^+); HRMS (EI): calcd for $C_{15}H_{28}Si$: 236.1960, found; 236.1970.
17. *Selected data for compound* **3b**: IR ν max 1646, 1721 and 3371 cm^{-1}; ^1H NMR ($CDCl_3$; 400 MHz) δ 4.79 (d, J = 2.3 Hz, 1H), 4.73 (d, J = 2.3 Hz, 1H), 4.26 (ddd, J = 6.3, 8.7, 8.7 Hz, 1H), 2.23–2.14 (m, 2H), 2.11–2.02 (m, 2H), 1.94 (d, J = 8.7 Hz, 1H), 1.69–1.54 (m, 3H), 1.51–1.31 (m, 4H), 1.27–1.22 (m, 1H), 0.97 (s, 3H); ^{13}C NMR ($CDCl_3$; 100 MHz) δ 146.9, 110.9, 75.1, 63.9, 42.2, 38.5, 34.5, 31.4, 30.8, 25.6, 23.6; MS (CI): 167 (M^++1); HRMS (CI): calcd for $C_{11}H_{18}O$+H: 167.1436, found; 167.1436.
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