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Synthesis and absolute configuration of serofendic acids

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Abstract—The first synthesis of serofendic acids A and B, novel neuroprotective substances isolated from fetal calf serum, is described. This efficient process, starting from (−)-isosteviol, not only provided substantial amounts of serofendic acids, but also established their absolute configuration.

Recently, we reported the discovery of novel neuroprotective substances, serofendic acids A (**1**) and B (**2**), in lipophilic extracts of fetal calf serum (FCS).[1] Serofendic acids exhibited potent protective action against neurotoxicity induced by glutamate and an NO donor. They were determined by modern NMR techniques to be members of a unique class of atisane-type diterpenoids having a methylsulfoxide moiety (Fig. 1). NOESY experiments revealed that these two compounds are epimers having opposite configuration at the sulfoxide group. However, their absolute configuration and the sterochemistry at sulfoxide group are still unknown. These compounds are of considerable chemical and pharmacological interest, so we designed a total synthesis to afford sufficient amounts of **1** and **2** for detailed characterization.

Our synthetic route is depicted in Scheme 1. Earlier reports have described the synthesis of atisane-type diterpenoids. Ihara and co-workers constructed the atisane skeleton by intramolecular Michael reaction and radical cyclization processes.[2] On the other hand, Coates and Bertram derived the skeleton from naturally available isosteviol (**3**).[3] We adopted intermediate **4** of Coates's synthetic route as our starting material because it possesses most of the stereogenic centers of serofendic acids. We planned to introduce the remaining stereogenic center with the assistance of the 16-position functional group.

Dehydration of **4** using thionyl chloride gave mainly a mixture of *exo*-olefin **5** and *endo*-olefin **6** in 1.3:1 ratio. The following oxidation provided a mixture of **7**, **8**, **9** and **6**. This result indicates that since **6** is less prone to oxidation, a chemoselective dehydration procedure is necessary. We found that when Martin's dehydrating agent[4] was used, preparation of the reagent and the dehydration reaction proceeded in one pot, and the olefins were obtained with high selectivity (5:6 = 13:1) and in high yield (96%). Treatment of **5** with selenium

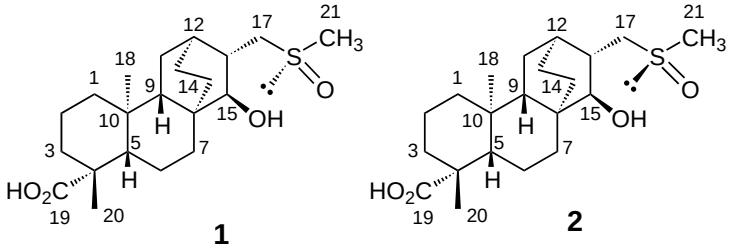

Figure 1. Structures of serofendic acids A (**1**) and B (**2**).

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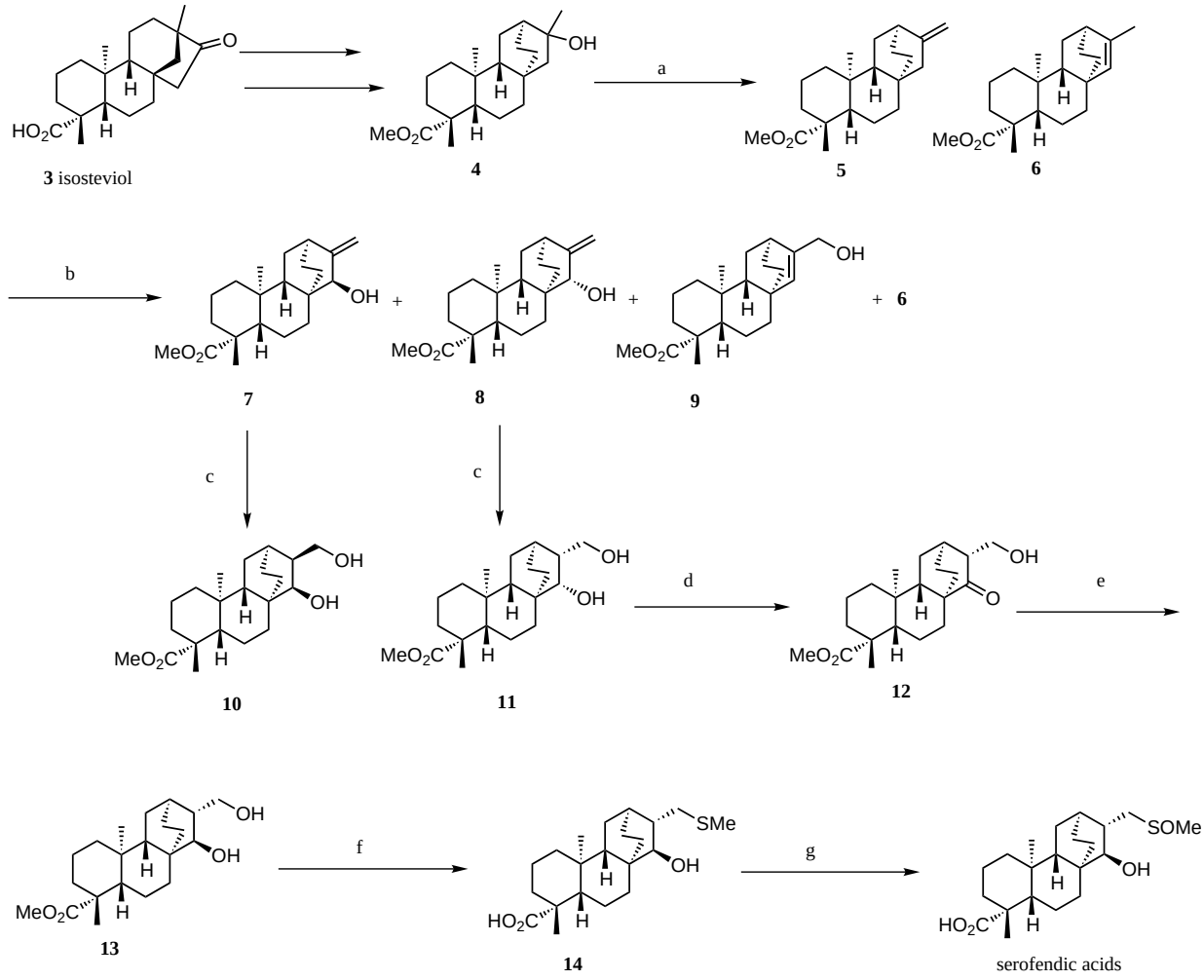

Scheme 1. (a) Ph-C$(CF_3)_2$-OK, $(Ph)_2S$, Br_2, $CHCl_3$, rt, 3 h then **4**, rt, 3 h, 96%, **5**:**6** = 13:1; (b) SeO_2, TBHP, CH_2Cl_2, rt, 5 h, 26% **7**, 28% **8**, 3% **9**; (c) BH_3–THF, THF, rt, 3 h then H_2O_2 aq., NaOH aq., rt, 2 h, 67% **10** from **7**, 84% **11** from **8**; (d) $NaBrO_3$, $NaHSO_3$, CH_3CN, H_2O, rt, 2 h; (e) $NaB(OAc)_3H$, AcOH, CH_3CN, 0°C, 5 h, 67% from **11**; (f) (i) TsCl, DMAP, pyridine, rt, 24 h, (ii) NaSMe, HMPA, 80°C, 48 h, 68%; (g) Davis's oxaziridine (2-benzenesulfonyl-3-phenyloxaziridine), CH_2Cl_2, 0°C, 30 min, 100%.

dioxide afforded **7** and **8** with **9** as a minor by-product. These alcohols were isolated and the stereochemistry of **7** and **8** was confirmed by means of NOESY experiments. Hydroboration of **7** and **8** gave the *syn*-diastereomer **10** and *syn*-diastereomer **11**, respectively. Thus, the borane reagent selectively approached from the opposite side to the secondary alcohol. Since the isomers did not exhibit natural configuration, the secondary alcohol of **11** was inverted by means of an oxidation and reduction process. The secondary alcohol of diol **11** was selectively oxidized by using $NaBrO_3$–$NaHSO_3$[5] to give the ketoalcohol **12**, which was then reduced with $NaB(OAc)_3H$ to yield the diol **13** in 67% overall yield. Selective tosylation of the resulting diol **13** followed by thiomethylation and simultaneous hydrolysis of the methyl ester with NaSMe gave the sulfide **14** in 68% overall yield.

Finally, oxidation of the sulfide group in **14** by using Davis's oxaziridine[6] quantitatively yielded serofendic acids A (**1**) and B (**2**) as a 1:2 mixture. After separation of the diastereomers by HPLC, the physico-chemical properties (^1H and ^{13}C NMR, HPLC t_R)[7] and biological activity of the synthetic isomers were found to be consistent with those of the natural isomers.

Since the amounts of natural serofendic acids available were insufficient for direct comparison of optical rotation data, the absolute stereochemistry was determined by chiral derivatization and HPLC–MS analysis.[8] The secondary alcohol of the synthetic **1** was derivatized with (*R*)- or (*S*)-α-methylbenzyl isocyanate to give the (*R*)-diastereomer (**1a**) and (*S*)-diastereomer (**1b**), respectively (Fig. 2a). These diastereomeric carbamates were separated by reversed-phase HPLC interfaced to a mass spectrometer operated under electrospray ionization (ESI) conditions. Detection of the protonated molecular ion (m/z 530) in the selected ion monitoring (SIM) mode allowed us to analyze samples of only a few micrograms without prior purification. As shown in Fig. 2b, the mass chromatographic peaks of **1a** and **1b** could be baseline-separated, and the retention time of

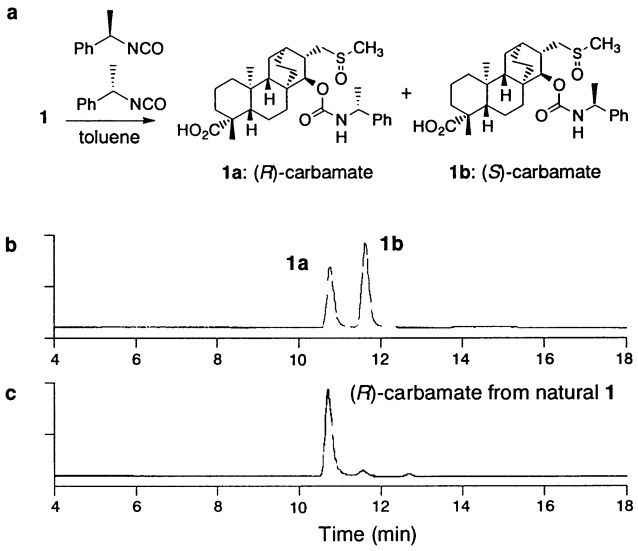

Figure 2. (a) Derivatization of serofendic acid A (**1**) with (*R*)- or (*S*)-α-methylbenzyl isocyanate. (b) Ion trace *m*/*z* 530 of (*RS*)-carbamate derivatives (**1a**, **1b**) prepared from synthetic **1**. (c) Ion trace *m*/*z* 530 of (*R*)-carbamate derivative prepared from natural **1**.

the (*R*)-carbamate prepared from the natural serofendic acid (**1**) was identical with that of synthetic reference compound **1a** (Fig. 2b). In the same manner, the (*S*)-carbamate derivatized from the natural **1** was found to correspond to **1b** (data not shown). Thus, serofendic acid A (**1**) proved to have identical absolute configuration with the synthetic **1** prepared from (–)-isosteviol. The absolute configuration of serofendic acid B (**2**) was also characterized in the similar manner.

The remaining problem was the stereochemical assignment of the sulfoxide group in serofendic acids. As is often the case with naturally occurring sulfoxides,[9] serofendic acids were found as an epimeric mixture due to the sulfoxide configuration. However, we considered that determination of the sulfoxide configuration would be significant for further investigations, especially for the structure–activity relationship studies. In order to determine the configuration at the sulfoxide group, we adopted the method developed by Kusumi and coworkers.[10] After protection of the secondary hydroxyl group and the carboxylic acid, synthetic **1** and **2** were converted to corresponding (*R*)-(methoxyphenylacetyl)sulfoximines **1c** and **2c**, and (*S*)-(methoxyphenylacetyl)sulfoximines **1d** and **2d**, respectively. The ^{1}H NMR chemical shift differences ($\Delta\delta = \delta_S - \delta_R$) for these sulfoximines are shown in Fig. 3. As expected, the apparent $\Delta\delta$ values were arranged with opposite signs on both sides of the *N*-(methoxyphenylacetyl)-sulfoximine group and the configurations were determined to be $(R)_S$ for **1** and $(S)_S$ for **2**, as shown in Fig. 1.

In conclusion, we have accomplished the first synthesis of serofendic acids, which are novel neuroprotective substances isolated from fetal calf serum, and their absolute configuration, including the sulfoxide stereochemistry, was determined. Detailed biological studies are under way.

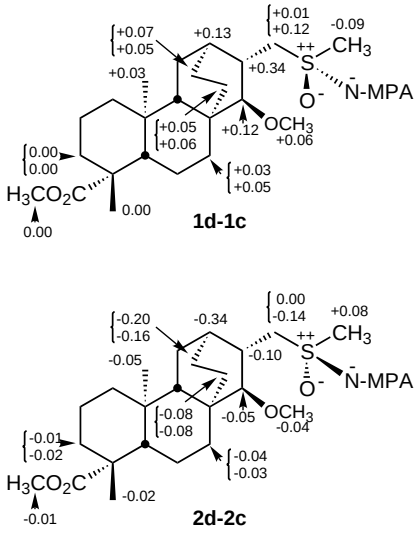

Figure 3. The $\Delta\delta$ values obtained for *N*-MPA-sulfoximines prepared from **1** and **2**. The ^{1}H NMR spectra were recorded at 600 MHz in $CDCl_3$.

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7. Serofendic acid A (**1**): HRFAB(+)MS: $(M+H)^+$ m/z 383.2246 ($C_{21}H_{35}O_4S$, Δ −1.0 mmu); $[\alpha]_D$ −122.9 (*c* 1.280, MeOH); mp 214–216°C; ^{1}H NMR (500 MHz, CD_3OD): 2.99 (1H, dd, $J=13.2$, 9.3 Hz, H17a), 2.97 (1H, d, $J=3.9$ Hz, H15), 2.87 (1H, dd, $J=13.2$, 6.3 Hz, H17b), 2.72 (3H, s, H21), 2.17 (1H, brd, $J=14.2$ Hz, H3α), 2.06 (1H, m, H14α), 1.95 (1H, m, H16), 1.92 (1H, m, H2β), 1.91 (1H, m, H6α), 1.83 (1H, m, H6β), 1.74 (1H, ddd, $J=13.2$, 13.2, 4.4 Hz, H7β), 1.70 (1H, m, H12), 1.69 (1H, m, H13α), 1.65 (1H, m, H1α), 1.62 (1H, m, H11β), 1.61 (1H, m, H9), 1.44 (1H, m, H11α), 1.42 (1H, m, H2α), 1.42 (1H, m, H13β), 1.24 (3H, s, H18), 1.11 (1H, ddd, $J=13.2$, 2.9, 2.9 Hz, H7α), 1.06 (1H, m, H3β), 1.07 (1H, m, H5), 1.00 (1H, m, H1β), 0.99 (3H, s, H20), 0.87 (1H, m, H14β); ^{13}C NMR (150 MHz, CD_3OD): 181.6 (C19), 81.3 (C15), 60.9 (C17), 57.8 (C5), 44.6 (C4), 44.5 (C16), 42.8 (C9), 41.2 (C1), 39.3 (C3), 39.2 (C10), 38.8 (C21), 37.7 (C8), 34.3 (C7), 32.1 (C12), 30.0 (C11), 29.5 (C18), 28.2 (C14), 22.2 (C13), 20.9 (C6), 20.0 (C2), 13.4 (C20). Serofendic acid B (**2**): HRFAB(+)MS: m/z 383.2277 ($C_{21}H_{35}O_4S$, Δ +2.1 mmu); $[\alpha]_D=-13.73$ ($c=1.408$, MeOH); mp 229–230°C; ^{1}H NMR (500 MHz, CD_3OD): 3.04 (1H, dd, $J=13.1$, 6.8, H17a), 2.96 (1H, d, $J=4.3$ Hz, H15), 2.91 (1H, dd, $J=13.1$, 9.2 Hz, H17b), 2.74 (3H, s, H21), 2.17 (brd, $J=14.0$ Hz, H3α), 2.07 (1H, ddd, $J=14.4$, 11.6, 3.0 Hz, H14α), 1.96 (1H, m, H2β), 1.92 (1H, m, H16), 1.90 (1H, m, H6α), 1.83 (1H, m, H6β), 1.80 (1H, m, H12), 1.74 (1H, ddd, $J=13.3$, 13.3, 4.4 Hz, H7β), 1.68 (1H, m, H13α), 1.67 (1H, m, H1α), 1.63 (1H, m, H11β), 1.62 (1H, m, H9), 1.46 (1H, m, H11α), 1.43 (1H, m, H13β), 1.42 (1H, m, H2α), 1.24 (3H, s, H18), 1.11 (1H, ddd, $J=13.3$, 2.9, 2.9 Hz, H7α), 1.06 (1H, m, H3β), 1.06 (1H, m, H5), 1.00 (1H, m, H1β), 0.99 (3H, s, H20), 0.86 (1H, ddd, m, H14β); ^{13}C NMR (125 MHz, CD_3OD): 181.6 (C19), 81.1 (C15), 59.8 (C17), 57.8 (C5), 44.6 (C4), 44.3 (C16), 42.9 (C9), 41.2 (C1), 39.3 (C3), 39.2 (C10), 38.3 (C21), 37.7 (C8), 34.3 (C7), 30.7 (C12), 29.9 (C11), 29.5 (C18), 28.4 (C14), 21.9 (C13), 20.9 (C6), 20.0 (C2), 13.5 (C20).
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