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# Asymmetric Pictet-Spengler Reactions:Synthesis of Tetrahydroisoquinoline Derivatives from L-DOPA

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**Abstract:** The *cis*-1-substituted-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid esters **3** can be obtained in a highly diastereoselective fashion through 1,3-induction Pictet- Spengler (P-S) cyclization of the L-DOPA (3,4-dihydroxyphenylalanine) methyl ester with aromatic or aliphatic aldehydes under acidic conditions. Their epimers **4** are also obtained as minor products.

**Keywords:** Asymmetric synthesis, Pictet-Spengler reaction, tetrahydroisoquinoline, 1,3-induction, L-DOPA.

1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acids constitute a class of compounds attracted increasing interest, due to their various biological activities including anti-arrhythmic activity, angiotensin-converting enzyme inhibition, antihypertensive activity, and antidepression[1]. Moreover, they are substructures of many naturally occurring alkaloids, such as *Ecteinascidins*, *Protokerberines*, *Berbines*, *Papaverolines*, *Yohimbines etc*[2]. Therefore, much effort has been devoted to the asymmetric synthesis of this kind of compounds.

Of particular interest to us was *cis*-1-substituted-6,7-dihydroxy-1,2,3,4-tetrahydro-isoquinoline-3-carboxylic acid esters, which was an essential building block for our synthesis of the analogs of anticancer marine alkaloid *Ecteinascidin*[3,4]. Using L-DOPA methyl ester **1** as starting material, we employed the classical P-S reaction to prepare the desired compounds *via* 1,3-asymmetric induction[5] (**Scheme 1**). Various solvent systems (benzene, dioxane, toluene, water, methanol-water, dichloromethane), different acids ($H_2SO_4$, TFA, ytterbium triflate) and temperatures have been reported to realize the P-S cyclization. However these conditions do not work well with L-DOPA. By simply stirring aldehyde **2c** and L-DOPA methyl ester with anhydrous NaOAc in HOAc at room temperature for 20 hours, we obtained the desired compound **3c** predominantly[6]. The epimer **4c** was also obtained.

Easy cyclization is of great significance in the chemistry of isoquinolines. This prompts us to investigate the applicability of this method in the synthesis of tetrahydroisoquinoline derivatives from L-DOPA with different aromatic and aliphatic aldehydes. As expected, the major products **3a-n** with *cis* configuration were obtained in

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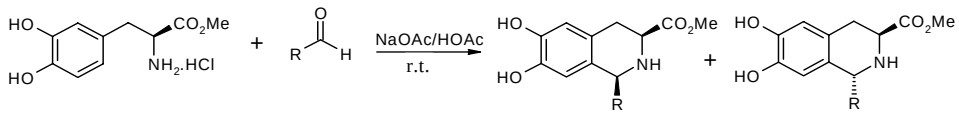
good to excellent yields. In the meantime, some of the epimers were isolated and confirmed to be the *trans*-1-substituted-6,7-dihydroxy-1,2,3,4-tetrahydro-isoquinoline-3-caboxylic acid esters **4a-n** (**Table1**).

**Scheme 1**




**1** **2** **3** (major) **4** (minor)

**Table 1** The preparation of 1-substituted-tetrahydroisoquinoline-3-carboxylic acid esters.

| Entry | R | Reaction Time (h) | Total Yield (%)[b] | Ratio of **3** and **3/4**[C] |
|---|---|---|---|---|
| a | $C_2H_5$- | 16 | 90 | 10:1[a] |
| b | *n*-$C_3H_7$- | 17 | 81 | 4:1[a] |
| c | 3,4,5-$(OCH_3)_3$-$C_6H_2$- | 20 | 95 | 20:1 |
| d | 2-$(OCH_3)$-4,5-$(O\text{-}CH_2O)$-$C_6H_2$- | 43 | 73 | >5:1[d] |
| e | 3-$(OCH_3)$-4-(OH)-$C_6H_3$- | 25 | 75 | >10:1[d] |
| f | 2,3,4-$(OCH_3)_3$-$C_6H_2$- | 15 | 95 | 10:1[d] |
| g | 4-Cl-$C_6H_4$- | 5 | 90 | 13:1 |
| h | 3-Br-$C_6H_4$- | 10 | 65 | 5:1 |
| i | 4-$(NO_2)$-$C_6H_4$- | 6 | 89 | 11:1 |
| j | 4-$(N(CH_3)_2)$-$C_6H_4$- | 20 | 89 | 13:1 |
| k | 4-$(OCH_3)$-$C_6H_4$- | 15 | 77 | >10:1[d] |
| l | 3-(OH)-4-$(OCH_3)$-$C_6H_3$- | 14 | 93 | 1:1[d] |
| m | 3,4-$(OCH_2O)$-$C_6H_3$- | 13 | 95 | 15:1 |
| n | $C_6H_5$- | 5 | 96 | 6:1 |

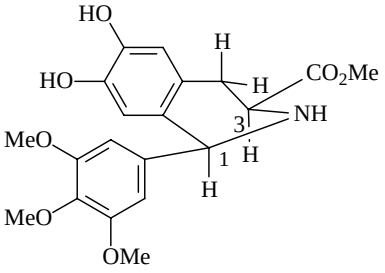
[a]They are hydrochloride. [b]The yields after column chromatography. [c]The diastereoisomer ratios refer to isolated ratios. [d]The minor products were not isolated, the diastereoisomer ratio were estimated by TLC.

$^1$H-NMR spectroscopic data unequivocally confirmed the structures of the tetrahydroisoquinolines **3** and **4**, whose stereochemistry were deduced by measurements of the difference nuclear overhauser effect (NOE)[7]. The difference in the distance of the H-1 and H-3 protons, which is the most distinctive feature, differentiating the proposed configurations, is supported by the significant positive or no NOE between these protons of the tetrahydroisoquinolines **3** and **4,** respectively. Thus, the existence of the NOE between H-3 and H-1 in **3c** verifies a *cis*-1,3-diaxial relationship between these protons. In contrast, in **4c**, H-1 is unaffected when H-3 is irradiated, and *vice versa*. These results are in good agreement with the following suggested preferential conformation of compounds **3c** and **4c** (**Figure 1**).

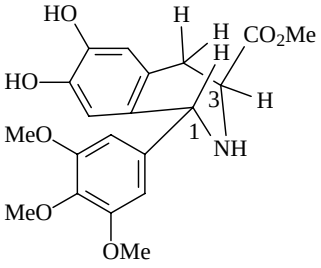
This method gave high yields of tetrahydroisoquinolines independing the substrates. Thus aromatic aldehydes with electron donating or as electron withdrawing substituents are all converted to the tetrahydroisoquinolines smoothly and efficiently. And the aliphatic aldehydes propylaldehyde **2a** and *n*-butylaldehyde **2b** are also converted to the corresponding tetrahydroisoquinolines. A mild and highly efficient methodology has

been developed for the construction of 1-substituted-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid esters. This method can be in to synthesis of variety new tetrahydro- isoquinolines from L-DOPA.

**Figure 1**




**3c**




**4c**

## General Procedure

A mixture of L-DOPA methyl ester **1** (1 mmol), anhydrous NaOAc (2 mmol) and HOAc (4 mL) were stirred under Ar protection. To this mixture was added dropwise a solution of aldehyde **2** (1.1 mmol) in HOAc (4 mL) over 5 min and the mixture was stirred at room temperature for 5 to 20 hours. Solvents were removed *in vacuo* and the residue dissolved in EtOAc. The precipitate was filtrated and the filtrate was evaporated. Column chromatography with dichloromethane-acetone gave the desired *cis*-1-substituted-6,7-dihydroxy-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid esters **3** and their epimers **4**.

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