Synthesis of Optically Active Methyl 7β-Hydroxykaurenoate with Potent Neuroprotective Activity

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Received June 11, 2004; accepted July 8, 2004

It has been suggested by a number of previous studies 1—4) that excess activation of glutamate receptors causes severe and irreversible damage to the mammalian central nervous system (CNS). Akaike and coworkers have recently reported the isolation of atisane diterpenes, serofendic acids A (1) and B (2) (Fig. 1), from fetal calf serum and described their potent protective activity in cortical neurons against both nitric oxide donor and glutamate cytotoxicity. 2,5) These observations prompted us to examine the possible neuroprotective activity of our synthetic compounds that have a variety of bridged skeletons. Here we report that kaurene derivatives act as potent neuroprotective agents.

Among the many compounds that we tested, racemates of 7β-hydroxykaurenoate (3) 6) and its 4-demethyl acetate (4) were both synthesized via methods that contained radical cyclization and intramolecular Diels–Alder reactions as key steps. Both compounds displayed potent neuroprotective activity against N-methyl-D-aspartate toxicity in cultured cortical neurons.

Key words kaurene diterpenoid; neuroprotective activity; chiral synthesis; radical cyclization

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overall yield of 62% (Chart 3). Following the exchange of the protecting group for a hydroxyl group via (−)-4, the resulting silyl ether 22 was methylated to generate 23 in an overall yield of 89% with high diastereoselectivity. Removal of the silyl group of 23 synthesized the compound (−)-3 in 93% yield.

Evaluation of the synthetic products 3 and 4 for possible neuroprotective activity was then carried out by examining the effects of these kaurene derivatives on NMDA toxicity in cultured cortical neurons. The neuronal cells were exposed to NMDA for 24 h, followed by the addition of the kaurene derivatives to the culture medium 24 h prior to the addition of NMDA. Racemates of both 3 and 4 at a concentration of 10 μM were found to inhibit NMDA toxicity in a dose-dependent manner to 56% and 51% of control levels, respectively, whereas the (−)-3 and (−)-4 derivatives inhibited this toxicity completely at the same dosages (Fig. 3). It is noteworthy that the optically active compound showed about twice the activity of the corresponding racemate.

An NMDA glutamate receptor subtype is thought to play a predominant role in triggering glutamate neurotoxicity, but kaurene derivatives did not block [3H]-NMDA binding using rat brain synaptosomes (data not shown). It has been reported that serofendic acid does not block glutamate receptor-mediated currents in cortical neurons, despite its pronounced activity in preventing glutamate neurotoxicity. Based upon these findings, it was speculated that the neuroprotective effects of these compounds do not involve the inhibition of glutamate receptor channel activities. The neuroprotective mechanisms of kaurene derivatives are still unknown. However, from our results showing that compounds (−)-3 and (−)-4 displayed more potent neuroprotective effects than the corresponding racemate products, we postulate that a receptor other than the NMDA receptor might be involved in the neuroprotective effects of these molecules.

Acknowledgments We thank Professor A. Akaike, Kyoto University, for his generous and helpful discussions.

References