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FOUR TETRAHYDROISOQUINOLINE-MONOTERPENE GLUCOSIDES FROM *CEPHAELIS IPECACUANHA*

NAOTAKA NAGAKURA, ATSUKO ITOH and TAKAO TANAHASHI

Kobe Women's College of Pharmacy, Higashinada-ku, Kobe 658, Japan

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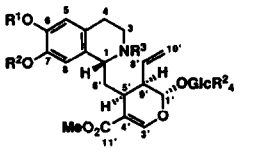
IN HONOUR OF PROFESSOR MEINHART ZENK'S SIXTIETH BIRTHDAY

Key Word Index—*Cephaelis ipecacuanha*; Rubiaceae; roots; tetrahydroisoquinoline-monoterpene glucosides; *trans*-cephaeloside; *cis*-cephaeloside; 6-*O*-methyl-*trans*-cephaeloside; 6-*O*-methyl-*cis*-cephaeloside.

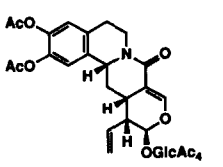
Abstract—Four new tetrahydroisoquinoline-monoterpene glucosides, *trans*-cephaeloside, *cis*-cephaeloside, 6-*O*-methyl-*trans*-cephaeloside and 6-*O*-methyl-*cis*-cephaeloside, have been isolated from the roots of *Cephaelis ipecacuanha*. Their structures have been elucidated on the basis of chemical and spectral data.

INTRODUCTION

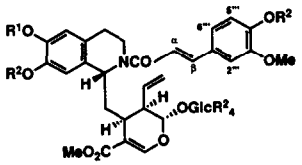
The crude drug 'Ipecac', which is defined as the dried roots of *Cephaelis ipecacuanha* A. Richard, has been used in therapy since the beginning of the 17th century as an emetic and expectorant, and was recommended as early as the 18th century for use against dysentery. The medicinal value of this drug rests mainly in its content of emetine and cephaeline, which are largely responsible for its pharmacological effects [1]. Thus, its alkaloidal constituents have been intensively investigated. The glucosidal constituents, by contrast, have not been chemically studied except for ipecoside (**1**) [2, 3]. Recently, we re-examined this crude drug and isolated from it 10 new monoterpene-isoquinoline glucosides along with ipecoside (**1**) and characterized six of them [4]. In continuation of this study, we report here the structure elucidation of the remaining four monoterpene-isoquinoline glucosides **3**–**6**, which possess *N*-feruloyl moieties instead of an *N*-acetyl group in ipecoside (**1**) and 6-*O*-methylipecoside (**2**).



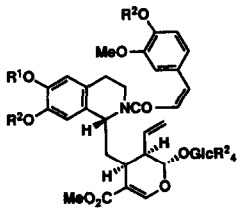
1 R^1=R^2=H, R^3=Ac
1a R^1=R^2=R^3=Ac
2 R^1=Me, R^2=H, R^3=Ac
2a R^1=Me, R^2=R^3=Ac
11 R^1=R^2=Ac, R^3=H



7



3 R^1=R^2=H
3a R^1=R^2=Ac
5 R^1=Me, R^2=H
5a R^1=Me, R^2=Ac



4 R^1=R^2=H
4a R^1=R^2=Ac
6 R^1=Me, R^2=H
6a R^1=Me, R^2=Ac

RESULTS AND DISCUSSION

trans-Cephaeloside (**3**), $C_{35}H_{41}NO_{14}$, was isolated as needles. It showed IR bands at 3412 (OH), 1700 (α,β-unsaturated ester), and 1636 cm^{-1} (amide). Its ^1H NMR spectrum exhibited signals for an olefinic proton at δ7.39 (*d*, J = 1.8 Hz), a carbomethoxy group at δ3.66 (*s*), two aromatic protons at δ6.49 and 6.51 (each *s*), and terminal vinyl protons at δ5.46 (*dd*, J = 10.0 and 1.8 Hz), 5.60 (*dd*, J = 17.2 and 1.8 Hz) and 5.79 (*dt*, J = 17.2 and 10.0 Hz). These spectral features were closely similar to those of ipecoside (**1**). The differences in their spectra could be accounted for by the substitution of their *N*-acylating unit. The ^1H NMR spectrum of **3** lacked a signal of the *N*-acetyl group such as was observed in **1**, but exhibited signals corresponding to a *trans*-methylcaffeoyl moiety, an aromatic methoxyl signal at δ3.93, a pair of doublets for *trans*-olefinic protons at δ7.06 and 7.51 (J = 15.5 Hz) and an AMX spin system from three aromatic protons (δ6.81–7.24). The presence of the methylcaffeoyl moiety was also supported by UV absorption at 315 nm.

Acetylation of **3** in Ac_2O–pyridine not only provided the expected acetate **3a**, but in addition a minor product

acetate **4a**. EI mass spectra of both compounds exhibited a $[M]^+$ at *m/z* 993 corresponding to $C_{49}H_{55}NO_{21}$ and a fragment at *m/z* 219 due to the *O*-acetyl-methylcaffeoyl group. The ^1H NMR data of **3a** and **4a**, excluding the signals attributable to the *N*-acyl groups, were in good agreement with those for ipecoside hexaacetate (**1a**). The ^1H NMR spectrum of **3a**, furthermore, exhibited a singlet for methoxyl at δ3.88, a pair of doublets for olefinic protons at δ7.02 and 7.57 (J = 15.2 Hz) and an AMX spin system from three aromatic protons (δ7.06–7.24), together with a residual singlet from a phenolic acetyl group. These signals could be assigned to the *O*-acetyl-*trans*-feruloyl group with the aid of a series of differential NOE experiments. Irradiation at δ3.88 (OMe) resulted in a 10% enhancement of the integral for H-2‴ at δ7.24 (*d*, J = 1.8 Hz) and irradiation of H-β at δ7.57 caused 8% and 12% increases of H-2‴ and H-6‴ (δ7.19, *dd*, J = 8.0 and 1.8 Hz), indicating the placement of the methoxyl group at C-3‴. Thus, the *O*-acetyl-*trans*-methyl-caffeoyl moiety in **3a** should be an *O*-acetyl-*trans*-feruloyl group rather than an *O*-acetyl-*trans*-isoferuloyl group. On the other hand, the acetate **4a** was determined to be the geometric isomer (*cis*-form) of **3a**, which was formed by acetylation with concomitant isomerization of the double bond, by the coupling constant of olefinic protons (J = 12.5 Hz) and by differential NOE experiments. These findings led us to conclude that **3** possesses a *N*-*trans*-feruloyl group in place of an *N*-acetyl group as in ipecoside (**1**). As further structural confirmation, **4a** was subjected to *N*-deacylation with triethyloxonium fluoroborate [5] followed by a sequence of treatments with $NaHCO_3$ and NH_4OH to give demethylalangiside hexaacetate (**7**) together with an isomeric mixture of ethyl *O*-acetylferulate (**8**). Consequently, the structure of the glucoside **3** was established as shown.

The second glucoside **4** was found to be isomeric with **3**, $C_{35}H_{41}NO_{14}$, from its elemental analysis. Its spectral features clearly demonstrated that **4** has a similar structure to **3**. In its ^1H NMR spectrum, however, the signals arising from the *trans*-feruloyl group were replaced by a methoxyl signal at δ3.22*, *cis*-coupled olefinic protons at δ6.06 and 6.61 (each *d*, J = 12.8 Hz) and an aromatic AMX system (δ6.69–6.86), suggesting the presence in **4** of a *cis*-feruloyl group instead of the *trans*-feruloyl moiety, as in **3**. This was substantiated by acetylation of **4** to yield two acetates, which were identical in all respects with **3a** and **4a** derived from **3**. Accordingly, the new glucoside **4** was characterized as *N*-*cis*-feruloyl-*N*-deacetyl-ipecoside, which was named as *cis*-cephaeloside.

The ^1H NMR spectra of **3** and **4** were fairly complicated as most signals were accompanied by weak ones. This phenomenon could be ascribed to rotational isomerism around the amidic bond [7]. To exclude the possibility that the weak peaks were due to a contaminant, compounds **3** and **4** were synthesized starting from ipecoside (**1**) and *trans*-ferulic acid as follows. Acetylation of *trans*-ferulic acid afforded *O*-acetyl-*trans*-ferulic acid (**9**), which was isomerized to *O*-acetyl-*cis*-ferulic acid (**10**) by irradiation. *N*-Deacetylipecoside hexaacetate (**11**), which was prepared from ipecoside hexaacetate (**1a**) through *N*-deacetylation with triethyloxonium fluoroborate, was condensed with **9** in the presence of DCC, yielding **3a**. Finally, **3a** was subjected to Zemplen reaction to give **3**. In a similar manner, **4** was prepared from **1a** and **10**. The ^1H NMR spectra of both products were superimposable with those of the isolates, indicating that they were present as mixtures of rotomers in solution.

Another set of closely related glucosides comprised the methylcephaelosides **5** and **6**. Each glucoside was assigned the molecular formula $C_{36}H_{43}NO_{14}$. Their spectral features closely resembled those of *trans*-cephaeloside (**3**) and *cis*-cephaeloside (**4**), respectively, except for the presence of an additional aromatic methoxyl signal in their ^1H NMR spectra. The compounds **5** and **6** were, therefore, assumed to be methylates of *trans*- and *cis*-cephaelosides. From the chemical shifts of the aromatic protons in both **5** and **6**, we could site the additional methoxyl group in the tetrahydroisoquinoline nucleus, i.e. at C-6 or at C-7 rather than in the feruloyl moiety. On conventional acetylation, each glucoside gave two isomeric acetates **5a** and **6a**, which were found to be *E* and *Z* isomers, respectively, as could be seen from the coupling constants of olefinic protons in their ^1H NMR spectra. The existence of an *O*-acetyl-*trans*-feruloyl group in **5a** and an *O*-acetyl-*cis*-feruloyl group in **6a** was also demonstrated by an EI mass fragment ion at *m/z* 219 and by comparison of the ^1H NMR data of **5a** and **6a** with those of **3a** and **4a**. These findings, together with coexistence of 6-*O*-methylipecoside (**2**) in this plant [4], suggested that the structural relationship between **3** and **5**, as well as that between **4** and **6**, was the same as that between ipecoside (**1**) and **2**. The additional methoxyl group in glucosides **5** and **6** was, therefore, tentatively placed at C-6. This assumption was finally confirmed by preparation of **5a** and **6a** from 6-*O*-methylipecoside pentaacetate (**2a**) [4] and ferulic acid in a similar way to that used for **3a** and **4a**. Thus, the structures of the two new glucosides **5** and **6** were established as 6-*O*-methyl-*trans*-cephaeloside and 6-*O*-methyl-*cis*-cephaeloside, respectively.

EXPERIMENTAL

Mps: uncorr. ^1H (200 or 500 MHz) NMR: TMS as int. standard. EIMS: 70 or 20 eV; FDMS: 20 mA (emitter current); SIMS: glycerol as matrix. TLC: silica gel.

Plant material and isolation of glucosides. The source of plant material and isolation of glucosides are described in a previous publication [4]. Compounds **A**, **B**, **C** and **D** in ref. [4] correspond to **4**, **3**, **6** and **5**, respectively.

trans-*Cephaeloside* (**3**). Needles, mp 170–172° (MeOH). $[\alpha]_D^{27}$ −193° (MeOH; *c* 1.0). UV λ_{max}^{EtOH} nm (log ε): 227sh (4.42), 276sh (4.08), 293 (4.14), 315 (4.09). IR ν_{max}^{KBr} cm^{-1}: 3412, 1700, 1636, 1615, 1598, 1518. ^1H NMR (CD_3OD): δ1.57 (1H, *ddd*, J = 14.5, 11.7, 3.2 Hz, H-6′),

*The methoxyl resonated at an anomalously high field. This could be explained by the conformation where this group lies over the plane of the aromatic system in the tetrahydroisoquinoline nucleus [6].

2.60 (1H, *ddd*, J = 14.5, 11.5, 2.2 Hz, H-6'), 2.85 (1H, *ddd*, J = 16.2, 12.0, 5.5 Hz, H-4), 3.12 (1H, *dd*, J = 9.0, 8.0 Hz, H-2''), 3.64, 3.66* and 3.67 (3H, each *s*, COOMe), 3.86 and 3.88* (1H, each *dd*, J = 12.0, 2.0 Hz, H-6''), 3.93 (3H, *s*, OMe), 4.30 (1H, *dd*, J = 14.0, 5.3 Hz, H-3), 4.55, 4.61* and 4.63 (1H, each *d*, J = 8.0 Hz, H-1''), 5.42* and 5.43 (1H, each *d*, J = 2.8 Hz, H-1'), 5.34 and 5.46* (1H, each *dd*, J = 10.0, 1.8 Hz, H-10'), 5.60 (1H, *dd*, J = 17.2, 1.8 Hz, H-10'), 5.69 (1H, *dd*, J = 11.5, 3.2 Hz, H-1), 5.79 (1H, *dt*, J = 17.2, 10.0 Hz, H-8'), 6.49*, 6.51*, 6.56 and 6.68 (2H, each *s*, 2 × ArH), 6.81* and 6.83 (1H, each *d*, J = 8.0 Hz, H-5'''), 6.98 and 7.06* (1H, each *d*, J = 15.5 Hz, H-α), 7.12* and 7.13 (1H, each *dd*, J = 8.0, 1.8 Hz, H-6'''), 7.23 and 7.24* (1H, each *d*, J = 1.8 Hz, H-2'''), 7.39*, 7.41 and 7.43 (1H, each *d*, J = 1.8 Hz, H-3'), 7.51* and 7.52 (1H, each *d*, J = 15.5 Hz, H-β). FDMS *m/z*: 722 $[M+Na]^+$, 700 $[M+H]^+$; HR-SIMS Found: 700.2621 $[M+H]^+$; $C_{35}H_{42}NO_{14}$ requires 700.2603.

cis-*Cephaeloside* (**4**). Needles, mp 164–165° (MeOH). $[\alpha]_D^{28}$ −183° (MeOH; *c* 1.0). UV λ_{max}^{EtOH} nm (log ε): 225sh (4.47), 277 (4.13), 295sh (4.07), 313 (3.91). IR ν_{max}^{KBr} cm^{-1}: 3392, 1684, 1640, 1600, 1520. ^{1}H NMR (CD_3OD): δ 1.57 (1H, *ddd*, J = 15.0, 12.0, 3.0 Hz, H-6'), 2.36 (1H, *ddd*, J = 16.0, 12.2, 6.5 Hz, H-4), 2.46 (1H, *dd*, J = 16.0, 4.5 Hz, H-4), 2.58 (1H, *ddd*, J = 15.0, 11.5, 2.0 Hz, H-6'), 3.19 (1H, *dd*, J = 9.0, 8.0 Hz, H-2''), 3.22* and 3.92 (3H, each *s*, OMe), 3.60, 3.64* and 3.68 (3H, each *s*, COOMe), 3.88* and 3.93 (1H, each *dd*, J = 12.0, 2.0 Hz, H-6''), 4.09 (1H, *dd*, J = 13.7, 6.5 Hz, H-3), 4.61, 4.63* and 4.64 (1H, each *d*, J = 8.0 Hz, H-1''), 5.42 and 5.43* (1H, each *d*, J = 3.0 Hz, H-1'), 5.47 (1H, *dd*, J = 10.0, 1.8 Hz, H-10'), 5.60 (1H, *dd*, J = 17.2, 1.8 Hz, H-10'), 5.67 (1H, *dd*, J = 11.5, 3.0 Hz, H-1), 5.80 (1H, *dt*, J = 17.2, 10.0 Hz, H-8'), 6.02 and 6.06* (1H, each *d*, J = 12.8 Hz, H-α), 6.24, 6,36*, 6.45, 6.48* and 6.50 (2H, each *s*, 2 × ArH), 6.61* and 6.68 (1H, each *d*, J = 12.8 Hz, H-β), 6.69* and 6.70 (1H, each *d*, J = 8.0 Hz, H-5'''), 6.80 (1H, *dd*, J = 8.0, 1.8 Hz, H-6'''), 6.86 (1H, *d*, J = 1.8 Hz, H-2'''), 7.38, 7.39 and 7.40* (1H, each *d*, J = 1.7 Hz, H-3'). FDMS *m/z*: 722 $[M+Na]^+$, 700 $[M+H]^+$. (Found: C, 57.77; H, 6.08; N, 1.93. $C_{35}H_{41}NO_{14}\cdot 3/2H_2O$ requires: C, 57.84; H, 6.10; N, 1.93%).

6-O-*Methyl*-trans-*cephaeloside* (**5**). Needles, mp 162–164° (MeOH). $[\alpha]_D^{22}$ −189° (MeOH; *c* 1.0). UV λ_{max}^{EtOH} nm (log ε): 222 (4.44), 232 (4.45), 293 (4.21), 323 (4.21). IR ν_{max}^{KBr} cm^{-1}: 3400, 1705, 1645, 1600, 1515. ^{1}H NMR (CD_3OD): δ 1.57 (1H, *ddd*, J = 14.3, 12.0, 3.5 Hz, H-6'), 2.62 (1H, *ddd*, J = 14.3, 11.5, 2.2 Hz, H-6'), 3.12 (1H, *dd*, J = 9.0, 8.0 Hz, H-2''), 3.64, 3.65* and 3.66 (3H, each *s*, COOMe), 3.80* and 3.83 (3H, each *s*, OMe), 3.87 (1H, *dd*, J = 12.0, 2.0 Hz, H-6''), 3.93 (3H, *s*, OMe), 4.33 (1H, *dd*, J = 14.0, 5.5 Hz, H-3), 4.53, 4.61* and 4.62 (1H, each *d*, J = 8.0 Hz, H-1''), 5.42* and 5.43 (1H, each *d*, J = 2.7 Hz, H-1'), 5.47 (1H, *dd*, J = 10.5, 1.8 Hz, H-10'), 5.61 (1H, *dd*, J = 17.2, 1.8 Hz, H-10'), 5.71 (1H, *dd*, J = 11.5, 2.8 Hz, H-1), 5.80 (1H, *dt*, J = 17.2, 10.5 Hz, H-8'), 6.48, 6.50*, 6.52, 6.65*, 6.70 and 6.71 (2H, each *s*, 2 × ArH), 6.80, 6.81* and 6.83 (1H, each *d*, J = 8.0 Hz, H-5'''), 6.99 and 7.08* (1H, each *d*, J = 15.2 Hz, H-α), 7.11 (1H, *dd*, J = 8.0, 1.7 Hz, H-6'''), 7.23, 7.24 and 7.25* (1H, each *d*, J = 1.7 Hz, H-2'''), 7.39*, 7.40 and 7.42 (1H, each *d*, J = 1.8 Hz, H-3'), 7.49, 7.52* and 7.53 (1H, each *d*, J = 15.2 Hz, H-β). FDMS *m/z*: 736 $[M+Na]^+$, 714 $[M+H]^+$; HR-SIMS found: 714.2749 $[M+H]^+$; $C_{36}H_{44}NO_{14}$ requires 714.2759.

6-O-*Methyl*-cis-*cephaeloside* (**6**). Needles, mp 154–155° (MeOH). $[\alpha]_D^{28}$ −157° (MeOH; *c* 1.0). UV λ_{max}^{EtOH} nm (log ε): 225sh (4.45), 277 (4.10), 293sh (4.04), 304sh (3.93), 312sh (3.87). IR ν_{max}^{KBr} cm^{-1}: 3416, 1706, 1634, 1610, 1600, 1516. ^{1}H NMR (CD_3OD): δ 1.57 (1H, *ddd*, J = 14.0, 12.0, 3.0 Hz, H-6'), 2.36 (1H, *ddd*, J = 16.0, 12.3, 6.5 Hz, H-4), 2.52 (1H, *dd*, J = 16.0, 4.5 Hz, H-4), 2.59 (1H, *ddd*, J = 14.0, 11.5, 2.0 Hz, H-6'), 3.19 (1H, *dd*, J = 9.0, 8.0 Hz, H-2''), 3.22* and 3.93 (3H, each *s*, OMe), 3.64* and 3.67 (3H, each *s*, COOMe), 3.77* and 3.79 (3H, each *s*, OMe), 3.88 (1H, *dd*, J = 12.0, 2.0 Hz, H-6''), 4.11 (1H, *dd*, J = 14.0, 6.5 Hz, H-3), 4.63* and 4.64 (1H, each *d*, J = 8.0 Hz, H-1''), 5.44* and 5.45 (1H, each *d*, J = 2.8 Hz, H-1'), 5.47 (1H, *dd*, J = 10.0, 1.8 Hz, H-10'), 5.61 (1H, *dd*, J = 17.2, 1.8 Hz, H-10'), 5.69 (1H, *dd*, J = 11.5, 3.0 Hz, H-1), 5.80 (1H, *dt*, J = 17.2, 10.0 Hz, H-8'), 6.04 and 6.06* (1H, each *d*, J = 12.5 Hz, H-α), 6.43, 6.45, 6.48*, 6.50* and 6.53 (2H, each *s*, 2 × ArH), 6.63* and 6.70 (1H, each *d*, J = 12.5 Hz, H-β), 6.68 (1H, *d*, J = 8.0 Hz, H-5'''), 6.80 (1H, *dd*, J = 8.0, 1.8 Hz, H-6'''), 6.86 (1H, *d*, J = 1.8 Hz, H-2'''), 7.40 and 7.41* (1H, each *d*, J = 1.8 Hz, H-3'). FDMS *m/z*: 736 $[M+Na]^+$, 714 $[M+H]^+$. (Found: C, 58.09; H, 6.28; N, 1.90. $C_{36}H_{43}NO_{14}\cdot 3/2H_2O$ requires: C, 58.37; H, 6.26; N, 1.89%.)

Acetylation of trans- *and* cis-*cephaelosides. trans*-Cephaeloside (**3**) (7.7 mg) was treated with Ac_2O–pyridine. The crude residue (12.5 mg) was purified by prep. TLC (Et_2O, 2 developments). Of the two major bands, the more mobile one gave **4a** (4.9 mg), the less mobile one affording **3a** (5.2 mg). In a similar way, *cis*-cephaeloside (**4**) (101.0 mg) was acetylated to afford identical products **3a** (13.9 mg) and **4a** (124.7 mg).

trans-*Cephaeloside heptaacetate* (**3a**). Needles, mp 133–134° (EtOH). $[\alpha]_D^{22}$ −135° ($CHCl_3$; *c* 0.3). UV λ_{max}^{EtOH} nm (log ε): 225sh (4.46), 278 (4.30), 310sh (4.11). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1760, 1710, 1650, 1635, 1605, 1510. ^{1}H NMR ($CDCl_3$): δ 1.52 (1H, *ddd*, J = 14.5, 12.0, 4.0 Hz, H-6'), 1.87, 1.96, 2.00, 2.09, 2.26, 2.27 and 2.32 (21H, each *s*, 7 × Ac), 2.61 (1H, *ddd*, J = 12.0, 5.8, 2.3 Hz, H-5'), 2.69 (1H, *ddd*, J = 14.5, 12.5, 2.3 Hz, H-6'), 2.82 (1H, *dd*, J = 16.5, 3.5 Hz, H-4), 2.95 (1H, *ddd*, J = 16.5, 12.0, 6.0 Hz, H-4), 3.28 (1H, *m*, H-9'), 3.65 (3H, *s*, COOMe), 3.66 (1H, *ddd*, J = 9.8, 4.2, 2.0 Hz, H-5''), 3.73 (1H, *ddd*, J = 14.5, 12.0, 3.5 Hz, H-3), 3.88 (3H, *s*, OMe), 4.12 (1H, *dd*, J = 12.2, 2.0 Hz, H-6''), 4.20 (1H, *dd*, J = 14.5, 6.0 Hz, H-3), 4.21 (1H, *dd*, J = 12.2, 4.2 Hz, H-6''), 4.76 (1H, *d*, J = 8.5 Hz, H-1''), 4.90 (1H, *dd*, J = 9.8, 8.5 Hz, H-2''), 5.00 (1H, *t*, J = 9.8 Hz, H-4''), 5.15 (1H, *t*, J = 9.8Hz, H-3''), 5.27 (1H, *d*, J = 2.0 Hz, H-1'), 5.44 (1H, *dd*, J = 7.5, 3.5 Hz, H-10'), 5.68 (2H, *m*, H-8' and H-10'), 5.84 (1H, *dd*, J = 12.5, 4.0 Hz, H-1), 6.79 and 6.91 (2H, each *s*, 2 × ArH), 7.02 (1H, *d*, J = 15.2 Hz, H-α), 7.06 (1H, *d*, J = 8.0 Hz, H-5'''), 7.19 (1H, *dd*, J = 8.0, 1.8 Hz, H-6'''), 7.24 (1H, *d*, J = 1.8 Hz, H-2'''), 7.30 (1H, *d*, J = 2.0 Hz, H-3'),

*Represents signals due to the major rotomer.

7.57(1H, *d*, J = 15.2 Hz, H-β). NOEs: OMe to H-2‴ (10%), H-β to H-2‴ (8%), H-β to H-6‴ (12%). EIMS *m/z* (rel. int.):993 $[M]^+$ (0.2), 951 (0.3), 774 [M − acetylferuloyl]$^+$ (1.6), 732 (1.7), 467 (17), 425 (24), 383 (9), 248 (17), 219 (12), 206 (14), 177 (27), 43 (94), 42 (100).

cis-Cephaeloside heptaacetate (**4a**). Powder, $[\alpha]_D^{20}$ −145° ($CHCl_3$; *c* 1.0). UV λ_{max}^{EtOH} nm (log ε): 257sh (4.12), 267sh (4.05), 297 (3.71), 308sh (3.57). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1765, 1705, 1635, 1510. ^1H NMR ($CDCl_3$): δ 1.49 (1H, *ddd*, J = 14.5, 12.8, 3.8 Hz, H-6′), 1.89, 2.01, 2.03, 2.13, 2.245, 2.248 and 2.26 (21H, each *s*, 7 × Ac), 2.33 (1H, *ddd*, J = 17.0, 11.3, 7.8 Hz, H-4), 2.54 (1H, *dddd*, J = 12.8, 5.7, 2.5, 2.0 Hz, H-5′), 2.59 (1H, *dd*, J = 16.5, 5.0 Hz, H-4), 2.65 (1H, *ddd*, J = 14.5, 12.5, 2.5 Hz, H-6′), 3.29 (3H, *s*, OMe), 3.32 (1H, *ddd*, J = 9.5, 5.7, 2.0 Hz, H-9′), 3.63 (1H, *ddd*, J = 14.2, 11.3, 5.0 Hz, H-3), 3.64 (3H, *s*, COOMe), 3.70 (1H, *ddd*, J = 9.8, 4.0, 2.0 Hz, H-5″), 4.12 (1H, *dd*, J = 14.2, 7.8 Hz, H-3), 4.15 (1H, *dd*, J = 12.3, 2.0 Hz, H-6″), 4.26 (1H, *dd*, J = 12.3, 4.0 Hz, H-6″), 4.76 (1H, *d*, J = 8.0 Hz, H-1″), 5.04 (1H, *dd*, J = 9.8, 8.0 Hz, H-2″), 5.11 (1H, *t*, J = 9.8 Hz, H-4″), 5.20 (1H, *t*, J = 9.8 Hz, H-3″), 5.29 (1H, *d*, J = 2.0 Hz, H-1′), 5.44 (1H, *dd*, J = 9.5, 3.0 Hz, H-10′), 5.64 (1H, *dt*, J = 17.0, 9.5 Hz, H-8′), 5.69 (1H, *dd*, J = 17.0, 3.0 Hz, H-10′), 5.79 (1H, *dd*, J = 12.5, 3.8 Hz, H-1), 6.44 (1H, *d*, J = 12.5 Hz, H-α), 6.67 (1H, *d*, J = 12.5 Hz, H-β), 6.74 and 6.78 (2H, each *s*, 2 × ArH), 6.86 (1H, *d*, J = 8.5 Hz, H-5‴), 6.88 (1H, *dd*, J = 8.5, 1.5 Hz, H-6‴), 6.93 (1H, *d*, J = 1.5 Hz, H-2‴), 7.30 (1H, *d*, J = 2.0 Hz, H-3′). NOEs: OMe to H-2‴ (16%), H-β to H-2‴ (2%), H-β to H-6‴ (9%), H-β to H-α (11%), H-α to H-β (14%). EIMS *m/z* (rel. int.): 993 $[M]^+$ (0.1), 951 (0.5), 774 [M − acetylferuloyl]$^+$ (1.7), 732 (3), 646 [M − OGlcAc$_4$]$^+$ (1.3), 604 (2), 467 (32), 425 (70), 383 (43), 248 (34), 219 (19), 206 (47), 177 (74), 43 (83), 42 (100).

Treatment of **4a** *with* $Et_3O \cdot BF_4$. To a soln of **4a** (100 mg) in ethylene dichloride (3 ml) was added a soln of $Et_3O \cdot BF_4$ (24.4 mg) in ethylene dichloride (0.5 ml) and the mixt. stirred at room temp. for 40 min. The reaction mixt. was treated with 5% $NaHCO_3$ aq. soln and extracted with $CHCl_3$. The washed and dried $CHCl_3$ layer was concd *in vacuo*. The resulting residue (102.2 mg) was redissolved in $CHCl_3$–MeOH–NH_4OH (90:9:1, 10 ml) and the mixt. stirred for 1 hr. After concn *in vacuo*, the residue was purified by prep. TLC ($CHCl_3$–MeOH, 99:1) to give **8** (11.9 mg), **4a** (15.6 mg) and demethylalangiside tetraacetate (**7**) (23.8 mg) [4]. The ^1H NMR spectrum ($CDCl_3$) showed **8** to be an inseparable mixt. of ethyl *O*-acetyl-*trans*-ferulate and ethyl *O*-acetyl-*cis*-ferulate. *trans* Isomer: δ 1.34 (3H, *t*, J = 7.1 Hz, OCH_2Me), 2.323 (3H, *s*, Ac), 3.864 (3H, *s*, OMe), 4.27 (2H, *q*, J = 7.1 Hz, OCH_2Me), 6.39 (1H, *d*, J = 15.9 Hz, H-α), 7.05 (1H, *d*, J = 8.2 Hz, H-5), 7.11 (1H, *d*, J = 2.0 Hz, H-2), 7.13 (1H, *dd*, J = 8.2, 2.0 Hz, H-6), 7.65 (1H, *d*, J = 15.9 Hz, H-β). *cis* Isomer: δ 1.26 (3H, *t*, J = 7.1 Hz, OCH_2Me), 2.317 (3H, *s*, Ac), 3.859 (3H, *s*, OMe), 4.18 (2H, *q*, J = 7.1 Hz, OCH_2Me), 5.94 (1H, *d*, J = 12.8 Hz, H-α), 6.87 (1H, *d*, J = 12.8 Hz, H-β), 7.01 (1H, *d*, J = 8.2 Hz, H-5), 7.14 (1H, *dd*, J = 8.2, 2.0 Hz, H-6), 7.58 (1H, *d*, J = 2.0 Hz, H-2).

Preparation of O-*acetyl*-cis-*ferulic acid* (**10**). *trans*-Ferulic acid (1.05 g) was acetylated with Ac_2O in pyridine to afford *O*-acetyl-*trans*-ferulic acid (**9**) (1.05 g) as needles, mp 196–197° (Me_2CO). A soln of **9** (100 mg) in MeOH (20 ml) was irradiated with a low-pressure Hg lamp at 45° for 3 hr. After concn of the soln, the resulting crystalline compound **9** (26.7 mg) was filtered off. The filtrate was concd *in vacuo* and purified by prep. TLC ($CHCl_3$–C_6H_6–HOAc, 24:4:1) to give **9** (11.4 mg) and **10** (51.6 mg). *O*-Acetyl-*cis*-ferulic acid (**10**): needles, mp 115–117° (MeOH). ^1H NMR ($CDCl_3$): δ 2.32 (3H, *s*, Ac), 3.83 (3H, *s*, OMe), 5.96 (1H, *d*, J = 12.8 Hz, H-α), 6.98 (1H, *d*, J = 12.8 Hz, H-β), 7.01 (1H, *d*, J = 8.5 Hz, H-5), 7.13 (1H, *dd*, J = 8.5, 1.8 Hz, H-6), 7.58 (1H, *d*, J = 1.8 Hz, H-2).

Preparation of compounds **3a** *and* **4a** *from* **1a**. To a soln of **1a** (500 mg) in ethylene dichloride (6 ml) was added a soln of $Et_3O \cdot BF_4$ (140 mg) in ethylene dichloride (2.5 ml) and the mixt. stirred at 40° for 1 hr. The reaction mixt. was treated with 5% aq. $NaHCO_3$ soln (10 ml) and extracted with $CHCl_3$. The washed and dried organic layer was concd *in vacuo* to yield crude *N*-deacetylipecoside hexaacetate (**11**) (469 mg). This product was immediately used for the next coupling reaction without further purification because of its lactamization in solvents and on silica gel. To an ice-cooled and stirred soln of crude **11** (469 mg) and DCC (126 mg) in THF (2 ml) was added a soln of **9** (144 mg) in THF (8 ml), and the mixt. stirred for a further 75 min. After removal of insol. material by filtration, the filtrate was concd *in vacuo* and submitted to CC eluting with C_6H_6–EtOAc (2:1) to give **3a** (146 mg) as needles, mp 136.5–138° (EtOH). $[\alpha]_D^{20}$ −131° ($CHCl_3$; *c* 1.0). This compound was identical with the acetate of natural **3** (IR, MS, ^1H NMR). Ipecoside hexaacetate (**1a**) (90 mg) was treated with $Et_3O \cdot BF_4$ (34 mg) in ethylene dichloride (2.2 ml) and worked-up in the same way described above. To a soln of the crude product (98 mg) and DCC (25 mg) in THF (2 ml) was added a soln of **10** (24 mg) in THF (1 ml) under ice-cooling. After stirring for 105 min, the reaction mixt. was purified by a combination of prep. TLC (1: C_6H_6–EtOAc, 1:2; 2: Et_2O; 3: $CHCl_3$–MeOH–NH_4OH, 49:4:0.1) to provide an acetate (12 mg). This compound was identical to **4a** {$[\alpha]_D^{27}$ −139° ($CHCl_3$; *c* 0.8), IR, ^1H NMR}.

Zemplen reaction of **3a** *and* **4a**. A soln of **3a** (20 mg) in dry MeOH (5 ml) and 0.06 N NaOMe (0.2 ml) was stirred at room temp. for 18 hr. The reaction mixt. was satd with CO_2 by addition of dry ice and evapd *in vacuo*. The resulting residue was subjected to prep. TLC ($CHCl_3$–MeOH, 17:3) to give **3** (5.8 mg). Compound **4a** (25 mg) was deacetylated and purified in the same way as described above to afford **4** (7.9 mg). These products had ^1H NMR spectra identical to those of isolates **3** and **4**.

Acetylation of **5** *and* **6**. Conventional acetylation of **5** (18.4 mg) and subsequent purification by prep. TLC (C_6H_6–EtOAc, 1:2) afforded **5a** (13.5 mg) and **6a** (2.1 mg). In a similar manner, **6** (20.0 mg) gave **5a** (3.5 mg) and **6a** (20.8 mg).

6-O-*Methyl*-trans-*cephaeloside hexaacetate* (**5a**). Powder, $[\alpha]_D^{22}$ −119° ($CHCl_3$; *c* 1.3). UV λ_{max}^{EtOH} nm (log ε): 217 (4.36), 225sh (4.35), 282 (4.18), 286sh (4.18), 311sh (3.96). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1760, 1706, 1646, 1635, 1608, 1510. ^1H NMR ($CDCl_3$): δ 1.51 (1H, *ddd*, J = 14.5, 12.5, 3.5 Hz, H-6′), 1.87, 1.96, 2.00, 2.10, 2.29 and 2.32 (18H, each *s*, 6

× Ac), 2.60 (1H, *ddd*, J = 12.5, 5.5, 2.5 Hz, H-5'), 2.65 (1H, *ddd*, J = 14.5, 12.0, 2.5 Hz, H-6'), 2.80 (1H, *dd*, J = 16.0, 3.5 Hz, H-4), 2.94 (1H, *ddd*, J = 16.0, 12.5, 6.0 Hz, H-4), 3.30 (1H, *m*, H-9'), 3.64 (3H, *s*, COOMe), 3.67 (1H, *ddd*, J = 9.5, 4.5, 2.0 Hz, H-5''), 3.73 (1H, *ddd*, J = 14.0, 12.5, 3.5 Hz, H-3), 3.78 (3H, *s*, OMe), 3.89 (3H, *s*, OMe), 4.13 (1H, *dd*, J = 12.5, 2.0 Hz, H-6''), 4.18 (1H, *dd*, J = 14.0, 6.0 Hz, H-3), 4.21 (1H, *dd*, J = 12.5, 4.5 Hz, H-6''), 4.76 (1H, *d*, J = 8.0 Hz, H-1''), 4.91 (1H, *dd*, J = 9.5, 8.0 Hz, H-2''), 4.99 (1H, *t*, J = 9.5 Hz, H-4''), 5.15 (1H, *t*, J = 9.5 Hz, H-3''), 5.27 (1H, *d*, J = 2.0 Hz, H-1'), 5.44 (1H, *dd*, J = 8.0, 4.0 Hz, H-10'), 5.68 (2H, *m*, H-8' and H-10'), 5.77 (1H, *dd*, J = 12.0, 3.5 Hz, H-1), 6.64 (2H, *s*, 2 × ArH), 7.03 (1H, *d*, J = 15.5 Hz, H-α), 7.06 (1H, *d*, J = 8.0 Hz, H-5'''), 7.19 (1H, *dd*, J = 8.0, 1.8 Hz, H-6'''), 7.25 (1H, *d*, J = 1.8 Hz, H-2'''), 7.30 (1H, *d*, J = 2.0 Hz, H-3'), 7.57 (1H, *d*, J = 15.5 Hz, H-β). EIMS *m/z* (rel. int.): 965 $[M]^+$ (0.4), 923 (0.4), 746 $[M-$acetylferuloyl$]^+$ (13), 704 (7), 618 $[M-OGlcAc_4]^+$ (3), 576 (3), 439 (63), 397 (77), 355 (25), 220 (100), 219 (16), 178 (56), 177 (68), 43 (34), 42 (26).

6-O-*Methyl*-cis-*Cephaeloside hexaacetate* (**6a**). Powder, $[\alpha]_D^{26}$ −143° ($CHCl_3$; *c* 1.0). UV λ_{max}^{EtOH} nm (log ε): 257sh (4.07), 268 (3.99), 285 (3.81), 297sh (3.67), 312sh (3.41). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1762, 1704, 1636, 1512. ^1H NMR ($CDCl_3$): δ 1.48 (1H, *ddd*, J = 14.5, 13.0, 3.8 Hz, H-6'), 1.89, 2.02, 2.03, 2.13, 2.24 and 2.29 (18H, each *s*, 6 × Ac), 2.18 (1H, *ddd*, J = 16.5, 12.5, 7.0 Hz, H-4), 2.51 (1H, *m*, H-5'), 2.51 (1H, *dd*, J = 16.5, 5.0 Hz, H-4), 2.62 (1H, *ddd*, J = 14.5, 12.5, 2.0 Hz, H-6'), 3.23 (3H, *s*, OMe), 3.35 (1H, *ddd*, J = 9.0, 6.0, 2.0 Hz, H-9'), 3.61 (1H, *ddd*, J = 13.8, 12.5, 5.0 Hz, H-3), 3.62 (3H, *s*, COOMe), 3.70 (1H, *ddd*, J = 9.8, 4.2, 2.0 Hz, H-5''), 3.75 (3H, *s*, OMe), 4.09 (1H, *dd*, J = 13.8, 7.0 Hz, H-3), 4.15 (1H, *dd*, J = 12.5, 2.0 Hz, H-6''), 4.27 (1H, *dd*, J = 12.5, 4.2 Hz, H-6''), 4.76 (1H, *d*, J = 8.2 Hz, H-1''), 5.05 (1H, *dd*, J = 9.8, 8.2 Hz, H-2''), 5.12 (1H, *t*, J = 9.8 Hz, H-4''), 5.21 (1H, *t*, J = 9.8 Hz, H-3''), 5.30 (1H, *d*, J = 2.0 Hz, H-1'), 5.44 (1H, *dd*, J = 9.0, 3.0 Hz, H-10'), 5.64 (1H, *dt*, J = 17.0, 9.0 Hz, H-8'), 5.69 (1H, *dd*, J = 17.0, 3.0 Hz, H-10'), 5.71 (1H, *dd*, J = 12.5, 3.8 Hz, H-1), 6.43 (1H, *d*, J = 12.8 Hz, H-α), 6.66 (1H, *d*, J = 12.8 Hz, H-β), 6.52 and 6.58 (2H, each *s*, 2 × ArH), 6.86 (1H, *d*, J = 8.0 Hz, H-5'''), 6.87 (1H, *br d*, J = 8.0 Hz, H-6'''), 6.94 (1H, *br s*, H-2'''), 7.29 (1H, *d*, J = 2.3 Hz, H-3'). EIMS *m/z* (rel. int.): 965 $[M]^+$ (0.5), 923 (0.9), 746 $[M-$acetylferuloyl$]^+$ (14), 704 (1.5), 618 $[M-OGlcAc_4]^+$ (3), 576 (2), 439 (79), 397 (89), 220 (100), 219 (12), 178 (9), 177 (25), 43 (57), 42 (41).

Preparation of compounds **5a** *and* **6a** *from* **2a**. To a soln of **2a** (91 mg) [4] in ethylene dichloride (2.5 ml) was added a soln of $Et_3O \cdot BF_4$ (21 mg) in ethylene dichloride (0.4 ml). After stirring at 40° for 1 hr, the reaction mixt. was worked-up to provide crude 6-*O*-methyl-*N*-deacetylipecoside pentaacetate (79 mg). This product was coupled with **9** (25 mg) and purified in the same way as described for **3a** to yield **5a** (23 mg), $[\alpha]_D^{28}$ −124° ($CHCl_3$; *c* 1.1). In a similar manner, **6a** (17 mg), $[\alpha]_D^{28}$ −141° ($CHCl_3$; *c* 0.9), was prepd from **2a** (116 mg) and **10** (30 mg). These synthesized products were identical with the acetates from natural **5** or **6** (IR, MS, ^1H NMR).

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