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Tetrahedron Letters
Tetrahedron Letters 46 (2005) 57–59

Total synthesis of dipiperamide A and revision of stereochemical assignment

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Received 8 October 2004; revised 25 October 2004; accepted 5 November 2004

Abstract—The first total synthesis of dipiperamide A has been achieved by employing a solid-state photodimerization of an (*E*)-cinnamic acid derivative. This critical step results in the cyclobutane ring, which exists in the natural product, with full control of the regio- and stereochemistry at the four stereogenic centers. Results from these studies indicate that the proposed stereostructure of natural dipiperamide A should be revised to the structure originally assigned to dipiperamide B.

Dipiperamides A and B,[1] isolated from the white pepper (*Piper nigrum* L.), are members of a new class of bisalkaloids[2] consisting of a characteristic cyclobutane ring, which were assigned structures **1** and **2**, respectively, on the basis of extensive NMR spectroscopic analyses.[1] These compounds, recognized as a dimer of piperine (**3**), are of interest both because of their unique structures and the fact that they show potent inhibitory activity against a drug metabolizing enzyme cytochrome P450 (CYP) 3A4.[1] The administration of a potent CYP inhibitor could lead to cost-saving for patients on medication with expensive drugs, and from the study of CYP inhibitors development of alternative treatment with reduced drug dosage is expected.[2c] To our knowledge, no report of synthesis of this class of alkaloids has appeared in the literature. Herein, we report the first total synthesis of dipiperamide A (compound **2**), including a stereochemical revision of the proposed structure **1** of natural dipiperamide A to structure **2** which had been incorrectly assigned to dipiperamide B in the original report (Fig. 1).

The reaction of (*E*)-cinnamic acids in the crystalline state are well-known examples of [2+2] photodimerization and the classic studies by Schmidt and co-workers have demonstrated that such reactions are strictly controlled by the packing arrangement of molecules in the crystals.[3–5] These acids are observed to crystallize in three polymorphic forms, namely α, β, and γ, and, on photolysis, the well-stacked molecules in the α- and β-type crystals react to give head-to-tail and head-to-head dimeric products, α-truxillic and β-truxinic acids (Ar = Ph for each acid in Fig. 2), respectively, but in the γ-type crystals the molecules do not overlap for dimerization to occur.[6] Based on these topochemical criteria, solid-state photodimerization of the crystalline α-form of an (*E*)-cinnamic acid derivative was considered for the synthesis of compound **2**, which is the structure assigned for dipiperamide B in the original report,[1] since the substitution pattern on the 1,2,3,4-tetrasubstituted cyclobutane ring and the stereochemistry of **2** correspond to those of the α-truxillic type dimer.

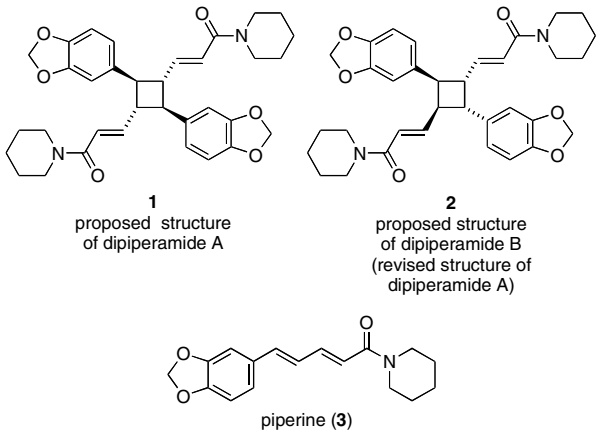

Figure 1. Proposed structures of dipiperamides A and B.

Keywords: Dipiperamide A; CYP inhibitor; Cyclobutane ring; Solid-state photodimerization.
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0040-4039/$ - see front matter © 2004 Published by Elsevier Ltd.
doi:10.1016/j.tetlet.2004.11.042

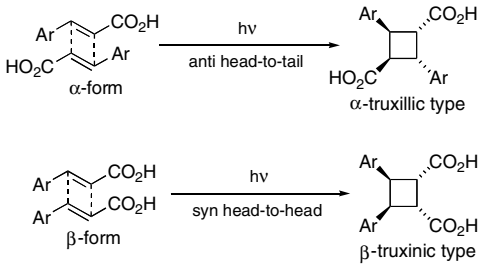
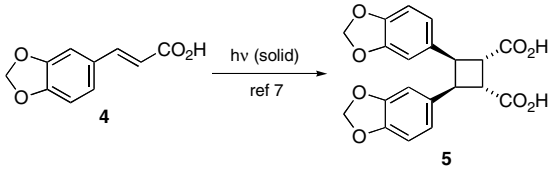


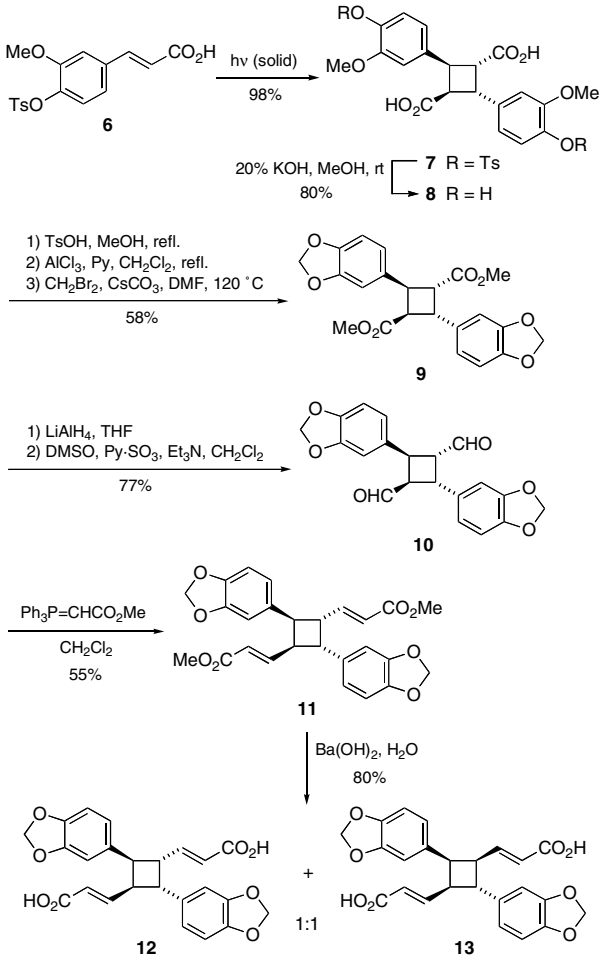
Figure 2. Topochemical [2+2] photocyclization of (*E*)-cinnamic acids in the solid-state.

As described above, the structures of photodimers can be predicted by the crystalline structures of cinnamic acids; however, it is difficult to form the desired type of crystalline structure, for the factors that control crystal packing are not yet well understood. In a series of 3,4-methylenedioxycinnamic acid derivatives, it has been observed experimentally that the molecules are arranged in a β-type packing to produce β-truxinic acids, for example, 3,4-methylenedioxycinnamic acid (**4**) → 3,3,4′,4′-bismethylenedioxy-β-truxinic acid (**5**) (Scheme 1),[7] which, however, is not responsible for the structure of **2**. We therefore focused our attention on the preparation and use of other crystalline derivatives of the 3,4-dioxygenated cinnamic acid with the α-type structure for the development of efficient synthesis of the α-truxillic acid. Thus, a number of the *O*-substituted derivatives of (*E*)-ferulic acid (4-hydroxy-3-methoxycinnamic acid) were synthesized and their crystal chemistry was explored. When the powdered crystals of these ferulic acid derivatives were suspended in hexane and subjected to UV irradiation through Pyrex, the best result, both in terms of crystalline formation in the head-to-tail α-modification and the yield of the photodimerization, was obtained with *O*-tosylferulic acid (**6**), leading stereospecifically to the α-truxillic acid **7** as a single isomer in 98% yield (Scheme 2). Confirmation of the α-truxillic stereochemistry of **7** was provided by a single crystal X-ray structure of the α-truxillaldehyde **10** derived from **7** (vide infra).

After removal of the tosyl group from **7** followed by esterification of the resultant bisphenol **8**, cleavage of the methoxy group with $AlCl_3$ and pyridine[8] gave the biscatechol, which was methylenated with CH_2Br_2 and $CsCO_3$ to yield the bismethylenedioxy ester **9** (Scheme 2). Reduction of **9** with $LiAlH_4$ and subsequent oxidation (DMSO, sulfur trioxide pyridine complex, Et_3N) of the bisalcohol afforded 3,3,4′,4′-bismethylenedioxy-α-truxillaldehyde (**10**), whose α-truxillic structure was unambiguously determined by X-ray analysis as



Scheme 1.



Scheme 2.

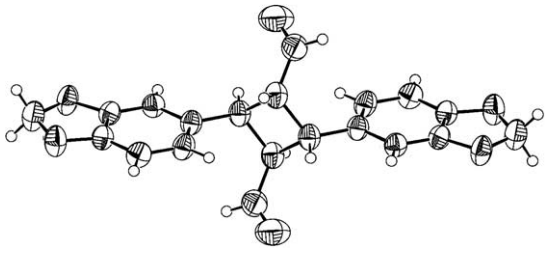
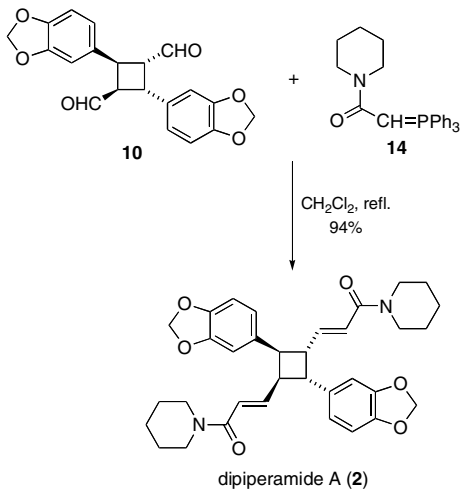


Figure 3. X-ray crystal structure of bisaldehyde **10**.

depicted in Figure 3. Wittig olefination of **10** with the triphenylphosphoranylidenacetate provided the unsaturated ester **11**. Since attempts to convert **11** into compound **2** by amidation with piperidine were unsuccessful, in anticipation of the DCC method for amide formation, ester hydrolysis of **11** was carried out with $Ba(OH)_2$ in water. However, in this hydrolysis epimerization was found to occur, resulting in an inseparable mixture of biscarboxylic acids **12** and **13** (ca. 1:1).

Conversion of **10** to compound **2** was successfully achieved in 94% yield without epimerization via Wittig olefination using 1-[(triphenylphosphoranylidene)acetyl]-piperidide (**14**), prepared[9] from chloroacetyl chloride,



Scheme 3.

piperidine, and PPh_3 (Scheme 3). Our synthetic sample of **2** showed mp 175–176 °C[10] and spectral data (^1H and ^{13}C NMR, and IR) that were clearly different from those reported[1] for natural dipiperamide B, but fully consistent with those reported[1] for natural dipiperamide A.

In conclusion, the first total synthesis of dipiperamide A (**2**) has been achieved by employing a solid-state photodimerization of the (*E*)-cinnamic acid derivative **6**. This critical step results in the formation of the cyclobutane ring with full control of the regio- and stereochemistry at the four stereogenic centers. Results from these studies indicate that the stereostructure **1** proposed for natural dipiperamide A should be revised to structure **2** originally assigned to dipiperamide B and, thus, the original stereostructure of dipiperamide B will also need to be revised.

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