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Desymmetrization of bicyclo[3.3.0]octane-3,7-dione by the Schmidt reaction: an easy synthesis of tecomanine †

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Abstract: The C_{2v} symmetry of *cis*-bicyclo[3.3.0]octane-3,7-dione **1** was altered by a selective Schmidt reaction to give the 3-azabicyclo[4.3.0]nonane building block **3b** which was employed in a short synthesis of (±)-tecomanine **4**. Asymmetric Schmidt reaction on **1**, employing (2*S*,4*R*)-2-azido-4-hydroxypentane **14** as a chiral inducer, showed encouraging levels of enantiotopic methylene group stereodifferentiation. © 1997 Elsevier Science Ltd

Versatile building blocks are of great importance for attaining efficiency and flexibility in organic synthesis. *cis*-Bicyclo[3.3.0]octane-3,7-dione **1**, easily available on a large scale by the Weiss reaction,[1] possesses many appealing features as a starting material for the synthesis of both natural and nonnatural cyclopentanoid compounds.[2] The presence of two carbonyl moieties at positions C-3 and C-7 on the carbon skeleton of **1** has indeed greatly facilitated the synthesis of several polyquinanes and polyquinenes in which the original diquinane structure of **1** has been preserved. However, the C_{2v} symmetry of **1** has often been a complicating factor in a more general use of this diketone in synthesis,[3,4] especially for preparing enantiomerically pure synthons. The problem has usually been circumvented by preparing the *meso* monoketal **2a** or **2b**,[5] before eliminating the plane of symmetry in an asymmetrically controlled manner. This has then been achieved either by asymmetric deprotonation of **2a,b** using chiral lithium amide bases[6] or by asymmetric Horner–Emmons reaction of **2a**,[7] or by asymmetric elimination of the OH group of the *endo* alcohol **2c**.[8] Unfortunately, these latter approaches based on **2a–c** require the synthesis and partial hydrolysis of the corresponding bisketals of **1** under carefully controlled conditions accompanied by a few recycling steps with subsequent loss of overall yields.[5]

A few years ago, we realized that the versatility of **1** in synthesis could be expanded by oxidative desymmetrization at one of the two homotopic carbonyl groups, while preserving a *cis*-disubstituted cyclopentane moiety in the modified structure. Following this approach the useful ketolactone (±)-**3a** was obtained by a ready (55–60% yield) selective Baeyer–Villiger oxidation of **1** which required no wasteful protective group.[9,10]

A logical extension of this strategy was the desymmetrization of diketone **1** to produce the bicyclic lactam **3b** *via* the formal insertion of a nitrogen atom into a carbon–carbon single bond adjacent to one carbonyl group. Compound **3b** is a useful building block since it possesses the 3-azabicyclo[4.3.0]nonane skeleton[11] occurring in several monoterpene alkaloids isolated from plants[12] or microorganisms[13] with varied physiological activity. This paper describes the successful achievement of this goal and the use of **3b** as a starting material for a short synthesis of (±)-tecomanine **4**. This alkaloid is naturally occurring as the (−)-enantiomer in *Tecoma stans*,[14] a bush common to Latin America, and has received special attention[15] for the powerful hypoglycemic activity of the salts.[16]

We also report our initial studies on the asymmetric Schmidt reaction on diketone **1** for which encouraging levels of enantiotopic group differentiation has been observed.

† This paper is dedicated to Prof. Paola Vita-Finzi on the occasion of her 65th birthday.

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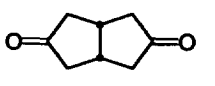
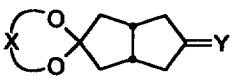
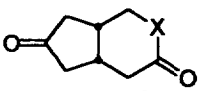


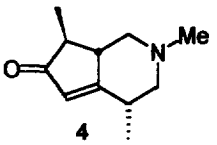
1



2a X = -CH_2CH_2- Y = O
2b X = -$CH_2CMe_2CH_2$- Y = O
2c X = -CH_2CH_2- Y = α-OH



3a X = O
3b X = NH



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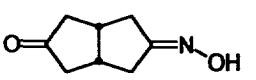

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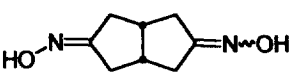

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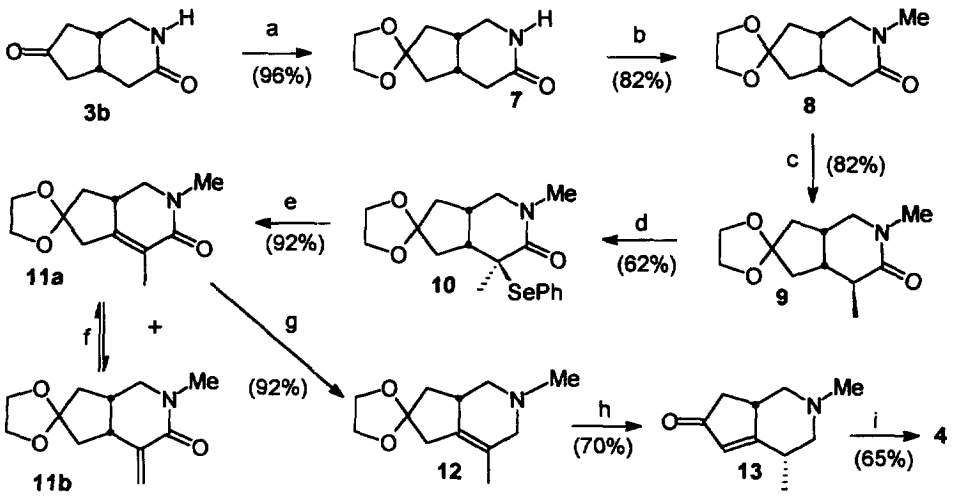
Results and discussion

Despite the development of a variety of new methods,[17] the Schmidt[18] and the Beckmann[19] reactions remain the most convenient and general protocols for converting cyclic ketones into lactams. In principle, Beckmann rearrangement of **1** to **3b** could conveniently be accomplished via the corresponding mono-oxime **5**; however, on exposure to hydroxylamine under different reaction conditions (solvent, pH, temperature) compound **1** afforded large amounts of bis-oxime **6** (mixture of *syn* and *anti* stereoisomers), making this approach to **3b** unfeasible.

No less frustrating were the initial attempts to produce **3b** through the selective addition of an azide ion to just one of the carbonyl groups of **1**.[18] Several strong acids (conc. H_2SO_4, TfOH, TsOH, $BF_3 \cdot Et_2O$) were tested as catalysts, either in CH_2Cl_2 or in a biphasic system (CH_2Cl_2–H_2O). Among them, $BF_3 \cdot Et_2O$ gave the best results. On treatment with NaN_3 (3 eqv) and $BF_3 \cdot Et_2O$ (1 eqv) in 1:1 CH_2Cl_2:H_2O for 3 h at 25°C diketone **1** afforded lactam **3b**, though in only 25% yield. Since protonated azides are primarily involved in the mechanism of the Schmidt rearrangement of ketones,[20] we reasoned that an increasing acid concentration could facilitate the conversion of **1** into **3b**. Indeed, after considerable experimentation we found that in a solution of 36% HCl, sodium azide rapidly added to **1**, lead to the desired lactam **3b** in about 50% yield. Interestingly, besides **3b** and unreacted diketone **1** (ca 25%), no dilactam resulting from the Schmidt rearrangement on the carbonyl group of **3b** could be detected in the reaction mixture.[21] Yields of **3b** were raised to 62–68% after recycling recovered **1**.

With compound **3b** finally available in a good amount, the synthetic route to (±)-tecomanine **4** was straightforward since lactam **3b** contained eight of the eleven carbons occurring in the targeted compound and was well structured for the regio- and stereoselective introduction of the remaining three methyl groups and the olefinic double bond. Acetalization of the ketone carbonyl group in **3b** followed by *N*-methylation with a phase transfer catalyst[22] afforded the crystalline lactam **8** in 79% yield (Scheme 1).[23] In principle, the latter compound could be converted into the α-methyl-α,β-unsaturated lactam **11a** via *syn* elimination of a proper phenylselenoxide.[24] Considering that nucleophiles should approach the enolate derived from the bicyclic structure **8** more easily from the convex than from the concave face, we realized that monoalkylation of **8** had to precede introduction of the α-phenylseleno group. In fact, this reaction sequence would have secured the required *syn* relationship between the α-phenylseleno substituent and the bridgehead proton in the β position to the lactam carbonyl group.[25] In the event, when LDA was used in the deprotonation step, monoalkylation of **8** proceeded in 82% yield affording a 14:1 mixture (NMR analysis) of lactone **9** and the corresponding *endo* stereoisomer. By employing $KN(SiMe_3)_2$ as a base, the reaction stereoselectivity was even higher (*exo*:*endo*, 28:1) but the yield of methyl derivative dropped to 60%. Alkylation of the mixture of monomethylated lactones with phenylselenyl bromide produced a 62% isolated yield of >92% diastereomerically pure (NMR) phenylselenyl derivative **10**. The latter upon conversion to the corresponding selenoxide afforded a chromatographically separable 3.6:1 mixture (NMR) of **11a** and α-methylenelactone **11b** in 92%

yield. The undesired minor lactone was equilibrated with $RhCl_3.3H_2O$ to produce a 1:4 mixture with the corresponding thermodynamically favored isomer **11a** whose overall yield was thus raised to 45% from **8**. Reduction of **11a** with $LiAlH_4$ afforded *N*-methyltetrahydropyridine **12** in 92% yield. Exposure of **12** to 70% $HClO_4$ brought about simultaneous cleavage of the ketal, migration of the double bond into conjugation with the carbonyl group, and subsequent equilibration at C(4) (tecomanine numbering) with formation of the diastereomerically pure (NMR) amine **13** in 70% isolated yield. That the methyl group at C(4) had the desired *endo* configuration was confirmed by NOE experiments and the value (2.0 Hz) of J_{4-5} in the ^{1}H-NMR spectrum of **13** which was consistent with the assigned stereochemistry.[26] Generation of the kinetic enolate of **13** and methylation with CH_3I in THF–DMPU at −78°C finally produced 95% diastereomerically pure (NMR) (±)-tecomanine **4** in 65% isolated yield (Scheme 1).[23] The spectral data (IR, ^{1}H-NMR, ^{13}C-NMR, mass spectra) of **4** were identical with those of an authentic sample of the natural alkaloid[27] and with literature data.[12d]



Reagents and conditions: (a) $HOCH_2CH_2OH$, p-TsOH (cat), C_6H_6, reflux; (b) CH_3I, KOH - Bu_4NI, THF, 20 °C; (c) (i) LDA, THF, -78 → 0 °C; (ii) CH_3I, -100 °C; (d) (i) LDA, THF, -78 → 0 °C; (ii) PhSeBr, -78 °C; (e) 30% H_2O_2, CH_2Cl_2-Py, 0 → 20°C; (f) $RhCl_3.3H_2O$, EtOH, $CaCO_3$, reflux; (g) $LiAlH_4$, THF, 0°C; (h) 70% $HClO_4$, CH_2Cl_2, 0 → 20 °C; (i) (i) LDA, THF, -78 °C, (ii) MeI, THF-DMPU, -78 °C.

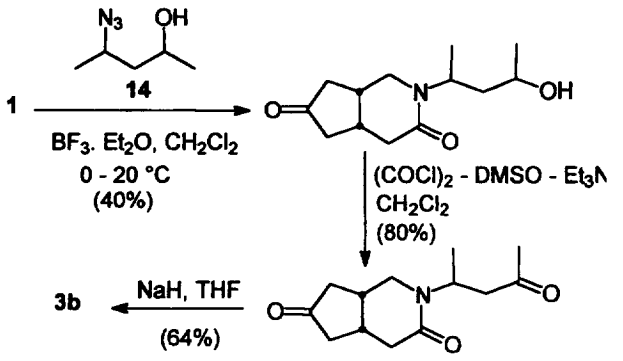
Scheme 1. [23]

In summary, (±)-tecomanine **4** was derived from the readily available diketone **1** and lactam **3b** in 9 and 8 steps, respectively, and in ca. 10% and 15% overall yields, respectively. This short, straightforward synthesis of **4** is amenable to scale up and adaptable for the synthesis of other members of the 3-azabicyclo[4.3.0]nonane based alkaloids.

Asymmetric Schmidt reaction on diketone 1

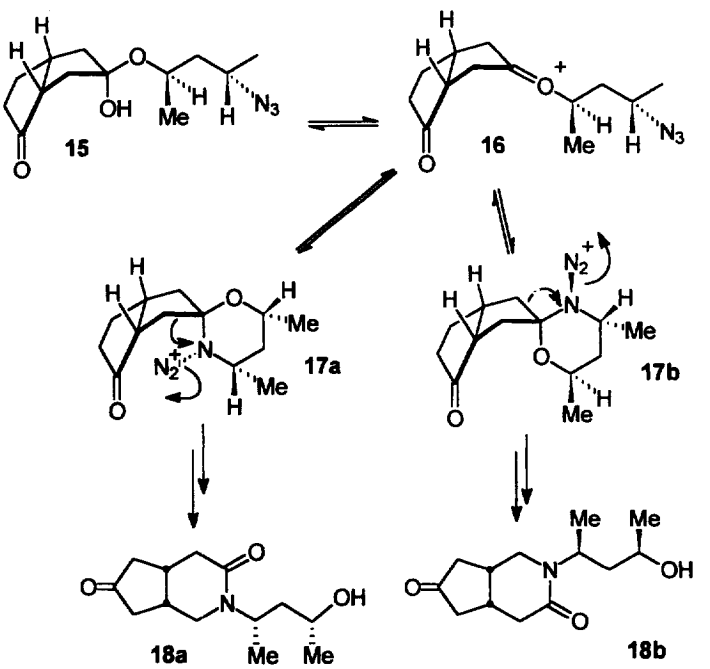
Recently, Aubé and collaborators reported an efficient intermolecular version of the Schmidt reaction in which hydrazoic acid or azido anion were replaced by 1,2- or 1,3-hydroxy azides.[28] This strategy was extended to chiral azido alcohols leading to the first known examples of an asymmetric Schmidt rearrangement.[28] These findings prompted us to employ the latter protocol for an enantioselective synthesis of the chiral lactam **3b**. Since the best results were obtained with 2-azido-4-hydroxypentane **14** as a partner of the reaction with prochiral ketones,[28] initially we used (±)-**14** (mixture of *threo* and *erythro* isomers), prepared[29] from commercially available (±)-2,4-pentanediol (mixture of isomers),

for optimizing reaction conditions on diketone **1**. Following Aubé's procedure[28] lactam (±)-**3b** was finally obtained in 24% overall yield from **1** (Scheme 2).[23]



Scheme 2. [23]

Asymmetric nitrogen insertion in **1** was then explored, relying on (2*S*,4*R*)-**14**[28,29] as a chiral inducer and $BF_3 \cdot OEt_2$ as a catalyst. In the event, stereodifferentiation of the enantiotopic methylene groups in **1** was inferior to our expectations, as revealed by the chromatographically inseparable 2:1 mixture of formed diastereomeric lactams **18a,b** (Scheme 3). This ratio was estimated by the intensity of the two pairs of methyl doublets at δ 1.12 and 1.21, and δ 1.16 and 1.19 ppm, respectively, in the ^1H NMR spectrum of the mixture **18a,b**. The ^{13}C NMR of **18a,b** showed four methyl singlets at δ 18.4, 18.6, 23.8 and 23.9 ppm, respectively. Running the same reaction in a solution of 36% HCl (no $BF_3 \cdot OEt_2$ added) a more encouraging level of stereoselectivity was observed since the diastereoisomeric ratio raised to 3.2:1 (d.e. 52%).



Scheme 3.

Even if the configuration of the major diastereomer could not be established unequivocally, a possible explanation for the observed modest stereoselectivity could be given (Scheme 3). According to Aubé's mechanistic proposals,[28] the initial hemiketal **15** should lead to the reversible formation of oxonium ion **16**; then, intramolecular attack of the azide on the carbocation is followed by irreversible migration of the pseudoaxial bond antiperiplanar to the departing N_2 substituent. Therefore, diastereotopic face differentiation in the step **16**→**17** would determine the stereochemical outcome of this Schmidt-like rearrangement on diketone **1**. In fact, migration of the stereoelectronically properly oriented methylene group in **17a** would eventually lead to **18a**, while rearrangement involving the alternative bond in **17b** would produce **18b** (Scheme 3).

On the basis of this mechanism the overall diastereoselectivity could depend on either kinetic or thermodynamic factors or a combination of both effects. Previous studies[6d,30] have shown that in certain cases nucleophilic attack on diketone **1** or related compounds may be modestly stereoselective, with the nucleophile preferring to approach from the less sterically hindered *exo* face. Such a preference should be even less pronounced for the intramolecular attack on oxonium ion **16** where the nucleophile being already linked to the oxygen atom would suffer less steric hindrance in approaching the *endo* face of the carbonyl group. On the other hand, molecular mechanics calculations[31] indicated only a small thermodynamic preference for the formation of one of the two possible intermediates **17a,b**, and then for one of the two final lactams **18a,b**.

In conclusion, although the synthetic route described here is still unsatisfactory for the synthesis of optically pure tecomanine **4**, this research has achieved, for the first time, promising results in the not-trivial operation of simultaneously removing the C_2 and S_1 axes of diketone **1**. Our efforts are now concentrated on developing a more efficient chiral auxiliary for asymmetric nitrogen insertion in diketone **1**.

Experimental

Melting points were determined on a Fisher–Johns hot plate and are uncorrected. Elemental analyses were performed in the Analytical Laboratory of the Department of Organic Chemistry, University of Pavia. All experiments were run in oven-dried glassware under an argon atmosphere. All commercial reagent grade solvents were dried and degassed by standard techniques just before use. ^{1}H NMR (300 MHz) and ^{13}C NMR (75 MHz) spectra were obtained in $CDCl_3$ unless otherwise indicated employing Me_4Si as the internal standard. The multiplicity (in parentheses) of each carbon atom was determined by DEPT experiments. Electron ionization mass spectra (direct inlet system) were recorded at 70 eV. Analytical TLC was carried out on 0.25 mm glass-supported silica gel plates and visualization was effected with short-wavelength UV light (254 nm) or with 0.5% vanillin solution in H_2SO_4–EtOH (4:1) followed by heating. Flash column chromatography was accomplished with 230–400 mesh silica gel.

(1R,6R*)-3-Azabicyclo[4.3.0]nona-4,8-dione* ***3b***

Solid NaN_3 (0.6 g, 9.1 mmol) was added portionwise over 20 min to a solution of **1** (1.0 g, 7.2 mmol) in 36% aqueous HCl (20 mL), while keeping the temperature below 35°C. The mixture was stirred for 3 h at rt and then brought to pH 10 with 20% aqueous NaOH at 0°C. Precipitated NaCl was filtered off and the aqueous layer was extracted continuously with $CHCl_3$ for 48 h. Drying of the organic phase over $MgSO_4$ and removal of solvent furnished a residue that was separated on a silica gel column (30 g). Elution with 15% Me_2CO–CH_2Cl_2 gave unreacted diketone **1** (240 mg) and lactam **3b** (576 mg, 52%), mp 120–122°C; IR (KBr) 3246, 2935, 1735, 1667, 1638, 1351, 1180 cm^{-1}; ^{1}H-NMR δ 2.10–2.30 (m, 3H), 2.40–2.90 (m, 5 H), 3.21 (ddd, 1 H, J=13.0, 6.8 and 3.0 Hz), 3.52 (ddd, 1 H, J=13.0, 5.8 and 3.5 Hz), 6.3 (br s, 1 H); ^{13}C NMR (D_2O) δ 223.7 (s), 175.4 (s), 43.6 (t), 41.9 (t), 40.9 (t), 31.9 (t), 31.3 (d), 30.7 (d); MS $C_8H_{11}NO_2$ *m/z* 153 (M^+, 100), 125 (10), 112 (33), 96 (35), 82 (53), 68 (33), 54 (84), 41 (78). Anal. Calcd for $C_8H_{11}NO_2$: C, 62.73; H, 7.24; N, 9.14. Found: C, 62.76; H, 7.21, N 9.11.

(1R,6R*)-8-Ethylenedioxy-3-azabicyclo[4.3.0]nona-4-one* **7**

To a solution of **3b** (1.0 g, 6.5 mmol) in benzene (30 mL) was added ethylene glycol (1 mL, 18 mmol) and *p*-TsOH (15 mg), and the mixture was refluxed using a Dean–Stark water separator for 15 h. The cooled reaction mixture was washed with aqueous $NaHCO_3$ and brine, and the aqueous layer was reextracted with CH_2Cl_2 (2×25 mL). The combined organic extracts were dried over $MgSO_4$. Removal of solvent furnished ketal **7** (1.24 g, 96%), which was immediately submitted to the following reaction. IR (KBr) 3260, 2936, 1655, 1334, 1091 cm^{-1}; ^{1}H-NMR δ 1.54–1.75 (m, 2H), 1.92–2.10 (m, 2H), 2.28 (dd, 1 H, J=15.0 and 6.0 Hz), 2.45 (dd, 1 H, J=15.0 and 6.0 Hz), 2.50–2.70 (m, 2H), 3.11 (ddd, 1 H, J=13.0, 6.0 and 3.5 Hz), 3.31 (dt, 1H, J=13.0 and 5.0 Hz), 3.92 (s, 4H), 6.10 (br s, 1 H); MS $C_{10}H_{15}NO_3$ *m/z* 197 (M^+, 90), 152 (25), 139 (88), 125 (65), 112 (88), 99 (85), 96 (100), 86 (70), 68 (42), 55 (34), 41 (87). Anal. Calcd for $C_{10}H_{15}NO_3$: C, 60.90; H, 7.67; N, 7.10. Found: C, 60.94; H, 7.64; N, 7.14.

(1R,6R*)-8-Ethylenedioxy-3-methyl-3-azabicyclo[4.3.0]nona-4-one* **8**

To a stirred solution of **7** (100 mg, 0.51 mmol) in dry THF (2 mL) under argon at rt was added CH_3I (79.5 mg, 0.56 mmol), followed by pulverized KOH (31.4 mg, 0.56 mmol) and Bu_4NI (37 mg, 0.1 mmol) in dry THF (3 mL). After 4 h additional CH_3I (79.5 mg, 0.56 mmol) was added, followed by pulverized KOH (31.4 mg, 0.56 mmol). After stirring overnight the reaction mixture was filtered and evaporated to give a residue which was redissolved in CH_2Cl_2, washed with aqueous $Na_2S_2O_3$, brine, and dried over $MgSO_4$. Removal of solvent and filtration through a silica gel column (2% MeOH–CH_2Cl_2) furnished **8** (88 mg, 82%) as colorless needles, mp 72–74°C. Sublimation at 0.002 mm Hg gave an analytical sample: mp 76°C; IR (KBr) 2943, 2871, 1639, 1431, 1336, 1229, 1095, 1004 cm^{-1}; ^{1}H-NMR δ 1.52–1.69 (m, 2 H), 1.93–2.05 (m, 2 H), 2.30 (dd, 1 H, J=15.0 and 6.0 Hz), 2.45 (dd, 1 H, J=15.0 and 6.0 Hz), 2.47–2.64 (m, 2 H), 2.98 (s, 3 H), 3.18 (dd, 1 H, J=13.0 and 6.0 Hz), 3.36 (dd, 1 H, J=13.0 and 5.0 Hz), 3.92 (s, 4 H); MS $C_{11}H_{17}NO_3$ *m/z* 211 (M^+, 42), 166 (8), 139 (30), 126 (13), 110 (100), 86 (16), 57 (10), 41 (16). Anal. Calcd for $C_{11}H_{17}NO_3$: C, 62.54; H, 8.11; N, 6.63. Found: C, 62.49; H, 8.16; N, 6.60.

(1R,5R*,6S*)-8-Ethylenedioxy-3,5-dimethyl-3-azabicyclo[4.3.0]nona-4-one* **9**

Freshly prepared LDA in THF (1 M, 2 mL, 2 mmol) was added slowly dropwise to a stirred solution of **8** (203 mg, 0.96 mmol) in dry THF (7 mL) under argon at −78°C. The solution was warmed to 0°C and stirred at this temperature for 75 min, then recooled to −100°C and CH_3I (546 mg, 3.84 mmol) was added rapidly. The reaction mixture was stirred for 3 h at −100°C and quenched with saturated aqueous NH_4Cl (3 drops), diluted with CH_2Cl_2, and dried over $MgSO_4$. Removal of solvent and filtration (EtOAc) through a silica gel column (20 g) furnished unreacted **8** (12 mg, 6%) and the methyl derivative **9** (177 mg, 82%): mp 42°C; IR (KBr) 2975, 1659, 1431, 1395, 1345, 1268, 1101, 1023, 984 cm^{-1}; ^{1}H-NMR δ 1.16 (d, 3H, J=6.5 Hz), 1.57 (ddd, 1 H, J=13.5, 7.0 and 1.5 Hz), 1.58–1.70 (m, 1 H), 1.97 (ddd, 1 H, J=13.5, 8.5 and 2.0 Hz), 2.0–2.15 (m, 2 H), 2.16–2.28 (m, 1 H), 2.42–2.58 (m, 1 H), 2.97 (s, 3 H), 3.22 (dd, 1 H, J=13.0 and 6.5 Hz), 3.33 (dd, 1 H, J=13.0 and 11.0 Hz), 3.92 (s, 4 H); ^{13}C NMR δ 174.4 (s), 116.7 (s), 64.7 (t), 64.2 (t), 51.7 (t), 40.9 (t), 40.6 (d), 40.2 (d), 38.6 (t), 34.7 (d), 34.5 (q), 14.3 (q); MS $C_{12}H_{19}NO_3$ *m/z* 225 (M^+, 29), 180 (6), 153 (13), 139 (14), 124 (100), 99 (7), 86 (10), 71 (7), 41 (9). Anal. Calcd for $C_{12}H_{19}NO_3$: C, 63.98; H, 8.50; N, 6.22. Found: C, 63.96; H, 8.48; N, 6.27.

(1R,5R*,6S*)-8-Ethylenedioxy-3,5-dimethyl-5-phenylseleno-3-azabicyclo[4.3.0]nona-4-one* **10**

Freshly prepared LDA in dry THF (1 M, 2.6 mL, 2.6 mmol) was added slowly dropwise to a solution of **9** (300 mg, 1.34 mmol) in dry THF (10 mL) under argon at−78°C. The solution was warmed to 0°C and stirred at this temperature for 75 min, then recooled to −78°C, and a solution of freshly prepared PhSeBr (656 mg, 2.76 mmol) in dry THF (2 mL) was rapidly added dropwise. The reaction mixture was stirred for 3 h at −78°C, quenched by addition of saturated aqueous NH_4Cl,

extracted with CH_2Cl_2 (3×25 mL), washed with brine, and dried over $MgSO_4$. Removal of solvent and filtration (10% hexane–EtOAc) through a silica gel column (30 g) furnished unreacted **9** (44 mg, 15%) and the seleno-derivative **10** (314 mg, 62%). IR (neat) 2927, 1647, 1436, 1336, 1115, 741, 692 cm^{-1}; ^{1}H-NMR δ 1.50 (s, 3 H), 1.54–1.60 (m, 1 H), 1.75 (dd, 1 H, J=13.5 and 6.5 Hz), 1.93 (ddd, 1 H, J=13.5, 8.0 and 2.0 Hz), 2.07 (ddd, 1 H, J=13.5, 7.5 and 2.0 Hz), 2.67–2.77 (m, 2 H), 2.94 (s, 3 H), 3.06 (dd, 1 H, J=13.0 and 3.8 Hz), 3.82–4.0 (m, 4 H), 4.12 (dd, 1 H, J=13.0 and 7.0 Hz), 7.25–7.60 (m, 5 H). CIMS (CH_4) $C_{18}H_{23}NO_3Se$ *m/z* 381 (M+ H, 100%).

(1R)-8-Ethylenedioxy-3,5-dimethyl-3-azabicyclo[4.3.0]non-5-en-4-one* ***11a*** *and (1R*,6S*)-8-ethylenedioxy-3-methyl-5-methylene-3-azabicyclo[4.3.0]nona-4-one* ***11b***

To a solution of **10** (240 mg, 0.63 mmol) in CH_2Cl_2 (8 mL) at 0°C was added pyridine (0.1 mL) followed by 30% aqueous H_2O_2 (0.080 mL). The reaction mixture was stirred at 0°C for 1 h, warmed to rt, quenched with saturated aqueous $Na_2S_2O_3$, extracted with CH_2Cl_2, dried over $MgSO_4$, and filtered through Celite (2 g). Removal of solvent and separation (EtOAc) over a silica gel column (20 g) furnished the α-methylenelactam **11b** (28 mg, 20%), and the corresponding *endo* isomer **11a** (101 mg, 72%). To a stirred solution of the undesired lactam **11b** (25 mg, 0.11 mmol) in EtOH (6 mL) under argon was added solid $CaCO_3$ (10 mg) followed by $RhCl_3.3H_2O$ (3 mg). The reaction mixture was heated at reflux for 48 h, cooled to rt, and taken to dryness. The residue was dissolved in CH_2Cl_2, filtered successively through Celite (0.5 g) and silica gel (2 g). Elution with EtOAc provided additional 20 mg (80%) of the desired lactam **11a**. Compound **11b**: IR (neat) 2939, 1659, 1608, 1431, 1342, 1081, 1020 cm^{-1}; ^{1}H-NMR δ 1.74 (dd, 1 H, J=14.0 and 5.0 Hz), 1.87 (dd, 1 H, J=13.5 and 11.0 Hz), 2.07 (ddd, 1 H, J=14.0, 7.5 and 1.5 Hz), 2.15 (ddd, 1 H, J=13.5, 8.0 and 1.5 Hz), 2.56 (m, 1 H), 3.02 (s, 3 H), 3.18 (m, 1 H), 3.25–3.34 (m, 2 H), 3.85–3.98 (m, 4 H), 5.27 (br s, 1 H), 6.14 (br s, 1 H). Compound **11a**: IR (neat) 2925, 1631, 1490, 1310, 1116, 1080, 1020 cm^{-1}; ^{1}H-NMR δ 1.62 (t, 1 H, J=12.5 Hz), 1.77 (dt, 3 H, J=2.5 and 1.8 Hz), 2.09 (ddd, 1 H, J=12.5, 7.5 and 1.8 Hz), 2.65 (d sext, 1 H, J=19.0 and 1.8 Hz), 2.73 (br d, 1 H, J=19.0 Hz), 2.98 (s, 3 H), 2.93–3.10 (m, 1 H), 3.25 (dd, 1 H, J=13.5 and 11.5 Hz), 3.35 (dd, 1 H, J=11.5 and 7.0 Hz), 3.85–4.05 (m, 4 H); MS $C_{12}H_{17}NO_3$ m/z 233 (M^+, 35), 180 (41), 161 (60), 146 (33), 137 (27), 108 (88), 96 (48), 86 (51), 79 (66), 73 (58), 41 (100). Anal. Calcd for $C_{12}H_{17}NO_3$: C, 64.55; H, 7.67; N, 6.27. Found: C, 64.50; H, 7.69; N, 6.24.

8-Ethylenedioxy-3,5-dimethyl-3-azabicyclo[4.3.0]non-5-ene ***12***

A solution of $LiAlH_4$ (1 M in THF, 0.26 mL, 0.26 mmol) was slowly added by syringe to a stirred solution of **11a** (30 mg, 0.13 mmol) in dry THF (4 mL) under argon at 0°C. After 90 min, saturated aqueous Na_2SO_4 (0.5 mL) was added dropwise. The reaction mixture was filtered through Celite, dried over $MgSO_4$, and the solvent was evaporated. The crude material was purified by silica gel flash chromatography (EtOAc) to give **12** (26 mg, 92%): IR (neat) 2930, 2781, 1460, 1310, 1121, 1080, 1035 cm^{-1}; ^{1}H-NMR δ 1.42 (t, 1 H, J=12.5 Hz), 1.55 (br s, 3 H), 1.83 (t, 1 H, J=10.2 Hz), 1.98 (ddd, 1 H, J=12.5, 7.5 and 1.5 Hz), 2.36 (s, 3 H), 2.47 (br d, 1 H, J=18.0 Hz), 2.55 (br d, 1 H, J=17.0 Hz), 2.60 (br d, 1 H, J=18.0 Hz), 2.72–2.87 (m, 1 H), 3.0 (dd, 1 H, J=10.2 and 5.5 Hz), 3.14 (br d, 1 H, J=17.0 Hz), 3.87–4.0 (m, 4 H); ^{13}C NMR δ 131.2 (s), 122.6 (s), 116.1 (s), 64.4 (t), 64.0 (t), 58.9 (t), 57.7 (t), 45.4 (d), 40.7 (t), 39.4 (t), 39.3 (q), 16.4 (q); MS $C_{12}H_{19}NO_2$ *m/z* 209 (M^+, 100), 194 (34), 166 (76), 122 (41), 108 (35), 99 (25), 94 (31), 79 (41), 43 (52), 41 (45). Anal. Calcd for $C_{12}H_{19}NO_2$: C, 68.87; H, 9.15; N, 6.69. Found: C, 68.84; H, 9.10; N, 6.73.

(1R,5S*)-3,5-Dimethyl-3-azabicyclo[4.3.0]non-6-en-8-one* ***13***

70% $HClO_4$ (0.05 mL) was added to a stirred solution of **12** (30 mg, 0.14 mmol) in CH_2Cl_2 (5 mL) at 0°C. After 30 min at 0°C followed by 2 h at rt, the reaction mixture was quenched with 10% NaOH. The basic phase was extracted with CH_2Cl_2 (3×10 mL) and the combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated. Amine **13** was purified by silica gel flash chromatography (1% Et_3N–EtOAc); yield 16.6 mg (70%); IR (neat) 2940, 2795, 1705, 1620, 1465, 1258, 1195, 1160, 1135 cm^{-1}; ^{1}H-NMR δ 1.17 (d, 3 H, J=6.5 Hz), 1.74 (t, 1 H, J=11.0 Hz), 1.76 (t,

1 H, J=11.0 Hz), 1.97 (ddd, 1 H, J=18.5, 2.5 and 1.0 Hz), 2.35 (s, 3 H), 2.55 (dd, 1 H, J=18.6 and 7.0 Hz), 2.68–2.81 (m, 1 H), 2.95–3.03 (m, 1 H), 3.03 (ddd, 1 H, J=11.0, 6.0 and 2.0 Hz), 3.20 (ddd, 1 H, J=11.0, 6.0 and 2.0 Hz), 5.88 (t, 1 H, J=2.0 Hz); ^{13}C NMR δ 207.8 (s), 185.8 (s), 125.1 (d), 63.1 (t), 62.5 (t), 45.1 (q), 40.7 (d), 39.1 (t), 35.1 (d), 14.8 (q). MS $C_{10}H_{15}NO$ *m/z* 165 (M^+, 63), 136 (14), 122 (17), 97 (40), 79 (42), 57 (100), 41 (38). Anal. Calcd for $C_{10}H_{15}NO$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.73; H, 9.11; N, 8.43.

(±)-Tecomanine ***4***

A solution of freshly prepared LDA (1 M in THF, 0.073 mL, 0.073 mmol) was slowly added by syringe to a stirred solution of **13** (10 mg, 0.061 mmol) in dry THF (2 mL) under argon at −78°C. After 30 min a solution of MeI (11 mg, 0.077 mmol) and DMPU (0.044 mL) in THF (0.5 mL) was added rapidly. After stirring at −78°C for an additional hour the reaction mixture was quenched with 2% HCl and extracted with CH_2Cl_2 to remove DMPU. The aqueous layer was alkalized with solid KOH and extracted exhaustively with CH_2Cl_2. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated. Tecomanine was purified by silica gel flash chromatography (1% Et_3N–EtOAc): yield 7.1 mg (65%); ^{1}H-NMR δ 1.17 (d, 3 H, J=6.5 Hz), 1.19 (d, 3 H, J=7.5 Hz), 1.78 (t, 2 overlapped H, J=11.0 Hz), 1.97 (qdd, 1 H, J=7.5, 3.0 and 1.0 Hz), 2.36 (s, 3 H), 2.56–2.65 (m, 1 H), 2.70–2.81 (m, 1 H), 3.04 (ddd, 1 H, J=11.0, 5.8 and 2.0 Hz), 3.28 (ddd, 1 H, J=11.0, 6.0 and 2.0 Hz), 5.88 (t, 1 H, J=2.0 Hz); ^{13}C NMR δ 14.7 (q), 14.8 (q), 34.8 (d), 44.9 (q), 45.2 (d), 49.2 (d), 61.6 (t), 62.8 (t), 124.2 (d), 183.1 (0), 210.2 (0); MS $C_{11}H_{17}NO$ *m/z* 179 (M^+ 37), 164 (23), 149 (13), 136 (20), 121 (20), 111 (34), 97 (22), 93 (18), 83 (19), 71 (29), 57 (100), 43 (40). Spectroscopic and chromatographic data of this product are identical with those of an authentic sample of natural (−)-tecomanine[27] and with literature data.[12d]

(2S,4R)-2-Azido-4-hydroxypentane (2S,4R)- ***14***

A solution of freshly distilled $SOCl_2$ (1.65 g, 13.8 mmol) in dry CH_2Cl_2 (2 mL) was added dropwise to a stirred solution of commercially available (2*R*,4*R*)-2,4-pentanediol (0.88 g, 8.5 mmol) in dry CH_2Cl_2 (6 mL) under argon at 0°C. The solution was heated at reflux for 1 h, cooled to rt, washed with 5% aqueous $NaHCO_3$ (1 mL) and then with brine. Drying ($MgSO_4$) and removal of the solvent gave an oily residue (1.08 g, 85%). [IR (neat) 2980, 1460, 1383, 1293, 1189, 1081, 926, 800 cm^{-1}] which was used immediately in the following step. To the thus prepared sulphite (0.435 g, 2.9 mmol) were added in the order MeCN (10 mL), CCl_4 (10 mL), and H_2O (15 mL). To the mixture cooled to 0°C was added $RuCl_3.3H_2O$ (5 mg) followed by solid $NaIO_4$ (1.25 g, 5.8 mmol), and vigorous stirring was continued at 0°C for 1 h. The aqueous layer was washed with CH_2Cl_2 and the combined organic extracts were washed with brine, filtered through Celite (3 g), and dried over $MgSO_4$. Removal of solvents furnished practically pure (2*R*,4*R*)-2,4-pentanediol sulphate (0.46 g, 96%): IR (neat) 2992, 2944, 1488, 1377, 1199, 1070, 930, 870, 840, 805, 778, 745 cm^{-1}; ^{1}H-NMR δ 1.60 (d, 6H, J=7.0 Hz), 2.03 (t, 2H, J=7.0 Hz), 5.08 (sxt, 2H, J=7.0 Hz). Anal. Calcd for $C_5H_{10}O_4S$: C, 36.14; H, 6.06; S, 19.29. Found C, 35.76; H, 6.36; S, 19.45. Solid NaN_3 (0.35 g, 5.4 mmol) was added portionwise to a solution of the previously prepared sulphate (0.45 g, 2.7 mmol) in dry DMF (15 mL) and the reaction mixture was stirred for 2 h at 70–80°C. Removal of the solvent under vacuum (0.2 mm Hg, 50°C) gave a residue which was redissolved into THF (20 mL). To the stirred solution was added H_2O (45 μL), followed by conc. H_2SO_4 (115 μL), and stirring was continued for 40 min at rt. Solid $NaHCO_3$ (0.5 g) was added and the mixture was stirred for an additional 20 min, filtered through Celite, and taken to dryness. The crude material was purified by silica gel flash chromatography (70% EtOAc–hexane) to give oily (2*S*,4*R*)-2-azido-4-hydroxypentane (0.31 g, 90%): $[\alpha]_D^{20}$ = +66.2 (CH_2Cl_2, *c*=1); IR (neat) 3346, 2972, 2117, 1454, 1377, 1248, 1148, 1039, 956, 925 cm^{-1}; ^{1}H-NMR δ 1.23 (d, 3H, J=7.0 Hz), 1.32 (d, 3H, J=7.0 Hz), 1.48–1.70 (2H, m), 3.60–3.80 (m, 1H), 3.90–4.05 (m, 1H). Anal. Calcd for $C_5H_{11}N_3O$: C, 45.10; H, 8.33; N, 10.52. Found C, 45.25; H, 8.51; N, 10.40.

(1R,6R)-N-[(2S,4R)-4-Hydroxy-2-pentanyl]-3-azabicyclo[4.3.0]nona-4,8-dione ***18a*** *and (1S,6S)-N-[(2S,4R)-4-hydroxy-2-pentanyl]-3-azabicyclo[4.3.0]nona-4,8-dione* ***18b***

(2*S*,4*R*)-**14** (62.2 mg, 0.48 mmol) was added to a solution of **1** (40.3 mg, 0.29 mmol) in 36% aqueous HCl (0.8 mL) while keeping the temperature at 0°C. After having been stirred for 2 h at 0°C and then for 4 h at rt, the mixture was brought to pH=9 with 10% aqueous NaOH, and the aqueous layer was saturated with NaCl and extracted continuously with CH_2Cl_2 for 24 h. Drying of the organic phase over $MgSO_4$ and removal of the solvent furnished a residue that was separated on a silica gel column (6 g) Elution with EtOAc gave unreacted diketone 1 (17.5 mg). Elution with 15% MeOH–EtOAc afforded a chromatographically inseparable 3.2:1 mixture of lactams **18a–b** (15.7 mg, 40% on reacted 1): IR (neat) 3417, 2971, 1735, 1640, 1488, 1477, 1368, 1243, 1174, 903 cm^{-1}; ^{1}H-NMR δ 1.12 (d, 3H, J=7.0 Hz),[a] 1.16 (d, 3H, J=7.0 Hz),[b] 1.19 (d, 3H, J=6.5 Hz),[b] 1.21 (d, 3H, J=6.5 Hz),[a] 1.48 (dt, 1H, J=14.0 and 5.0 Hz), 1.55–1.70 (m, 1H), 2.0–2.22 (m, 2H), 2.30 (dd, 1 H, J=14.0 and 6.0 Hz), 2.40–2.85 (m, 6H), 3.0–3.10 (m, 1H), 3.40 (dd, 1 H, J=12.0 and 5.0 Hz), 3.75–3.90 (m, 1H), 4.75–4.90 (m, 1H); ^{13}C NMR δ 216.6 (s), 170.5 (s),[a] 170.4 (s),[b] 66.0 (d),[a] 65.9 (d),[b] 45.9 (d),[b] 45.8 (d),[a] 44.0 (t),[b] 43.9 (t),[a] 43.0 (t), 42.9 (t), 41.9 (t),[a] 41.6 (t),[b] 36.6 (t), 33.7 (d),[b] 33.3 (d),[a] 31.2 (d),[b] 31.1 (d),[a] 23.9 (q),[b] 23.8 (q),[a] 18.6 (q),[a] 18.4 (q)[b] [[a] signals attributable to the major diastereomer; [b] signals assignable to the minor diastereomer. The relative intensity between corresponding signals was 3.2:1]; MS $C_{13}H_{21}NO_3$ *m/z* 239 (M^+, 16), 221 (17), 206 (10), 194 (35), 192 (32), 180 (100), 152 (30), 138 (15), 95 (18). Anal. Calcd for $C_{13}H_{21}NO_3$: C 65.25, H 8.84, N 5.85. Found C, 65.18, H, 8.93; N, 5.70.

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29. In separate experiments, commercially available (±)-2,4-pentanediol and (2*R*,4*R*)-pentanediol (97% ee, GLC) were converted into (±)- and (2*S*,4*R*)-2-azido-4-hydroxypentane,[28] respectively, in four steps and *ca* 68% overall yield: (a) $SOCl_2$, CH_2Cl_2, 40°C; (b) $NaIO_4$, $RuCl_3.3H_2O$, CH_3CN–H_2O, 25°C; (c) NaN_3, DMF, 75°C; (d) 10% H_2SO_4–THF, 20°C.
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31. **17b** is slightly favored over **17a** by 1.1 kcal/mol at 20°C. Molecular mechanics calculations were performed with the MM^+ force fields of *Hyper-Chem* (Release 3 for Windows), AUTODESK (1993).

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