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Stereoselective synthesis of the *cis*-decalin subunit of vinigrol via three pericyclic reactions in cascade

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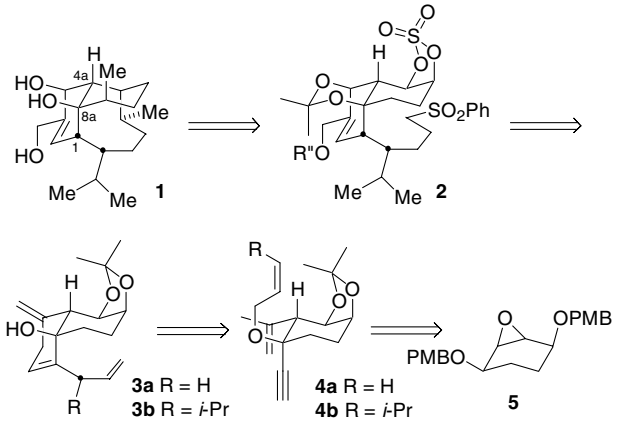
Abstract—Synthesis of the *cis*-decalin portion of vinigrol using a tandem oxy-Cope/Claisen/ene reaction is described. This three pericyclic reaction cascade proves to be a valuable synthetic tool in the construction of such systems.

Vinigrol (**1**) is a diterpenoid isolated from *Virgaria nigra*, which contains a unique tricyclo[4.4.4.0^{4a,8a}]-tetradecane framework (Scheme 1).[1] This architecturally complex natural product possesses antihypertensive and anti-platelet aggregating properties.[2] In 1991, Norris et al. discovered that vinigrol (**1**) is a powerful tumor necrosis factor (TNF) antagonist capable of arresting the progression of AIDS-related complex to AIDS.[3] Its promising biological activities along with its structural complexity have stimulated the disclosure of several synthetic approaches.[4]



Scheme 1.

Our retrosynthetic analysis depicted in Scheme 1 reveals that the eight-membered ring surmounting the *cis*-decalin in **1** could be created via an intramolecular S_N2 displacement of the cyclic sulfate at C5 by a sulfone anion. Since *cis*-decalins can exist in two conformations, the acetonide moiety in **2** is essential to lock the *cis*-decalin **2** into the conformer prone to cyclization. The latter was obtained from *cis*-decalin **3**, which could be realized in one step from a tandem oxy-Cope/Claisen/ene reaction of allyl ether **4**.[5] The tandem reaction precursor **4** was generated from the known epoxide **5**, which is readily prepared from commercially available 1,3-cyclohexadiene.[6]

The synthesis commenced by the epoxide opening of *meso*-***5*** with an organocuprate generated from isopropenyl magnesium bromide and CuI in THF to afford the corresponding homoallylic alcohol in 95% yield (Scheme 2). The latter was treated with I_2 in MeOH[7] to provide compound (±)-***6*** free of benzyl groups in 85%. Following the protection of the *cis*-1,2-diol moiety in **6** with 2,2-dimethoxypropane and a catalytic amount of PTSA in acetone (72%), the corresponding acetonide was then oxidized using Dess–Martin's periodinane to provide ketone **7** in 87% yield.[8] Installation of the acetylene group on tandem reaction precursor **4a** required the addition of lithium trimethylsilylacetylide to **7** in THF (84%, dr>25:1) followed by treatment with fluoride ions to give alcohol **8** in 74% yield as the sole isomer. Allylation of tertiary alcohol **8** with allyl

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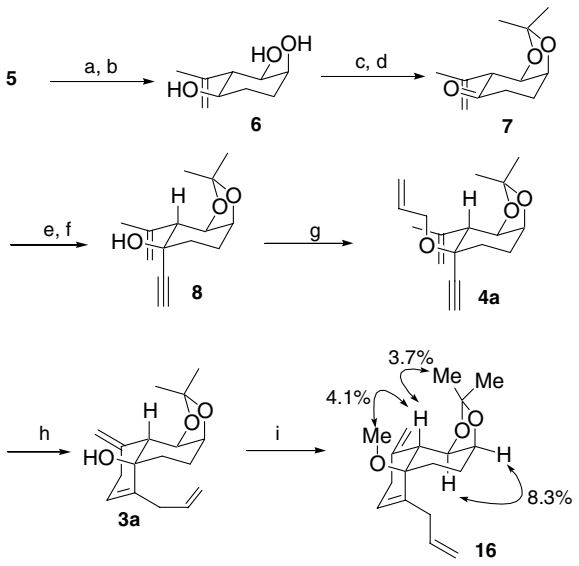

Scheme 2. Reagents and conditions: (a) $CH_2{=}C(CH_3)MgBr$, CuI, THF, 95%; (b) I_2, MeOH, 85%; (c) 2,2-dimethoxypropane, PPTS (5 mol%), acetone, 72%; (d) Dess–Martin periodiane, CH_2Cl_2, 87%; (e) TMS–acetylene, BuLi, −78 to 25 °C, 84%; (f) TBAF, THF, 74%; (g) $CH_2{=}CHCH_2Br$, NaH, THF–DMF (3:1), 100%; (h) 180 °C, toluene, 80%; (i) NaH, MeI, DMF–THF (2:1), 86%.

bromide and sodium hydride in THF–DMF (3:1) gave allyl ether **4a** in 100% yield.

Compound **4a** was dissolved in degassed toluene and subjected to microwave irradiation (180 °C) for 1 h to give the desired *cis*-decalin **3a** in 80% yield.[9,10] The relative stereochemistry of **3a** was established by ^{1}H NMR COSY and NOESY experiments on methyl ether derivative **16**. From 1D NOE experiments, NOEs between H-4a and H-methyl acetonide (3.7%), H-4a and CH_3O at C8a (4.1%), H-5 and H-6 (8.3%) clearly indicate that **3a** possesses a *cis*-ring junction.

The high diastereoselectivity of the tandem process can be rationalized by the reaction mechanism proposed in Figure 1. At first glance, allyl ether **4a** can undergo an oxy-Cope rearrangement via two possible transition states, **A** and **B**. Assuming that a rapid equilibrium exists between the conformers, only the energy difference between the transition states will account for the diastereomeric ratio.[11] A close examination of transition state **B** reveals the existence of severe 1,3-diaxial interactions between the allyl ether whereas in **A** the allyl ether chain is oriented in an equatorial position. This favors the formation of **9** over **12**. This is supported by the fact that no *trans*-decalins **14** or **15** were observed resulting from the transannular ene reaction of **13**. The highly strained macrocyclic allene **9** undergoes a Claisen [3,3]-shift, which generates in situ the 10-membered ring enone **10**. The latter is poised to cyclize via a transannular carbonyl-ene reaction. This concerted reaction can adopt two possible reactive macrocyclic

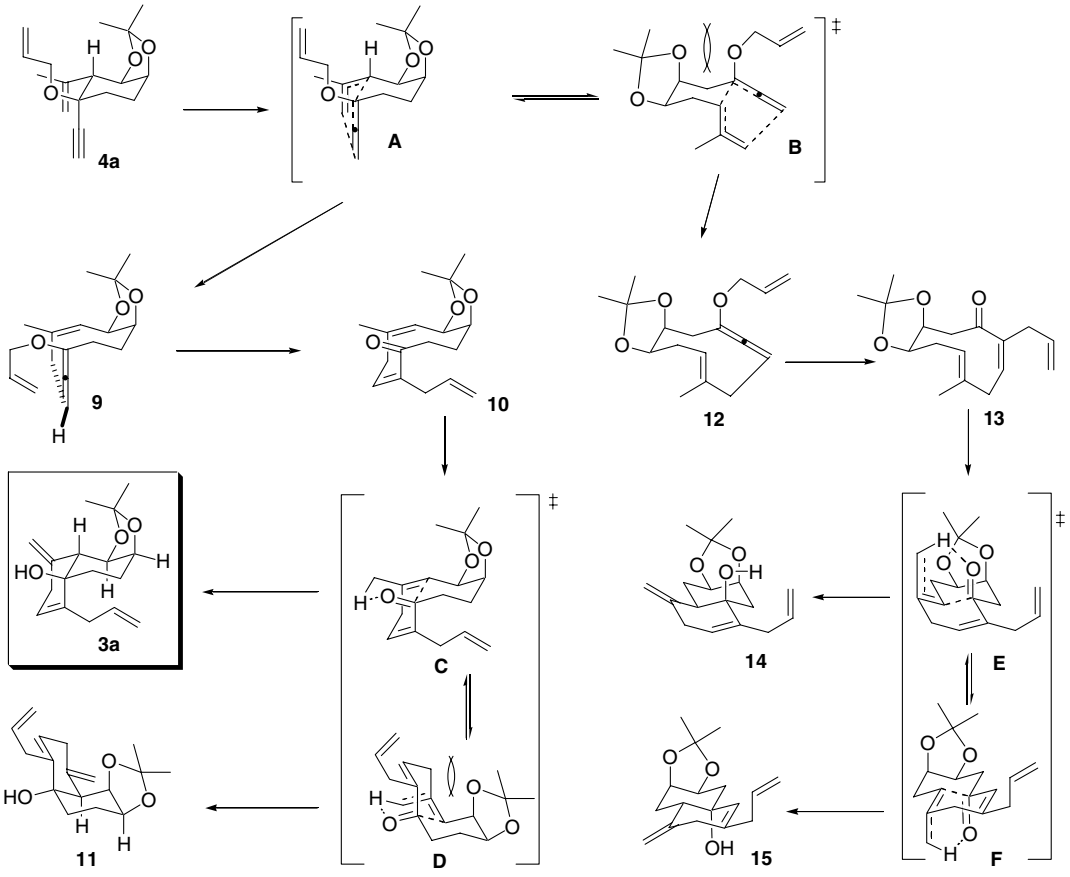

Figure 1. Proposed mechanism for the tandem oxy-Cope/Claisen/ene reaction.

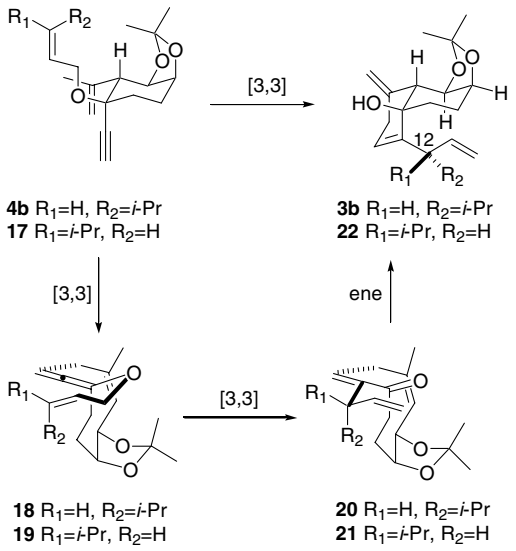

Figure 2.

conformations, **C** and **D**, at the transition states. An inspection of transition state **D** reveals strong 1,3-diaxial methylene *O*-acetonide interactions, which favor the transition state **C** over **D** as the reactive conformer to provide decalin **3a** as the sole isomer. The preferential formation of **3a** over decalins **11**, **14**, and **15** is thus explained.

At this stage, implementation of the isopropyl group on the allylic side chain in **3b** was investigated. Assuming that macrocyclic **18** is formed during the oxy-Cope process, Claisen rearrangement following by ene reaction of **18** should give the desired product **3b** bearing the proper stereochemistry at C12 (Fig. 2). To this end, precursor **4b** was readily prepared from alcohol **8**, sodium hydride, and *cis*-1-mesylate-4-methyl-2-pentene in 100% yield.[12] Irradiation of **4b** at temperature ranging from 160 to 200 °C gave a complex mixture of products from which no decalin product **3b** was isolated. At first glance, steric interactions between the isopropyl group and the ring in **18** could elevate the activation energy of the rearrangement process thereby favoring other undesired lower energetic processes. Similar results were reported by Hanna and co-workers when attempting to rearrange *cis*-isopropyl tertiary bicyclo[2.2.2]octenols to vinigrol skeleton via an anionic or thermal oxy-Cope reaction.[13] However, they found that the *trans*-isopropyl isomer proceeded without any difficulties.

trans-Allyl ether **17** was thus prepared and submitted to microwave irradiation.[14] Surprisingly, no product **22** resulting from a tandem oxy-Cope/Claisen/ene reaction was observed. According to these results, it is clear that large substituents at the terminal position are detrimental to the rearrangement sequence. Studies of the tandem process with various groups on allyl moiety as well as the synthesis of vinigrol are currently in progress and will be reported in due course.

Acknowledgements

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