

论文

(-)-14-去甲基石杉碱甲的不对称全合成及其乙酰胆碱酯酶抑制活性老年痴呆症药物石杉碱甲类似物研究VI.(-)-14-去甲基石杉碱甲的不对称全合成及其乙酰胆碱酯酶抑制活性

何煦昌;于更立;白东鲁;

中国科学院 上海生命科学院,上海药物研究所,上海 200031

摘要:

目的(-)-14-去甲基石杉碱甲的合成及其抑制乙酰胆碱酯酶活性研究。方法从β-酮酯3与2-亚甲基-1,3-丙二醇双醋酸酯4在手性膦配体钯催化下,对映选择性的形成双环化合物5,双键移位后得到关键中间体6,进而复结晶富集后,得到光学纯6。经Wittig反应,得双键化合物7,酯基水解后,得到相应酸8。经改良的Curtius重排,产生氨基甲酸酯9。除去保护后,得目标化合物2。结果(-)-14-去甲基石杉碱甲仅是天然(-)-石杉碱甲抑制乙酰胆碱酯酶活性1/8。结论由电鳐乙酰胆碱酯酶与(-)-石杉碱甲复合物X-射线衍射结构分析揭示,14-甲基与酶形成氢键是(-)-石杉碱甲高抑制活性的一个必要基团。

关键词: (-)-石杉碱甲 不对称合成 乙酰胆碱酯酶抑制剂 手性二茂铁膦配体

Studies on analogues of huperzine A for treatment of senile dementia VI. Asymmetric total synthesis of 14-nor-huperzine A and its inhibitory activity of acetylcholinesterase

HE Xu-chang; YU Geng-li; BAI Dong-lu

Abstract:

AimTo study asymmetric total synthesis of 14-nor-huperzine A 2 and its inhibitory activity on acetylcholinesterase. MethodsHighly enantioselective synthesis of compound 5 from β-keto-ester 3 and 2-methylene-1,3-propanediol diacetate 4 by palladium-catalyzed bicycloannulation was carried out using new chiral ferrocenylphosphine ligands, such as 10, 11, followed by regioselective double-bond migration to produce compound 6. Optically pure 6 was obtained after enantio-enrichment recrystallization. Then, according to similar procedures of huperzine A synthesis, the target compound 14-nor-huperzine A 2 was prepared. The inhibitory activity was tested with rat erythrocyte membrane acetylcholinesterase. ResultsThe inhibitory activity of synthetic (-)-14-nor-huperzine A was 8 fold less potent than that of (-)-huperzine A. Conclusion A hydrogen-bond between 14-methyl group of (-) huperzine A and the main-chain oxygen of His 440 is necessary for the highly acetylcholinesterase inhibitory activity of huperzine A.

Keywords: asymmetric synthesis acetylcholinesterase inhibitor chiral ferrocenylphosphine ligands huperzine A

收稿日期 2002-06-10 修回日期 网络版发布日期

DOI:

基金项目:

通讯作者: 白东鲁

作者简介:

参考文献:

本刊中的类似文章

文章评论 (请注意:本站实行文责自负, 请不要发表与学术无关的内容!评论内容不代表本站观点.)

扩展功能

本文信息

- ▶ Supporting info
- ▶ PDF(145KB)
- ▶ [HTML全文]
- ▶ 参考文献

服务与反馈

- ▶ 把本文推荐给朋友
- ▶ 加入我的书架
- ▶ 加入引用管理器
- ▶ 引用本文
- ▶ Email Alert
- ▶ 文章反馈
- ▶ 浏览反馈信息

本文关键词相关文章

- ▶ (-)-石杉碱甲
- ▶ 不对称合成
- ▶ 乙酰胆碱酯酶抑制剂
- ▶ 手性二茂铁膦配体

本文作者相关文章

- ▶ 何煦昌
- ▶ 于更立
- ▶ 白东鲁

PubMed

- ▶ Article by
- ▶ Article by
- ▶ Article by

反馈人	<input type="text"/>	邮箱地址	<input type="text"/>
反馈标题	<input type="text"/>	验证码	<input type="text"/> 5998