A Facile Synthesis of Methyl (3-isocyano-2-cyclopent-2-enyl) acetate

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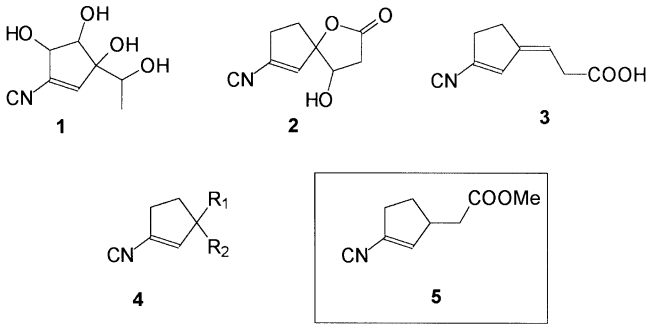
During the course of our current program on the design and synthesis of melanin biosynthesis inhibitors, we have been interested in cyclopentenoid isonitriles **1**, **2** and **3** which were isolated from cultures of *Tricoderma hamatum* (Bon) bain Aggr.[1] All of these compounds have cyclopentenyl isonitrile moiety **4** and show high inhibitory activity against mushroom tyrosinase, a key enzyme for melanin biosynthesis.[2]



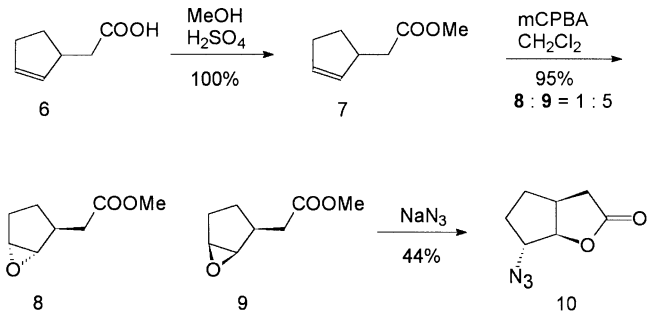
Little is known about the origin of the inhibitory activity of these derivatives. One point of the interest is the effect of cyclopentenyl isonitrile moiety **4** on the activities of compounds **1**, **2** and **3**. To examine this effect, we have prepared simple ester **5** which contains cyclopentenyl isonitrile moiety **4** and compared the inhibitory effect of ester **5** with those of compounds **1**, **2** and **3**.

The synthetic pathway to ester **5** began with commercially available 2-cyclopentenyl-1-acetic acid **6** (Scheme 1). Esterification of acid **6** with methanol gave methyl ester **7** in quantitative yield. Epoxidation of ester **7** with mCPBA gave *syn*-epoxide **9** as a major component (>5:1 by ^{1}H NMR) in 95% yield. Presumably the directing effect of the ester group overcomes any steric hindrance that would, otherwise, favor formation of the anti diastereomer **8**.[3] Treatment of purified *syn*-epoxide **9** with sodium azide yielded undesired lactone **10** as a major product in 44% yield.[4]

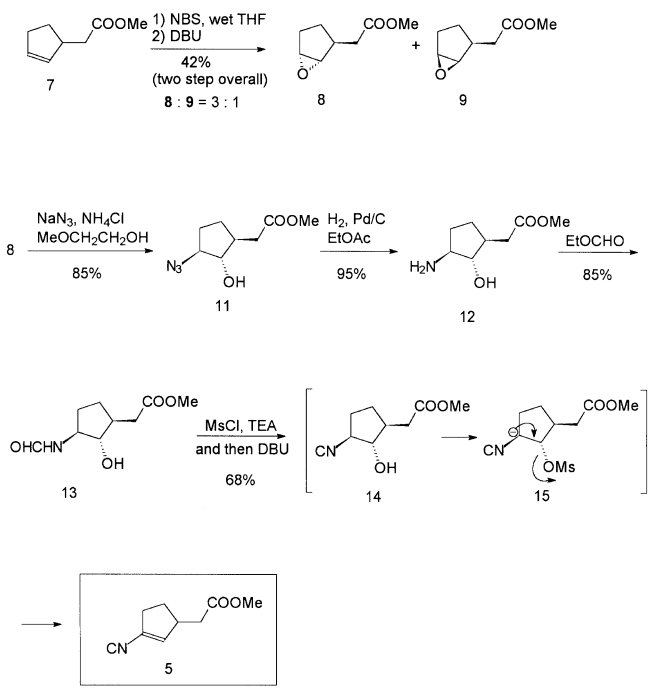
Because of the difficulties in further manipulation of lactone **10** towards the target molecule **5**, we turned our attention to indirect epoxidation *via* halohydrin formation (Scheme 2), in the hope of enhancing selectivity toward *anti*-epoxidation.[5] By treating alkene **7** with *N*-bromosuccinimide in wet THF, followed by ring-closure of the resultant bromohydrin, desired *anti*-epoxide **8** was obtained as a major compoent in approximately 3:1 ratio.

Treatment of *anti*-epoxide **8** with sodium azide and ammonium chloride in ethylene glycol monomethylether gave vicinal *trans*-azidoalcohol **11** in 85% yield without any lactone formation. In DMF solvent instead of ammonium chloride in ethylene glycol monomethylether, unchanged epoxide **8** was only recovered. Vicinal amino alchol **12** was obtained by reduction of *trans*-azidoalcohol **11**. When amino alcohol **12** was treated with ethyl formate according to the procedure described by Seebach *et al.*, only its amino group was formylated to produce hydroxy formamide **13** in 85% yield.[6]

Conversion of hydroxy formamide **13** to ester **5** was supposed to be straightforward using the Baldwin and Fukuyama's stepwise procedure[7] *via* the isolation of intermediates **14** and/or **15**. However, due to the instability of intermediate **14** and **15** which were easily hydrolized during the purification, our modified one-pot procedure was



Scheme 1



Scheme 2

Table 1. Inhibitory activity against mushroom tyrosinase

Material	IC_{50}(μg/mL)	ref
1	6.7	2
2	1.6×10^{-2}	2
3	2.4×10^{-1}	2
5	5×10^{-3}	-

much more effective than stepwise procedure. The one-pot conversion was accomplished by treatment of hydroxy formamide **13** with MsCl Et_3N (excess) in CH_2Cl_2 at -10 °C, followed by addition of DBU (excess) at 25 °C in 68% overall yield.

The inhibitory effect of vinyl isonitrile ester **5** on the mushroom tyrosinase system was determined by a standard method[8] and the observed figure (IC_{50}=5 ng/mL) was found to be comparable with that of the most effective cyclopentenyl isonitrile **3**.[2] It can therefore be concluded that cyclopentenyl isonitrile moiety makes a major contribution to the activities of compounds **1**, **2** and **3**.

Experimental Section

Ring Opening of Epoxide 8. Epoxide **8** (656 mg, 4.20 mmole) in 6 mL of an $CH_3OCH_2CH_2OH$-H_2O (5 : 1) solution was refluxed with NaN_3 (1.5 g, 23.07 mmole) and solid NH_4Cl (1.2 g) for 5h. The reaction mixture was then cooled to room temperature and concentrated. The residue was extracted with ether (20 mL × 3), and the organic layer was dried with Na_2SO_4 and evaporated to give a thick syrup which was chromatographed with EtOAc : Hexane (1 : 10) solution to afford 710 mg (3.56 mmole, 85%) azido alcohol **11**. ^{1}H NMR ($CDCl_3$): δ 3.70 (3H, s), 3.75 (1H, m), 3.30 (1H, br), 2.51 (2H, dd, *J*=1.5, *J*=6.6 Hz), 2.00-2.30 (3H, m), 1.35-1.73 (2H, m).

Hydrogenation of Azido-alcohol 11. Azido alcohol **11** (0.636 mg, 3.19 mmole) in ethanol (20 mL) was hydrogenated at 1 atm and room temperature over 10% Pd/C catalyst (20 mg) for 5h. After removal of the catalyst by filtration, the ethanol was evaporated to give 524 mg (3.02 mmole, 95%) of amino alcohol **12.** ^{1}H NMR ($CDCl_3$): δ 3.75 (3H, s), 3.32 (1H, t, *J*=9 Hz), 3.09 (1H, q, *J*=9 Hz), 2.48 (2H, dd, *J*=4.8, *J*=6.7 HZ), 1.31 (2H, m).

Formylation of Amino-alcohol 12. A solution of amino alcohol **12** (515 mg, 2.97 mmole) in ethyl formate (20 mL) was refluxed for 2h. Excess ethyl formate was evaporated to give a thick syrup. Flash-chromatography (SiO_2, EtOAc : Hex=1 : 1) gave 510 mg (2.53 mmole, 85%) of hydroxy formate **13.** ^{1}H NMR ($CDCl_3$): δ 8.15 (1H, s), 5.97 (1H, br), 3.96 (1H, m), 3.67 (3H, s), 3.64 (1H, t, *J*=6Hz), 2.64 (1H), 2.35 (1H), 1.92-2.32 (3H, m), 1.35-1.60 (2H, m).

Synthesis of Methyl (3-isocyano-2-cyclopent-2-enyl) Acetate 5. To a solution of hydroxy formate **13** (481 mg, 2.39 mmole) and triethylamine (1 mL) in 5 mL of dichloromethane at -10 °C was added methanesulfonylchloride (500 mg) over a period of 10 min. After stirring for additional 2h at -10 °C, 2 mL (12.9 mmol) of DBU was added dropwise and the reaction mixture was allowed to warm to room temperature for 5h. After evaporation of solvent, The reaction mixture was directly purified by flash chromatography to afford 268 mg (1.62 mmole, 68%) of vinyl isonitrile **5**. IR ($CHCl_3$): 2117 (characteristic peak corresponding to the -NC group), 1725 cm^{-1}; MS (EI): m/e=165; ^{1}H NMR ($CDCl_3$): δ 5.93 (1H, br), 3.69 (3H, s), 3.20 (1H, br), 2.57 (2H, m), 2.40 (2H, dd, *J*=3, *J*=7 Hz), 2.29 (1H, m), 1.63 (1H, m).

Inhibitory activity

Inhibitory activity against mushroom tyrosinase were determined at the Cosmetic Research Institute, LG Chemical Ltd., Korea, according to the procedure described by K. Tomita *et al.*[8]

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