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Synthesis of the naringinase inhibitors L-swainsonine and related 6-*C*-methyl-L-swainsonine analogues: (6*R*)-*C*-methyl-L-swainsonine is a more potent inhibitor of L-rhamnosidase by an order of magnitude than L-swainsonine

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Abstract—Efficient syntheses are reported of the α-L-rhamnosidase inhibitors L-swainsonine [(1*R*,2*S*,8*S*,8a*S*)-octahydroindolizine-1,2,8-triol], (6*R*)-*C*-methyl-L-swainsonine (1*R*,2*S*,6*R*,8*S*,8a*S*)-6-methyloctahydro-indolizine-1,2,8-triol, (6*S*)-*C*-methyl-L-swainsonine (1*R*,2*S*,6*S*,8*S*,8a*S*)-6-methyloctahydro-indolizine-1,2,8-triol and related 6-*C*-methyl hydroxycastanospermines [(1*R*,2*S*,6*R*,7*R*,8*R*,8a*R*)-6-methyl-octahydroindolizine-1,2,6,7,8-pentaol and (1*R*,2*S*,6*S*,8*S*,8a*S*)-6-methyloctahydro-indolizine-1,2,8-triol]. (6*R*)-*C*-Methyl-L-swainsonine [$K_i = 0.032$ μM] is a significantly more potent naringinase inhibitor than L-swainsonine [$K_i = 0.45$ μM].

D-Swainsonine, a natural product isolated[1] from *Swainsona canescens*, is a powerful inhibitor of α-mannosidases—in particular a mannosidase of glycoprotein processing[2]—and may be regarded as a mimic of mannofuranose. Swainsonine is a potential chemotherapeutic agent for the treatment of cancer[3] and accordingly has attracted much synthetic effort.[4] Swainsonine is an example of a carbohydrate mimic in which the ring oxygen of a sugar is replaced by nitrogen;[5,6] such alkaloids have considerable therapeutic potential.[7] Enantiomers of iminosugars frequently show potent biological activity;[8,9] D-imino sugar mimics usually inhibit D-glycosidases competitively while their L-enantiomers are generally more potent non-competitive inhibitors.[10]

L-Swainsonine **1** is a potent inhibitor of naringinase (an L-rhamnosidase);[11] inhibition of enzymes that process non-mammalian sugars may provide new strategies for the treatment of diseases such as those induced by mycobacteria.[12] In contrast, there are only a few syntheses[13] of L-swainsonine **1**. This Letter reports a very efficient synthesis of L-swainsonine **1**. There have been limited studies on the effect of alkyl branches on iminosugars which usually cause significant loss of glycosidase inhibition.[14] Introduction of carbon substituents at C-6 and C-7 of D-swainsonine leads to some reduction in the efficacy of α-mannosidase inhibition.[15] This Letter also describes the synthesis of epimeric 6-*C*-methyl L-swainsonines **2** and **3**, in which the 6(*R*)-epimer **2** is the best inhibitor of naringinase yet reported and shows the first example of significant enhancement of glycosidase inhibition by the introduction of a branching alkyl group. Synthetic dihydroxyswainsonines [hydroxycastanospermines] have been known for some time;[16,17] two such pentahydroxyindolizidines were isolated from the leaves of *Eugenia uniflora*[18] but some doubt has been cast on the proposed structures.[19] This Letter also describes the first syntheses of carbon branched

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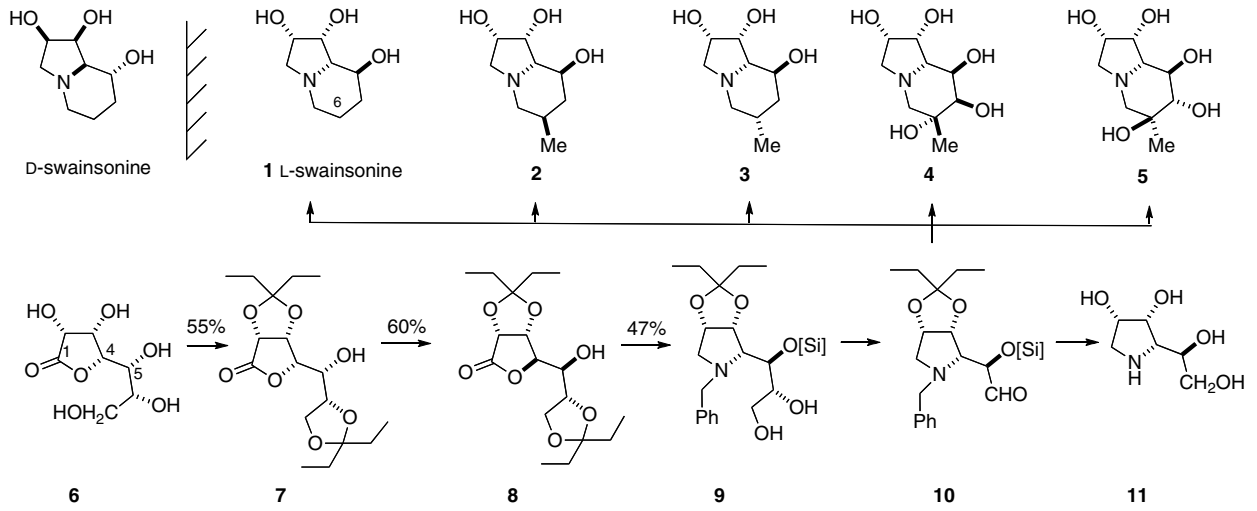
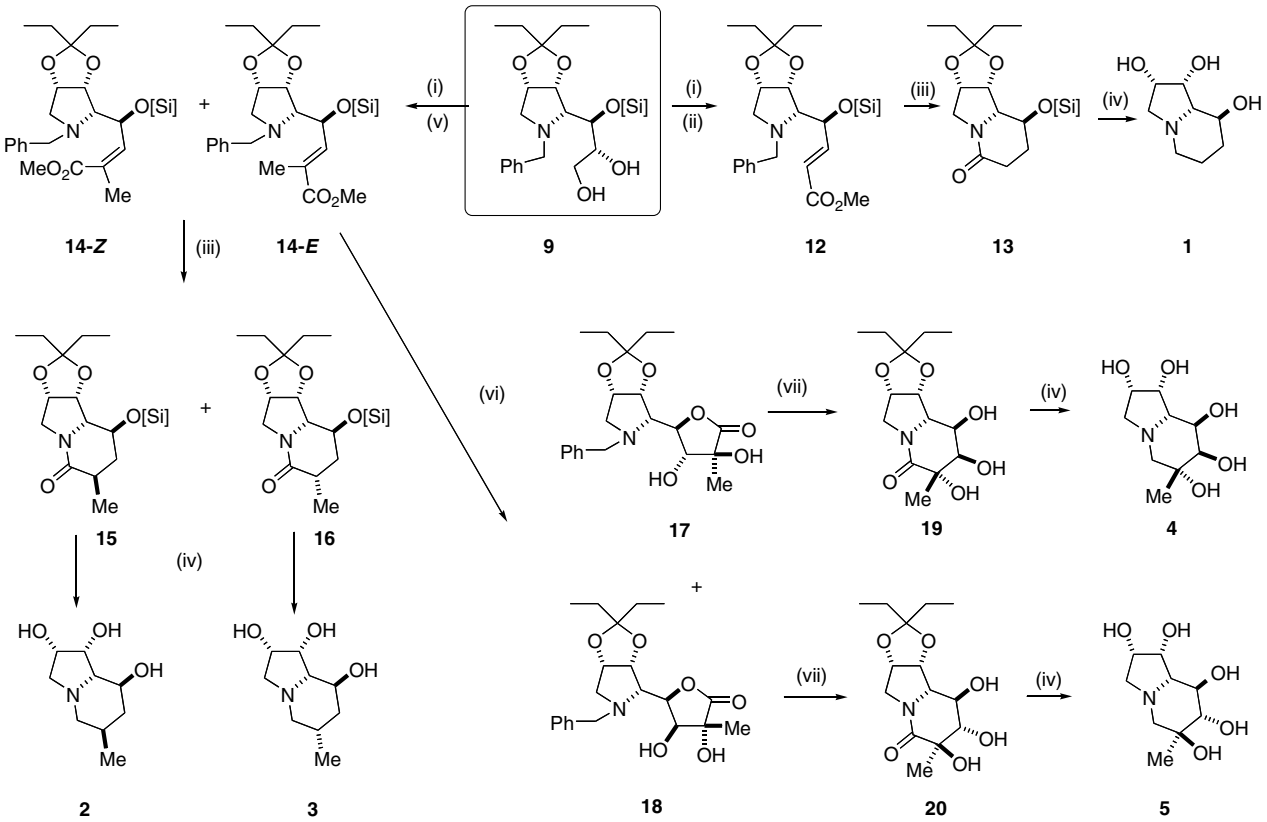
pentahydroxyindolizidines, 6(*R*)- **4** and 6(*S*)-**5** L-dihydroxyswainsonines; again the substitution of a methyl group at C-6 of L-swainsonine significantly enhances inhibition of naringinase.

Diol **9**, the key intermediate for the synthesis of all the L-swainsonine derivatives described in this Letter, has been used for the synthesis of the potent rhamnosidase inhibitor L-DIM **11** and may be prepared from the readily available glucoheptonolactone **6** (Scheme 1).[20] Initial protection of lactone **6** using pentan-3-one as described by Burke[21] allowed access to the C-5 hydroxyl function (55% yield) to give **7**, and to lactone **8**[22] [60% yield] in which the configuration of both C-4 and C-5 had been inverted. Further functional group manipulation gave diol **9** on a multigram scale in 47% yield (28% from **7**; 15% from **6**). Periodate cleavage of **9** gave aldehyde **10** which on in situ treatment with the stabilised Wittig reagent $Bu_3P{=}CHCO_2Me$ afforded the *E*-enoate **12** as an oil, $[\alpha]_D^{22}$ −8.5 (*c*, 1.0, $CHCl_3$), in 81% yield (Scheme 2).



Scheme 1. For details of conversion of **6** to **9**, see Ref. 20.



Scheme 2. Reagents: (i) $NaIO_4$, MeOH, H_2O; (ii) $Bu_3P{=}CHCO_2Me$ (81% over two steps); (iii) H_2, $Pd(OH)_2$, dioxane/H_2O, 6:1 (95%); (iv) BH_3, THF; then CF_3CO_2H:H_2O, 9:1 (82%); (v) $Bu_3P{=}C(Me)CO_2Me$ (81% over two steps); (vi) TBAF, pyridinium chloride, THF; K_2OsO_4, NMO, $(DHQ)_2AQN$; (vii) H_2, $Pd(OH)_2$, dioxane/H_2O, 6:1; then K_2CO_3, MeOH.

Hydrogenation of **12** in aqueous dioxane in the presence of palladium hydroxide on carbon gave lactam **13** in 95% yield. Reduction of the amide **13** with borane in THF, followed by deprotection of the product with aqueous trifluoroacetic acid formed L-swainsonine **1** in 82% yield (9.8% overall from **6**, 17.9% from **7**).[23] This synthetic route allows the preparation of significant amounts of crystalline L-swainsonine **1**.

For the synthesis of the branched 6(*R*)- **2** and 6(*S*)-**3** *C*-methylswainsonines, diol **9** was cleaved by periodate and then treated in situ with $Bu_3P{=}C(Me)CO_2Me$ to give a mixture of enoates **14-*Z*** and **14-*E*** in a ratio of 1:4 and 81% combined yield. Hydrogenation of the mixture **14** in aqueous dioxane in the presence of palladium hydroxide on carbon gave lactams **15** and **16** as separable oils in 43% and 28% yields, respectively; the stereochemistry at C-6 of **15** and **16** was deduced from the products of subsequent reactions. The reduction of **15** by borane in THF, followed by deprotection of the crude product with aqueous trifluoroacetic acid, afforded 6*R*-*C*-methyl-L-swainsonine **2**[24] in 77% yield. Similar treatment of **16** gave 6*S*-*C*-methyl-L-swainsonine **3**[25] in 81% yield, the structure of which was firmly established by X-ray crystallographic analysis.[26] 6*R*-*C*-Methyl-L-swainsonine **2** is the most potent inhibitor of L-rhamnosidase yet reported.

The solution NMR structures of the methyl substituted compounds **2** and **3** were compared with that of L-swainsonine **1**. Full ^1H and ^{13}C assignments for all three compounds are given in Tables 1–3.

The $^3J_{HH}$ coupling constant values are sensitive to both the relative configurations of the ring protons and to the ring conformation.[27] The values of the C7H/H′–C8H–C8aH–C1H–C2H–C3H/H′ coupling constants are very similar for **1**, **2** and **3** (Table 2) indicating the same relative configurations at these carbons and that all three compounds adopt the same ring conformation, with the C7H′, C8H and C8aH protons axial and the C7H and C1H protons equatorial. The large C5H′–C6H–C7H′ couplings in **2** indicate that these three protons are all axial, and so the C6 methyl group is equatorial. The lack of a large coupling between C6H and either C5H, C5H′, C7H or C7H′ in **3** indicates that C6H is equatorial, and so the C6 methyl group is axial. These patterns of coupling constants and the patterns of NOEs (not shown) for all three compounds are fully consistent with the ring conformation, or its enantiomer, reported for the crystal structure of swainsonine diacetate.[28] Thus, methylation at the C6 position has no effect on the overall ring conformation of **1**.

The 6(*R*)- **4** and 6(*S*)- **5** *C*-methyl dihydroxyswainsonines were also prepared. Attempts at dihydroxylation

Table 1. ^1H NMR (500 MHz) assignments (ppm) of **1**, **2** and **3** in ^2H_2O at pH 9, referenced to acetone at 2.220 ppm

	1	2	3
C5H	2.912[a]	2.870	2.749
C5H′	1.964[a]	1.640	2.135
C6H	1.716	1.71	2.07
C6H′	1.514	—	—
$C6CH_3$	—	0.899	1.048
C7H	2.054	2.059	1.882
C7H′	1.234	0.962	1.424
C8H	3.798	3.826	4.018
C8aH	1.925[a]	1.883	1.843
C1H	4.254	4.240	4.235
C2H	4.347	4.349	4.331
C3H	2.889[a]	2.863	2.850
C3H′	2.566	2.531	2.493

[a] Chemical shifts determined from HSQC because of overlap in the ^1H 1D spectrum.

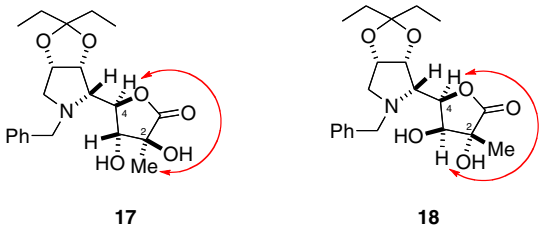
Table 2. $^3J_{HH}$ NMR coupling constants (Hz) of **1**, **2** and **3** in ^2H_2O at pH 9

	1	2	3
C5H–C5H′	nd	−10.9	−11.2
C5H–C6H	nd	3.0[b]	1.5[b]
C5H′–C6H	nd	10.9	3.7
C6H–$C6CH_3$	—	6.5	7.4
C6H–C7H	nd	4.2	2.0[b]
C6H–C7H′	nd	11.4	5.3
C7H–C7H′	nd	−12.3	−12.6
C7H–C8H	4.3	4.6	4.5
C7H′–C8H	10.6	11.0	11.3
C8H–C8aH	9.8[a]	9.7	9.6
C8aH–C1H	3.3	3.7	3.7
C1H–C2H	5.7	5.9	6.0
C2H–C3H	1.6[a]	2.5	2.4
C2H–C3H′	8.3	7.9	8.0
C3H–C3H′	−10.7	−11.0	−11.0

[a] Couplings determined from HSQC because of overlap in the ^1H 1D spectrum.
[b] Couplings estimated by simulation of the 1D spectrum.

Table 3. ^{13}C NMR (125.7 MHz) assignments (ppm) of **1**, **2** and **3** in ^2H_2O at pH 9, referenced to acetone at 30.90 ppm

	1	2	3
C5	51.93	59.20	58.07
C6	23.43	29.63	28.86
$C6CH_3$	—	18.63	19.11
C7	32.73	41.52	38.49
C8	66.61	66.21	63.66
C8a	73.07	72.72	73.88
C1	69.95	69.69	70.12
C2	69.31	69.55	69.53
C3	60.85	60.62	61.65



17 **18**

Figure 1. NOEs used to determine the relative stereochemistries of **17** and **18**.

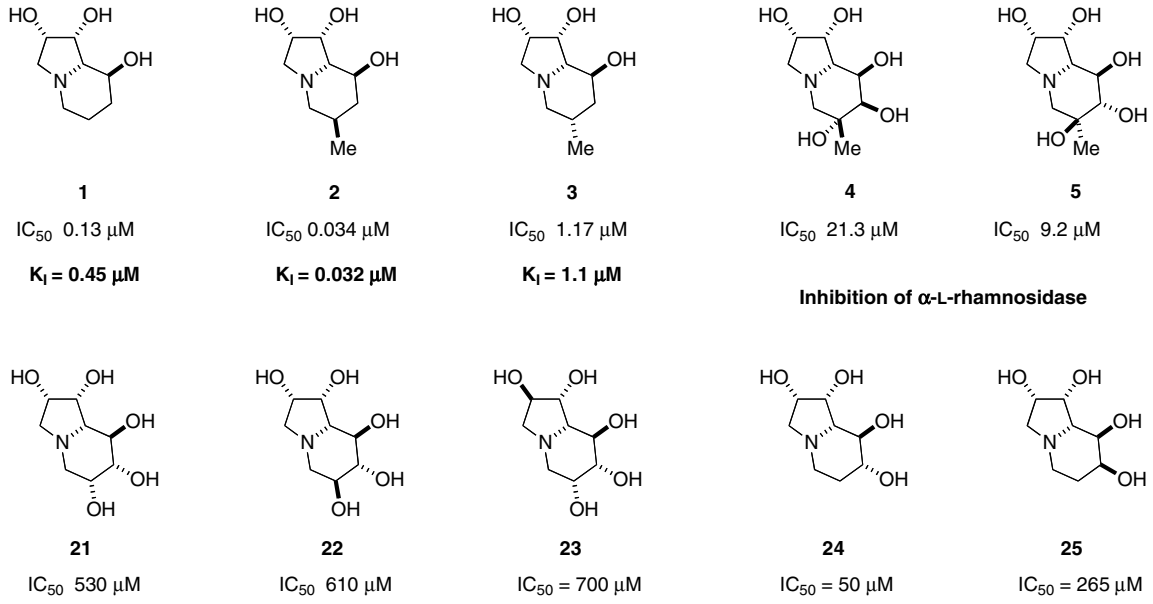


Figure 2. IC_{50} (μM) of naringinase inhibition by L-swainsonine analogues.

of the major enoate **14-*E*** under a number of different conditions failed; however, initial deprotection of the silyl ether in **14-*E*** using tetrabutylammonium fluoride (TBAF) and pyridinium chloride in THF (76% yield), followed by dihydroxylation with potassium osmate and *N*-methylmorpholine-*N*-oxide (NMO) in the presence of $(DHQ)_2AQN$, afforded the separable lactones **17**[29] and **18**[30] in a combined yield of 72% in a ratio of 3:1 (Fig. 1).

The stereochemical outcome was assigned by the NOE experiments indicated in Figure 2, since the cis-hydroxylation of the *E*-enoate **14-*E*** guaranteed a trans-relationship between the hydroxyl substituents in the lactone ring. Hydrogenation of **17**, the major product, in the presence of Pearlman's catalyst (20% $Pd(OH)_2$/C) in dioxane, followed by treatment with potassium carbonate in methanol promoted rearrangement of lactone **17** to lactam **19**; reduction of lactam **19** with borane in THF, followed by deprotection with aqueous trifluoroacetic acid afforded the 6(*R*)-methyl branched dihydroxyswainsonine **4**.[31] A similar sequence of reactions on **18** gave, via lactam **20**, the 6(*S*)-epimer **5**[32] in 22% yield.

The L-swainsonine analogues **1**–**5** were evaluated as naringinase inhibitors and compared to the unbranched analogues **21**–**25** reported previously;[17] none of the L-swainsonine analogues showed any significant inhibition of α-D-mannosidase.[33] While L-swainsonine **1** showed potent inhibition activity towards *Penicillium decumbens* α-L-*rhamnosidase* (K_i 0.45 μM), the introduction of a 6*R*-*C*-methyl group **2** led to a significant increase in potency of rhamnosidase inhibition (K_i 0.032 μM) (Fig. 2). The 6*S*-epimer **3** (K_i 1.1 μM) was only a marginally weaker inhibitor than **1** (K_i 0.45 μM). All the unbranched dihydroxyswainsonines **21**–**25** were much weaker inhibitors than **1**. However introduction of a C-6 methyl group to dihydroxyswainsonines **4** and **5** caused a significant increase in their inhibitory potency; thus, whereas dihydroxyswainsonine **22** showed an IC_{50} value of 610 μM, the introduction of a 6*S*-methyl group in **5** lowered the IC_{50} value to 9.2 μM.

In summary, this Letter reports an efficient synthesis of L-swainsonine **1** and several analogues with a branching C-6 methyl group. The introduction of a methyl group at C-6 in most L-swainsonine analogues increases the α-L-rhamnosidase inhibition and, in particular, the 6*R*-*C*-methyl analogue **2** is the most potent naringinase inhibitor yet described.

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23. Selected data for L-swainsonine **1**: mp 143–144 °C; $[\alpha]_D^{20}$ +79.5 (*c* 2.65, H_2O) {lit.[17] mp 143–145 °C; $[\alpha]_D^{21}$ +84.3 (*c*, 1.02, H_2O)}. For NMR data, see Tables 1–3.
24. Selected data for 6*R*-*C*-methyl-L-swainsonine **2**: mp 166–167 °C (H_2O); $[\alpha]_D^{22}$ +77.5 (*c* 2.57, H_2O); for NMR data, see Tables 1–3.
25. Data for 6*S*-*C*-methyl-L-swainsonine **3**: mp 148–150 °C (decomp., H_2O); $[\alpha]_D^{22}$ + 43.7 (*c* 1.72, H_2O); For NMR data, see Tables 1–3.
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29. Data for **17**: $R_f = 0.20$ (EtOAc/cyclohexane, 1:2); $[\alpha]_D^{20}$ +23.2 (*c* 2.32, $CHCl_3$); IR (film) $\nu = 3440$ (OH), 1785 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) $\delta = 7.33–7.21$ (m, 5H, Ar*H*), 4.81 (d, $J_{3,4} = 7.7$ Hz, 1H, H-3), 4.70–4.64 (m, 2H, H-6, H-7), 4.61 (br s, 1H, OH), 4.47 (dd, $J =$ 1.0 Hz, $J_{3,4} = 7.7$ Hz, 1H, H-4), 3.99 (d, $J_{ArCHa,ArCHb} =$ 13.4 Hz, 1H, ArC*H*a), 3.07 (app d, $J = 12.5$ Hz, 2H, H-8a, ArC*H*b), 2.95–2.93 (m, 1H, H-5), 2.75 (br s, 1H, OH), 2.13 (dd, $J_{7,8b} = 4.9$ Hz, $J_{8a,8b} = 11.5$ Hz, 1H, H-8b), 1.94–1.74 (m, 2H, $C(CH_2CH_3)_2$), 1.68–1.53 (m, 2H, $C(CH_2CH_3)_2$), 1.49 (s, 3H, 2-Me), 1.02 (t, $J_{Et} = 7.5$ Hz, 3H, $C(CH_2CH_3)_2$), 0.87 ppm (t, $J_{Et} = 7.5$ Hz, 3H, $C(CH_2CH_3)_2$); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 177.3$ (C=O), 138.0, 128.4, 128.4, 127.2 (Ar*C*), 116.4 ($C(CH_2CH_3)_2$), 81.4 (C-4), 80.8 (C-7), 77.5 (C-6), 76.3 (C-2), 72.7 (C-3), 67.5 (C-5), 60.1 (C-8), 58.6 ($ArCH_2$), 28.5, 28.3 ($C(CH_2CH_3)_2$), 19.3 (2-Me), 8.5, 7.6 ppm ($C(CH_2CH_3)_2$); HRMS *m*/*z* (ESI +ve): $[M+H]^+$ calcd for $C_{21}H_{30}NO_6$, 392.2068; found, 392.2067.
30. Data for **18**: $R_f = 0.28$ (EtOAc/cyclohexane, 1:2); $[\alpha]_D^{20}$ +31.8 (*c* 2.06, $CHCl_3$); IR (film) $\nu = 3418$ (OH), 1784 (C=O) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) $\delta = 7.34–7.22$ (m, 5H, Ar*H*), 5.03 (dd, $J_{4,5} = 1.5$ Hz, $J_{3,4} = 2.8$ Hz, 1H, H-4), 4.80 (dd, $J_{5,6} = 5.0$ Hz, $J_{6,7} = 6.4$ Hz, 1H, H-6), 4.63–4.59 (m, 2H, H-3, H-7), 4.47 (d, $J_{ArCHa,ArCHb} =$ 12.8 Hz, 1H, ArC*H*a), 3.28 (dd, $J_{4,5} = 1.4$ Hz, $J_{5,6} = 5.0$ Hz, 1H, H-5),3.07 (d, $J_{8a,8b} = 11.9$ Hz, 1H, H-8a), 3.05 (d, $J_{ArCHa,ArCHb} = 12.8$ Hz, 1H, ArC*H*b),

2.08 (dd, $J_{7,8b} = 5.1$ Hz, $J_{8a,8b} = 11.9$ Hz, 1H, H-8b), 1.83 (q, $J_{Et} = 7.6$ Hz, 2H, C(CH_2CH_3)$_2$), 1.58 (s, 3H, 2-Me), 1.60–1.52 (m, 2H, C(CH_2CH_3)$_2$), 0.99 (t, $J_{Et} = 7.6$ Hz, 3H, C(CH_2CH_3)$_2$), 0.86 ppm (t, $J_{Et} = 7.6$ Hz, 3H, C(CH_2CH_3)$_2$); ^{13}C NMR (100 MHz, $CDCl_3$) $\delta = 176.5$ (C=O), 136.7, 128.8, 128.6, 127.5 (Ar*C*), 116.3 (*C*(CH_2CH_3)$_2$), 80.8 (C-6), 79.5 (C-3), 78.2 (C-4), 77.6 (C-2), 77.0 (C-7), 68.4 (C-5), 60.3 (Ar*C*H_2), 59.4 (C-8), 28.3, 26.6 (C(*C*H_2CH$_3$)$_2$), 17.6 (2-Me), 8.6, 8.4 ppm (C(CH_2*C*H_3)$_2$); HRMS *m*/*z* (ESI +ve): $[M+H]^+$ calcd for $C_{21}H_{30}NO_6$, 392.2068; found, 392.2068.

31. 6(*R*)-Methyl branched dihydroxyswainsonine **4**: $[\alpha]_D^{20}$ +36.2 (*c* 1.05, H_2O); ^{1}H NMR (400 MHz, D_2O) $\delta = 4.36$ (ddd, $J_{2,3} = 2.8$ Hz, $J_{1,2} = 5.7$ Hz, $J_{2,3'} = 8.5$ Hz, 1H, H-2), 4.18 (dd, $J_{1,8a} = 3.7$ Hz, $J_{1,2} = 5.7$ Hz, 1H, H-1), 4.11 (dd, $J_{7,8} = 3.3$ Hz, $J_{8,8a} = 10.4$ Hz, 1H, H-8), 3.61 (d, $J_{7,8} = 3.3$ Hz, 1H, H-7), 2.88 (dd, $J_{2,3} = 2.8$ Hz, $J_{8,8a} = 10.9$ Hz, 1H, H-3), 2.69–2.62 (m, 2H, H-3′, H-5), 2.37–2.29 (m, 2H, H-5′, H-8a), 1.21 ppm (s, 3H, 6-Me); ^{13}C NMR (100 MHz, D_2O) $\delta = 74.5$ (C-7), 72.7 (C-6), 70.2 (C-1), 69.7 (C-2), 65.5 (C-8), 64.8 (C-8a), 59.5 (C-3), 56.6 (C-5), 23.1 ppm (6-Me); HRMS *m*/*z* (ESI +ve): $[M+H]^+$ calcd for $C_9H_{18}NO_5$, 220.1179; found, 220.1188.
32. 6(*S*)-Methyl branched dihydroxyswainsonine **5** $[\alpha]_D^{20}$ +27.7 (*c* 0.85, H_2O); ^{1}H NMR (400 MHz, D_2O) $\delta = 4.38$–4.31 (m, 1H, H-2), 4.18 (dd, $J = 3.5$ Hz, $J = 5.8$ Hz, 1H, H-1), 3.60 (app t, $J = 10.0$ Hz, 1H, H-8), 3.32 (d, $J = 9.3$ Hz, 1H, H-7), 2.87–2.81 (m, 2H, H-3, H-5), 2.52 (dd, $J_{2,3'} = 8.1$ Hz, $J_{3,3'} = 10.7$ Hz, 1H, H-3′), 2.10–2.01 (m, 2H, H-5′, H-8a), 1.23 ppm (s, 3H, 6-Me); ^{13}C NMR (100 MHz, D_2O) $\delta = 80.9$ (C-7), 72.7 (C-6), 71.7 (C-8a), 70.0 (C-2), 69.6 (C-1), 68.2 (C-8), 62.0 (C-5), 60.2 (C-3), 20.3 ppm (6-Me); HRMS *m*/*z* (ESI −ve): $[M-H]^-$ calcd for $C_9H_{16}NO_5$, 218.1023; found, 218.1023.
33. For details of the enzyme assays see Ref. 20.