Coordination of Sodium Cation to an Oxygen Function and Olefinic Double Bond to Form Molecular Adduct Ion in Fast Atom Bombardment Mass Spectrometry

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Steroidal allylic alcohols formed Na^+ adduct ion peaks $[M+Na]^+$ by the addition of NaCl in FAB mass spectrometry. A comparison of the intensities of the adduct ion peaks of allylic alcohols with those of the corresponding saturated alcohols and olefin suggested that the olefinic double bond and the proximal hydroxyl group had coordinated to Na^+. The adduct ion was stable and did not undergo dehydroxylation. We suggest that the Na^+ adduct ion will be useful for the molecular weight determination of allylic alcohols which are susceptible to dehydroxylation under FAB mass spectrometric conditions. Na^+ adduct ions of α,β-unsaturated carbonyl compounds were also investigated.

Key words cation-π interaction; FAB-MS; Na^+ adduct ion; allylic alcohol; α,β-unsaturated carbonyl compound

One of the most important uses of mass spectrometry in organic chemistry is in the determination of molecular weight (MW: M). In fast atom bombardment (FAB) mass spectrometry,[1—3] molecular-related ion peaks of organic compounds are generally observed as $[M+H]^+$, $[M]^+$, $[M-H]^+$ or $[M+2H]^+$ (for positive ion), depending on the structures. However, compounds which decompose during the analyses show only very weak or no molecular-related ion peaks. In such cases, addition of an alkali metal salt to the compounds sometimes helps to induce adduct ion peaks $[M+A]^+$ (A: atomic weight of alkali metal), and these peaks have also been used for molecular weight determination in FAB mass spectrometry.[4—7]

Alkali metal adduct ions of organic compounds are observed in FAB mass analyses of various compounds, especially polyoxygenated compounds such as saccharides[8—11] and polyethers,[12—15] and polyfunctional compounds such as peptides.[16—19] We previously reported the structural requirements of oxygen functional groups for stabilization of the adduct ions in FAB mass spectra of a variety of diols and related compounds with the addition of NaCl.[7] Compounds with two proximal oxygens efficiently coordinated to Na^+, and afforded the adduct ion peaks $[M+Na]^+$ [Chart 1a]. However, compounds with an isolated hydroxyl group or ether oxygen hardly formed a complex with Na^+, and the intensities of the Na^+ adduct ion peaks were negligible compared to those of diols, including *n*-hexadecane-1,2-diol (**12**), which formed stable Na^+ adduct ions.[7]

The affinity of alkali metal cations to π-electrons has been extensively investigated on the basis of cation π-interactions.[20—28] Experiments to determine the binding energies of alkali metal cations with benzene and ethylene in the gas phase have been carried out by mass analyses of ion-molecule binding under solvent-free conditions and without counter ion influence.[22—24] Theoretical studies have also been carried out to calculate the binding energies of alkali metal cations to aromatic compounds.[25—27] As described above, our previous studies showed that compounds with an isolated hydroxyl group hardly formed a complex with Na^+ under FAB mass spectrometric conditions.[7] However, if an olefinic double bond and Na^+ could interact, allylic alcohols might form a complex with Na^+ by the participation of both the hydroxyl group and the olefinic double bond to yield $[M+Na]^+$ ion peaks effectively [Chart 1b]. Allylic alcohols are susceptible to dehydroxylation (protonation followed by dehydration to form the allylic cation) under FAB mass spectrometric conditions, but if the hydroxyl group and olefinic double bond were coordinated to Na^+, the complex might not readily undergo dehydroxylation, as in the case of 1,2-diols.[7] This paper reports the interactions of Na^+ with allylic alcohols in FAB mass spectrometry. Steroidal allylic alcohols, in which α,β-unsaturated hydroxyl groups were located in ring A or in the side chain, were chosen as test compounds. Interactions of Na^+ with steroidal α,β-unsaturated carbonyl compounds were also investigated [Chart 1c].

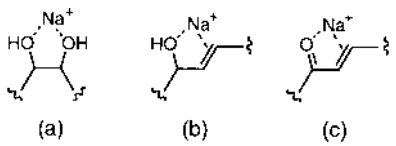

Chart 1

Results and Discussion

In order to examine Na^+ coordination effects, a steroidal olefin (**1**), allylic alcohols (**3**, **5**), α,β-unsaturated ketones (**7**, **9**), an α,β-unsaturated ester (**11**), and corresponding saturated compounds (**2**, **4**, **6**, **8**, **10**) were prepared (Table 1) (see Experimental). These steroidal derivatives were employed because they are nonvolatile and soluble in *m*-nitrobenzyl alcohol (*m*NBA), which was used as the matrix in FAB mass spectrometry.[7]

First, FAB mass spectra of the olefin **1**, the saturated alcohol **2** and the allylic alcohol **3** were measured in *m*NBA containing NaCl. Figure 1 shows the spectra with addition of 0.5 equivalents of NaCl.[29] The olefin **1** did not show an Na^+ adduct ion peak at *m*/*z* 393 (Fig. 1a), and the alcohol **2** showed only a weak adduct ion peak at *m*/*z* 411 (Fig. 1b). In

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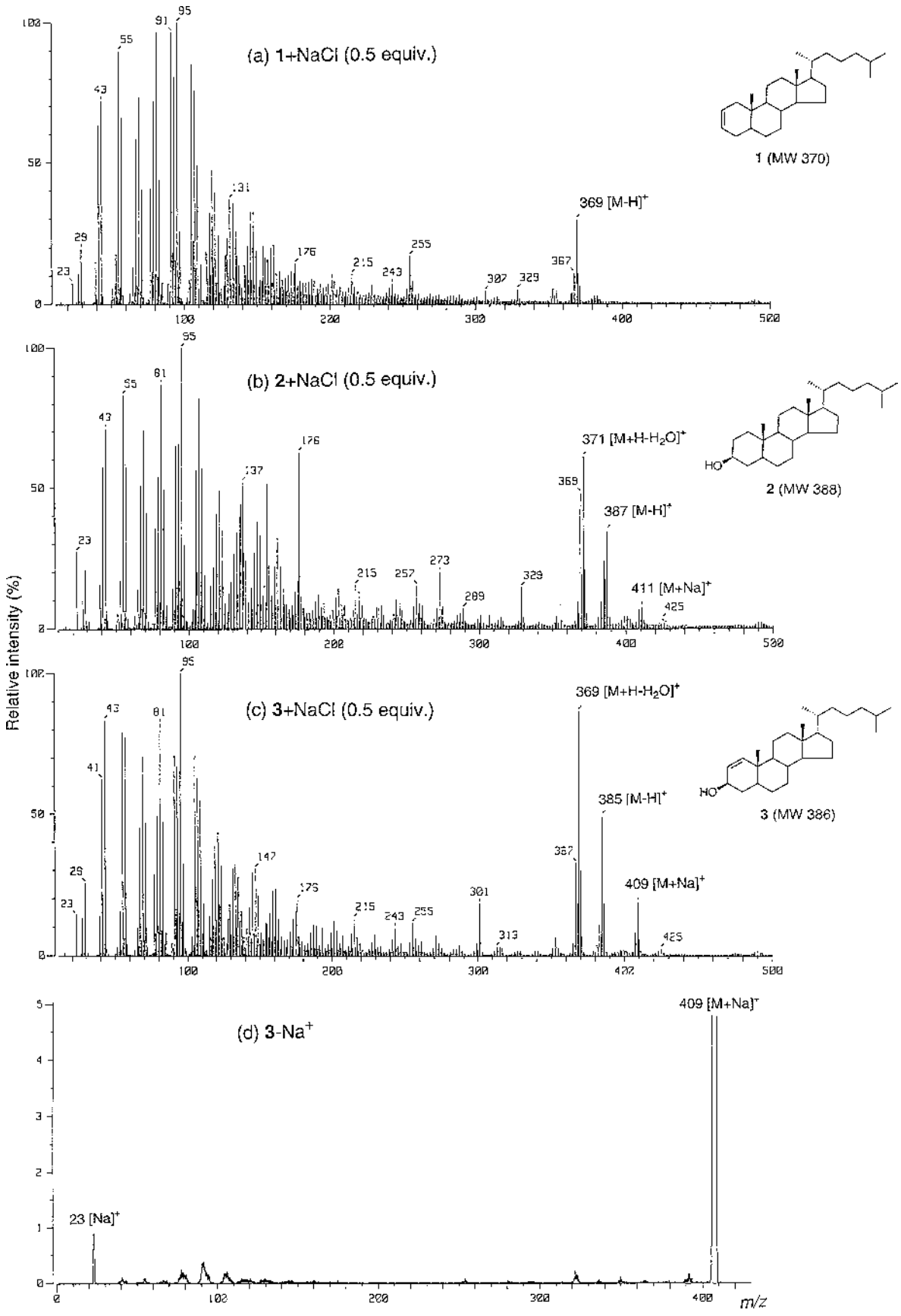

Fig. 1. (a—c) Positive Ion FAB Mass Spectra of Compounds **1**, **2** and **3** with 0.5 eq of NaCl[29]
Matrix, *m*-nitrobenzyl alcohol.

(d) Collisionally Activated Dissociation (CAD) Spectrum of Na^+ Adduct Ion of **3** at *m*/*z* 409

contrast, the allylic alcohol **3** formed a more intense adduct ion peak at *m/z* 409 (Fig. 1c). The intensity of the Na^+ adduct ion peak of **3** increased with the amount of NaCl added from 0.2 to 1.0 equivalents.[29] These results suggested that Na^+ coordinated with both the hydroxyl group and the olefinic double bond of **3**, and that the coordination contributed to the formation of the adduct ion $[M+Na]^+$ in the FAB mass spectrum. The time-course of the intensity of the adduct ion of **3** was followed, and the data are shown in Fig. 2, with the intensity of the ion $[M-H]^+$. The Na^+ adduct ion seemed to be rather stable, because rapid decrease of this ion was not observed. The stability of the Na^+ adduct ion of **3** was confirmed by the collisionally activated dissociation (CAD) spectrum of the adduct ion (Fig. 1d). The spectrum gave an Na^+ ion peak and weak fragment peaks of the steroidal skeleton or side chain, without showing the dehydroxylated ion peak at *m/z* 369. This implies that the coordination of the hydroxyl group and the olefinic double bond of **3** with Na^+ prevented dehydroxylation, as in the case of the coordination of the 1,2-diol **12** with Na^+.[7]

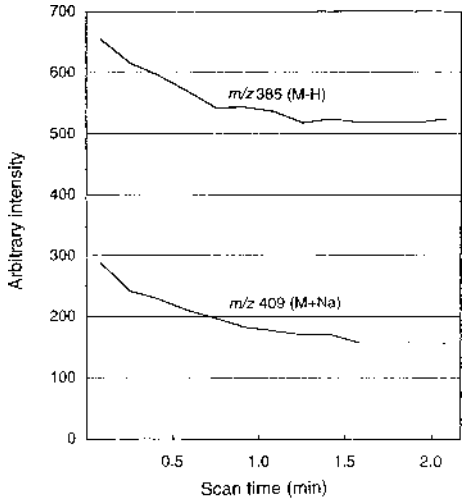

Fig. 2. Intensities of Ions $[M+Na]^+$ at *m/z* 409 and $[M-H]^+$ at *m/z* 385 during the FAB Mass Analysis of **3** with 0.5 eq of NaCl

Next, in order to generalize the coordination effect of an oxygen function and an olefinic double bond with Na^+, the intensities of the adduct ion peaks of allylic alcohols, α,β-unsaturated ketones, an α,β-unsaturated ester, and the corresponding saturated compounds were examined. The amount of ions formed in FAB mass spectrometry varies with the molecular size and functional groups of the analytes. Therefore, the test compounds were grouped into five categories, and the intensities of the $[M+Na]^+$ ion peaks of structurally related compounds were compared (Table 1). The relative in-

Table 1. Relative Intensity Values of Sodium Adduct Ions in FAB Mass Spectrometry[a]

Group No.	Compound	Standard compound[b]
1	**1** < 0.01; **2** 0.17; **3** 1.00	**13** 0.87
2	**4** 0.44; **5** 1.00	—[c]
3	**6** 0.57; **7** 1.00	**12** 0.43
4	**8** 0.84; **9** 1.00	**14** 1.1
5	**10** 0.88; **11** 1.00	**14** 2.9

a) Eech value was obtained by the analysis of a mixture of a test compound, a standard compound and NaCl (1 : 1 : 0.4). The data were normalized so that the maximum value of a test compound was 1.00. Matrix: *m*-nitrobenzyl alcohol. For details of sample preparation and measurement, see Experimental. *b*) The relative intensity value of **13** to **12** was 0.06[7] and that of **14** to **12** was 0.14. *c*) Intensity values of compounds **4** and **5** were compared directly by analyzing a mixture of **4**, **5** and NaCl (1 : 1 : 0.4).

tensity of the Na^+ adduct ion peak of each compound was determined by the concomitant analysis of a standard diol, **12**, **13**[30,31] or **14**,[32] which is able to form a complex with Na^+ by coordinating with the two hydroxyl groups.[7] The amount of NaCl added was fixed at 0.2 equivalents with respect to the sample. FAB mass spectra were measured in *m*NBA solution containing one of the test compounds (**2**—**3**, **6**—**11**), a standard compound (**12**, **13** or **14**), and NaCl in a molar ratio of 1 : 1 : 0.4. A standard compound for each group was selected according to the intensity of the Na^+ adduct ion of the test compound. Intensities of Na^+ adduct ions of **4** and **5** were directly compared without the standard diol by analyzing a mixture of **4**, **5** and NaCl (1 : 1 : 0.4), because the Na^+ adduct ion of **4** $[M+Na\ (m/z\ 383)]^+$ coincided with the dehydrated ion of the standard compound **14** $[M+H-2H_2O\ (m/z\ 383)]^+$. The intensity of the Na^+ adduct ion of compound **1** was determined by comparison of separately recorded FAB mass spectra of **1** and standard compound **13**, both containing 0.2 equivalents of NaCl.

Relative intensity values of Na^+ adduct ion peaks are summarized in Table 1. The relative intensities have been normalized so that the maximum value of any test compound in a group was set to be 1.00.

Compounds in group 1 include the olefin **1**, the saturated alcohol **2**, and the allylic alcohol **3**, containing the functional groups in the steroidal ring A. They were analyzed with the diol **13** as the standard compound. As described above, no Na^+ adduct ion peak of **1** was detected in the FAB mass spectrum upon addition of NaCl. The relative intensity value also showed that the intensity of the Na^+ adduct ion of **1** was negligible. The intensity value (1.00) of the allylic alcohol **3** was higher than the value (0.17) of the saturated alcohol **2**, which suggests the coordination of Na^+ with the olefinic double bond and the proximal hydroxyl group of the allylic alcohol **3** to be bidentate in character (Chart 1b). The coordination of **3** with Na^+ afforded the ion $[M+Na]^+$. Compounds **4** and **5** in group 2 are 5-en-3β-ol steroids containing a saturated alcohol and an allylic alcohol moiety in the steroidal side chain. In these cases, the same coordination effect as in the allylic alcohol **3** was observed. Comparison of the relative intensity values of the saturated alcohol **4** (0.44) and the allylic alcohol **5** (1.00) suggests the coordination of the olefinic double bond and the hydroxyl group of **5** to Na^+. These results for group 1 and 2 indicate that addition of NaCl to form an $[M+Na]^+$ ion peak is useful for the analyses of both cyclic and linear allylic alcohols which are susceptible to dehydroxylation under FAB mass spectrometric conditions.

Compounds in groups 3, 4 and 5 include those with the saturated ketone **6** and the enone **7** in the ring system, the saturated ketone **8** and the enone **9** in the side chain of steroidal 5-en-3β-ol series, and the saturated ester **10** and the α,β-unsaturated ester **11** in the side chain of the steroidal 5-en-3β-ol series. The ketone **6** and the enone **7** in group 3

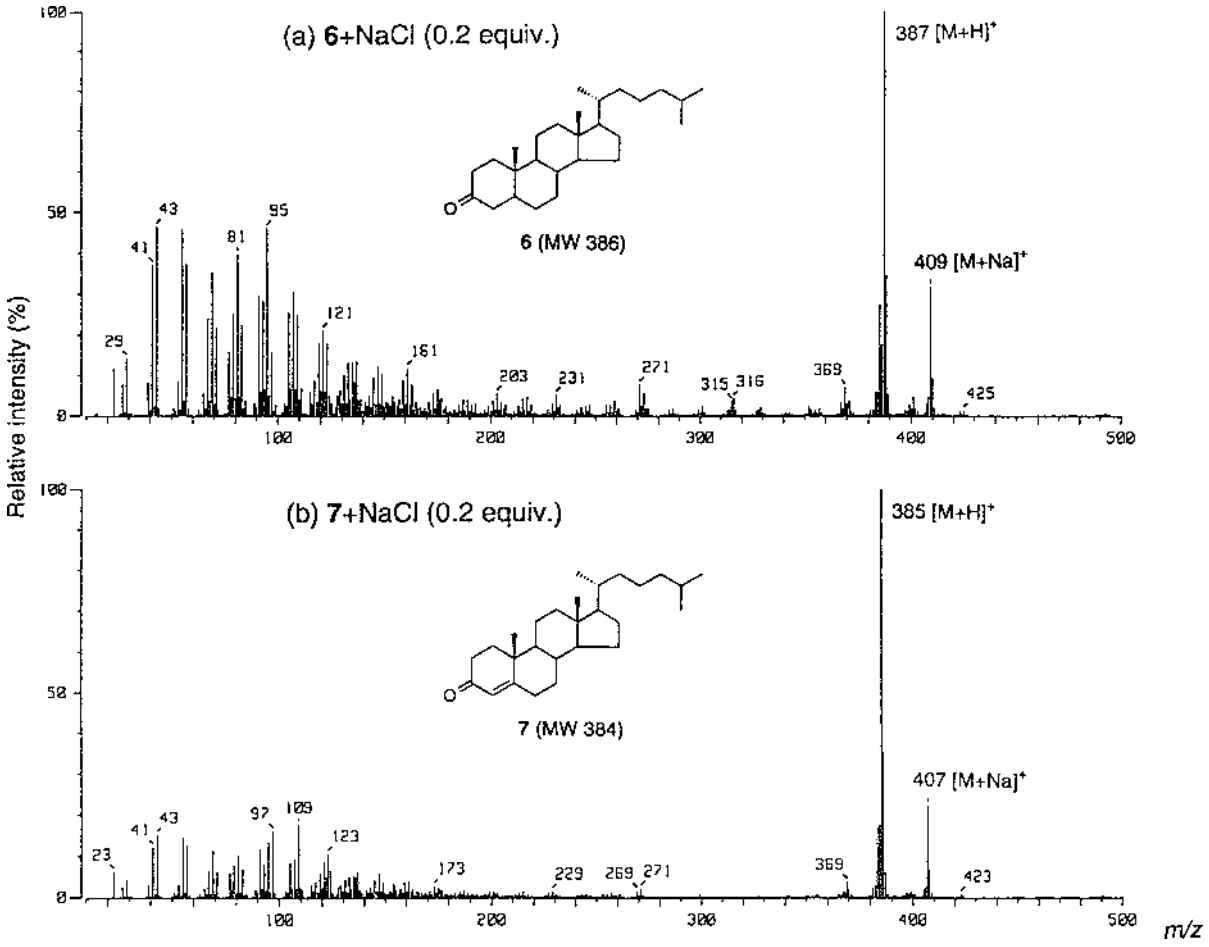

Fig. 3. Positive Ion FAB Mass Spectra

(a) Compound **6** with 0.2 eq of NaCl. (b) Compound **7** with 0.2 eq of NaCl. Matrix, *m*-nitrobenzyl alcohol.

were analyzed with the diol **12** as the standard compound. In contrast with the saturated alcohol **2**, the saturated ketone **6** formed an Na^+ adduct ion, as did the enone **7** (Fig. 3). Even so, the intensity value of the enone **7** (1.00) was higher than that of the ketone **6** (0.57), and the difference may reflect the relative strength of the coordination of the carbonyl group and olefinic double bond of **7** to Na^+, as compared with **6** (Chart 1c). The higher value of the enone **9** (1.00) than the ketone **8** (0.84) in group 4, and also that of the unsaturated ester **11** (1.00) compared with the ester **10** (0.88) support the coordination of the olefinic double bond and the carbonyl group to Na^+.

In conclusion, steroidal allylic alcohols, α,β-unsaturated ketones and an α,β-unsaturated ester afforded Na^+ adduct ion peaks in FAB mass spectrometry. The adduct ions were suggested to be formed by coordination of the olefinic double bond and the proximal oxygen function to Na^+, in which the cation-π interaction plays an important role. Participation of the olefinic double bond in the stabilization of Na^+ adduct ions of type b and c in Chart 1 may be attributed to the delocalization of positive charge. In this regard, Adams and Gross studied the lithiation of mono-unsaturated oleyl alcohol, finding that the spatially separated hydroxyl group and olefinic double bond were unable to form a complex with Li^+, and that the double bond was not lithiated.[33] Rubino *et al.* suggested the participation of olefinic π-electrons and a hydroxyl group of sphingosine to form a complex with Li^+.[34] Addition of sodium salt to allylic alcohols to form stable $[M+Na]^+$ ion peaks will be useful in molecular weight determination in FAB mass spectrometry.

Experimental

Instrumentation and Sample Preparation FAB mass spectra were recorded on a JEOL JMS-HX110 double-focusing mass spectrometer of EBE arrangement with a JMS-DA7000 data system. The ion acceleration voltage was 10 kV, and xenon gas was accelerated at a voltage of 6 kV. *m*-Nitrobenzyl alcohol (*m*NBA) was used as the matrix, and NaCl was used as the sodium cation source. The CAD spectrum was obtained with helium as the collision gas, which was metered to cause about 20% attenuation of the main beam.

Sample solutions for the FAB mass analyses, containing 0.5 equivalents of NaCl, were prepared by mixing 5 μl each of 0.1 M sample compound in $CHCl_3$–CH_3OH (1 : 1), 0.05 M NaCl in H_2O–CH_3OH (1 : 9) and *m*NBA.[7] Solutions for experiments to obtain the relative intensities of sodium adduct ions were prepared by mixing 5 μl each of 0.1 M test compound and 0.1 M standard compound [hexadecene-1,2-diol (**12**),[7] 5α-cholestane-1α,3β-diol (**13**),[7,30,31] or (20*R*,22*R*)-cholest-5-ene-3β,20,22-triol (**14**)[7,32]], 10 μl of 0.02 M NaCl, and 10 μl of *m*NBA. An aliquot of the mixture was applied to the target tip for FAB mass analyses. FAB mass spectra were obtained by means of a 5.2 s scan from *m*/*z* 10 to 1900. Three values at 20, 30, and 40 s from the start of the scanning, were averaged. Each sample was measured at least twice.

Materials The structures of compounds **1**—**11** and standard compounds **12**—**14** are listed in Table 1. 5α-Cholestan-3β-ol (**2**) and *m*-NBA were purchased from Tokyo Kasei Kogyo Co., Ltd. 5α-Cholestan-3-one (**6**) and 1,2-hexadecanediol (**12**) were purchased from Sigma Chemical Co. and Aldrich Chemical Co., Inc., respectively. Compounds **1**,[35,36] **7**,[37] **8**,[38] **13**,[30,31] and **14**[32] were prepared by the reported methods. Compound **9**[39] was synthesized by reaction of $(C_6H_5)_3AsCH_2COCH(CH_3)_2Br$[40] with the aldehyde **15**[41] (Chart 2) followed by aqueous acid treatment.[42] Compound **11**[43] was prepared from the aldehyde **15** by reaction with $(C_6H_5)_3P{=}CHCOOCH_3$ to afford the α,β-unsaturated ester, followed by aqueous acid treatment. Compound **5** was obtained by reduction of the α,β-unsaturated ester described above with diisobutylaluminum hydride, followed by aqueous acid treatment. Compound **10**[44,45] was obtained by esterification of cholenic acid **16** (purchased from Steraloids Inc. Wilton, NH, U.S.A., Chart 2) with trimethylsilyldiazomethane.[46] Compound **4**[47] was prepared by $LiAlH_4$ reduction of compound **10**. Compound **3**[48] was obtained by reduction of 5α-cholest-1-en-3-one[49] with $NaBH_4$ in the presence of $CeCl_3$.[50,51] All compounds prepared were characterized by ^{1}H-NMR (JEOL JNM A-500 NMR spectrometer, 500 MHz) and FAB mass spectrometry.

^{1}H-NMR ($CDCl_3$) of **3**: δ 0.64 (3H, s), 0.84 (3H, d, J=6.5 Hz), 0.85 (3H, d, J=6.5 Hz), 0.88 (3H, d, J=6.0 Hz), 0.89 (3H, s), 4.28 (1H, dddd, J=9.0, 7.0, 1.5, 1.5 Hz), 5.46 (1H, ddd, J=10.0, 1.5, 1.5 Hz), 5.90 (1H, dd, J=10.0, 1.5 Hz). **4**: δ 0.66 (3H, s), 0.92 (3H, d, J=6.5 Hz), 0.99 (3H, s), *ca.* 3.5 (1H, m), *ca.* 3.6 (2H, m), 5.33 (1H, m). **5**: δ 0.68 (3H, s), 0.99 (3H, s), 1.02 (3H, d, J=6.5 Hz), 3.35 (1H, m), 4.04 (2H, m), 5.33 (1H, m), 5.53 (2H, m). **9**: δ 0.70 (3H, s), 0.99 (3H, s), 1.08 (9H, d, J=*ca.* 7.0 Hz), 3.51 (1H, m), 5.33 (1H, m), 6.05 (1H, d, J=15.5 Hz), 6.70 (1H, dd, J=15.5, 9.0 Hz). **10**: δ 0.66 (3H, s), 0.91 (3H, d, J=6.7 Hz), 0.99 (3H, s), 3.50 (1H, m), 3.64 (3H, s), 5.33 (1H, m). **11**: δ 0.70 (3H, s), 0.99 (3H, s), 1.07 (3H, d, J=6.5 Hz), 3.50 (1H, m), 3.70 (3H, s), 5.33 (1H, m), 5.73 (1H, d, J=15.5 Hz), 6.82 (1H, dd, J=15.5, 9.0 Hz).

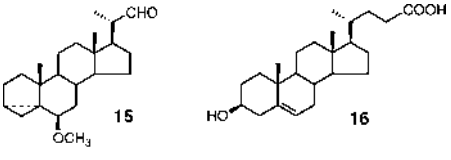

Chart 2

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