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Practical deracemization of NM-3, a synthetic angiogenesis inhibitor

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Abstract—The practical deracemization of the angiogenesis inhibitor NM-3 is described. The transformation features the diastereoselective addition of optically active pantolactone to a ketene intermediate and hydrolysis of the pantolactone ester.

Angiogenesis, the process of new blood vessel formation and proliferation, has been known to be associated with diseases such as rheumatoid arthritis, psoriasis, diabetic retinopathy, and solid tumors.[1] Therefore, anti-angiogenesis therapy is thought to be clinically useful for the treatment of these diseases. In 1999, a synthetic isocoumarin derivative, NM-3 **1** (Fig. 1), was reported by the Mercian group in Japan to have an anti-angiogenic activity in the mouse dorsal air sac assay system.[2,3] In addition to the anti-angiogenic activity, its high physicochemical stability and pharmacological properties made NM-3 **1** a promising candidate as an anticancer drug, especially for solid tumor treatment. Although this compound has already been used as a racemate for clinical testing, it is necessary to obtain it in an enantiomerically pure form for further research.

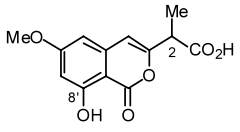

Figure 1. Chemical structure of NM-3.

The diastereoselective addition of a chiral alcohol to a ketene was reported as early as 1919,[4] and then developed by several groups including Larsen et al. at Merck.[5] Houk et al. recently explored this reaction using quantum mechanical calculations and provided a quantitative model.[6] Because the ketene formation and addition of an alcohol can be done in one pot and the products can be hydrolyzed without significant racemization, the Merck process is useful for transforming racemic α-substituted carboxylic acids to their enantiomerically pure form. This process is thought to be general for preparing various types of chiral α-substituted carboxylic acids. Indeed, there are examples which include the syntheses of chiral α-arylcarboxylic acids,[7,8] α-aryloxypropionic acids,[9] α-chlorocarboxylic acids,[9] and α-amino acids.[10–12] In this communication, we wish to report the deracemization of the racemic NM-3 (±)-**1** to its optically active form using this process. To the best of our knowledge, this is the first example of the application of the Merck process to isocoumarin compounds.

We first converted the racemic NM-3 (±)-**1** into 8′-*O*-acetyl NM-3 **2** to avoid side reactions including the condensation of phenol with the acid chloride in the next ketene formation step (Scheme 1). Indeed, treatment of (±)-**1** with oxalyl chloride and DMF did not

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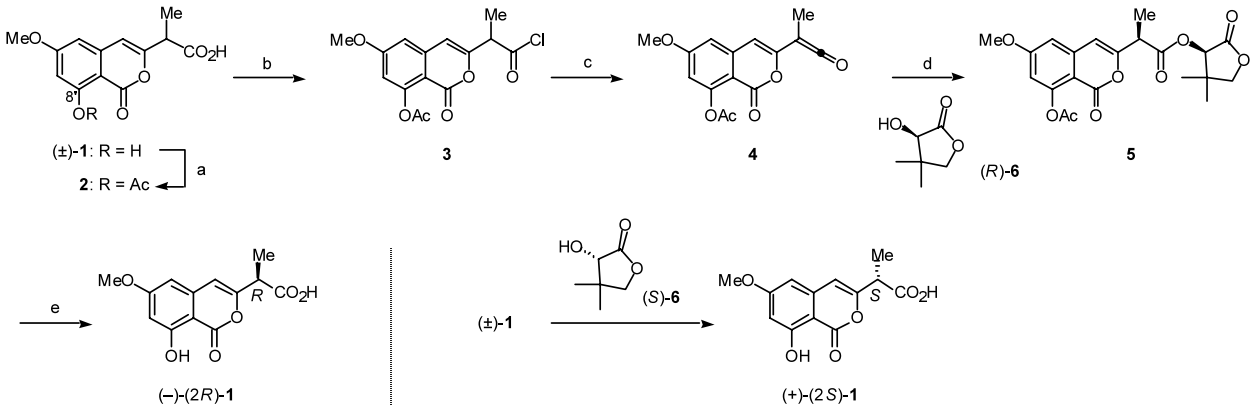
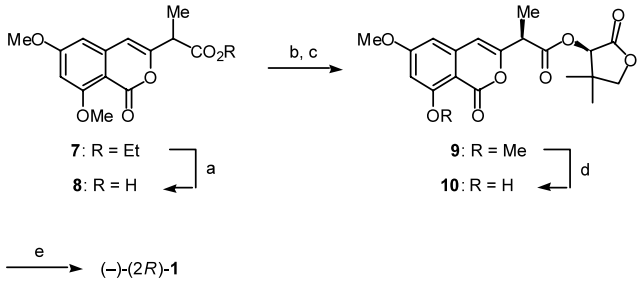


Scheme 1. Deracemization of NM-3. *Reagents and conditions*: (a) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 0°C, 1 h; (b) cat. DMF, oxalyl chloride, toluene, rt, 1 h; (c) *N*,*N*-dimethylethylamine, 0°C, 15 min; (d) (*R*)-pantolactone **6**, 15 min (85% from (±)-**1**, 94% de); (e) 1 M aq. HCl–AcOH (2:5), 110°C, 8 h (82%, 88% ee).

yield acid chloride. Reaction of acetate **2** with oxalyl chloride in the presence of a catalytic amount of DMF produced acid chloride **3**. After azeotropic removal of the excess oxalyl chloride with toluene, acid chloride **3** was treated with 1.2 equiv. of *N*,*N*-dimethylethylamine in toluene at 0°C to generate ketene **4** in situ. A sharp signal at 2119 cm^{-1} was observed in the infrared spectrum of the reaction mixture, suggesting the formation of ketene **4** from acid chloride **3**.[5] Addition of (*R*)-pantolactone **6** to the reaction mixture gave pantolactone ester **5** in 85% yield from (±)-**1**. The diastereomeric excess of **5** was determined to be 94% by ^1H NMR analysis. It is worth noting that when *N*-methylpyrrolidine or an excess amount of *N*,*N*-dimethyethylamine was used instead of 1.2 equiv. of *N*,*N*-dimethyethylamine, racemization occurred and the diastereomeric purity of the product decreased to 13–48%. Among several conditions tried (e.g. HCl–acetic acid, BCl_3, BBr_3, TMSCl–NaI, $HClO_4$–acetic acid), hydrolysis of the pantolactone ester and C8′-acetyl group in **5** was best achieved using 1 M aqueous HCl and acetic acid at 110°C to afford (−)-(2*R*)-**1** in 82% yield and 88% ee. The enantiomeric purity of (−)-(2*R*)-**1** was determined by chiral HPLC analysis using an ULTRON ES-OVM column (ϕ 4.6×150 mm: Shinwa Chemical Industries) and 0.02 M KH_2PO_4–H_3PO_4 buffer (pH 3)–MeOH (3:1) as the solvent. (+)-(2*S*)-**1** was also obtained in almost the same total yield (82% from (±)-**1**) and enantioselectivity (86%) when (*S*)-pantolactone was used in the ketene addition step. The absolute configuration was determined by X-ray crystallographic analysis of the amide derived from (+)-**1** and (2*R*)-2-phenylethylamine.[13]

To improve the enantiomeric excess of this process, we examined several protecting groups for the phenolic hydroxy group. The best result was obtained when the methyl group was used for this purpose (Scheme 2). Methyl ether **8** was prepared by acid hydrolysis of the known ethyl ester **7**, which is currently used as an intermediate of the (±)-NM-3 synthesis.[13] By using the same procedure described above, methyl ether **8** was converted to pantolactone ester **9** in 95% yield and 97%



Scheme 2. Transformation of **7** to (−)-**1**. *Reagents and conditions*: (a) 1 M aq. HCl–AcOH (2:5), 110°C, 8 h (57%); (b) cat. DMF, oxalyl chloride, toluene, rt, 2 h; (c) *N*,*N*-dimethylethylamine, toluene, −40°C, 15 min, then (*R*)-**6**, −40°C, 100 min (95% from (±)-**1**, 97% de); (d) MgI_2, THF, rt, 6 h (77%, 97% de); (e) 0.25 M aq. HCl–AcOH (2:5), 110°C, 5 h (83%, 94% ee).

de. Selective cleavage of the C8′ methyl ether was accomplished using magnesium iodide in THF to give the NM-3 pantolactone ester **10** in 77% yield without racemization. Final removal of the pantolactone moiety with 0.25 M aq. HCl–AcOH at 110°C afforded (−)-(2*R*)-**1** in 83% yield and 94% ee.

In conclusion, the practical deracemization of NM-3 has been accomplished using the diastereoselective addition of pantolactone to the ketene intermediate as the key step. Using this process, a reasonable amount of both enantiomers of NM-3 can be obtained. These materials will be useful for further clinical testing and basic research.

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