New access to chiral pyrrolidine and piperidine β-enamino ketones. Application to the enantioselective synthesis of (–)-hygroline

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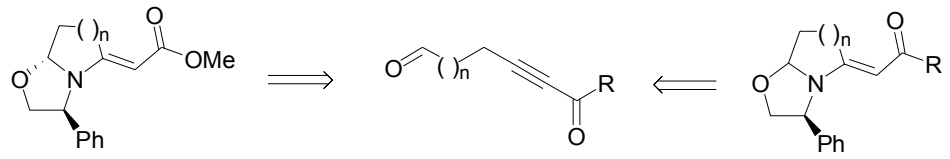
Abstract
We report here a new access to chiral pyrrolidine and piperidine β-enamino ketones by condensation of (*S*)-phenylglycinol with ω-oxo alkynones. As an illustration of the synthetic potential of the target compounds, the total enantioselective synthesis of alkaloid (–)-hygroline was achieved.

Keywords: β-Enamino ketone, pyrrolidine, piperidine, hygroline

Introduction

Synthesis of β-enaminones has attracted much interest because of their intrinsic biological properties.[1] Moreover, β-enaminones constitute useful precursors for the preparation of a number of heterocycles and natural products. Indeed, due to their versatile reactivity, they can be condensed to fused heterocycles[2] or be reduced into either β-amino carbonyl derivatives[3] or 1,3-amino alcohols.[4] In our continuing efforts towards the synthesis of natural products, we have been interested in the enantioselective preparation of heterocyclic β-enaminones bearing an exocyclic double bond. The classical general method for the preparation of such compounds relies on the Eschenmoser sulphide contraction.[3a,3b,5] Alternative procedures have been developed to synthesize morpholinone,[6] pyrrolidine[7] and piperidine[4a,7] derivatives. More recently, we described the preparation of chiral bicyclic pyrrolidine and piperidine β-enamino esters (7a*R*)-**1** and (8a*R*)-**2**, by condensation of (*S*)-phenylglycinol with ω-oxo alkynoates **3** and **4** (R = OMe)[8] (Scheme 1). During the course of this work, we realized that our strategy could be extended towards the obtention of oxazolidine β-enamino ketone analogues **5** and **6** (Scheme 1). Herein, we wish to report our study concerning the synthesis of these compounds by the condensation of the same chiral amine with various ω-oxo alkynones **3** and **4** (R = alkyl, aryl)

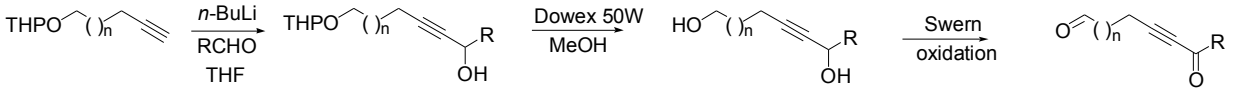
(Scheme 1). The interest of such compounds as precursors of chiral amino alcohols will be demonstrated by the total enantioselective synthesis of the pyrrolidine alkaloid (–)-hygroline.



Scheme 1

Results and Discussion

To evaluate the feasibility of our approach, we carried out the present study using various alkyl and phenyl alkynones **3** (R = Me, Ph) and **4** (R = Me, Ph, *n*-Pr, *i*-Pr) as the starting products (Scheme 2). The resulting pyrrolidine and piperidine enamino ketones were viewed as useful building blocks for the total synthesis of various alkaloids.[9] The required dioxo alkynes **3a-b** and **4a-d** were easily obtained in four steps starting from the tetrahydropyrannyl ether[10] of pent-4-yn-1-ol **7** and hex-5-yn-1-ol **8** (Scheme 2). Condensation of the acetylide anions on the various aldehydes afforded the corresponding propargyl alcohols **9a-b** and **10a-d** in high yields. Subsequent deprotection of the ω-hydroxy functions was performed using Dowex W50 in methanol to give the corresponding diols **11a-b**[11] and **12a-d**. During these studies, we noted that the benzylic alcohol (**9b** and **10b**) were prone to solvolysis by methanol.[12] Indeed, we observed the formation of the corresponding methyl ethers after prolonged reaction times.[12] Consequently, the reaction was monitored by gas chromatography and stopped before the appearance of these by-products, even if some unreacted starting material remained. The latter was however easily recovered after column chromatography. Finally, double oxidation of the previously obtained diols was efficiently achieved using Swern conditions[13] to yield the expected ketoaldehydes **3a-b** and **4a-d** (Scheme 2).



n = 1 **7**
n = 2 **8**

n = 1	**9a**	(R = Me)	(86%)
	9b	(R = Ph)	(88%)
n = 2	**10a**	(R = Me)	(85%)
	10b	(R = Ph)	(94%)
	10c	(R = *n*-Pr)	(87%)
	10d	(R = *i*-Pr)	(90%)

n = 1	**11a**	(R = Me)	(97%)
	11b	(R = Ph)	(82%)*
n = 2	**12a**	(R = Me)	(90%)
	12b	(R = Ph)	(90%)*
	12c	(R = *n*-Pr)	(97%)
	12d	(R = *i*-Pr)	(94%)

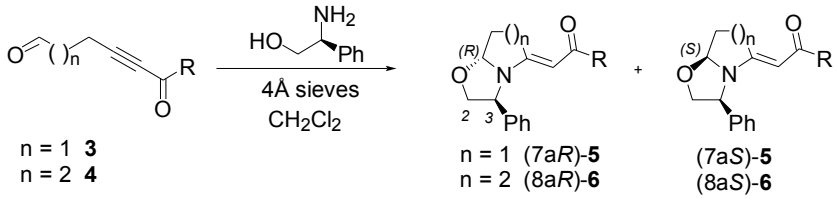
n = 1	**3a**	(R = Me)	(84%)
	3b	(R = Ph)	(82%)
n = 2	**4a**	(R = Me)	(76%)
	4b	(R = Ph)	(73%)
	4c	(R = *n*-Pr)	(75%)
	4d	(R = *i*-Pr)	(79%)

*: calculated yields based on reacted starting material.

Scheme 2

With the required linear precursors in hands, we turned our attention to their condensation with (*S*)-phenylglycinol. The results obtained starting from the various substituted ketoaldehydes are summarized in Table 1.

Table 1. Synthesis of oxazolidine β-enamino ketones **5**-**6** by condensation of keto aldehydes **3**-**4** with (*S*)-phenylglycinol



Entry	n	R	**3** or **4**	Ratio[a] (7a*R*)-**5**:(7a*S*)-**5** or (8a*R*)-**6**:(8a*S*)-**6**	**5** or **6** (Yield)[b]
1	1	CH_3	**3a**	75:25	(7a*R*)-**5a** (48%)
					(7a*S*)-**5a** (18%)
2	1	Ph	**3b**	85:15	(7a*R*)-**5b** (66%)
					(7a*S*)-**5b** (11%)
3	2	CH_3	**4a**	100:0	(8a*R*)-**6a** (62%)
4	2	Ph	**4b**	100:0	(8a*R*)-**6b** (72%)
5	2	$-(CH_2)_2CH_3$	**4c**	100:0	(8a*R*)-**6c** (70%)
6	2	$-CH(CH_3)_2$	**4d**	100:0	(8a*R*)-**6d** (75%)

[a]determined by GC and NMR. [b] Isolated yields.

When reacted in CH_2Cl_2 in the presence of the chiral amine and 4Å molecular sieves at room temperature, ketoaldehyde **3a** afforded the expected chiral β-enamino ketone **5a** as a mixture of epimers at C-7a in a 75:25 ratio (estimated by GC and NMR) and 66% overall yield (Table 1, entry 1). Column chromatography readily afforded the isolation of the two diastereomers in respectively 48% and 18% yields. The configuration at C-7a of the major isomer of **5a** was assigned to (*R*), by analogy with analogous pyrrolidine β-enaminoester **1**[8] (Scheme 1), based on the comparison of their chemical shifts in ^{13}C NMR. In particular, similar chemical shifts for C-2 and C-3 were observed for the major isomer of **5a** and for (7a*R*)-**1**. In contrast, the (7a*S*) minor isomer of **5a** displayed very different chemical shifts (Table 2).

Likewise, when reacted with (*S*)-phenylglycinol the phenylketone **3b** gave rise to a 85:15 mixture of β-enaminoketones (7a*R*)-**5b** and (7a*S*)-**5b** that were subsequently isolated in 66% and 11% respective yields (Table 1, entry 2). The absolute configurations of both isomers were assigned as above by comparison of the chemical shifts of C-2 and C-3 (Table 2). It was of note that the minor diastereomer (7a*S*)-**5b** slowly isomerized in $CDCl_3$ solution into (7a*R*)-**5b**, which in turn evolved to the corresponding pyrrole derivative as substantiated by the characteristic ^1H

NMR aromatic signals at 6.05, 6.24 and 6.95 ppm. However, the ratio of the two diastereomers does not evolve after prolonged reaction time in CH_2Cl_2.

Table 2. Characteristic ^{13}C NMR chemical shifts for oxazolo piperidines **1** and **5**

Compounds	δ C-2 (ppm)	δ C-3 (ppm)
(7a*R*)-**1**	76.3	63.4
(7a*R*)-**5a**	76.3	62.9
(7a*R*)-**5b**	76.0	62.4
(7a*S*)-**5a**	78.8	58.9
(7a*S*)-**5b**	79.2	59.2

As for the homologous ketoaldehydes **4a-d**, their condensation with (*S*)-phenylglycinol afforded the corresponding piperidine β-enaminoketones **6a-d** respectively as single isomers, in high isolated yields (Table 1, entries 3-6). X-ray analysis[14] performed on crystalline **6b** allowed us to assign the (8a*R*) absolute configuration. The same stereochemistry was attributed to piperidine compounds **6a, 6c** and **6d**, based on the comparison of ^{13}C NMR spectroscopic data. Indeed, compounds **6a-d** and the piperidine β-enaminoester (8a*R*)-**2** displayed similar chemical shifts for C-2 and C-3 (Table 3).

Table 3. Characteristic ^{13}C NMR chemical shifts for oxazolo piperidines **2** and **6**

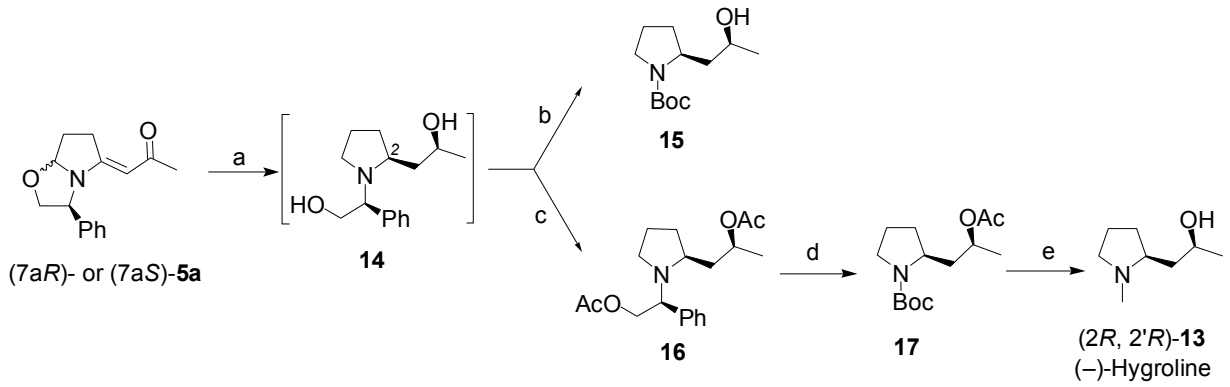
Compounds	δ C-2 (ppm)	δ C-3 (ppm)
(8a*R*)-**2**	73.4	61.6
(8a*R*)-**6a**	73.4	61.5
(8a*R*)-**6b**	73.7	62.3
(8a*R*)-**6c**	73.4	61.6
(8a*R*)-**6d**	73.5	61.9

In the above study, we demonstrated that the present methodology consisting in the condensation of a chiral amine with alkynoates could be successfully extended to alkynones, allowing the efficient synthesis of the target pyrrolidine and piperidine β-enamino ketones. Noteworthy, as conjugated alkynones reacted much faster than the corresponding alkynoates, the follow-up of the reaction by NMR experiment that would give clues on the involved intermediates proved impossible. As for the ester analogue, piperidine derivatives **6a-d** were obtained with excellent diastereoselectivities. In contrast, poorer diastereomeric excesses were obtained for pyrrolidine compounds **5a** and **5b** (d.e. 50 to 70%) for unclear reasons.

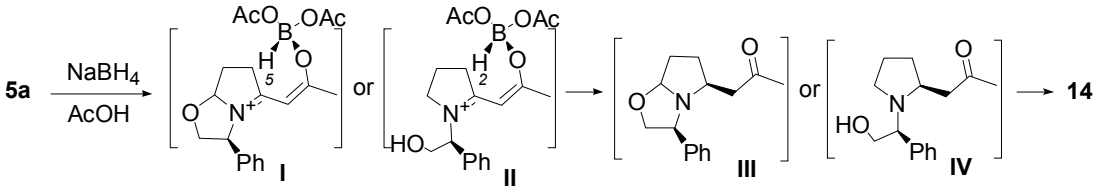
Reduction of β-enamino ketones may lead to γ-amino alcohols some of which are interesting for their biological and pharmaceutical properties as well as their wide application in synthesis.[15] In this context, the previously synthesized chiral β-enamino ketones appear as convenient precursors of chiral pyrrolidine and piperidine γ-amino alcohols. In this work, we turned our

attention towards the total synthesis of 2-(2-hydroxypropyl)-1-methylpyrrolidine **(13)** (Scheme 3) whose four enantiomers have been described,[16] three of them being natural products. Starting from enantiopure pyrrolidine β-enaminoketone (7a*R*)-**5a,** the key step of our synthesis relied on a diastereoselective reduction. The absolute configurations of the two newly created stereogenic centers were to be assigned based on the identification of the final generated product(s). Various methods including catalytic hydrogenations,[4b] dissolving metal reduction,[17] and treatment with $LiBH_4/CeCl_3$[18] or with $NaBH_4$ in glacial acetic acid[19] have been described to afford predominantly *syn* amino alcohols. We decided to perform the reduction with *in situ* generated sodium triacetoxy borohohydride in acetic acid, as this method had been successfully used in our laboratory to reduce pyrrolidine β-enamino ester **1** into the corresponding β-amino ester with a high diastereoselectivity.[3c] To our delight, these reaction conditions applied to compound (7a*R*)-**5a** cleanly led to the reduction of the C-C double bond and of the ketone moiety along with the cleavage of the oxazolidine ring to give pyrrolidine diol **14**, as a single isomer according to NMR. Noteworthy, the reduction performed on isomer (7a*S*)-**5a** yielded to the same diastereomer **14**, showing that the lack of diastereoselectivity during the formation of the oxazolidine **5a** is of little importance in this case. Compound **14** was submitted to debenzylation (H_2, $Pd(OH)_2/C$) followed by the *in situ* carbamatation in the presence of Boc_2O, to give amino alcohol **15**. Unfortunately, column chromatography did not allow the separation of the latter from 2-phenylethanol. To allow easier isolation, compound **14** was thus subjected to a bis-acetylation to give pyrrolidine acetate **16** in 46% overall yield from **5a**. Debenzylation of compound **16** (H_2, $Pd(OH)_2/C$) followed by the *in situ* carbamatation in the presence of Boc_2O, gave rise to acetate **17** in 85% yield. Treatment with lithium aluminium hydride led to the simultaneous reduction of the carbamate and to the deprotection of the alcohol function to yield the expected compound **13** in 88% yield. The spectroscopic data[16,20] and the optical rotation of this compound {$[\alpha]_D^{24}$ –50 (c 1.28, MeOH)} were identical with those reported in the literature for the (2*R*,2'*R*)-**13** diastereomer { $[\alpha]_D^{22}$ –49 (c 0.4, EtOH)[20] ; $[\alpha]_D^{20}$ –50.2 (c 0.466, EtOH)[21] ; $[\alpha]_D^{25}$ –53 (c 1.025, EtOH)[16] }, (–)-hygroline, an alkaloid isolated from *Eryhroxylum coca*.[22] This result allowed us to assign the (2*R*, 2'*R*) absolute stereochemistry to compounds **14**–**17** (Scheme 3).

As for mechanistic considerations, the observation that both (7a*R*) and (7a*S*) isomers of compound **5a** were reduced into the same diastereomer showed that the geometry of the ring fusion did not control the stereochemistry at the C-2 center of pyrrolidine **14**. So, we reasoned that the control of the stereochemistry of the latter was induced by the chiral center bearing the phenyl substituent, the oxazolidine moiety being initially cleaved or not. The key step of the reaction would then consist in the reduction of the iminium moiety of intermediate boro enolates **I** or **II**[23] *via* an hydride transfer from the less hindered face (*Re* face at C-5 or C-2 respectively) *anti* to the phenyl substituent (Scheme 4). In our scenario, subsequent reduction of the resulting ketone moiety of intermediates **III** or **IV** would lead to a *syn* 1,3-amino alcohol, as previously reported for the reduction of linear β-enaminoketones.[20]



Scheme 3. *Reagent and conditions:* (a) $NaBH_4$, AcOH, CH_3CN; (b) H_2, $Pd(OH)_2/C$, Boc_2O, AcOMe, 63% (calculated yield for 2 steps); (c) Ac_2O, NEt_3, DMAP, CH_2Cl_2, 46% (2 steps); (d) H_2, $Pd(OH)_2/C$, Boc_2O, AcOMe, 85%;(e) $LiAlH_4$, THF, 88%.



Scheme 4

Conclusions

In conclusion, we developed a valuable methodology for the synthesis of chiral oxazolo pyrrolidine and piperidine β-enamino ketones by condensation of (*S*)-phenylglycinol with ω-oxo alkynones. The synthetic potential of these compounds was illustrated by the total enantioselective synthesis of alkaloid (–)-hygroline.

Experimental Section

General Procedures. Unless otherwise specified, materials were purchased from commercial suppliers and used without further purification. THF was distilled from sodium/ benzophenone ketyl immediately prior to use. CH_2Cl_2 was distilled from calcium hydride. All reactions were carried out under argon. Thin layer chromatography analyses were performed on Merck precoated silica gel (60 F_{254}) plates and column chromatography on silica gel Gerudan SI 60 (40-60 μm) (Merck). Melting points are uncorrected. IR: Philips PU 9700. Gas chromatographies were performed on a capillary Chrompack CP-SIL5. Optical rotation: Perkin-Elmer 241 polarimeter. Elemental analysis: Service de Microanalyse de l'ICSN (Gif sur Yvette). HMRS

were recorded on a JEOL MS 700 mass spectrometer and a Thermo Electron Orbitrap mass spectrometer. NMR: Bruker ARX 250 spectrometer (250 MHz and 62.9 MHz for ^{1}H and ^{13}C, respectively). Spectra were recorded in $CDCl_3$ as solvent. Chemical shifts (δ) were expressed in ppm relative to TMS at $\delta = 0$ for ^{1}H and to $CDCl_3$ at $\delta = 77.16$ for ^{13}C and coupling constants (J) in Hertz.

General procedure for the preparation of compounds 9a-b and 10a-d

To a solution of alkyne **7** or **8** (10 mmol) in anhydrous THF (40 mL) at –78 °C was added dropwise *n*-BuLi (2.5 M in hexanes, 1.1 equiv). The reaction mixture was stirred at this temperature for 30 min and the required aldehyde (3 equiv of acetaldehyde and 1.1 equiv of the other aldehydes) was subsequently added dropwise. The reaction mixture was allowed to warm to room temperature and after stirring for 5 h, quenched with a saturated aqueous NH_4Cl solution (20 mL). The solvent was removed *in vacuo* and the aqueous layer was extracted with CH_2Cl_2 (5×20 mL). The combined organic layers were washed with water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. Silica gel column chromatography of the residue (AcOEt:cyclohexane 2:8) afforded the pure expected compounds as oils.

7-(Tetrahydro-2*H*-pyran-2-yloxy)hept-3-yn-2-ol (9a). Colorless oil (86%); IR (neat) 3400, 2250 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.42 (d, J = 6.5 Hz, 3H), 1.50–1.85 (m, 8H), 2.03 (br s, 1H), 2.33 (dt, J = 2 and 7 Hz, 2H), 3.43–3.54 (m, 2H), 3.77–3.87 (m, 2H), 4.48–4.53 (m, 1H), 4.59–4.61 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 15.5, 19.3, 24.6, 25.4, 28.7, 30.5, 58.1, 62.0, 65.8, 82.8, 83.3, 98.6; HRMS (ESI$^+$) calcd for $C_{12}H_{20}O_3Na$ $(M+Na)^+$: 235.1305, found: 235.1304.

1-Phenyl-6-(tetrahydro-2*H*-pyran-2-yloxy)hex-2-yn-1-ol (9b). Colorless oil (88%); IR (neat) 3400, 2240, 2200 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.47–1.88 (m, 8H), 2.35–2.43 (m, 3H), 3.43–3.52 (m, 2H), 3.79–3.88 (m, 2H), 4.58 (t, J = 3 Hz, 1H), 5.43–5.45 (m, 1H), 7.31–7.56 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 15.6, 19.2, 25.3, 28.5, 30.4, 61.9, 64.3, 65.7, 80.6, 86.2, 98.5, 126.5, 127.9, 128.3, 141.4; HRMS (ESI$^+$) calcd for $C_{17}H_{22}O_3Na$ $(M+Na)^+$: 297.1461, found: 297.1460.

8-(Tetrahydro-2*H*-pyran-2-yloxy)oct-3-yn-2-ol (10a). Colorless oil (85%); IR (neat) 3400, 2220 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.42 (d, J = 6.5 Hz, 3H), 1.49–1.82 (m, 10H), 2.03 (br s, 1H), 2.24 (dt, J = 2 and 7 Hz, 2H), 3.37–3.53 (m, 2H), 3.72–3.87 (m, 2H), 4.48–4.52 (m, 1H), 4.57–4.60 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 18.6, 19.7, 24.8, 25.5, 25.6, 29.0, 30.8, 58.6, 62.4, 67.0, 82.7, 84.4; 98.9; HRMS (ESI$^+$) calcd for $C_{13}H_{22}O_3Na$ $(M+Na)^+$: 249.1461, found: 249.1460.

1-Phenyl-7-(tetrahydro-2*H*-pyran-2-yloxy)hep-2-yn-1-ol (10b). Colorless oil (94%); IR (neat) 3400, 2230 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.49–1.82 (m, 10H), 2.28–2.33 (m, 2H), 2.65 (br s, 1H), 3.35–3.50 (m, 2H), 3.70–3.86 (m, 2H), 4.56 (t, J = 3 Hz, 1H), 5.42 (s, 1H), 7.26–7.54 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 18.8, 19.6, 25.4, 25.5, 29.0, 30.7, 62.3, 64.7, 67.0, 80.5, 87.1, 98.8, 126.7, 128.2, 128.6, 141.4; HRMS (ESI$^+$) calcd for $C_{18}H_{24}O_3Na$ $(M+Na)^+$: 311.1617, found: 311.1618.

10-(Tetrahydro-2*H*-pyran-2-yloxy)dec-5-yn-4-ol (10c). Colorless oil (87%); IR (neat) 3400 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.92 (t, J = 7.25 Hz, 3H), 1.39–1.73 (m, 14H), 2.03 (s, 1H), 2.23 (dt, J = 6.5 and 1.5 Hz, 2H), 3.37–3.50 (m, 2H), 3.69–3.84 (m, 2H); 4.30–4.57 (m, 1H), 4.55–4.58 (m,

1H); ^{13}C NMR ($CDCl_3$) δ 13.9, 18.6, 19.7, 25.5, 29.0, 30.8, 40.4, 62.4, 62.5, 67.1, 81.8, 85.1, 98.9; HRMS (ESI^+) calcd for $C_{15}H_{26}O_3Na$ $(M+Na)^+$: 277.1774, found: 277.1772.

2-Methyl-9-(tetrahydro-2*H*-pyran-2-yloxy)non-4-yn-3-ol (10d). Colorless oil (90 %); IR (neat) 3400 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.96 (d, *J* = 6.75 Hz, 3H), 0.99 (d, *J* = 6.75 Hz, 3H), 1.51–1.90 (m, 12H), 2.26 (dt, *J* = 2 and 7 Hz, 2H), 3.37–3.53 (m, 2H), 3.72–3.86 (m, 2H), 4.13–4.16 (m, 1H), 4.57–4.60 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 17.5, 18.2, 18.6, 19.6, 25.5, 28.9, 30.7, 34.7, 62.2, 67.0, 68.0, 80.3, 85.6, 98.8; HRMS (ESI^+) calcd for $C_{15}H_{26}O_3Na$ $(M+Na)^+$: 277.1774, found: 277.1774.

General procedure for the deprotection of compounds 9a-b and 10a-d

A solution of the substrate (10 mmol) in MeOH (60 mL) was stirred at room temperature in the presence of Dowex 50W (2.5 g). The resulting reaction was monitored by tlc or GC (reaction time: 6 h for **9a** and **10a,c,d** and 4 h for **9b** and **10b**). The reaction mixture was filtered and concentrated in vacuo. Silica gel column chromatography (AcOEt:cyclohexane 1:1) afforded pure diols as oils.

Hept-4-yne-1,6-diol (11a). Colorless oil (97%); IR (neat) 3340, 2260 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.43 (dd, *J* = 1 and 6.5 Hz, 3H), 1.71–1.81 (m, 2H), 2.31–2.40 (m, 4H), 3.76 (t, *J* = 6 Hz, 2H), 4.47–4.53 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 15.1, 24.5, 31.0, 58.0, 60.9, 82.9, 83.4; HRMS (ESI^+) calcd for $C_7H_{12}O_2Na$ $(M+Na)^+$: 151.0729, found: 151.0727.

1-Phenylhex-2-yne-1,6-1-diol (11b). Colorless oil (74% along with 10% recovered starting material **9b**). The spectroscopic data are in accordance with that reported in the literature.[10]

Oct-5-yne-1,7-diol (12a). Colorless oil (90%); IR (neat) 3320, 2250, 2220 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.41 (d, *J* = 6.5 Hz, 3H), 1.54–1.70 (m, 4H), 2.21–2.66 (m, 2H), 3.63 (t, *J* = 6 Hz, 2H), 3.80 (br s, 2H), 4.45–4.53 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 18.4, 24.6, 24.8, 31.4, 58.0, 61.8, 82.8, 83.8; HRMS (ESI^+) calcd for $C_8H_{14}O_2Na$ $(M+Na)^+$: 165.0886, found: 165.0884.

1-Phenylhept-2-yne-1,7-diol (12b). Colorless oil (65% along with 27% recovered starting material **10b**); IR (neat) 3340, 2240, 2200 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.55–1.71 (m, 4H), 2.25–2.31 (m, 2H), 2.75 (br s, 2H), 3.60 (t, *J* = 6 Hz, 2H), 5.41 (s, 1H), 7.26–7.53 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 18.7, 24.9, 31.7, 62.2, 64.7, 80.6, 87.1, 126.7, 128.2, 128.6, 141.4; HRMS (ESI^+) calcd for $C_{13}H_{16}O_2Na$ $(M+Na)^+$: 227.1042, found: 227.1041.

Dec-5-yne-1,7-diol (12c). Colorless oil (97%); IR (neat) 3340 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.91 (t, *J* = 7.25 Hz, 3H), 1.38–1.50 (m, 2H), 1.52–1.68 (m, 6H), 2.22 (dt, *J* = 7 and 2 Hz, 2H), 2.59 (br s, 2H), 3.63 (t, *J* = 6.25 Hz, 2H), 4.31 (td, *J* = 6.5 and 2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 13.9, 18.5, 18.6, 25.0, 31.7, 40.3, 62.2, 62.4, 82.0, 84.9; HRMS (ESI^+) calcd for $C_{10}H_{18}O_2Na$ $(M+Na)^+$: 193.1199, found: 193.1198.

8-Methylnon-5-yne-1,7-diol (12d). Colorless oil (94%); IR (neat) 3320 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.95 (d, *J* = 6.75 Hz , 3H), 0.97 (d, *J* = 6.75 Hz, 3H), 1.55–1.70 (m, 4H), 1.78–1.88 (m, 3H), 2.23–2.91 (m, 2H), 3.67 (t, *J* = 6 Hz, 2H), 4.13–4.16 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 17.5, 18.2, 18.4, 24.9, 31.5, 34.6, 61.9, 67.8, 80.3, 85.4; HRMS (ESI^+) calcd for $C_{10}H_{18}O_2Na$ $(M+ Na)^+$: 193.1199, found: 193.1200.

General procedure for the oxidation of compounds 11a-b and 12a-d

To a cooled –78 °C solution of $(COCl)_2$ (16 mmol, 3.2 equiv) in dry CH_2Cl_2 (70 mL) was slowly added DMSO (26.5 mmol, 5.3 equiv). The mixture was stirred at this temperature for 15 min, then the required diol (5 mmol, 1 equiv) dissolved in CH_2Cl_2 (10 mL) was added dropwise. The reaction mixture was stirred at –78 °C for 30 min, then at –50 °C for 30 min more. The solution was cooled to –78 °C, and NEt_3 (55 mmol, 11 equiv) was added. The reaction mixture was allowed to warm to room temperature over 3 h. Water (40 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3×30 mL). The combined organic layer was washed with water and brine, dried over Na_2SO_4 and concentrated *in vacuo*. Silica gel column chromatography of the residue (AcOEt/Cyclohexane 3:7) afforded the pure expected ketoaldehydes as oils.

6-Oxohept-4-ynal (3a). Colorless oil (84%); IR (neat) 1670, 1720, 2205 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.32 (s, 3H), 2.67–2.71 (m, 2H), 2.77–2.79 (m, 2H), 9.80 (t, *J* = 0.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 11.5, 32.3, 41.0, 81.0, 91.3, 184.2, 199.0; HRMS (CI) calcd for $C_7H_9O_2$ $(M+H)^+$: 125.0597, found: 125.0600.

6-Oxo-6-phenylhex-4-ynal (3b). Pale-yellow oil (82%); IR (neat) 1630, 1710, 2200, 2250 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.78–2.92 (m, 4H), 7.27–7.64 (m, 3H), 8.09–8.13 (m, 2H), 9.86 (d, *J* = 0.5 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 12.0, 41.4, 79.6, 94.0, 128.5, 129.4, 134.0, 136.5, 177.8, 199.0; HRMS (CI) calcd for $C_{12}H_{11}O_2$ $(M+H)^+$: 187.0759, found: 187.0760.

.**7-Oxooct-5-ynal (4a).** Pale-yellow oil (76%); IR (neat) 2220, 1720, 1680 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.95 (q, *J* = 7 Hz, 2H), 2.33 (s, 3H), 2.54 (t, *J* = 7Hz, 2H), 2.63 (t, *J* = 7 Hz, 2H), 9.81 (d, *J* = 0.75 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 18.1, 20.0, 32.7, 42.3, 81.9, 92.2, 184.6, 201.1; HRMS (CI) calcd for $C_8H_{11}O_2$ $(M+H)^+$: 139.0759, found: 139.0757.

7-Oxo-7-phenylhept-5-ynal (4b). Pale-yellow oil (73%); IR (neat) 2220, 2180,1725, 1645 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.00 (quint, *J* = 7 Hz, 2H), 2.59 (t, *J* = 7 Hz, 2H), 2.69 (t, *J* = 7 Hz, 2H), 7.45–7.61 (m, 3H), 8.10–8.13 (m, 2H), 9.83 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 18.5, 20.3, 42.5, 80.3, 94.9, 128.6, 129.6, 134.1, 136.7, 178.0, 201.1; HRMS (CI) calcd for $C_{13}H_{13}O_2$ $(M+H)^+$: 201.0916, found: 201.0921.

7-Oxodec-5-ynal (4c). Yellow oil (75 %); IR (neat) 1665, 1720, 2200 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.88 (t, *J* = 7.5 Hz, 3H), 1.63 (q, *J* = 7.5 Hz, 2H), 1.85 (q, *J* = 7 Hz, 2H), 2.37–2.48 (m, 4H), 2.58 (t, *J* = 7 Hz, 2H), 9.75 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.4, 17.5, 18.2, 20.1, 42.4, 47.3, 81.4, 92.2, 188.1, 201.1; HRMS (ESI^+) calcd for $C_{10}H_{14}O_2Na$ $(M+Na)^+$: 189.0886, found: 189.0885.

8-Methyl-7-oxonon-5-ynal (4d). Colorless oil (79 %); IR (neat) 1660, 1710, 2180 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.12 (d, *J* = 7 Hz, 3H), 1.13 (d, *J* = 7 Hz, 3H), 1.87 (q, *J* = 7 Hz, 2H), 2.42 (t, *J* = 7 Hz, 2H), 2.54–2.62 (m, 3H), 9.75 (d, *J* = 1 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 17.9, 18.3, 20.2, 42.4, 42.9, 80.4, 93.2, 192.1, 201.1; HRMS (ESI^+) calcd for $C_{10}H_{14}O_2Na$ $(M+Na)^+$: 189.0886, found: 189.0888.

General procedure for the preparation of 5a-b and 6a-d

A mixture of the required ketoaldehyde (5 mmol) **3a-b** or **4a-d** in CH_2Cl_2 (50 mL), (*S*)-phenylglycinol (1.1 equiv) and 4 Å molecular sieves (10 g) was stirred at room temperature for 4

h. The reaction mixture was filtered over a Celite® pad. The cake was washed with CH_2Cl_2 and the combined filtrates were evaporated *in vacuo*. Silica gel column chromatography (AcOEt/cyclohexane 1:1) allowed the isolation of the expected compounds.

(1*E*)-1-[(3*S*,7a*R* and 7a*S*)-3-Phenyltetrahydropyrrolo[2,1-*b*]oxazol-5(6*H*)-ylidene]acetone (5a). For (7a*R*)-**5a**: White solid (48%); mp 90–91 °C (from cyclohexane); $[\alpha]_D^{24}$ + 359 (*c* 1.18, $CHCl_3$); IR ($CHBr_3$) 1655 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 1.98–2.11 (m, 1H), 2.04 (s, 3H), 2.35–2.48 (m, 1H), 3.06–3.32 (m, 1H), 3.70–3.83 (m, 2H), 4.55–4.72 (m, 2H), 5.16 (s, 1H), 5.35 (dd, *J* = 4.25 and 6 Hz, 1H), 7.25–7.43 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 27.8, 30.8, 33.0, 62.9, 76.3, 95.4, 96.9, 125.7, 127.9, 129.1, 139.1, 165.9, 196.1. For (7a*S*)-**5a**: Yellow solid (18%); mp 106.5 °C (from cyclohexane:AcOEt); $[\alpha]_D^{24}$ – 115 (*c* 1.025, $CHCl_3$); IR ($CHBr_3$) 1650 cm^{-1} ; ^1H NMR ($CDCl_3$) δ 1.71 (s, 3H), 1.88–2.04 (m, 1H), 2.26–2.36 (m, 1H), 2.92–3.07 (m, 1H), 3.76–3.87 (m, 1H), 4.18 (d, *J* = 8.25 Hz, 1H), 4.43–4.53 (m, 3H), 5.32 (dd, *J* = 5.5 and 7.5 Hz, 1H), 7.16–7.34 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 27.9, 30.1, 34.5, 58.3, 78.8, 95.2, 96.3, 127.1, 127.7, 128.2, 137.9, 157.3, 194.6; Anal. Calcd for $C_{15}H_{17}NO_2$: C, 74.05; H, 7.04; N, 5.76. Found: C, 73.65; H, 6.91; N, 5.59.

(2*E*)-1-Phenyl-2-[(3*S*,7a*R* and 7a*S*)-3-phenyltetrahydropyrrolo[2,1-*b*]oxazol-5(6*H*)-ylidene]ethanone (5b). For (7a*R*)-**5b**: Pale-yellow oil (66%); $[\alpha]_D^{20}$ + 408 (*c* 1.02, $CHCl_3$); IR (neat) 1640 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.00–2.15 (m, 1H), 2.38–2.51 (m, 1H), 3.22–3.37 (m, 1H), 3.77–3.99 (m, 2H), 4.66–4.74 (m, 2H), 5.39 (dd, *J* = 4.5 and 6 Hz, 1H), 5.86 (s, 1H), 7.27–7.39 (m, 8H), 7.75–7.79 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 27.5, 33.4, 62.4, 76.0, 91.2, 96.6, 125.4, 127.0, 127.6, 127.8, 128.7, 130.7, 138.6, 140.3, 167.5, 188.4. For (7a*S*)-**5b**: White solid (11%); mp 153 °C (from cyclohexane:AcOEt); $[\alpha]_D^{20}$ – 94 (*c* 1.04, $CHCl_3$); IR ($CHBr_3$) 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.66–2.08 (m, 1H), 2.32–2.42 (m, 1H), 3.10–3.25 (m, 1H), 3.76–3.87 (m, 1H), 4.26 (d, *J* = 8.75 Hz, 1H), 4.45–4.57 (m, 2H), 5.04 (s, 1H), 5.38 (dd, *J* = 5.5 and 7.5 Hz, 1H), 7.15–7.38 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 28.6, 35.6, 59.2, 79.2, 93.2, 97.1, 127.3, 127.9, 128.4, 129.0, 130.7, 138.3, 141.1, 159.7, 199.7; Anal. Calcd for $C_{20}H_{19}NO_2$: C, 78.66; H, 6.27; N, 4.59. Found: C, 78.43; H, 6.31; N, 4.45.

(1*E*)-1-[(3*S*,8a*R*)-3-Phenylhexahydro-5*H*-[1,3]oxazolo[3,2-*a*]pyridine-5-ylidene]acetone (6a). Pale-yellow oil (62%); $[\alpha]_D^{20}$ + 171 (*c* 1.055, $CHCl_3$); IR ($CHBr_3$) 1630 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.48–1.66 (m, 2H), 1.85 (s, 3H), 1.93–2.03 (m, 1H), 2.30–2.46 (m, 1H), 2.95–3.10 (m, 1H), 3.27–3.35 (m, 1H), 3.61 (t, *J* = 8.5 Hz, 1H), 4.55 (t, *J* = 8.5 Hz, 1H), 4.75 (t, *J* = 8 Hz, 1H), 4.85 (s, 1H), 4.91 (dd, *J* = 4.5 and 9 Hz, 1H), 7.19–7.41 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 16.9, 27.9, 28.1, 31.4, 61.5, 73.4, 89.25, 95.6, 125.7, 127.9, 129.2, 138.6, 158.5, 194.9; HRMS (ESI^+) calcd for $C_{16}H_{20}NO_2$ $(M+H)^+$: 258.1488, found: 258.1487.

(2*E*)-1-Phenyl-2-[(3*S*,8a*R*)-3-phenylhexahydro-5*H*-[1,3]oxazolo[3,2-*a*]pyridine-5-ylidene]ethanone (6b). White solid (72%); mp 152 °C (from cyclohexane:AcOEt); $[\alpha]_D^{20}$ + 248 (*c* 1.065, $CHCl_3$); IR ($CHBr_3$) 1615 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.56–1.73 (m, 2H), 2.03–2.09 (m, 1H), 2.36–2.42 (m, 1H), 3.13–3.28 (m, 1H), 3.41–3.44 (m, 1H), 3.67 (t, *J* = 8.75 Hz, 1H), 4.61 (t, *J* = 8.75 Hz,1H), 4.84 (t, *J* = 8.25 Hz, 1H), 5.05 (dd, *J* = 4 and 9.25 Hz, 1H), 5.51 (br s, 1H), 7.23–7.43 (m, 10H); ^{13}C NMR ($CDCl_3$) δ 17.3, 28.2, 28.4, 62.3, 62.3, 73.7, 89.7, 93.3, 126.2,

127.3, 128.1, 128.3, 129.5, 130.5, 138.6, 142.1, 160.2, 188.2; HRMS (ESI^+) calcd for $C_{21}H_{22}NO_2$ $(M+H)^+$: 320.1645, found: 320.1643.

(1*E*)-1-[(3*S*,8a*R*)-3-Phenylhexahydro-5*H*-[1,3]oxazolo[3,2-*a*]pyridine-5-ylidene]pentan-2-one (6c). Yellow oil (70%); $[\alpha]_D^{20}$ +175 (*c* 1.11, $CHCl_3$); IR (neat) 1635 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.75 (t, *J* = 7.5 Hz, 3H); 1.32–1.67 (m, 4H); 1.93–2.07 (m, 3H); 2.30–2.35 (m, 1H); 3.00–3.11 (m, 1H); 3.28–3.37 (m, 1H); 3.63 (t, *J* = 8.5 Hz, 1H); 4.55 (t, *J* = 8.5 Hz, 1H); 4.75 (t, *J* = 8 Hz, 1H); 4.83 (s, 1H), 4.89–4.95 (m, 1H), 7.20–7.41 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 13.9, 17.0, 19.1, 27.9, 28.1, 46.2, 61.6, 73.4, 89.3, 95.4, 125.8, 127.9, 129.1, 138.7, 158.2, 197.9; HRMS (ESI^+) calcd for $C_{18}H_{24}NO_3$ $(M+H)^+$: 286.1802, found: 286.1800.

(1*E*)-3-Methyl-1-[(3*S*,8a*R*)-3-phenylhexahydro-5*H*-[1,3]oxazolo[[3,2-*a*]pyridine-5-ylidene]butan-2-one (6d). White solid (75%); mp 75 °C (from cyclohexane); IR (neat) 1620 cm^{-1}; $[\alpha]_D^{20}$ +171 (*c* 0.955, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 0.82 (d, *J* = 7 Hz, 3H), 0.88 (d, *J* = 7 Hz, 3H), 1.50–1.62 (m, 2H), 1.95–1.98 (m, 1H), 2.22 (s, *J* = 7 Hz, 1H), 2.28–2.36 (m, 1H), 3.00–3.10 (m, 1H), 3.28–3.37 (m, 1H), 3.65 (t, *J* = 8.5Hz, 1H), 4.54–4.60 (m, 1H), 4.75 (t, *J* = 8 Hz, 1H), 4.83 (s, 1H), 4.91–4.96 (m, 1H), 7.21–7.41 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 17.2, 19.5, 19.8, 28.0, 28.2, 41.5, 61.9, 73.5, 89.4, 94.1, 125.9, 128.0, 129.2, 138.8, 158.6, 201.9 ; HRMS (ESI^+) calcd for $C_{18}H_{24}NO_2$ $(M+H)^+$: 286.1802, found: 286.1804.

***tert*-Butyl (2*S*)-2-[(2*S*)-2-hydroxypropyl]pyrrolidine-1-carboxylate (15).** A solution of $NaBH(OAc)_3$ was prepared by portionwise addition of $NaBH_4$ (0.23 g, 6 mmol) to a mixture of glacial acetic acid (3.5 mL, 60 mmol) and CH_3CN (1.5 mL) at 0°C. After hydrogen evolution had ceased (30 min), a solution of **5a** (0.30 g, 1.22 mmol) in CH_3CN (9 mL) was added. After stirring for 3 h at room temperature, water (50 mL) was added and solid Na_2CO_3 was added until pH = 9. The aqueous layer was extracted with CH_2Cl_2 (3×50 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. ^{13}C NMR ($CDCl_3$) of the crude diol **14**: δ 23.8, 24.6, 30.1, 40.4, 53.6, 59.6, 63.2, 65.0, 69.1, 127.8, 128.3, 129.3, 138.5. The residue was dissolved in AcOMe (30 mL) and subjected to hydrogenation (1 atm) in the presence of $Pd(OH)_2/C$ (0.15 g) and Boc_2O (0.52 g, 2.4 mmol) at room temperature for 12 h. The reaction mixture was filtered, the residue thoroughly washed with methyl acetate and the combined filtrates were concentrated *in vacuo*. Silica gel column chromatography (AcOEt/cyclohexane 2:8) yielded compound **15** along with unseparable 2-phenylethanol (0.28 g overall, 63% calculated yield for **15**). From a mixture with 2-phenylethanol: ^1H NMR ($CDCl_3$) δ 1.17 (d, *J* = 6.5 Hz, 3H), 1.46 (s, 9H), 1.37–1.60 (m, 3H, 1.82–1.96 (m, 3H), 3.29–3.35 (m, 2H), 3.68–3.86 (m, 1H), 3.90 (br s, 1H), 4.10–4.25 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 22.6, 23.5, 28.5, 31.2, 45.6, 46.5, 53.9, 63.8, 79.9, 156.6.

(1*S*)-2-{(2*S*)-1-[(1*S*)-2-(Acetoxy)-1-phenylethyl]pyrrolidin-2-yl}-1-methylethyl acetate (16). A solution of $NaBH(OAc)_3$ was prepared by portionwise addition of $NaBH_4$ (0.42 g, 11.1 mmol) to a mixture of glacial acetic acid (6.4 mL, 111 mmol) and CH_3CN (2.5 mL) at 0°C. After hydrogen evolution had ceased (30 min), a solution of **5a** (0.54 g, 2.22 mmol) in CH_3CN (10 mL) was added. After stirring for 3 h at room temperature, water (50 mL) was added and solid

Na_2CO_3 was added until pH = 9. The aqueous layer was extracted with CH_2Cl_2 (3×50 mL) and the combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The residue was dissolved in CH_2Cl_2 (12 mL), Ac_2O (1.26 mL, 13.3 mmol), NEt_3 (2.15 mL, 15.5 mmol) and DMAP (27 mg, 0.22 mol) were then added. The reaction mixture was stirred at room temperature for 12 h. A saturated aqueous NH_4Cl solution (20 mL) was added and the resulting aqueous layer was extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo*. Silica gel column chromatography (AcOEt/cyclohexane 3:7) yielded compound **16** (0.34 g, 46%) as a colorless oil. $[\alpha]_D^{24}$ –24 (*c* 0.975, $CHCl_3$); IR (neat) 1750 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.99 (d, *J* = 6.25 Hz, 3H); 1.42–1.85 (m, 6H); 1.96 (s, 6H); 2.56–2.66 (m, 1H), 2.85–2.92 (m, 2H), 3.85–3.92 (m, 1H), 4.34–4.41 (m, 1H), 4.49–4.56 (m, 1H), 4.70–4.78 (m, 1H), 7.22–7.36 (m, 5H); ^{13}C NMR ($CDCl_3$) δ 19.7, 20.6, 21.1, 23.2, 30.2, 41.5, 49.7, 58.7, 63.8, 64.9, 69.4, 127.2, 128.1, 128.2, 140.4, 170.1, 170.4; Anal. Calcd for $C_{19}H_{27}NO_4$: C, 68.44; H, 8.16; N, 4.20. Found: C, 68.53; H, 8.17; N, 4.28.

***tert*-Butyl (2*S*)-2-[(2*S*)-2-(acetoxy)propyl]pyrrolidine-1-carboxylate (17).** A solution of compound **16** (0.32g, 0.96 mmol) in methyl acetate (30 mL) was subjected to hydrogenation (1 atm) in the presence of $Pd(OH)_2/C$ (0.016 g, 0.5 equiv in weight) and Boc_2O (0.44 g, 2 mmol), at room temperature for 12 h. The reaction mixture was filtered, the residue thoroughly washed with methyl acetate and the combined filtrates were concentrated *in vacuo*. Silica gel column chromatography (AcOEt/cyclohexane 1:9) yielded compound **17** (0.22g, 85%) as a colorless oil. $[\alpha]_D^{21}$ –54 (*c* 1.015, $CHCl_3$); IR (neat) 1690, 1735 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.15 (d, *J* = 6.25 Hz, 3H), 1.36 (s, 9H), 1.46–1.85 (m, 6H), 1.92 (s, 3H), 3.20–3.25 (m, 2H), 3.60–3.70 (m, 1H), 4.74–4.82 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 20.0, 21.3, 23.3, 28.5, 30.6, 40.6, 45.9, 54.9, 69.4, 79.1, 154.3, 170.4; Anal. Calcd for $C_{14}H_{25}NO_4$: C, 61.97; H, 9.29; N, 5.16. Found: C, 62.13; H, 9.36; N, 5.39.

(–)-Hygroline (13). To a suspension of $LiAlH_4$ (310 mg, 8.10 mmol) in dry THF (10 mL) was added dropwise a solution of compound **16** (0.22g, 0.81 mmol) in THF (4 mL). The reaction mixture was refluxed for 12 h. After cooling to 0 °C, water (0.31 ml), 15% NaOH solution (0.31 mL), water (0.93 mL) and anhydrous K_2CO_3 were successively added. The resulting reaction mixture was stirred at room temperature for 1 h and then filtered on a glass-frit. The residue was washed with THF. The solvent was carefully removed at room temperature under reduced pressure (110 mm Hg) to yield the expected compound (102 mg, 87%). The spectroscopic data are in accordance with that of the literature.[16, 20, 21] $[\alpha]_D^{24}$ –50 (*c* 1.28, MeOH).

References and Notes

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