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Rapid synthesis of methoxyconidiol and conitriol stereoisomers

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ABSTRACT

We describe the diastereoselective synthesis of the marine meroterpenes methoxyconidiol and conitriol in their trans form from the readily available 1-bromo-2,5-dimethoxybenzene in only three steps. The choice of the protective group strategy influenced not only the overall reaction yields but also the diastereoisomeric ratio. In addition, we describe the synthesis of natural conitriol (cis form) for the first time.

The term meroterpenoids was initially proposed in 1968 by Cornforth as 'Compounds containing terpenoid elements along with structures of different biosynthetic origin'.[1] Many meroterpenes have been characterized in both terrestrial and marine sources with the terpenoid moiety ranging in size from one to nine isoprene units. Concerning marine organisms, these compounds are mainly found not only in brown algae[2] but also in microorganisms[3] and invertebrates such as sponges,[4] ascidians,[5] or octocorals.[6]

Among ascidians, the genus *Aplidium* was found to produce a variety of diprenylated hydroquinone derivatives with a range of structural diversity generated by cyclization between hydroquinone and terpene parts and/or within the two isoprenoid units. The bicyclic or tricyclic systems obtained are formed via the common intermediate geranylhydroquinone **1** which is also isolated from an *Aplidium* species, *Aplidium antillense*.[7] Some of these meroterpenes were described to possess moderate antibacterial and antiproliferative activities but they were often tested as racemic mixtures.

We reported[8] the isolation and structural elucidation of the new meroterpenes methoxyconidiol **3** and didehydroconicol **5**, together with the known compounds cordiachromene **2** and epiconicol **4**,[9] extracted from a colonial ascidian *Aplidium aff. densum*. In this series (Fig. 1), the relative stereochemistry of both α-terpineol derivatives **3**[8] and **6**[9] was assumed to be the same with a cis orientation of H1′ and H6′ protons whereas the chromenes **4** and **7** are two epimers at C1′. Conicol **7** was described to have a *trans*-diaxial relationship between H1′ and H6′, identical to tetrahydrocannabinol **8** another well-known natural diprenylated hydroquinone. The presence of both stereoisomers conidiol and epiconicol in the same species *Aplidium conicum* indicates that the C1′–C6′ cyclization to the α-terpineol six-membered ring lacks stereospecificity.

Primary screening has shown that methoxyconidiol has a moderate antiproliferative activity against bacteria.[8] We further demonstrated that methoxyconidiol **3** presents an antimitotic action on the first division of sea urchin embryos.[10] The results of this study suggested that the mechanism of the action of methoxyconidiol might be mediated by disruption of microtubule dynamics. These promising results led us to synthesize methoxyconidiol together with epiconicol and didehydroconicol.[11] The diastereoselective synthesis of methoxyconidiol **3** with the cis orientation of

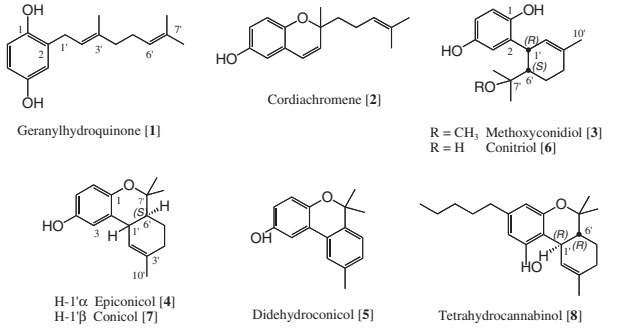

Figure 1. Structures of natural meroterpenes isolated from ascidians of the genus *Aplidium*. Configurations indicated for C1′ and C6′ in compounds **3**, **6**, **4**, and **7** are relative configurations.

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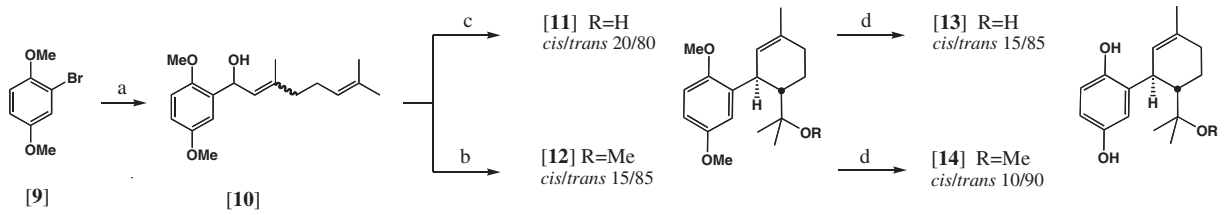


Scheme 1. Diastereoselective synthesis of *trans*-methoxyconidiol **14** and *trans*-conitriol **13**. Configurations indicated in compounds **11**, **12**, **13**, and **14** are relative configurations. Reagents and conditions: (a) (i) *n*-BuLi, Et_2O, −78 °C, 1 h, (ii) citral, −78 °C to rt, 1 h; 85%, (b) AcCl/MeOH, rt, 12 h; 73%, (c) HCl 12 M, THF, rt, 12 h; 82%, (d) (i) CAN, CH_3CN/H_2O:1/1, rt, 15 min, (ii) $Na_2S_2O_4/H_2O$, THF, 15 min; 85%.

H1′ and H6′ protons was achieved in three steps from 4-hydroxyphenol: (i) protection of the aromatic hydroxyl group as methoxymethyl ethers (ii) aromatic lithiation followed by the addition of citral (iii) acidic treatment affording the 6-membered ring by intramolecular cyclization.

Here we report, for the first time, the synthesis of conitriol **6** and a new and short diastereoselective synthesis toward the trans isomers of methoxyconidiol and conitriol.

trans-Methoxyconidiol and *trans*-conitriol were synthesized, as pairs of enantiomers, starting from commercially available 1-bromo-2,5-dimethoxybenzene **9** (Scheme 1). Firstly, a bromine-lithium exchange[12] followed by the addition of citral (*E*-geranial/*Z*-neral 1/1)[13] afforded the alcohol **10**[14] in 85% yield (*Z*/*E* 30/70). The subsequent acidification of the product with either aqueous HCl (path c) or methanolic HCl (path b) resulted in the formation of the desired 6-membered ring **11**[14] (cis/trans 20/80) and **12**[14] (cis/trans 15/85) in 82% and 73% yield, respectively. Finally, the oxidation-reduction sequence with ceric ammonium nitrate (CAN)[15] followed by treatment with sodium dithionite ($Na_2S_2O_4$) afforded the deprotected 4-hydroxyphenolic products *trans*-conitriol **13**[16] (cis/trans 15/85) and *trans*-methoxyconidiol **14**[17] (cis/trans 10/90) both in 85% yield.

trans-Methoxyconidiol **14** was obtained as an isomeric mixture in 52% overall yield as a white powder with a molecular formula of $C_{17}H_{24}O_3$ confirmed by HRMS. The ^{1}H NMR spectroscopic data showed a coupling constant $^3J_{1',6'}$ value of 1 Hz indicating a trans relationship between the H1′ and the H6′ protons. By contrast, the vicinal coupling constant in *cis*-methoxyconidiol was found to be 4.6 Hz.[8] Moreover, the 9′ methyl group appeared at δ 0.78 ppm, which was downfield compared to the previously reported chemical shift of δ 0.54 ppm. This was presumably caused by a weaker interaction between the 9′ methyl group and the hydroquinone ring's π-cloud in the trans configuration (Fig. 2).[19] Finally, in the ^{1}H NMR spectrum of the mixture of the methoxyconidiol diastereoisomers, a major sharp singlet attributed to 4-OH of the trans isomer was found at δ 8.46 ppm and a minor singlet attributing to 4-OH of the cis isomer was found at δ 4.05 ppm (90:10 ratio), the later was consistent with the 4-OH found at δ 4.27 ppm in the ^{1}H NMR of methoxyconidiol isolated from *Aplidium aff. densum*.[8] All these singlets disappeared when a deuterium exchange experiment was performed.

trans-Conitriol **13** was obtained as a colorless oil with a molecular formula of $C_{16}H_{22}O_3$ confirmed by HRMS. The ^{1}H NMR spectroscopy[16] enabled us to prove again a trans relationship between H1′ and H6′, in contrast with conitriol **6** previously characterized by Salvà and collaborators.[9] As for *trans*-methoxyconidiol, the trans relationship was supported by the $^3J_{1',6'}$ coupling constant value of 1 Hz together with the chemical shift of the sharp singlet attributed to 4-OH at δ 8.53 ppm.

In addition, we also synthesized *cis*-conitriol for the first time.[18] The compound was obtained as a colorless oil following the protocol we described in Ref. 11,18. All the spectroscopic data were identical with those previously published for the natural product.[9]

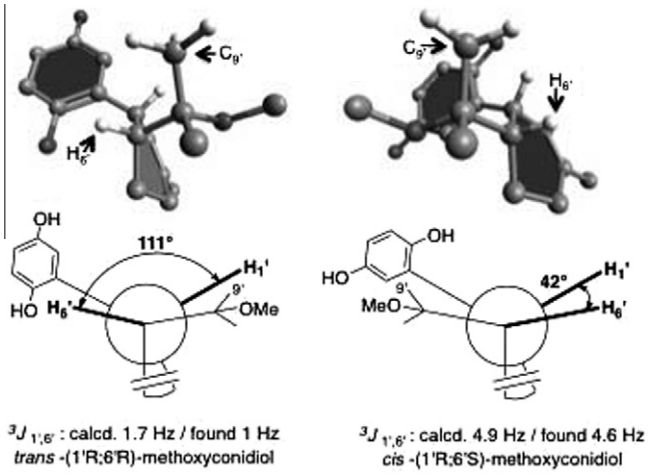
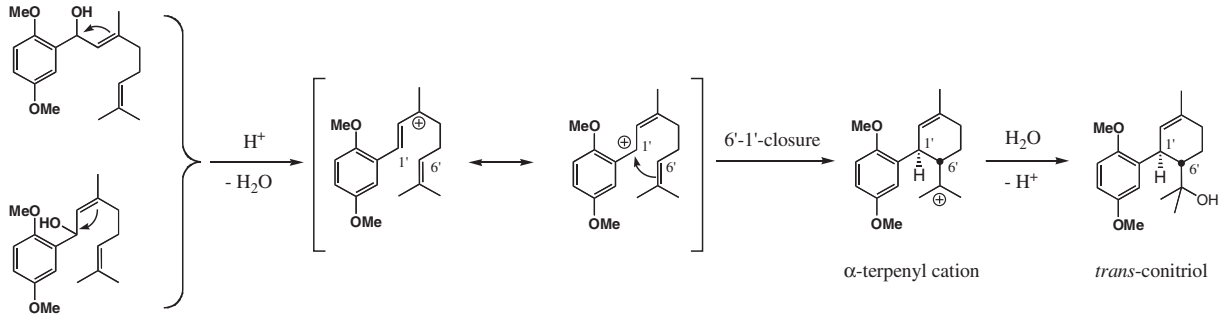


Figure 2. An energy-minimized structure[20] of *cis*- and *trans*-methoxyconidiol showing the dihedral angles[21] between H1′ and H6′ along with the orientation of C9′ in relation with the aromatic ring. Indicated configurations are relative.

We postulated that the formation of the 6-membered rings **11** and **12** involved OH-protonation followed by water elimination to give the α-terpinyl tertiary carbocation stabilized by a benzyl/allyl effect. The transient carbocation was then trapped by nucleophiles such as water (path c) or methanol (path b) forming the dimethoxybenzene α-terpineol derivatives **11** (cis/trans 20/80) and **12** (cis/trans 15/85).

The alcohol **10** is a mixture of *Z* (nerol-methoxyhydroquinone) and *E* (geraniol-methoxyhydroquinone) isomers (*Z*/*E* 30/70). The C2′–C3′ double bond of nerol-methoxyhydroquinone has the same *Z* configuration as that of *trans*-conitriol but not geraniol-methoxyhydroquinone, which represents 70% of the starting mixture. We propose that *trans*-conitriol (or *trans*-methoxyconidiol) is formed via a common intermediate, the stabilized benzylic/allylic cation, in the reactions of both *Z*- and *E*-isomers of alcohol **10** (Scheme 2). This intermediate was suggested for the biosynthesis of Δ^1-THCA by Δ^1-THCA synthase.[21]

This mechanism can explain the 1′–6′ cyclization but not the diastereoselective ratio in favor of the trans configuration. Indeed, we obtained preferentially the cis isomer (cis/trans 80/20) in the synthesis of methoxyconidiol described precedently.[11] The diastereoisomeric ratio is completely reversed in the strategy described here for the synthesis of *trans*-methoxyconidiol (cis/trans 10/90). In the same way, with the first synthesis protocol we obtained preferentially conitriol (cis/trans 80/20)[18] whereas *trans*-conitriol was prepared with high diastereoselectivity (cis/trans 15/85) with the protocol described here. The role of parameters that can influence conformational mobility of the isoprenic chain such as the protecting group (methoxy vs methoxymethyl) or *E*/*Z* ratio in alcohol **10**, together with work-up procedure, toward the diastereoselectivity cis/trans is still under investigation regarding stereochemical outcome of the reaction.



Scheme 2. Postulated mechanism accounting for the formation of *trans*-conitriol **13**.

In conclusion, we have described an efficient route for the synthesis of the meroterpenes *trans*-methoxyconidiol **14** and *trans*-conitriol **13** previously isolated from Ascidian species as their cis form. It should be noted that, to the best of our knowledge, the synthesis of conitriol is described for the first time in this article. With the synthetic method presented here compounds **13** and **14** were obtained in high yields in less than 12 h, at room temperature, without any side products and with a high diastereoselectivity.

Acknowledgments

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14. All new compounds were fully characterized on the basis of ^{1}H NMR, ^{13}C NMR, and mass spectroscopic data. Data for major product (*E*)-**10** ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 7.03 (s, 1H, H-3); 6,81 (m, 2H, H-5 H-6); 5.80 (d,1H, H-2′); 5.20 (m, 2H, H-1′ H-6′); 3.83 (s, 6H, 1-OMe 4-OMe); 2.00 (m, 3H, H-4′ H-5′ 1′-OH); 1.83–1.80 (m, 9H, 8′-CH_3 8′-CH_3 9′-CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 153.9 (C-4), 151.3 (C-1), 137.0 (C-3′), 130.8 (C-7′), 127.1 (C-2), 125.0 (C-6′), 121.5 (C-2′), 112.0 (C-3 C-5 C-6), 72,6 (C-1′), 55,0 (1-OMe 4-OMe), 42,6 (C-4′), 24,6 (C-5′), 22,6 (C-8′ C-9′), 16,4 (C-10′). HRMS ESI^{+}: $(C_{18}H_{26}O_3+Na)^{+}$: 313.1780 (Calcd), 313.1774 (Found). Data for major product *trans*-**11** ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 6.96 (s, 1H, H-3), 6.77 (m, 2H, H-5 H-6); 5.37 (s, 1H, H-2′); 4.64 (s, 1H, 7′-OH); 3.82 (s, 6H, 1-OMe 4-OMe); 3.23 (d, 1H, H-1′, $^{3}J_{1',6'}$ = 1.25 Hz); 2.31 (d, 1H, H-6′); 2.12–1.51 (m, 4H, H-4′ H-5′); 1.82 (s, 3H, H-10′); 1.24 (s, 6H, H-8′ H-9′). ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 152.7 (C-4), 148.5 (C-1), 135.3 (C-3′), 126.4 (C-2), 123.9 (C-2′), 116.0 (C-3), 112.0 (C-5 C-6), 70.6 (C-7′), 55.9 (1-OMe 4-OMe), 45.6 (C-6′), 31.5 (C-4′), 28.0 (C-8′ C-9′), 26.4 (C-1′), 24.9 (C-5′), 22.3 (C-10′). HRMS ESI^{+}: $(C_{18}H_{26}O_3+Na)^{+}$: 313.1780 (Calcd), 313.1777 (Found). Data for major product *trans*-**12** ^{1}H NMR (DMSO-d_6, 400 MHz) δ (ppm): 6.95 (s, 1H, H-3); 6.75 (m, 2H, H-5 H-6); 5.80 (s, 1H, H-2′); 3.83 (s, 6H, 1-OMe 4-OMe); 3.31 (s, 3H, 7′-OMe); 3.21 (d, 1H, H-1′, $^{3}J_{1',6'}$ = 1.43 Hz); 2.33 (d, 1H, H-6′); 2.10–1.52 (m, 4H, H-4′ H-5′); 1.80 (s, 3H, H-10′); 1.23 (s, 6H, H-8′ H-9′). ^{13}C NMR (DMSO-d_6, 100 MHz) δ (ppm): 152.6 (C-4), 148.6 (C-1), 134.8 (C-3′), 132.1 (C-2), 124.4 (C-2′), 118.5 (C-3), 111.0 (C-5 C-6), 77.1 (C-7′), 55.6 (1-OMe 4-OMe), 45.1 (7′-OMe), 36.1 (C-6′), 31.1 (C-4′), 23.7 (C-8′ C-9′), 23.0 (C-1′ C-5′), 22.9 (C-10′). HRMS ESI^{+}: $(C_{19}H_{28}O_3+Na)^{+}$: 327.1936 (Calcd), 327.1943 (Found).
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16. Data for major product *trans*-**13** ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.65 (s, 1H, 1-OH); 8.53 (s, 1H, 4-OH); 6.55–6.50 (m, 3H, H-3 H-5 H-6); 5.35 (s, 1H, H-2′); 4.50 (s, 1H, 7′-OH); 3.90 (d, 1H, H-1′, $^{3}J_{1',6'}$ = 1 Hz); 2.10 (s, 1H, H-4′); 2.02 (d, 1H, H-6′); 1.82 (s, 3H, H-10′); 1.65 (s, 1H, H-5′); 1.24 (s, 3H, H-8′); 0.98 (s, 3H, H-9′). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 149.1 (C-4), 148.1 (C-1), 134.2 (C-3′), 128.1 (C-2), 124.1 (C-2′), 118.3 (C-3), 116.0 (C-5 C-6), 73.5 (C-7′), 46.2 (C-6′), 33.1 (C-1′), 30.5 (C-4′), 29.3(C-8′); 23.2 (C-9′); 22.5 (C-10′), 20.6 (C-5′). HRMS ESI^{+}: $(C_{16}H_{22}O_3+Na)^{+}$: 285.1467 (Calcd), 285.1475 (Found). Data for minor product *cis*-**6**: see Ref. 9.
17. Data for major product *trans*-**14** ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm): 8.55 (s, 1H, 1-OH); 8.46 (s, 1H, 4-OH); 6.58–6.52 (m, 3H, H-3 H-5 H-6); 5.90 (s, 1H, H-2′); 3.76 (d, 1H, H-1′, $^{3}J_{1',6'}$ = 1.11 Hz); 3.13 (s, 3H, 7′-OMe); 2.12 (s, 1H, H-4′); 2.10 (d, 1H, H-6′); 1.69 (s, 3H, H-10′); 1.63 (s, 1H, H-5′); 0.89 (s, 3H, H-8′); 0.78 (s, 3H, H-9′). ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 152.1 (C-4), 147.9 (C-1), 131.2 (C-3′), 128.1 (C-2), 125.2 (C-2′), 119.3 (C-3), 115.0 (C-5 C-6), 77.5 (C-7′), 48.0 (7′-OMe), 45.2 (C-6′), 33.1 (C-1′), 30.5 (C-4′), 22.0 (C-8′ C-10′), 20.9 (C-5′), 19.5 (C-9′). HRMS ESI^{+}: $(C_{17}H_{24}O_3+Na)^{+}$: 299.1623 (Calcd), 299.1629 (Found). Data for minor product *cis*-**3**: see Ref. 8.
18. For the first and the second steps of the synthesis, see Ref. 11. Typical procedure for the third step: to a stirred solution of 1-[2,5-bis(methoxymethyloxy)phenyl]-3,7-dimethyl-2,6-octadien-1-ol (0.1 g, 0.28 mmol) in THF/H_2O (2:1, 10 mL) was added dropwise 12 N hydrochloric acid (1.6 mL). The mixture was stirred at 8 °C for 18 h then concentrated in vacuo. The crude was diluted with CH_2Cl_2 (10 mL), washed with water (2 × 10 mL), dried (Na_2SO_4), and concentrated. The residue was purified by silica gel chromatography (heptane/ethyl acetate, 7:3) to give conitriol as a colorless oil (15 mg, 20%).
19. The energy-minimized structures were computed using the following software: Avogadro: an open-source molecular builder and visualization tool. Mac OS X Version 1.0.1 http://avogadro.openmolecules.net.
20. The dihedral angles values were determined in silico using the Avogadro software. The estimated ^{3}J values were obtained from the dihedral angles values using the following software: Sweet J: a desktop calculator for the Karplus equation. Mac OS X Version 2.2; http://www.inmr.net/sweetj.html.
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