Synthesis of Monoterpene Piperidines from the Iridoid Glucoside Antirrhinoside

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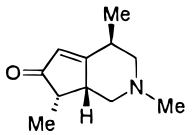
Synthesis of five novel piperidine monoterpene alkaloids (**17**−**21**) using the iridoid glucoside antirrhinoside (**4**) as a synthon is described. Two strategies for their preparation were investigated: the first possible pathway involved an intermediate diol, **13**, from which the piperidine ring was expected to be constructed via reaction of its ditosylate with an amine; the second strategy involved a double reductive amination as the key step to the piperidine ring, which proved successful. The stereochemistry of C-5 and C-9 in the obtained piperidine monoterpenes was the same as that reported for α-skytanthine (**3**), a known isolate from *Skytanthus acutus* (Apocynaceae).

Monoterpene alkaloids have been the subject of much interest because they often exhibit pharmacological activity.[1] The piperidine alkaloids especially, from *Skytanthus acutus* and *Tecoma stans*[2] have been studied intensively, and tecomanine (**1**) has been shown to have hypoglycemic activity.[3−5] Also, incarvilline (**2**) and related compounds from *Incarvillea sinensis*[6−9]—used in the Chinese traditional medicine to treat rheumatism and to relieve pain—have been investigated.

Advanced synthetic pathways to such compounds have been reported; for example, (+)-**1** has been synthesized enantioselectively.[10,11] Moreover, (+)-α-skytanthine (**3**) has been prepared by cyclization of an intermediate cyclopentanoid ditosylate with methylamine,[12] and a hydroxylated 3-azabicyclo[4.3.0]nonane, racemic isooxyskytanthine, has been prepared using a photocyclization step.[13] Recently, a Mitsunobu-type cyclization has been employed for the formation of the piperidine ring in **3**.[14] Finally, there have been several reports[15−19] on the synthesis of simple 3-azabicyclo[4.3.0]nonanes.



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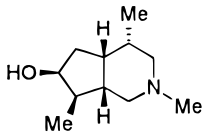

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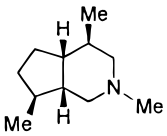

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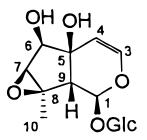
The biological activity known for some natural piperidine monoterpenes encouraged us to synthesize enantiomerically pure analogues. Utilizing the chirality already present in the iridoid aglucone, steps involving expensive chiral catalysts or reagents, as well as separations of racemates, may be avoided. Previously, one of us has reported[20] on the conversion of antirrhinoside (**4**) into the pyridine **5**. As a part of our current investigation of **4** as a synthon for cyclopentanoids, we have synthesized five novel piperidine monoterpenes with the same stereochemistry at C-5 and C-9 as **2** and **3**, but lacking the methyl group at C-4.

Results and Discussion

Multigram amounts of antirrhinoside (**4**) can readily be obtained from *Antirrhinum majus* L. (Scrophulariaceae). The commercial varieties "White Wonder" and "Bright Eyes" are preferred because of their high content (1.5% of fresh wt) of **4** and the presence of only small amounts of the closely eluting antirrhide (**6**) and 5-glucosylantirrhinoside (**7**). Isolation was performed by reversed-phase chromatography of the H_2O-soluble part of the crude EtOH extract as earlier described.[21]



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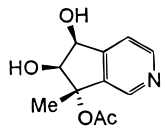

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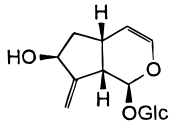

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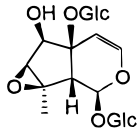

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In the present work utilizing **4** as a synthon for cyclopentanoids, our first goal was to make a synthetically useful intermediate. Since our primary aim was piperidines, tosylation[22] or mesylation[23] of the diol **13** (see Scheme 1) and subsequent treatment with an appropriate amine seemed the most straightforward method for achieving this.

Previously, a $SnCl_2$-catalyzed reaction of **4** has been reported[24] to yield the 5,6-monoisopropylidene derivative **10** directly in 49% yield. However, in our hands this reaction gave a complex mixture of products. Attempts with mild ketalization methods[25−27] (as **4** degraded under conditions using strong acids) showed that the sugar 4′,6′-diol moiety was reacting faster (with **8** as an isolable intermediate) than the aglucone 5,6-diol. This problem was overcome by first preparing the diisopropylidene derivative (**9**) using pyridinium *p*-toluenesulfonate (PPTS) and 2,2-dimethoxypropane in Me_2CO[27] and subsequently removing the 4′,6′-isopropylidene group by heating at 60 °C in dilute HOAc. Thus, a 72% overall yield of **10** was obtained. Now, to avoid the inherent problem of cyclobutane formation[28] during $NaBH_4$ reduction of the aglucone of 5,6-isopropylidene antirrhinoside (**10**), hydrogenation of **11** was performed prior to enzymatic cleavage by β-glucosidase,

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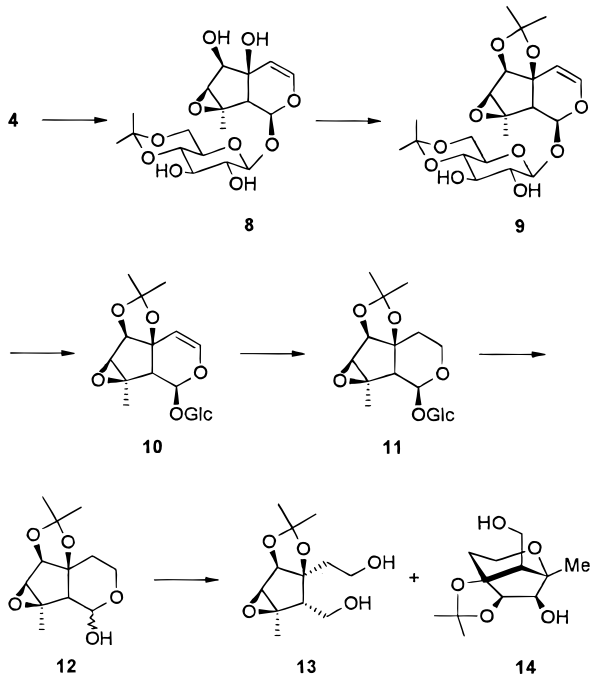
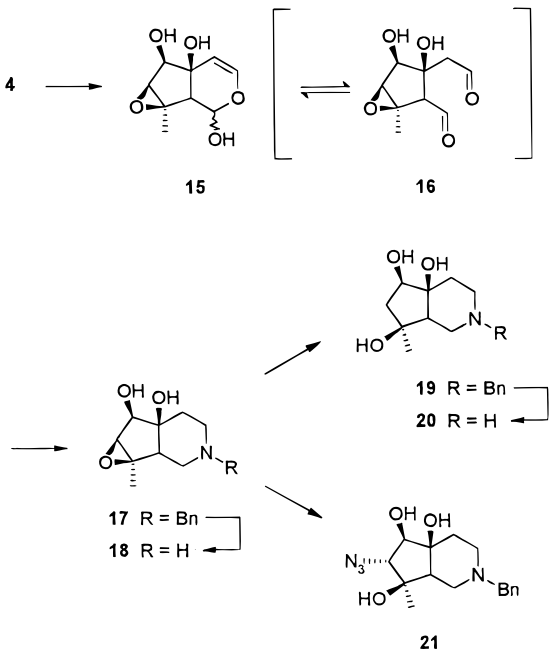
Scheme 1. Preparation of a Precursor (**13**) of Piperidines



Scheme 2. Piperidine Synthesis via Double Reductive Amination



which next afforded the crystalline hemiacetal **12** in 85% overall yield. Reduction of **12** with $NaBH_4$ (in MeOH or dioxane$-H_2O$) was anticipated to furnish the intermediate diol **13**. However, in addition to the expected diol **13**, a less polar by-product, **14**, was isolated in varying amounts, and it was occasionally the main product. Analysis of the ^{1}H-NMR spectrum of **14** showed that the epoxide had been opened (H-7 at δ 3.16 with $J_{6,7} = 1.5$ Hz in **13** was shifted downfield to δ 3.92 with $J_{6,7} = 6$ Hz in **14**), and usual acetylation conditions gave only a diacetate with H-7 shifted further downfield to δ 4.78 ($J_{6,7} = 6$ Hz). Together, these facts were taken as evidence for the tricyclic structure **14** proposed for the by-product; cyclization had proceeded via attack of the primary 3-OH group (iridoid numbering is preserved for aglucone derivatives) at the more hindered position of the epoxide. Thus, it was possible to obtain the desired product **13**, but, due to the disadvantage of its lability towards weakly basic conditions, for example, acylation (benzoylation and tosylation) in pyridine as well as weak acids (dilute HOAc), we decided to abandon the above synthetic scheme and try another strategy for piperidine synthesis from **4**.

Because antirrhinoside aglucone (**15**) in principle is in equilibrium with the dialdehyde form **16** (although not observable by NMR spectroscopy), a double reductive amination[29−31] seemed a promising alternate pathway to piperidines. Thus, after enzymatic removal of the sugar moiety, almost pure antirrhinoside aglucone was obtained in reasonable yield (74%) using continuous extraction, and the crystalline compound could be obtained after reversed-phase chromatography (58% overall). The reductive amination of **15** was performed with $NaCNBH_3$ and benzylamine hydrochloride in MeOH solution. Benzylamine was chosen as the amine because the benzyl group was expected to confer sufficient hydrophobicity on the resulting piperidine to facilitate purification of the reaction mixture. Indeed, it was found that the only major apolar impurity present in the crude product was the readily separable benzylamine itself. Even though the yield of *N*-benzylated piperidine **17** was modest (37%) the route was attractive because of its few steps. No significant improvements were achieved by changing: (a) the amount of reductant, (b) the amount of benzylamine hydrochloride, or (c) the reaction time; however, it was found that slow addition of the reductant was important.

The piperidine (**17**) was modified by opening of the epoxide in two different ways. First a $LiAlH_4$ reduction[32] yielded selectively the 8-OH compound, **19**, in reasonable yield. In addition, an azide functionality could be introduced by azidolysis[33] of the epoxide to give the azido derivative, **21**. Both the original piperidine **17** and the modifications **19** and **21** were hydrogenated under Pd/C catalysis to remove the *N*-benzyl protective group. However, only the two former gave pure debenzylated products (i.e., **18** and **20**), whereas the azido compound **21** gave a mixture of partially reduced products in low yield. (See Scheme 2.)

Thus, we have shown that an iridoid aglucone of the decarboxylated type may be converted smoothly into a piperidine compound in only two steps. This was substantiated by an additional small-scale experiment in which the aglucone of another iridoid, catalpol, was shown to be able to undergo a similar reaction to give a piperidine. The intermediate hemiacetal **12** may also prove useful for synthesis of, for example, prostaglandin analogues. Furthermore, we are currently investigating the synthesis of the corresponding pyrrolidines (i.e., after loss of C-3) from **10**.

Experimental Section

General Experimental Procedures. Antirrhinoside (**4**) was isolated[21] from *Antirrhinum majus*. The β-glucosidase was purchased from Sigma Chemical Co. THF was distilled from sodium and stored over molecular (4 Å) sieves until use. Elemental analyses were performed by the Microanalytical Department at the H.C. Ørsted Institute (University of Copenhagen). Optical rotations (10^{-1} deg cm^2 g^{-1}) were measured on a

Table 1. ^{13}C NMR of Antirrhinoside Derivatives (in Me_2CO-d_6)

carbon	**4**[a]	**8**	**9**	**10**	**11**
1	95.01	95.52	95.38	95.17	95.86
3	143.04	141.71	143.05	142.88	60.53
4	106.99	107.86	109.22	109.18	33.41
5	74.36	73.84	87.66	87.78	89.50
6	76.74	75.42[b]	86.22	86.33	85.03
7	66.29	65.81	63.68	63.73	64.45
8	65.09	63.20	67.36	67.56	67.25
9	51.99	53.06	53.26	53.41	53.78
10	16.98	17.74	18.03	18.07	17.33
$(CH_3)_2\mathbf{C}<$			113.99	114.02	113.47
$(\mathbf{CH_3})_2C<$			28.02	28.06	28.24
			29.58	29.60	30.33
1′	99.29	99.98	99.82[c]	99.25	98.71
2′	73.41	75.42[b]	75.43	74.60	74.53
3′	77.08	74.32	74.31[d]	77.77	78.07
4′	70.41	74.32	74.52[d]	71.62	71.59
5′	76.38	68.38	68.38	77.94	77.59
6′	61.49	62.65	62.64	62.98	62.86
$(CH_3)_2\mathbf{C}<$		99.90	99.82[c]		
$(\mathbf{CH_3})_2C<$		19.33	19.33		
		29.46	29.48		

[a] In D_2O. [b,c] Double intensity. [d] Signals interchangeable.

Perkin-Elmer 241 polarimeter. Melting points are uncorrected. TLC was performed on Merck Si gel 60 F_{254} aluminium sheets with detection by charring with H_2SO_4, or by UV light when applicable. Medium-pressure Liquid chromatography (MPLC) was performed on a Merck Lobar Lichroprep RP-18 C-column. VLC (vacuum liquid chromatography) was performed on predried (120 °C; >24 h) Merck Si gel 60H (0.04−0.06 mm); the column size is given as height × diameter (cm). NMR spectra were recorded on a Bruker AM-500 or HX-250 spectrometer. Chemical shifts are given in parts per million, using the solvent peaks as internal standards (Me_2CO-d_6: δ 2.05, MeOH-d_4: δ 3.31, D_2O: δ 4.75, $CDCl_3$: δ 7.27). *J* values are given in Hertz. For all compounds assignments of ^1H-NMR spectra were based on 1D homonuclear decoupling experiments, while ^{13}C-NMR spectra were assigned using carbon−proton shift-correlation spectra. Mass spectra (positive mode electron impact) were obtained on a VG Trio-2 apparatus.

5,6:4′,6′-Di-*O*-Isopropylidene Antirrhinoside (9). To **4** (1.50 g, 4.14 mmol) in MeCO (35 mL) was added 2,2-dimethoxypropane (10.2 mL, 82.8 mmol) and PPTS (2.07 g, 8.28 mmol). Stirring at room temperature for 1 h was followed by 30 min at 40 °C, then Et_3N (1.72 mL, 12.4 mmol) was added and the reaction mixture concentrated. The oily residue was purified by MPLC (two runs) to yield **9** (1.45 g, 77%) as a hygroscopic foam; $[\alpha]^{23}_D$ −107° (*c* 0.44, MeOH); ^1H NMR (Me_2CO-d_6, 500 MHz,) δ 6.42 (1H, d, *J* = 6 Hz, H-3), 5.17 (1H, d, *J* = 8 Hz, H-1), 5.09 (1H, d, *J* = 6 Hz, H-4), 4.79 (1H, d, *J* = 8 Hz, H-1′), 4.46 (1H, d, *J* = 2 Hz, H-6), 3.84 (1H, dd, *J* = 10.5, 5 Hz, H-6a′), 3.73 (1H, t, *J* = 10.5 Hz, H-6b′), 3.53 (2H, m, H-3′ and H-4′), 3.34 (1H, m, H-2′), 3.29 (1H, d, *J* = 2 Hz, H-7), 3.28 (1H, m, H-5′), 2.51 (1H, d, *J* = 8 Hz, H-9), 1.47, 1.45 (each 3H, s, isopropylidene), 1.40 (3H, s, H-10), 1.33 (6H, br s, isopropylidene); ^{13}C NMR, see Table 1; *anal.* C 55.86%, H 6.74%, calcd for $C_{21}H_{30}O_{10}\cdot{}^1/_2H_2O$, C 55.87%, H 6.92%.

5,6-*O*-Isopropylidene Antirrhinoside (10). Diacetonide **9** (980 mg, 2.22 mmol) was heated in 1% aqueous HOAc (10 mL) at 60 °C for 5 h, at which point no more starting material could be detected by TLC ($CHCl_3$−MeOH 9:1, R_f 0.70 and 0.19 for diacetonide and monoacetonide, respectively). The reaction mixture was made alkaline with Et_3N (0.36 mL) and concentrated. The residue was purified by MPLC to yield **10** (830 mg, 93%) as a hygroscopic foam; $[\alpha]^{23}_D$ −100° (*c* 0.48, MeOH); ^1H NMR (Me_2CO-d_6, 500 MHz) δ 6.42 (1H, d, *J* = 6 Hz, H-3), 5.31 (1H, d, *J* = 7 Hz, H-1), 5.08 (1H, d, *J* = 6 Hz, H-4), 4.72 (1H, d, *J* = 7.5 Hz, H-1′), 4.44 (1H, d, *J* = 1.5 Hz, H-6), 3.86 (1H, m, H-6a′), 3.62 (1H, m, H-6b′), 3.43 (1H, m, H-3′), 3.36 (2H, m, H-4′ and H-5′), 3.28 (1H, d, *J* = 1.5 Hz, H-7), 3.25 (1H, m, H-2′), 1.46 (3H, s, isopropylidene), 1.43 (3H, s, H-10), 1.33 (3H, s, isopropylidene); ^{13}C NMR, see Table 1; *anal.* C 52.14%, H 6.50%, calcd for $C_{18}H_{26}O_{10}\cdot{}^1/_2H_2O$, C 52.54%, H 6.63%.

3,4-Dihydro-5,6-*O*-isopropylidene Antirrhinoside (11). To **10** (4.39 g, 10.92 mmol) in MeOH (50 mL) was added Pt/C (5%, 440 mg). The suspension was stirred vigorously under hydrogen (1 atm). When the consumption of H_2 had subsided, the mixture was filtered through activated charcoal over Celite and concentrated to yield **11** (4.09 g, 93%) as a hygroscopic foam; $[\alpha]^{23}_D$ −101° (*c* 0.65, MeOH); ^1H NMR (Me_2CO-d_6, 500 MHz) δ 5.19 (1H, d, *J* = 3 Hz, H-1), 4.64 (1H, d, *J* = 1.5 Hz, H-6), 4.64 (1H, d, *J* = 8.5 Hz, H-1′), 4.01 (1H, ddd, *J* = 11.5, 7, 1.5 Hz, H-3a), 3.85 (1H, dd, *J* = 11.5, 2.5 Hz, H-6a′), 3.68 (1H, m, *J* = 13, 11.5, 5 Hz, H-3b), 3.67 (1H, m, *J* = 11.5, 5.5 Hz, H-6b′), 3.45 (1H, t, *J* = 8.5 Hz, H-3′), 3.37 (1H, t, *J* = 8.5 Hz, H-4′), 3.34 (1H, m, H-5′), 3.30 (1H, d, *J* = 1.5 Hz, H-7), 3.28 (1H, t, *J* = 8.5 Hz, H-2′), 2.42 (1H, dt, *J* = 13, 13, 7 Hz, H-4a), 3.29 (1H, d, *J* = 3 Hz, H-9), 1.84 (1H, ddd, *J* = 13, 5, 1.5 Hz, H-4b), 1.46 (3H, s, isopropylidene), 1.39 (3H, s, H-10), 1.31 (3H, s, isopropylidene); ^{13}C NMR, see Table 1; *anal.* C 52.45%, H 6.83%, calcd for $C_{18}H_{28}O_{10}\cdot{}^1/_2H_2O$, C 52.29%, H 7.07%.

3,4-Dihydro-5,6-*O*-isopropylidene Antirrhinoside Aglucone (12). Compound **11** (4.09 g, 10.1 mmol) was dissolved in H_2O (50 mL) and β-glucosidase (212 mg; Sigma) was added. The mixture was stirred at room temperature for 3 days. The volume was reduced to 20 mL and extracted with EtOAc (6 × 100 mL). Drying (Na_2SO_4), filtration, and concentration of the organic layers yielded **12** (2.22 g, 91%) as a crystalline residue, which was recrystallized (Me_2CO−hexane) to give white needles, mp 104−106 °C; $[\alpha]^{23}_D$ +53° initially, changing to +13° due to mutarotation (*c* 0.73, MeOH); ^1H NMR (Me_2CO-d_6, 500 MHz) δ 5.28 (1H, m, H-1), 4.46 (1H, d, *J* = 1.5 Hz, H-6), 3.86 (1H, ddd, *J* = 10.5, 4.5, 6 Hz, H-3a), 3.67 (1H, ddd, *J* = 10.5, 9.5, 4 Hz, H-3b), 3.21 (1H, d, *J* = 1.5 Hz, H-7), 2.43 (1H, ddd, *J* = 14, 9.5, 4.5 Hz, H-4a), 2.35 (1H, br d, *J* = 4 Hz, H-9), 1.82 (1H, ddd, *J* = 14, 6, 4 Hz, H-4b), 1.41 (3H, s, H-10), 1.47, 1.32 (each 3H, s, isopropylidene), only very slow mutarotation was seen in Me_2CO; ^{13}C NMR, see Table 1; *anal.* C 59.58%, H 7.47%, calcd for $C_{12}H_{18}O_5$, C 59.48%, H 7.49%.

Reduction of 3,4-Dihydro-5,6-isopropylidene Antirrhinoside Aglucone (12). The aglucone **12** (183 mg, 0.76 mmol) was dissolved in MeOH−H_2O (10:1, 27.5 mL) and $NaBH_4$ (29 mg, 0.76 mmol) was added. The reaction mixture was stirred at room temperature for 4 h. Neutralization with 10% HOAc was followed by addition of H_2O (5 mL). The MeOH was evaporated and the residue diluted with H_2O to 30 mL. Activated charcoal (3 g) was added, and after being stirred for 30 min, the mixture was filtered through a layer of Celite

Table 2. ^{13}C NMR of Iridoid Aglucone Derivatives (in Me_2CO-d_6)

carbon	**12**	**13**	**14**	α-**15**	β-**15**
1	91.00	59.10[a]	58.11	91.80	95.17
3	58.36	59.67[a]	61.78	140.41	142.37
4	35.96	38.53	28.75	105.88	106.86
5	87.68	92.29	88.16	70.90	74.22
6	87.31	87.57	80.82	78.58	78.94
7	64.56	63.48	74.25	67.14	65.97
8	66.96	67.17	86.72	63.77	63.30
9	51.61	51.45	49.45	52.11	54.98
10	16.50	17.22	18.88	15.62	18.11
$(CH_3)_2$**C**<	112.91	112.26	114.89		
(**CH₃**)$_2$C<	28.47	28.46	28.72		
	30.38	30.40	27.44		

[a] Signals interchangeable.

on a glass filter, washing with additional H_2O. The cake was eluted with MeOH, and concentration gave crude **13** (161 mg, 88%), which was unstable towards further purification (partial cyclization to **14**); ^1H NMR (MeCO-d_6, 500 MHz) δ 4.27 (1H, d, J = 1.5 Hz, H-6), 3.96 (1H, dd, J = 11, 2.5 Hz, H-1a), 3.80 (1H, dd, J = 11, 3 Hz, H-1b), 3.77 (1H, m, H-3a), 3.70 (1H, ddd, J = 11, 9, 6 Hz, H-3b), 3.16 (1H, d, J = 1.5 Hz, H-7), 2.31 (1H, ddd, J = 14.5, 8, 6 Hz, H-4a), 2.24 (1H, br t, J = 2.5 Hz, H-9), 1.93 (1H, ddd, J = 14.5, 9, 6 Hz, H-4b), 1.48 (3H, s, isopropylidene), 1.44 (3H, s, H-10), 1.35 (3H, s, isopropylidene); ^{13}C NMR, see Table 2.

The aglucone **12** (106 mg, 0.438 mmol) in dioxane−H_2O (5.5 mL) was cooled to 0 °C, and $NaBH_4$ (17 mg, 0.438 mmol) was added under stirring. The mixture was allowed to reach 15 °C. The reaction was followed by TLC ($CHCl_3$−MeOH 9:1, R_f 0.58, 0.50, and 0.40 for **12**, **14** and **13**, respectively). After 150 min no starting material was left, and the reaction was neutralized with 10% HOAc. Then EtOAc (25 mL) and H_2O (5 mL) were added. After separation, the organic layer was dried (Na_2SO_4), filtered, and concentrated (at 30 °C) to yield crude **14** (67 mg, 63%); TLC showed that ring-closure only occurred during concentration; crystallization (Me_2-CO) gave needles, mp 144−146 °C; $[\alpha]^{23}_D$ −23° (*c* 0.53, MeOH); ^1H NMR (Me_2CO-d_6, 500 MHz) δ 4.33 (1H, d, J = 6 Hz, H-6), 3.98 (1H, dd, J = 11, 8 Hz, H-1a), 3.97 (1H, dd, J = 12, 6.6 Hz, H-3a), 3.92 (1H, d, J = 6 Hz, H-7), 3.88 (1H, dd, J = 11, 5.7 Hz, H-1b), 3.55 (1H, dt, J = 12, 12, 4.5 Hz, H-3b), 2.38 (1H, dt, J = 12, 12, 7 Hz, H-4a), 2.11 (1H, ddd, J = 8, 5.7, 2 Hz, H-9), 1.59 (3H, s, isopropylidene), 1.46 (1H, ddd, J = 12, 4.5, 2 Hz, H-4b), 1.43 (3H, s, isopropylidene), 1.23 (3H, s, H-10); ^{13}C NMR, see Table 2; *anal.* C 58.94%, H 8.15%, calcd for $C_{12}H_{20}O_5$, C 58.98%, H 8.26%.

Acetylation (pyr−Ac_2O 2:1, 2 h at room temperature) of **14** gave a crude diacetate, ^1H NMR ($CDCl_3$, 500 MHz) δ 4.78 (1H, d, J = 6 Hz, H-7), 4.38 (1H, dd, J = 11.5, 7.5 Hz, H-1a), 4.35 (1H, d, J = 6 Hz, H-6), 4.24 (1H, dd, J = 11.5, 6 Hz, H-1b), 3.98 (1H, dd, J = 12.5, 7 Hz, H-3a), 3.57 (1H, dt, J = 2 × 12.5, 4.5 Hz, H-3b), 2.33 (1H, ddd, J = 7.5, 6, 1.5 Hz, H-9), 2.19 (1H, dt, J = 2 × 12.5, 7 Hz, H-4a), 2.10, 2.03 (each 3H, s, AcO), 1.46, 1.32 (each 3H, s, isopropylidene), 1.41 (1H, ddd, J = 12.5, 4.5, 1.5 Hz, H-4b), 1.17 (3H, s, H-10).

Antirrhinoside Aglucone (15). To **4** (10.7 g, 30 mmol) in H_2O (100 mL) was added β-glucosidase (200 mg), and the mixture was stirred at 38 °C in an ether-extractor under continuous extraction with EtOAc (1 drop/sec). After 24 h the EtOAc extracts (~3 L) were dried (Na_2SO_4), filtered, and concentrated to yield crude **15** (4.37 g, 74%), which was purified by MPLC to yield crystalline **15** (3.44 g, 58% overall); mp 117−119 °C; $[\alpha]^{23}_D$ +130° (*c* 0.62, Me_2CO); ^1H NMR (Me_2CO-d_6, 500 MHz), major anomer (α-) δ 6.17 (1H, d, J = 6.5 Hz, H-3), 5.94 (1H, br s, 1-OH), 5.50 (1H, t, J = 3.5 Hz, H-1), 4.86 (1H, d, J = 6.5 Hz, H-4), 4.20 (1H, d, J = 9 Hz, H-6), 3.73 (1H, d, J = 9 Hz, 6-OH), 3.34 (1H, br s, H-7), 3.28 (1H, s, 5-OH), 2.40 (1H, d, J = 4 Hz, H-9), 1.45 (3H, s, H-10); minor anomer (β-) δ 6.29 (1H, d, J = 6.5 Hz, H-3), 6.18 (1H, obscured by H-3 of the major anomer, 1-OH), 4.97 (1H, dd, J = 9.5, 6.5 Hz, H-1), 4.82 (1H, d, J = 6.5 Hz, H-4), 4.03 (1H, d, J = 8.5 Hz, H-6), 3.85 (1H, d, J = 8.5 Hz, 6-OH), 3.39 (1H, br s, H-7), 3.36 (1H, s, 5-OH), 2.23 (1H, d, J = 9.5 Hz, H-9), 1.50 (3H, s, H-10); ^{13}C NMR, see Table 2; *anal.* C 52.02%, H 6.09%, calcd for $C_9H_{12}O_5 \cdot {}^1/_2H_2O$, C 51.67%, H 6.26%.

Table 3. ^{13}C NMR Data for Piperidine Derivatives

carbon	**17**[a]	**18**[b]	**19**[a]	**20**[b]	**21**[c]
C-1	54.11	47.75	52.91	44.17	52.20[f]
C-3	50.15	44.14	50.03	42.05	50.82[f]
C-4	30.56	32.98	31.87	31.15	33.63
C-5	74.07	76.34	80.35[d]	80.15[e]	76.81[g]
C-6	72.14	74.25	72.55	72.53	79.62[h]
C-7	64.77	67.31	47.95	46.44	79.50[h]
C-8	64.65	67.58	80.03[d]	79.88[e]	80.69[g]
C-9	47.66	49.84	54.60	54.18	54.85[f]
C-10	15.12	16.49	23.84	23.55	19.73
Ph-**CH₂**	62.53		62.69		63.78
Ph-CH_2	137.89		138.06		138.96
	128.79		128.84		130.38
	128.33		128.26		129.32
	127.21		127.12		128.34

[a] In $CDCl_3$. [b] In D_2O. [c] Due to a general low solubility no CH-correlated spectrum was obtained; in CD_3OD. [d-h] Signals may be interchanged.

Double Reductive Amination of Aglucone 15. Aglucone **15** (8.01 g, 40 mmol) was dissolved in MeOH (50 mL) and $BnNH_3Cl$ (5.74 g, 40 mmol) was added. The mixture was stirred at room temperature for 3 h. Addition of $NaCNBH_3$ (2.52 g, 40 mmol) in MeOH (40 mL) was performed with an automatic syringe pump (0.17 mL h^{-1}). After 3 days the reaction mixture was concentrated, and the residue was dissolved in CH_2Cl_2 (5 mL) and loaded onto a VLC column (6.5 × 5 cm). Gradient elution with hexane (150 mL), hexane−EtOAc 4:1 to 1:1 yielded piperidine **17** (4.05 g, 37%) as a crystalline residue. Recrystallization (Me_2CO−hexane 1:10) gave needles, mp 134−136 °C; $[\alpha]^{23}_D$ −54° (*c* 0.45, MeOH); ^1H MNR ($CDCl_3$, 500 MHz) δ 7.35−7.25 (5H, m, *Ph*-CH_2), 4.09 (1H, br s, H-6), 3.52 (2H, higher order coupling, Ph-C*H₂*), 3.45 (1H, br s, H-7), 2.94 (1H, ddd, J = 12, 7, 2 Hz, H-1a), 2.83 (1H, ddt, J = 13, 5, 2 × 2.5 Hz, H-3a), 2.34 (1H, br dd, J = 12, 7 Hz, H-9), 1.94 (1H, dt, J = 2 × 13, 2.5 Hz, H-3b), 1.81 (1H, dt, J = 13, 2 × 2.5 Hz, H-4a), 1.69 (1H, dt, 2 × 13, 5 Hz, H-4b), 1.63 (1H, dt, J = 2 × 12, 3 Hz, H-1b), 1.33 (3H, s, H-10); ^{13}C NMR, see Table 3; a*nal.* C 69.98%, H 7.65%, N 5.09%, calcd for $C_{16}H_{21}O_3N$, C 69.78%, H 7.69%, N 5.09%.

$LiAlH_4$ Reduction of Piperidine 17. Compound **17** (390 mg, 1.42 mmol) was dissolved in dry THF (10 mL) and added to a suspension of $LiAlH_4$ (160 mg, 4.24 mmol) in dry THF (10 mL). The mixture was refluxed (80 °C) for 2.5 h. Excess $LiAlH_4$ was quenched with EtOAc (10 mL). Upon addition of H_2O (50 mL), the mixture was neutralized by passing CO_2 through the solution. The volume was increased to 200 mL with

H_2O. The filtrate was extracted with EtOAc (3 × 200 mL), and the aqueous layer was made alkaline (pH 10) with 1 M NaOH and extracted once more with EtOAc (2 × 200 mL). Drying and concentration of the combined organic layers yielded a crude product (370 mg), which was purified on a VLC column (4 × 2 cm). Gradient elution with hexane (50 mL), hexane−EtOAc 3:2 to 1:1 afforded crystalline **19** (290 mg, 74%); mp 121−124 °C; $[\alpha]^{23}_D$ −17° (*c* 0.38, MeOH); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.34−7.23 (5H, m, *Ph*-CH_2), 4.18 (1H, dd, J = 9.5, 5 Hz, H-6), 3.55, 3.48 (each 1H, d, J = 13.5 Hz, Ph-C*H*$_2$), 2.78 (2H, m, H-1a, H-3a), 2.30 (1H, dd, J = 15.5, 9.5, H-7a), 2.15 (1H, ddd, J = 12, 6, 2 Hz, H-9), 2.05 (1H, ddd, J = 12, 8.5, 6.5 Hz, H-3b), 1.88 (1H, ddd, J = 15.5, 5, 2, H-7b), 1.79 (2H, m, H-4), 1.63 (1H, t, J = 12, H-1b), 1.15 (3H, s, H-10); ^{13}C NMR, see Table 3; *anal.* C 69.34%, H 8.37%, N 5.03%, calcd for $C_{16}H_{23}O_3N$, C 69.27%, H 8.36%, N 5.05%.

Azidolysis of Piperidine 17. A solution of **17** (300 mg, 1.09 mmol) in 80% aqueous MeOH (5 mL) was treated with NaN_3 (355 mg, 5.45 mmol) and NH_4Cl (128 mg, 2.40 mmol) at 80 °C for 21 h. The reaction mixture was diluted with EtOAc (50 mL) and washed with an alkaline aqueous solution (50 mL saturated aqueous $NaHCO_3$ and 10 mL of 1 M NaOH) and H_2O (50 mL). Drying (Na_2SO_4) and concentration of the organic layer yielded crystalline **21** (310 mg, 89%). Recrystallization (MeOH) yielded an analytical sample of **21**; mp 171−174 °C; $[\alpha]^{23}_D$ −37° (*c* 0.35, MeOH); ^{1}H NMR (MeOH-d_4, 500 MHz) δ 7.33−7.22 (5H, m, *Ph*-CH_2), 3.85 (1H, d, J = 7 Hz, H-6), 3.78 (1H, dd, J = 7, 1.5 Hz, H-7), 3.52, 3.49 (each 1H, d, J = 13 Hz, Ph-C*H*$_2$), 2.69 (2H, m, H-1a, H-3a), 2.13 (1H, dt, J = 2 × 11.5, 3.5 Hz, H-3b), 2.02 (1H, ddd, J = 11, 6.5, 1.5 Hz, H-9), 1.88 (1H, dd, J = 12, 11 Hz, H-1b), 1.82 (1H, dt, J = 13.5, 2 × 4 Hz, H-4a), 1.73 (1H, ddd, J = 13.5, 11, 4.5 Hz, H-4b), 1.15 (3H, s, H-10); ^{13}C NMR, see Table 3; *anal.* C 60.29%, H 7.04%, N 17.40%, calcd for $C_{16}H_{22}O_3N_4$, C 60.35%, H 6.97%, N 17.60%.

Hydrogenolysis of *N*-Benzylated Piperidine 17. Compound **17** (336 mg, 1.22 mmol) was dissolved in MeOH (5 mL). Pd/C 5% (10 mg) was added and H_2 was introduced to the mixture under vigorous stirring. When the H_2 consumption had subsided the mixture was filtered through activated C and Celite and concentrated to give pure crystalline **18** (188 mg, 83%); mp 140−142 °C; $[\alpha]^{23}_D$ −57° (*c* 0.46, MeOH); ^{1}H NMR (D_2O, 500 MHz) δ 4.38 (1H, br s, H-6), 3.66 (1H, br s, H-7), 3.21 (1H, dd, J = 19, 13 Hz, H-1a), 3.04 (1H, br dd, J = 13.5, 5 Hz, H-3a), 2.52 (1H, dt, J = 2 × 13.5, 3 Hz, H-3b), 2.23 (2H, m, H-1b, H-9), 1.86 (1H, br dd, J = 13.5, 3 Hz, H-4a), 1.45 (1H, dt, J = 2 × 13.5, 5 Hz, H-4b), 1.40 (3H, s, H-10); ^{13}C NMR, see Table 3; a*nal.* C 58.04%, H 8.09%, N 7.20%, calcd for $C_9H_{15}O_3N$, C 58.36%, H 8.16%, N 7.56%.

Hydrogenolysis of *N*-Benzylated Piperidine 19. Compound **19** (155 mg, 0.560 mmol) was treated as described for **17**. This gave **20** (89 mg, 85%) as an amorphous solid; $[\alpha]^{23}_D$ −17° (*c* 0.49, MeOH); ^{1}H NMR (D_2O, 500 MHz) δ 4.40 (1H, dd, J = 9.5, 6.5 Hz, H-6), 3.19 (1H, dd, J = 13, 6.5 Hz, H-1a), 3.16 (1H, m, H-3b), 2.77 (1H, dt, J = 2 × 12.5, 3.5 Hz, H-3b), 2.48 (1H, dd, J = 15, 9.5 Hz, H-7a), 2.40 (1H, t, J = 13, H-1b), 2.06 (1H, dd, J = 12, 6.5 Hz, H-9), 1.98 (1H, overlapped, H-4a), 1.96 (1H, overlapped, H-7b), 1.74 (1H, ddd, J = 14, 12.5, 5 Hz, H-4b), 1.28 (3H, s, H-10); ^{13}C NMR, see Table 3; EIMS *m*/*z* 187 $[M]^+$, 170, calcd for $C_9H_{17}O_3N$, 187.24.

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