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Deracemization of 5-(4-hydroxyphenyl)-5-phenylhydantoin (HPPH): practical synthesis of (−)-(*S*)-HPPH

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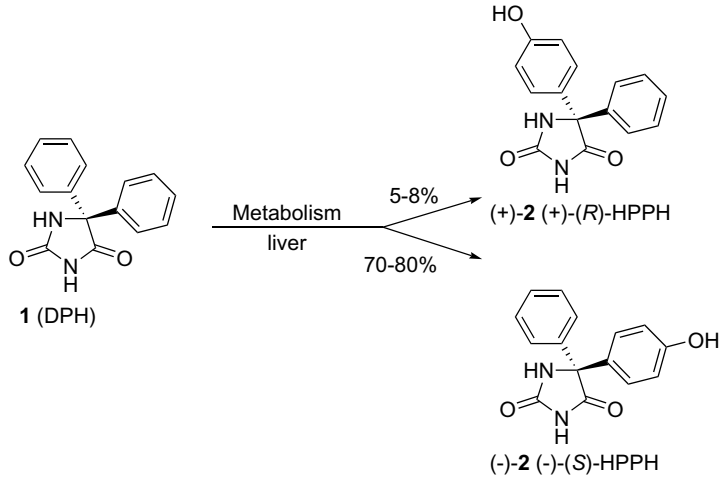
Abstract—In the presence of 10% NaOH in boiling MeOH enantiomerically enriched HPPH is racemized. This permits the deracemization of HPPH in the presence of brucine, giving enantiomerically pure (−)-(*S*)-HPPH [(−)-(*S*)-5-(4-hydroxyphenyl)-5-phenylhydandoin].

1. Introduction

Phenytoin **1** (5,5-diphenylhydantoin, PHT) is a well-known anticonvulsant employed for the treatment of epileptic seizures and was first introduced as an antiepileptic drug in 1938.[1] It still remains a drug of first choice for epilepsy, especially for grand mal, temporal lobe, and psychomotor seizures.[2] It has been demonstrated (Scheme 1) that phenytoin is extensively metabolized in the liver by microsomal enzymes and the major metabolites are (*S*)-5-(4-hydroxyphenyl)-5-phenylhydantoin (−)-**2** or (*S*)-HPPH (70–80%) and (*R*)-5-(4-hydroxyphenyl)-5-phenylhydantoin (+)-**2** or (*R*)-HPPH (5–8%).[3] It has been shown that (±)-HPPH (±)-**2** does not possess any anticonvulsant properties. However, there is currently a growing interest in studying the pharmacological properties of both (+)-(*R*)-HPPH and (−)-(*S*)-HPPH. Comparing the (+)-(*R*)-HPPH (+)-**2**



Scheme 1.

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levels in patients treated with PHT, it has been shown that in patients presenting gingival hyperplasia (GH) (+)-(*R*)-HPPH levels were much higher than in patients not presenting these symptoms.[4] In the light of this, it is believed that (+)-(*R*)-HPPH (+)-**2** could play a vital role in PHT induced wound healing.[5] In the case of the (*S*)-enantiomer (−)-**2**, there is a growing interest to understand its potential role in the treatment of neuropathic pain.

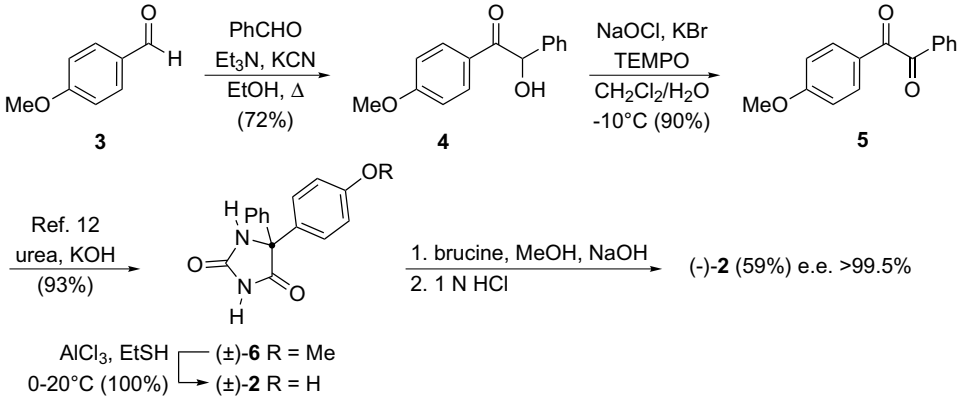
In 1975, Claesen et al.[6] resolved (±)-**2** in low yield (9%) by fractional crystallization of the diastereomeric brucine salts and established their absolute configuration by X-ray single-crystal diffraction of the (+)-10-camphorsulfonate of (+)-**2**. Several chromatographic methods have been reported for the resolution of (+)-**2** and (−)-**2**.[7] More recently super/subcritical fluid chromatography separations has been claimed to be amenable to preparative resolution of (±)-**2**.[8,9] We report herein an unprecedented deracemization of (±)-**2**, which allows one to prepare (−)-**2** in large amounts, readily.

2. Results and discussion

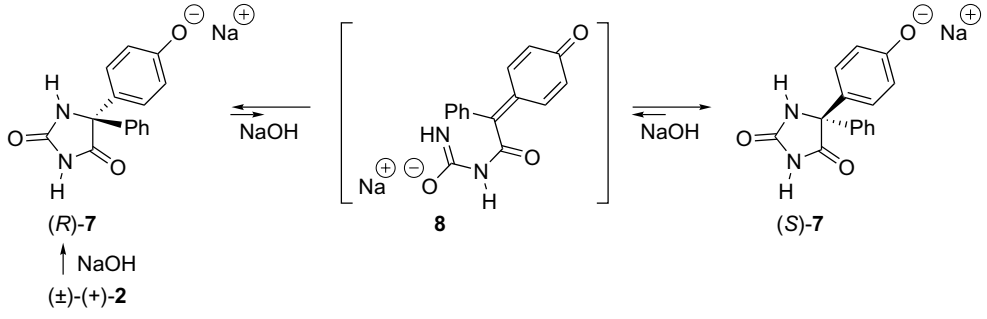
Racemic HPPH (±)-**2** can be obtained in one step (44% yield from 4-hydroxybenzophenone and NH_4CO_3, EtOH, KCN, 120 °C, 18 h) through a modified Bucherer–Lieb[10] synthesis, or according to the Biltz route[11] (Scheme 2), which is better suited for large-scale production because it does not require pressurized vessels and uses only catalytical amounts of KCN. We modified the last route by using a NaOCl/TEMPO oxidation of acyloin (±)-**4** and a two-phase system consisting of *n*-BuOH/KOH and PEG600 as phase transfer catalyst, as suggested by Poupaert et al.,[12] for the conversion of diketone **5** into the methyl ether (±)-**6**.

Deracemization of compounds containing one stereogenic center requires a reversible epimerization process that can be coupled with an irreversible enantioselective reaction (dynamic kinetic resolution).[13] Most common procedures use enantioselective protonation of enolates[14] or carbanions,[15] oxidation/reduction sequence for secondary alcohols and amines[16] or allylic rearrangements.[17] Deracemization of systems with quaternary carbon centers is less common.[18] As the latter systems cannot be deprotonated or oxidized to generate prochiral sp^2-C intermediates, heterolyses must be applied to equilibrate them with either a carbenium or a carbanion ion intermediate or with an alkenyl system through an elimination. We have found that the latter process can be applied for the deracemization of (±)-**2**. We observed that enantiomerically enriched (+)-**2** or (−)-**2** were racemized under basic conditions (0.5 N NaOH) at room temperature most probably following the mechanism shown in Scheme 3.

In the presence of an excess of NaOH, (+)-**2** generates phenolate (*R*)-**7** that undergoes C–N heterolysis (E_{1cb}-like elimination) giving intermediate **8**, which equilibrates by intramolecular nucleophilic addition with



Scheme 2.



Scheme 3. Racemization of HPPH.

(*R*)-**7** and (*S*)-**7**. In the presence of a catalytic amount (10%) of NaOH in MeOH, racemization of (+)-**2** is slow at room temperature, but fast in boiling MeOH. This has allowed one to find a procedure in which the brucine-(−)-**2** complex precipitates from a boiling MeOH solution of (±)-**2**. After decomplexation with 1 N HCl (solid/H_2O–HCl extraction), pure (−)-**2** was obtained in 59% yield and ee >99.5% (by chiral HPLC[7j]).

3. Conclusion

A very simple procedure has been found to deracemize (±)-5-(4-hydroxyphenyl)-5-phenylhydantoin (±)-**2** into (−)-(*S*)-**2** with good yield and high enantiomeric purity. Using other homochiral bases than brucine (+)-(*R*)-**2** might be obtained in a similar way. The deracemization of (±)-**2** relies probably on a C–N heterolytical process that is analgous to a E_{1cb}-elimination, with generation of a *para*-quinomethane intermediate.

4. Experimental

General, see Ref. 19.

4.1. (±)-5-(4-Hydroxyphenyl)-5-phenylhydantoin (+)-2

Method A: To a solution of (±)-**6**[20] (15.0 g, 53 mmol) in EtSH (105 mL) was added at 0 °C $AlCl_3$ (21.2 g, 159 mmol). The reaction was stirred at room temperature for 2 h. Ice water was added and the precipitated compound was isolated by filtration (14.2 g, 100%). Mp 306 °C decomp. (lit.[20] 220–221 °C). ^{1}H NMR (400 MHz, DMSO-d_6) δ 6.77 (d, 2H, ^3J = 8.9 Hz, Ar*H*), 7.13 (d, 2H, ^3J = 8.9 Hz, Ar*H*), 7.34–7.40 (m, 5H, Ph), 9.19 (s, 1H, NH), 9.61 (br s, 1H, PhO*H*), 11.02 (br s, 1H, NH). ^{13}C NMR (100 MHz, DMSO-d_6) 75.1, 120.3, 131.8, 133.1, 133.6, 135.5, 145.4, 161.2, 162.3, 180.5.

Method B: A high pressure reactor was charged with 4-hydroxybenzophenone (8.00 g, 40 mmol), KCN (3.2 g, 49 mmol), ammonium carbonate (11.6 g, 121 mmol), EtOH (30 mL), and H_2O (30 mL). The reactor was sealed and heated to 120 °C for 18 h. H_2O (150 mL) was added and the mixture was boiled without reflux for 20 min, cooled, and filtered. The solids were recrystallized from EtOH yielding white crystals (4.8 g, 44%) with identical physical and spectroscopical properties as above.

4.2. (−)-(*S*)-5-(4-Hydroxyphenyl)-5-phenylhydantoin (−)-2

Brucine (4.41 g, 11.2 mmol) (±)-**2** (3.00 g, 11.2 mmol) and NaOH (45 mg, 1.2 mmol) were dissolved in the minimum amount of boiling MeOH. The resulting hydantoin–brucine complex crystallized slowly. It was decomplexed by solid liquid extraction with 1 N HCl giving (−)-**2** (1.77 g, 59%). $[\alpha]_{546}^{25} = -22.4$ (*c* 0.50, MeOH). The ee was determined according to Yao and Zeng[7j] to be >99.5% in favor of the (*S*)-enantiomer.

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