Pergamon

Tetrahedron Letters 39 (1998) 9681–9682

TETRAHEDRON LETTERS

First Total Synthesis of (-)-8-*epi*-9-Deoxygoniopypyrone

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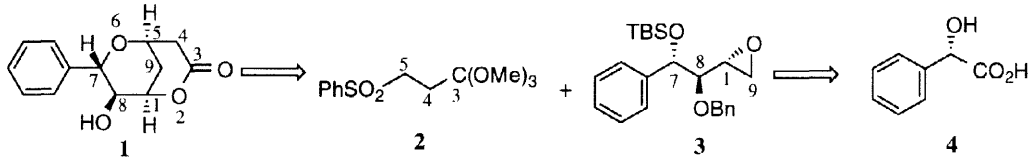
Received 25 September 1998; accepted 22 October 1998

Abstract : The structure and absolute configuration of natural 8-*epi*-9-deoxygoniopypyrone have been confirmed by an efficient and highly diastereoselective synthesis in 15 steps from (*S*)-mandelic acid with an overall yield of 43%.

Keywords : bicyclic heterocyclic compounds, cleavage reactions, hydroxylation, styryllactones.

In 1995, (-)-8-*epi*-9-deoxygoniopypyrone **1**[1] was isolated along with other antitumor styryllactones from the stem bark of *Goniothalamus dolichocarpus*.[2] The structure of 8-*epi*-9-deoxygoniopypyrone was determined as (1*R**,5*R**,7*R**,8*R**)-8-hydroxy-7-phenyl-2,6-dioxabicyclo[3.3.1]nonan-3-one **1** based on two-dimensional NMR studies and by comparison of its NMR spectra with those of its epimer, (+)-9-deoxygoniopypyrone, the structure of which was established by X-ray crystallographic analysis.[3]

In the course of our program directed toward the stereoselective synthesis of styryllactones, we have recently completed the total synthesis of nine of them.[4] Herein, we described the first synthesis of **1** which is identical to the natural (-)-8-*epi*-9-deoxygoniopypyrone, thereby confirming its structure and absolute configuration. As outlined in Scheme 1, one of the key element of our synthetic strategy for **1** involves a coupling between the sulfone **2** and the epoxyde **3**, readily available from (*S*)-mandelic acid **4** which authorizes the rapid construction of the 2,6-dioxabicyclo[3.3.1]nonan-3-one framework of **1**.



1 **2** **3** **4**

Scheme 1

As already described for its (*R*)-enantiomer, (*S*)-mandelic acid was readily transformed to the enantiopur (*E*)-α,β-unsaturated ester **5** in four steps and 72% overall yield (Scheme 2).[4c] Introduction of C-1-C-8 stereogenic centers of compound **1** was effected by the Sharpless asymmetric dihydroxylation (AD) using AD-mix-α in the presence of methanesulfonamide.[5] The dihydroxylation of **5** proceeded with a perfect matching double stereoselectivity to give exclusively the desired diol **6**.[6] Then, protection of the diol as a benzylidene acetal followed by reduction of the ester function by lithium aluminium hydride at 0°C furnished **7** in 99% yield. Hydroxy-directed regioselective reductive benzylidene cleavage in **8** with the $BH_3.Me_2S$-$BF_3.Et_2O$ system gave the benzyl ether **9** in 88% yield.[7] The stage was now set up for the introduction of the epoxyde functionality with concomitant inversion of the stereogenic center at C-3. To this event, the primary hydroxyl group of the diol **9** was selectively protected as a pivaloate group and the C-3 alcohol function transformed to a leaving group by treatment with methanesulfonyl chloride in the presence of an excess of triethylamine. Subsequent oxirane ring formation mediated by sodium methoxide, *via* the saponification of the pivaloate, afforded the α-epoxide **3** in 82% yield for the three-reaction sequence. The next task of the synthesis of **1**, the introduction of the C-3-C-5 fragment bearing a lactone unit was realized using the Ghosez's methodology.[8] Thus, addition of the lithium salt of methyl 3-phenylsulfonyl orthopropionate **2** to the epoxide **3**, in the presence of $BF_3.Et_2O$, followed by acid treatment which effected cleavage of the silyl protecting group and lactone formation. Exposure of the crude mixture to an excess of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) led to the bicyclic lactone **12** *via* $PhSO_2H$ elimination and concomitant intramolecular Michael addition of the benzylic hydroxyl function to the resulting α,β-unsatured-γ-lactone.

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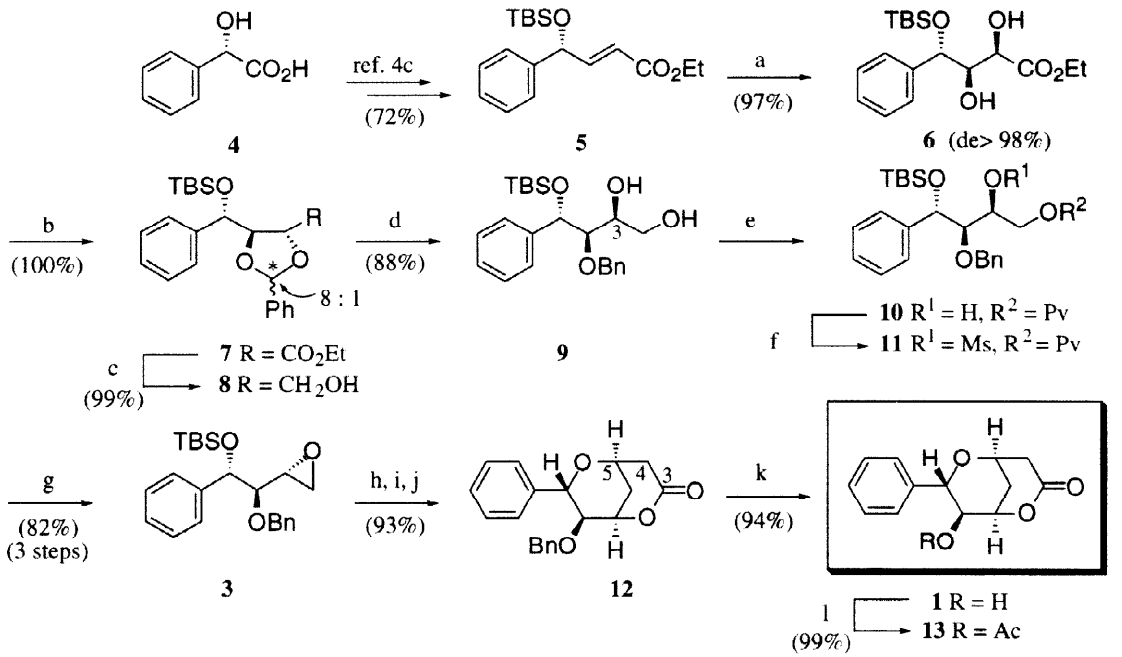
0040-4039/98/$ - see front matter
PII: S0040-4039(98)02269-2



Scheme 2: (a) AD-mix-α, $MeSO_2NH_2$, *t*-BuOH-H_2O (1:1), RT, 36h; (b) $PhCH(OMe)_2$, CSA, benzene, reflux, 1h; (c) $LiAlH_4$, Et_2O, 0°C, 5min; (d) $BH_3.Me_2S$, CH_2Cl_2, 60 min then $BF_3.Et_2O$, 0°C, 15 min; (e) *t*-BuCOCl, DMAP, CH_2Cl_2, RT, 15 min; (f) CH_3SO_2Cl, Et_3N, CH_2Cl_2, RT, 30 min; (g) MeONa, Et_2O-MeOH, RT, 5h; (h) $PhSO_2(CH_2)_2C(OMe)_3$ **2**, *n*BuLi, $BF_3.Et_2O$, THF, -78°C, 1h; (i) CF_3CO_2H-H_2O (9:1), RT, 3h; (j) DBU, CH_2Cl_2, 0°C, 1 h; (k) $TiCl_4$, CH_2Cl_2, RT, 30 min; (l) Ac_2O, DMAP, CH_2Cl_2, RT, 1h.

Finally, quantitative debenzylation with $TiCl_4$[9] afforded (-)-8-*epi*-9-deoxygoniopypyrone **1** (mp 130-131°C (AcOEt-hexane), $[\alpha]^{20}_D$ -90 (c 0.7, $CHCl_3$)). The spectra and the physical data of the corresponding acetate of synthetic **1** (compound **13**) are in accord with those of the natural material. [2,10] In conclusion, we have accomplished the first total synthesis of (-)-8-*epi*-9-deoxygoniopypyrone **1** in a highly stereocontrolled manner thereby establishing its relative and absolute configuration.

Acknowledgments : We wish to thank Professor J. Goré for useful discussions and the Ministère de l'Enseignement Supérieur et de la Recherche for a fellowship to JPS

References and notes

1. This name, numbered in accordance with IUPAC rules, should be preferred to (-)-*iso*-5-deoxygoniopypyrone.[2]
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