Stereocontrolled Total Synthesis of Antimalarial (+)-Axisonitrile-3

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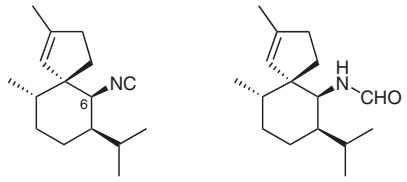
Abstract: Here we describe the total synthesis of the antimalarial sesquiterpene, (+)-axisonitrile-3. Three key features of this synthesis are: (i) non-Evans *syn*-aldol reaction of an isovaleric acid derivative bearing a chiral oxazolidinethione and crotonaldehyde with high diastereoselectivity, (ii) Claisen rearrangement of alkenyl dihydropyran affording spiro[4.5]decane with requisite functionalities, and (iii) highly stereoselective reduction in the sterically congested *O*-methyl oxime system.

Key words: antimalarial activity, (+)-axisonitrile-3, Claisen rearrangement, *O*-methyl oxime, total synthesis

The axane sesquiterpene, (+)-axisonitrile-3 (**1**), was isolated from the marine sponge *Axinella cannabina* in 1973. X-ray crystallographic analysis of **1** showed it to possess an isocyano group at the C6 position in the spiro[4.5]decane motif as well as four contiguous stereogenic carbon atoms involving a quaternary carbon center (Figure 1).[1,2] While it has a simple scaffold, (+)-**1** is found to exhibit potent antimalarial activity.[3] Related biologically active spirocyclic sesquiterpene (–)-axamide-3 (**2**) is also produced by marine organisms, and it possesses antifouling activity against *Barnacle larvae*.[4] Although nitrogen-containing axane sesquiterpenes have attracted considerable attention, only one example of the synthesis has been published. In 1978, Caine and co-workers achieved the first synthesis of (–)-**1**, an antipode of the natural product, from (+)-dihydrocarvone.[5] The absolute stereochemistry of natural compound was determined by comparison of the specific rotation of the synthetic **1**. Herein we wish to describe the first total synthesis of natural (+)-**1**. The synthesis involves several key features, including a non-Evans *syn*-aldol reaction of an isovaleric acid derivative bearing a chiral oxazolidinethione and crotonaldehyde with high diastereoselectivity. The spiro[4.5]decane containing all the functionalities is afforded by Claisen rearrangement of alkenyl dihydropyran. Finally, a highly stereoselective reduction in the sterically congested *O*-methyl oxime system is achieved.

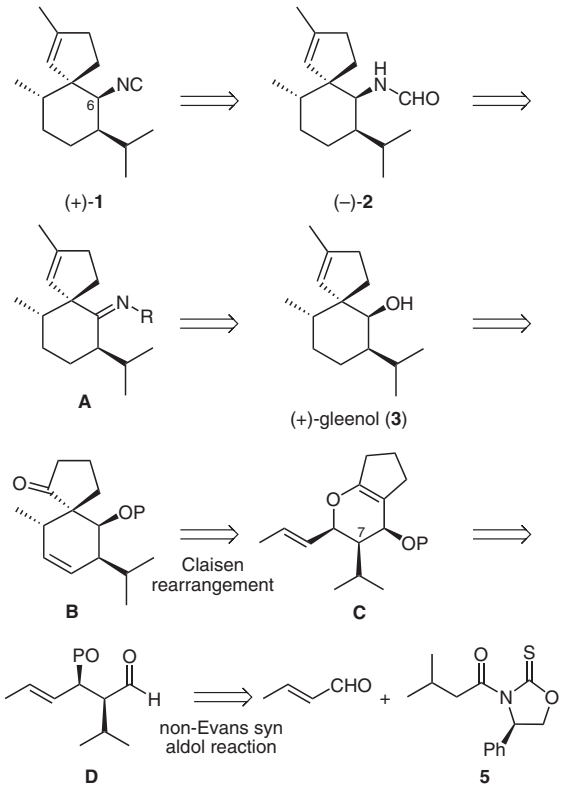
Scheme 1 represents the synthetic strategy for (+)-**1** through (+)-gleenol (**3**) as a versatile intermediate. Isocyanide **1** can be obtained from formamide **2** through dehydration, which in turn can be synthesized via an imine derivative **A** with an appropriate reductant for the stereoselective reaction of the sterically hindered imino group.



(+)-axisonitrile-3 (**1**) (–)-axamide-3 (**2**)

Figure 1 Structures of axane sesquiterpenes (+)-**1** and (–)-**2**

Imine derivative **A** can be derived from (+)-gleenol (**3**), which is stereoselectively accessible using our established strategy for its antipode (–)-**3**.[6b] Thus, the functionalized spiro[4.5]decane **B**, a precursor of (+)-**3**, can be obtainable from enantioenriched 2-(propenyl)dihydropyran **C** by means of a Claisen rearrangement as a crucial step. The C7 and an allylic center is then introduced from the (2*S*,3*R*)-aldol **D**. In the present study, we attempted a preparation of **D** by a $TiCl_4$-mediated non-Evans *syn*-aldol reaction[7] of an isovaleric acid derivative **5** bearing an oxazolidinethione chiral auxiliary, because we encountered some difficulties in the previous protocol.[6b,8]



Scheme 1 Synthetic strategy of (+)-**1**

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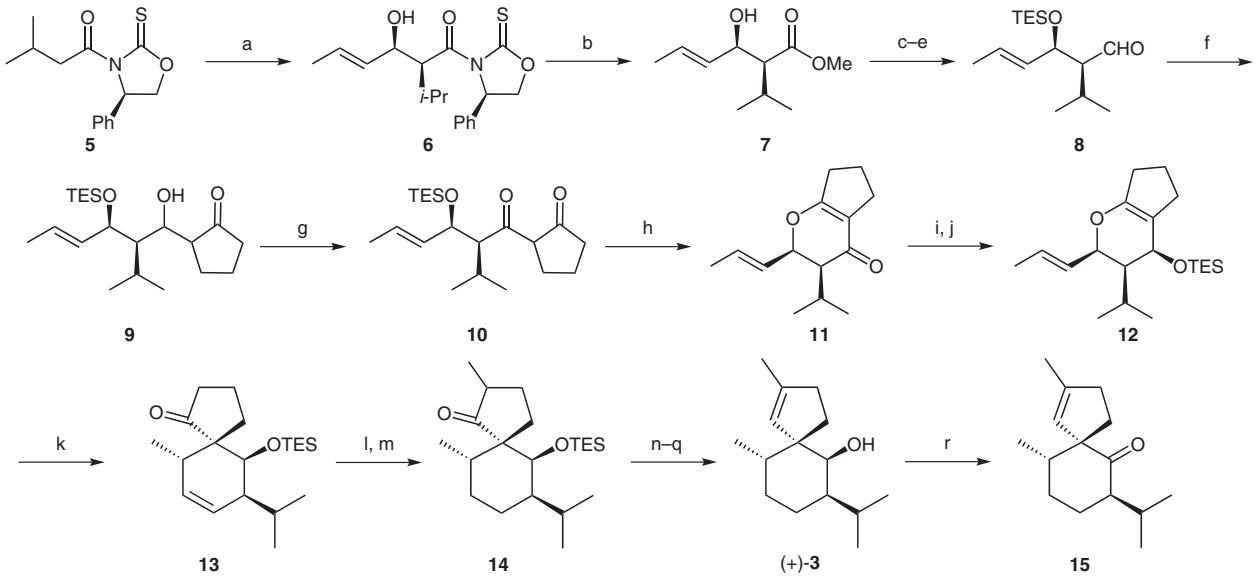


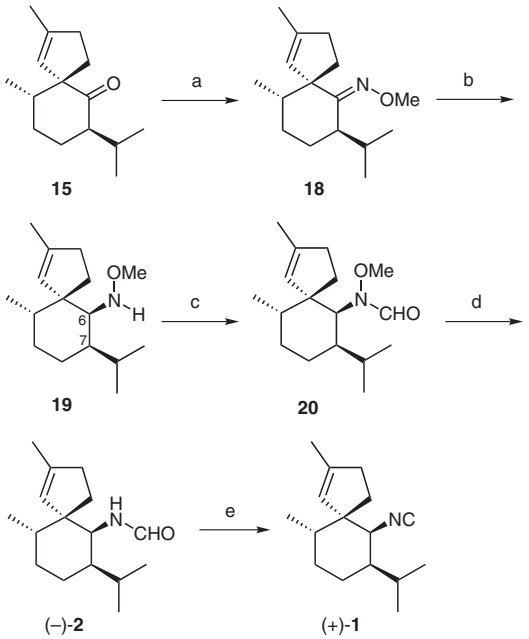
Scheme 2 Stereocontrolled syntheses of ketone **15** through (+)-gleenol (**3**). *Reagents and conditions*: (a) (i) $TiCl_4$, *i*-Pr_2NEt, CH_2Cl_2, 0 °C, 1 h; (ii) –78 °C, 40 min; (iii) crotonaldehyde, –78 °C, 25 h, 81% (non-Evans *syn*/*anti* = 94:6); (b) NaOMe, MeOH, r.t., 35 min, 58%; (c) TESOTf, 2,6-lutidine, CH_2Cl_2, –78 °C, 35 min, quant.; (d) DIBAL, CH_2Cl_2, –78 °C, 30 min, 80% (>95% dr); (e) Dess–Martin periodinane, CH_2Cl_2, 0 °C to r.t., 2 h, quant.; (f) (i) LDA, cyclopentanone, THF, –78 °C, 2 h; (ii) aldehyde **8**, –78 °C, 6 h, 91%; (g) (i) TFAA, DMSO, CH_2Cl_2, –78 °C, 50 min; (ii) Et_3N, –60 °C, 12 h, 98%; (h) 0.01 N HCl in EtOH, r.t., 23 h 25 min, 96%; (i) $LiAlH_4$, Et_2O, 0 °C, 35 min; (j) TESCl, imidazole, DMAP, CH_2Cl_2, 0 °C to r.t., 17 h, 73% (2 steps); (k) triglyme, 250 °C, 1 h, 84% (>95% dr); (l) H_2 (1 atm), $[Ir(cod)(PCy_3)py]PF_6$, CH_2Cl_2, r.t., 14 h, quant.; (m) LDA, MeI, THF, –78 °C, 12 h, 90%; (n) $LiAlH_4$, THF, –78 °C, 5 h; (o) MsCl, pyridine, 0 °C, 22 h; (p) DBU, toluene, 150 °C, 16 h; (q) TBAF, THF, r.t., 17 h, 93% (4 steps); (r) Dess–Martin periodinane, CH_2Cl_2, r.t., 3 h, 92%.

In addition, this type of non-Evans *syn*-aldol reaction using an acyl imide bearing a bulky group, such as an isopropyl group, is unprecedented. Thus, much attention is centered on its stereochemical outcome.

Stereocontrolled synthesis of ketone **15** through (+)-gleenol (**3**) was conducted based on our reported method with several modifications (Scheme 2). The synthesis commenced with the preparation of (2*S*,3*R*)-aldol adduct **6** through the non-Evans *syn*-reaction, which was carried out according to Crimmins' protocol with slight modifications.[7] Thus, treatment of an isovaleric acid derivative **5** bearing an oxazolidinethione chiral auxiliary[9] derived from D-phenylglycine with 1.1 equivalents of $TiCl_4$ and 1.1 equivalents of *i*-Pr_2NEt in CH_2Cl_2 at –78 °C led to the corresponding titanium enolate. The in situ generated enolate was then treated with 1.1 equivalents of crotonaldehyde at the same temperature affording the desired (2*S*,3*R*)-aldol adduct **6** in 81% yield with high stereoselectivity (non-Evans *syn*/*anti* = 94:6).[10] To achieve good levels of conversion and diastereoselectivity, a prolonged mixing time of **5** with $TiCl_4$ and base was required. Removal of the chiral auxiliary from the obtained aldol adduct **6** was achieved by using NaOMe in methanol to provide the corresponding methyl ester **7** in 58% yield. The yield of the oxidation of the second aldol adduct **9** was improved (98% yield) when the reaction was conducted at –60 °C. Furthermore, improved yield of the silyl ether **12** was achieved in CH_2Cl_2 rather than DMF (42% yield), which might be attributed to a decrease in the decomposition of both allyl alcohol and the TES ether **12** using the less polar solvent. The key Claisen rearrangement of 2-(propenyl)dihydropyran **12** was complete within 1 hour, affording spiro[4.5]decane **13** in 84% yield. The enantiomeric excess of (+)-gleenol (**3**) was confirmed by chiral HPLC analysis to be 97.8%.

Having obtained the requisite ketone, we then examined the introduction of a nitrogen group at the C6 position by means of stereoselective reduction of *O*-methyl oxime (Scheme 3).[11,12] Exposure of ketone **15** with methoxyamine hydrochloride in pyridine at 65 °C provided *O*-methyl oxime **18** in 97% yield. The reaction resulted in the exclusive formation of an *E*-isomer, which was confirmed by NOE correlation between a methoxy group and an isopropyl group. Diastereoselective reduction of **18** with various reductants was then examined. However, conventional reagents, such as L-Selectride, $LiAlH_4$ and $AlH_3{\cdot}EtNMe_2$, were found to be ineffective in this system. To our delight, the reaction of **18** with $NaBH_3CN$ in AcOH[12] at room temperature resulted in the formation of the corresponding methoxyamine **19** in 84% yield as a single diastereomer. Gratifyingly, the stereochemistry of newly generated C6 atom was assigned as the desired *S*-configuration on the basis of a small coupling constant (2.6 Hz) of H6 and H7. This result indicates that the reduction might proceed from the less hindered face in more favorable conformer **A**. Although conformer **A** seems unfavorable due to 1,3-diaxial interaction, conformer **B** suffers from a severe allylic strain between the methoxy group and the C7 isopropyl group (Figure 2).[13] It is worth noting that the methoxy group plays an important role throughout the reduction, although several extra steps are required to remove it.

Completion of the total synthesis of (+)-**1** through (–)-**2** was achieved from methoxyamine **19**. Exposure of **19** to acetic formic anhydride and warming from room temperature to 70 °C provided formamide **20** in excellent yield. The SmI_2-mediated N–O bond cleavage and dehydration of the resulting (–)-axamide-3 (**2**) using TsCl in pyridine at room temperature afforded (+)-axisonitrile-3 (**1**) in good overall yield.[14] Spectroscopic data of the synthesized (+)-**1** coincided with those of the natural product.[1,15]



Scheme 3 Completion of the total synthesis. *Reagents and conditions*: (a) $MeONH_2$·HCl, pyridine, 65 °C, 72 h, 97% (>95% *E*); (b) $NaBH_3CN$, AcOH, r.t., 2.5 h, 84% (>95% dr); (c) (i) AcOCHO, r.t., 12 h; (ii) 70 °C, 96 h, 98%; (d) SmI_2, THF, r.t., 2.5 h, 79%; (e) TsCl, pyridine, r.t., 3 h, 87%.

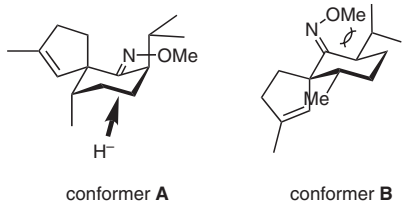
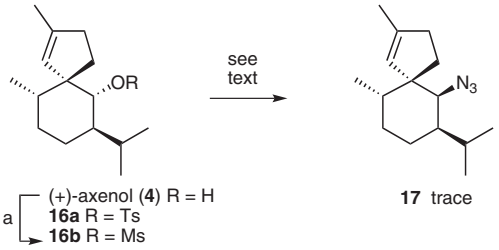


Figure 2 Two possible conformations of *O*-methyl oxime **18**

In conclusion, we accomplished the total synthesis of (+)-axisonitrile-3 via (–)-axamide-3 and (+)-gleenol. The synthesis involves (i) non-Evans *syn*-aldol reaction of an isovaleric acid derivative bearing oxazolidinethione and crotonaldehyde in good yield with high diastereoselectivity, (ii) Claisen rearrangement of 2-(*E*-propenyl)dihydropyran affording spiro[4.5]decane with the requisite functionalities, and (iii) highly stereoselective reduction in a sterically congested *O*-methyl oxime system.



Scheme 4 Attempted introduction of a nitrogen atom at C6 via an S_N2 reaction. *Reagents and conditions*: (a) Ms_2O, pyridine, 65 °C, 1 h, quant.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(8) In the previous synthesis of (–)-gleenol, the use of SuperQuat-type oxazolidine-2-one was necessary to minimize the cleavage of the oxazolidin-2-one during the removal of chiral auxiliary. Even employing SuperQuat, substantial amount of undesired byproduct caused by the ring opening of SuperQuat was formed.
(9) Wu, Y.; Yang, Y.-Q.; Hu, Q. *J. Org. Chem.* **2004**, *69*, 3990.
(10) The absolute stereochemistry of (2*S*,3*R*)-aldol adduct **6** was established by comparison of the specific rotation of the primary alcohol derived from ester **7**.
(11) An S_N2 reaction of tosylate **16a** prepared from axenol **4** with potassium azide has been reported by Caine and co-workers (Scheme 4).[5] However, we were unable to observe the formation of tosylate **16a** using their protocol. Thus we chose mesylate as an alternative leaving group. Unfortunately, azidation of **16b** under various reaction conditions (i.e., NaN_3, 15-crown-5, benzene, 80 °C; NaN_3, DMF, 100 °C; aq LiN_3, DMF, 100 °C; *n*-Bu_4NCl, NaN_3, NMP, 60 °C) was found to be unsuccessful. In each case, only a trace amount of the desired azide **17** was detected. Therefore we chose an alternative approach as shown in Scheme 3.

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(13) NOESY analysis of *O*-methyl oxime **18** indicated that **18** exists predominantly as the chair conformer **A** at r.t. in a $CDCl_3$ solution, see Supporting Information. Further, molecular mechanics calculations (SPARTAN) also supported the above observation.

(14) **Spectral Data for (+)-1**
White solid; mp 94–95 °C; $[\alpha]_D^{24}$ +54.4 (*c* 0.107, $CHCl_3$); lit.[1] $[\alpha]_D$ +68.4 (*c* 1.0, $CHCl_3$); lit.[15] $[\alpha]_D$ +43.4 (*c* 0.006, $CHCl_3$); R_f = 0.45 (hexane–*i*-Pr_2O = 20:1). ^1H NMR (400 MHz, $CDCl_3$): δ = 5.14 (q, *J* = 1.4 Hz, 1 H), 3.59 (br s, 1 H), 2.31–2.17 (m, 2 H), 2.01–1.90 (m, 2 H), 1.85–1.76 (m, 2 H), 1.74 (d, *J* = 1.4 Hz, 3 H), 1.59 (dqq, *J* = 9.4, 6.7, 6.7 Hz, 1 H), 1.51 (ddt, *J* = 13.4, 4.0, 3.5 Hz, 1 H), 1.33 (ddt, *J* = 12.8, 4.0, 13.4 Hz, 1 H), 1.20–1.11 (m, 1 H), 1.06 (ddt, *J* = 12.8, 4.0, 13.4 Hz, 1 H), 0.94 (d, *J* = 6.7 Hz, 3 H), 0.91 (d, *J* = 6.7 Hz, 3 H), 0.77 (d, *J* = 6.7 Hz, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.7, 144.8, 123.6, 64.5, 57.1, 43.8, 35.8, 34.9, 34.3, 31.2, 29.7, 24.9, 20.7, 20.3, 16.9, 16.1. IR (neat): 2925, 2131, 1541, 1456 cm^{-1}. ESI-HRMS: *m/z* calcd for $C_{16}H_{26}N$: 232.2055; found: 232.2059.

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