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Stereospecific synthesis of oxazolo[3,4-*b*]tetrahydroisoquinolin-3-ones, analogs of podophyllotoxin, via benzotriazole methodology

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Abstract

A stereospecific synthesis of 2-azapodophyllotoxin analogues based on benzotriazole methodology is reported. Intramolecular Friedel–Crafts reactions of benzotriazole Mannich adducts **2**/**3b**–**l** afforded 5-substituted oxazolo[3,4-*b*]tetrahydroisoquinolines **5b–l** as pure stereoisomers. © 1999 Elsevier Science Ltd. All rights reserved.

1. Introduction

Podophyllotoxin (**A**) analogues (Fig. 1) are of pharmacological interest as antitumor agents.[1] 2-Azapodophyllotoxin (**B**) is configurationally stable, resistant to epimerization and displays space filling properties similar to podophyllotoxin according to molecular mechanics analysis.[2] Synthetic 2-azapodophyllotoxins[2,3] are active as inhibitors of KB cells in vivo against P-388 in mice[4] and of cells derived from carcinoma of the nasopharynx.[5]

Accordingly, efficient asymmetric syntheses of analogs of 2-azapodophyllotoxin are of interest. Here, we report a general stereospecific route to 5-substituted oxazolo[3,4-*b*]tetrahydroisoquinolin-3-ones **5** using benzotriazole methodology.

2. Results and discussion

Various aldehydes, both aromatic and aliphatic, gave the corresponding Mannich adducts **2**/**3a**–**k** in good to excellent yields by reaction with 5(*S*)-benzyl-1,3-oxazolan-2-one and benzotriazole (BtH) in

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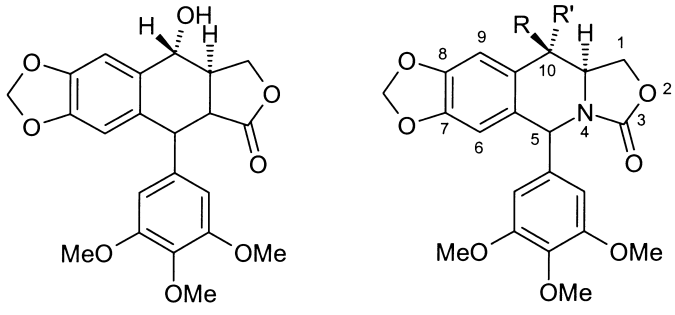


Figure 1.

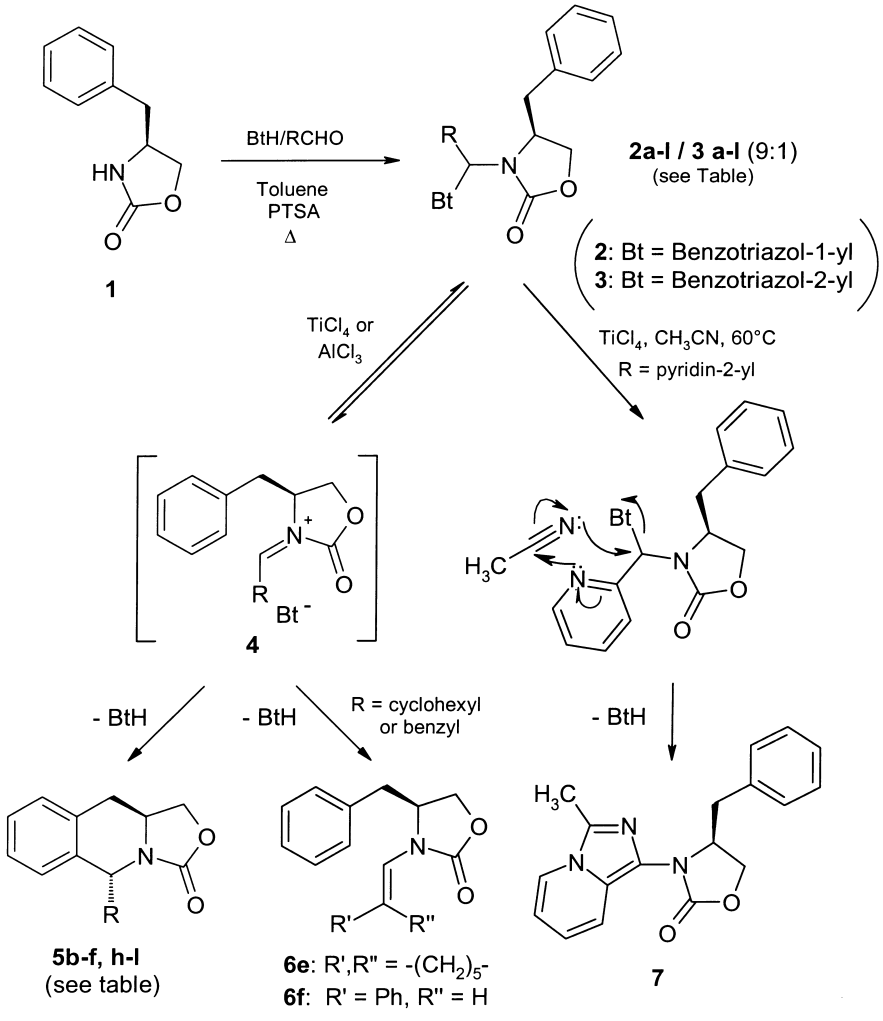
toluene using a Dean–Stark trap in the presence of a catalytic amount of PTSA (see Scheme 1). The products were obtained as isomeric mixtures of Bt-1 (**2a**–**k**) and Bt-2 (**3a**–**k**) (ratio ca. 9:1) compounds. The reactivity of the aliphatic aldehydes was dependent on the structure. The reaction with formaldehyde was complete after 30 min, to provide products **2**/**3a** in 96% yield. By contrast, trimethylacetaldehyde did not react at all. When cyclohexylcarboxaldehyde was used under the above conditions, elimination product **6e** (Scheme 1) was obtained in 27% yield along with expected products **2**/**3e** in 60% yield.

Phenylacetaldehyde gave elimination product **6f** (Scheme 1) in 62% yield when toluene was used as solvent, but when heated for three days at reflux temperature in methylene chloride the desired compounds **2**/**3f** (60%) were produced along with 7% of **6f**.

Aromatic aldehydes with electron-deficient rings including 2-pyridinecarboxaldehyde, *p*-nitrobenzaldehyde and *p*-trifluoromethylbenzaldehyde gave good yields of products **2**/**3i**, **2**/**3j** and **2**/**3k**. Benzaldehyde afforded 60% yield of **2**/**3h**, along with a small amount of **5h** (13%), after 60 h reaction. *p*-Anisaldehyde, with an electron-donor substituent in the phenyl ring, formed compound **5l** directly (isolated in 31% yield), along with traces of **2**/**3l** after 65 h. The latter two cases can easily be explained by the lower reactivity of those aldehydes as well as by stabilization of the iminium salt intermediate **4** which leads to compound **5** (see Scheme 1).

As demonstrated in our previous work,[6] both Bt-1 and Bt-2 groups are good leaving groups and can easily form iminium salts in the presence of a Lewis acid. Hence, the mixtures of Bt-1 **2** and Bt-2 **3** isomeric benzotriazole adducts were directly treated with a strong Lewis acid ($TiCl_4$ or $AlCl_3$) in acetonitrile to give the oxazolo[3,4-*b*]tetrahydroquinolin-3-ones **5** as single diastereomers in good yields (Scheme 1 and Table 1). The stereochemistry of compounds **5** was determined by X-ray crystallography of compound **5h**. Fig. 2 shows a perspective view of the structure of **5h** which reveals that the configuration of the newly-formed stereocenter has the *R*-configuration. For steric reasons, the plane of the phenyl ring is approximately orthogonal to the plane of the rest of the molecule.

The treatment of the pyridin-2-yl derivative **2**/**3i** in acetonitrile at 60°C in the presence of a Lewis acid gave the imidazo[1,5-*a*]pyridine compound **7** in 78% yield instead of the expected product **5i**. The structure of compound **7** was confirmed by X-ray crystallography (Fig. 3): **7** crystallizes with four molecules in the asymmetric unit, each exists in a conformation with the imidazo[1,5-*a*]pyridine group, approximately orthogonal to the attached oxazolidinone ring, but they differ in the relative orientations of the phenyl rings of the benzyl substituents. The geometry of the imidazo[1,5-*a*]pyridine moiety in **7** is similar to that in the only other previously reported crystal structure of this heterocyclic ring system.[7] The formation of compound **7** results from a [3+2] intermolecular cyclization, in which the Lewis acid activates the nucleophilic attack by the lone pair of the pyridine towards acetonitrile, forming a quite reactive zwitterion intermediate which displaces the benzotriazolyl residue (Scheme 1). This



Scheme 1.

type of heterocyclic system has been previously prepared via intramolecular[8] or [4+1] intermolecular[9] cyclization from 2-aminomethylpyridine derivatives.

Tamioka et al.[4] reported that the reaction of 5(*S*)-benzyl-1,3-oxazolan-2-one and 2,3,4-trimethoxybenzaldehyde led to a diastereomeric mixture in a 93:3 ratio; the direct reaction between ethyl glyoxylate and 5(*S*)-benzyl-1,3-oxazolan-2-one yielded a diastereomer mixture in a 95:5 ratio (GC–MS analysis). By contrast, using benzotriazole methodology, the reaction provided a single diastereomer; direct GC–MS analysis of the reaction mixture of **2**/**3b** with $TiCl_4$ showed that one diastereomer dominated by at least 100:1.

In summary, reaction of benzotriazole, 4(*S*)-benzyloxazolan-2-one and diverse aldehydes gave (4*S*)-3-(α-benzotriazolylalkyl)-4-benzyl-1,3-oxazolan-2-ones (**2**/**3**), which directly reacted with a Lewis acid to diasterospecifically produce chiral 5-substituted oxazolo[3,4-*b*]tetrahydroquinolin-3-ones **5**, analogues of the natural product podophyllotoxin.

Table 1
Preparation of products **2/3** and oxazolo[3,4-*b*]tetrahydroquinolin-3-ones **5**

		Compounds **2/3**		Compound **5**	
Entry	R	Time (h)	Yield (%)	Time (h)	Yield (%)
a	H	0.5	96		
b	COOEt	7.5	94	40	78
c	Pr	3	89[a]	72	70
d	$CH_3(CH_2)_{10}$	30	80[a]	72	62
e	cyclohexyl	24	60[a]	24	59[b]
f	benzyl	48	60[c]	144	55
g	*t*-Bu	48	no reaction		
h	Ph	60	60	24	78
i	2-Py	72	66	96	50[d]
j	*p*-CF_3-C_6H_4	50	80	24	89
k	*p*-NO_2-C_6H_4	30	80	60	90
l	*p*-MeO-C_6H_4	65	-[e]		

[a] further addition of aldehyde was made to inhibit the undesired condensation reactions.
[b] 7% of compound **6e** was also isolated.
[c] the reaction was done in methylene chloride under reflux.
[d] methylene chloride under reflux, instead of acetonitrile, was used. Using aluminum chloride with methylene chloride under reflux after 72 h gave 54% of **5i**.
[e] 31% of **5l** was isolated, and traces of products **2/3l** were detected in some chromatographic fractions.

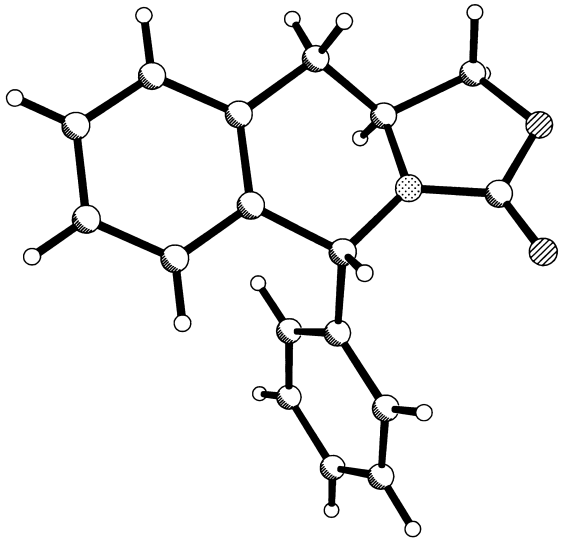


Figure 2. Perspective view of the X-ray crystal structure of **5h**

3. Experimental

3.1. General

^1H (300 MHz) and ^{13}C (75 MHz) NMR spectra were recorded in $CDCl_3$ with TMS or $CDCl_3$ as internal reference. Elemental analyses were performed on a Carlo Erba-1106 instrument. High resolution mass spectra were measured on a Kratos/AE1-MS 30 mass spectrometer. $[\alpha]_D$ were recorded on a

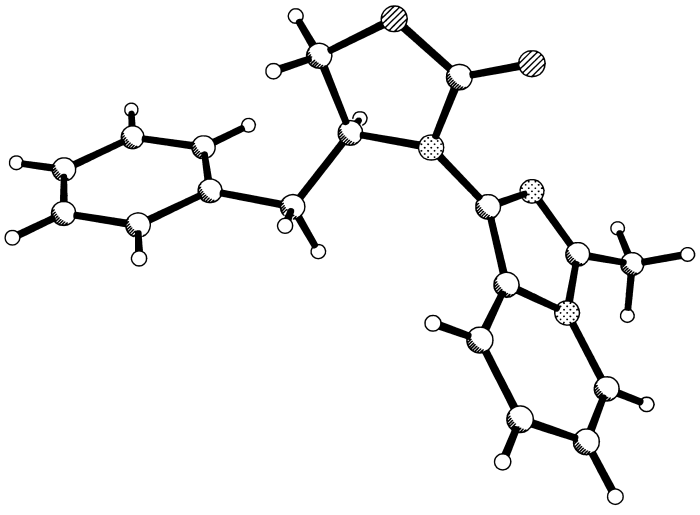


Figure 3. Perspective view of the X-ray crystal structure of **7**

Perkin–Elmer 341 polarimeter at 20°C, c=1 g/100 ml in methylene chloride. GC–MS analyses were run on a Hewlett Packard 5890 Series II Gas Chromatograph HP-5 (30 m×0.32 mm×0.25 μm) capillary column with a HP 5972 Series Mass Selective Detector.

*3.2. General procedure for syntheses of (4S)-3-[α-1,2,3-benzotriazolylalkyl]-4-benzyl-1,3-oxazolan-2-ones **2/3***

To a suspension of benzotriazole (10 mmol), 5(*S*)-benzyl-1,3-oxazolan-2-one (10 mmol) and PTSA (1 mmol) in dry toluene (50 ml), under nitrogen, was added the corresponding aldehyde (10 mmol). The mixture was then heated to reflux temperature with a Dean–Stark trap for between 1 h and 3 days. Further addition of aldehyde in the cases of butyraldehyde, cyclohexylcarboxaldehyde, dodecylaldehyde and 2-pyridinylcarboxaldehyde was needed to inhibit undesired condensation reactions. The reaction mixture was then washed with aqueous NaOH (2 N, 2×25 ml) and aqueous ammonium chloride (satd, 2×25 ml). The organic layer was dried over anhydrous sodium sulfate. After removal of the solvent, products **2**/**3** were obtained. When necessary, further purification was achieved using a silica gel column eluted with mixtures of hexanes:ethyl acetate (8:1 to 3:2).

*3.3. (4S)-3-[1H-1,2,3-Benzotriazol-1-ylmethyl]-4-benzyl-1,3-oxazolan-2-one (**2a**)*

Using formaldehyde gave 3.1 g of products **2**/**3a** (96%) after 1 h. The Bt-1 isomer **2a** was separated on a silica gel column eluted with hexanes:ethyl acetate, 3:2. Colorless solid, mp 85–86°C, yield 86%, $[\alpha]_D$=+65.4. ^{1}H NMR δ: 2.67 (dd, *J*=9.6 and 13.2 Hz, 1H), 3.49 (dd, *J*=4.0 and 13.2 Hz, 1H), 3.85–3.95 (m, 1H), 3.95–4.05 (m, 2H), 6.03 (d, *J*=14.6 Hz, 1H), 6.32 (d, *J*=14.7 Hz, 1H), 7.16 (d, *J*=7.5 Hz, 2H), 7.15–7.35 (m, 3H), 7.42 (t, *J*=7.7 Hz, 1H), 7.54 (t, *J*=7.7 Hz, 1H), 7.91 (d, *J*=8.2 Hz, 1H), 8.07 (d, *J*=8.2 Hz, 1H). ^{13}C NMR δ: 37.7, 53.9, 54.8, 67.4, 110.4, 119.6, 124.4, 127.2, 128.2, 128.8, 128.9, 132.1, 134.5, 146.0, 157.6. Anal. calcd for $C_{17}H_{16}N_4O_2$: C, 66.22; H, 5.24; N, 18.17. Found: C, 66.30; H, 5.31; N, 17.86.

*3.4. General procedure for syntheses of 5-substituted-3-oxo-1,5,10,10a-tetrahydro[1,3]oxazolo[3,4-b]isoquinolines **5b–l***

To a solution of compound **2**/**3** in acetonitrile, or methylene chloride in the case of **2**/**3i**, (5 ml per 1 mmol of **2**/**3**) 1.5 equiv. of $TiCl_4$ were added dropwise, and the mixture stirred at 60°C for between 1 and 5 days. Afterwards, the reaction was quenched with water (5 ml), and the mixture extracted with diethyl ether (2×10 ml). The combined organic extracts were washed with aqueous NaOH (2 N, 2×10 ml) and aqueous ammonium chloride (satd, 2×10 ml), and then dried over anhydrous sodium sulfate. After removal of the solvent, the residue was separated by silica gel column chromatography, with mixtures of hexanes:ethyl acetate in ratios of between 4:1 and 3:2, to give products **5b**–**k**.

*3.5. Ethyl (5S,10aS)-3-oxo-1,5,10,10a-tetrahydro[1,3]oxazolo[3,4-b]isoquinoline-5-carboxylate (**5b**)*

Yellowish oil, yield 78%, $[\alpha]_D$=−128.7. ^{1}H NMR δ: 1.21 (t, *J*=7.2 Hz, 3H), 2.77 (dd, *J*=11.0 and 15.6 Hz, 1H), 2.95 (dd, *J*=4.2 and 15.7 Hz, 1H), 4.05 (t, *J*=7.8 Hz, 1H), 4.13 (q, *J*=7.2 Hz, 2H), 4.30–4.45 (m, 1H), 4.60 (t, *J*=8.1 Hz, 1H), 5.35 (s, 1H), 7.09 (d, *J*=3.5 Hz, 1H), 7.20–7.35 (m, 2H), 7.50 (t, *J*=4.4 Hz, 1H). ^{13}C NMR δ: 13.9, 33.4, 49.3, 54.7, 61.8, 69.1, 126.9, 127.2, 128.0, 128.5, 129.6, 131.8, 156.9, 169.7. Anal. calcd for $C_{14}H_{15}NO_4$: C, 64.35; H, 5.80; N, 5.36. Found: C, 64.62; H, 6.09; N, 5.76. MS: 188 (100), 144, 128, 117, 91, 77, 63.

*3.6. (5R,10aS)-5-Propyl-1,5,10,10a-tetrahydro[1,3]oxazolo[3,4-b]isoquinolin-3-one (**5c**)*

Colorless prismatic crystals, mp 85–86°C, yield 70%, $[\alpha]_D$=−148.6. ^{1}H NMR δ: 0.98 (t, *J*=7.4 Hz, 3H), 1.35–1.55 (m, 2H), 1.65–1.80 (m, 1H), 1.80–1.95 (m, 1H), 2.80–2.95 (m, 2H), 3.95–4.07 (m, 1H), 4.13 (dd, *J*=2.8 and 8.5 Hz, 1H), 4.54 (t, *J*=8.5 Hz, 1H), 4.89 (dd, *J*=3.6 and 9.6 Hz, 1H), 7.15–7.25 (m, 4H). ^{13}C NMR δ: 13.8, 19.3, 33.7, 39.3, 48.1, 52.5, 68.1, 126.7, 126.8, 129.2, 131.3, 136.2, 157.1. Anal. calcd for $C_{14}H_{17}NO_2$: C, 72.69; H, 7.42; N, 6.06. Found: C, 72.87; H, 7.63; N, 6.10. MS: 188 (100), 144, 128, 117, 91, 77, 65.

*3.7. (5R,10aS)-5-Undecyl-1,5,10,10a-tetrahydro[1,3]oxazolo[3,4-b]isoquinolin-3-one (**5d**)*

Colorless oil, yield 62%, $[\alpha]_D$=−98.1. ^{1}H NMR δ: 0.88 (t, *J*=6.2 Hz, 3H), 1.15–1.55 (m, 18H), 1.65–1.80 (m, 1H), 1.80–195 (m, 1H), 2.80–2.95 (m, 2H), 4.00–4.10 (m, 1H), 4.13 (dd, *J*=2.5 and 8.5 Hz, 1H), 4.54 (t, *J*=8.1 Hz, 1H), 4.88 (dd, *J*=3.3 and 9.6 Hz, 1H), 7.05–7.25 (m, 4H). ^{13}C NMR δ: 14.0, 22.6, 26.0, 29.2, 29.35, 29.4, 29.5 (b), 31.8, 33.8, 37.1, 48.2, 52.7, 68.1, 126.7, 126.8, 129.3, 131.3, 136.3, 157.1. Anal. calcd for $C_{22}H_{33}NO_2$: C, 76.92; H, 9.70; N, 4.08. Found: C, 76.51; H, 10.13; N, 4.53. MS: 188 (100), 144, 128, 117, 91, 77.

*3.8. (5R,10aS)-5-Cyclohexyl-1,5,10,10a-tetrahydro[1,3]oxazolo[3,4-b]isoquinolin-3-one (**5e**)*

Colorless prismatic crystals, mp 138–139°C, yield 59%, $[\alpha]_D$=−129.5. ^{1}H NMR δ: 0.95–1.50 (m, 6H), 1.60–2.00 (m, 5H), 2.80–2.95 (m, 2H), 4.00–4.15 (m, 2H), 4.56 (t, *J*=8.0 Hz, 1H), 4.89 (d, *J*=3.8 Hz, 1H), 7.10 (d, *J*=7.2 Hz, 1H), 7.15–7.30 (m, 3H). ^{13}C NMR δ: 26.2, 26.4, 26.5, 28.1, 30.9, 33.6, 45.15, 50.4, 57.55, 67.9, 126.7, 126.9, 129.2, 132.2, 134.8, 158.0. Anal. calcd for $C_{17}H_{21}NO_2$: C, 75.24; H, 7.82; N, 5.16. Found: C, 75.28; H, 8.02; N, 5.20. MS: 188 (100), 144, 128, 117, 91, 77, 65.

*3.9. (5*R*,10a*S*)-5-Benzyl-1,5,10,10a-tetrahydro[1,3]oxazolo[3,4-*b*]isoquinolin-3-one (**5f**)*

Brown gum, yield 55%, $[\alpha]_D$=−62.0. ^{1}H NMR δ: 2.73 (d, *J*=7.6 Hz, 2H), 3.16 (dd, *J*=5.9 and 13.9 Hz, 1H), 3.25–3.40 (m, 2H), 3.97 (dd, *J*=3.8 and 10.1 Hz, 2H), 4.33 (t, *J*=8.2 Hz, 1H), 5.22 (t, *J*=5.5 Hz, 1H), 6.95–7.10 (m, 3H), 7.15–7.25 (m, 6H). ^{13}C NMR δ: 33.6, 41.9, 48.5, 53.1, 68.1, 126.6, 126.7, 127.0, 127.05, 128.2, 129.3, 129.5, 131.9, 134.6, 136.9, 156.7. HRMS (FAB): found 280.1333, required for $C_{18}H_{18}NO_2$ (M^++1) 280.1338.

*3.10. (5*R*,10a*S*)-5-phenyl-1,5,10,10a-tetrahydro[1,3]oxazolo[3,4-*b*]isoquinolin-3-one (**5h**)*

Colorless prismatic crystals, mp 154–156°C, yield 69%, $[\alpha]_D$=−242.9. ^{1}H NMR δ: 2.90–3.10 (m, 2H), 4.00–4.15 (m, 2H), 4.44 (t, *J*=8.0 Hz, 1H), 6.04 (s, 1H), 6.98 (d, *J*=7.2 Hz, 1H), 7.15–7.40 (m, 8H). ^{13}C NMR δ: 34.3, 48.05, 56.3, 68.4, 126.8, 127.3, 127.9, 128.55, 128.7, 129.2, 132.3, 133.9, 142.05, 156.5. Anal. calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.71; N, 5.28. Found: C, 76.59; H, 5.79; N, 5.43. MS: 265 (100), 220, 204, 192, 188, 179, 165, 144, 115, 91, 77, 63.

*3.11. (5*S*,10a*S*)-5-(2-Pyridinyl)-1,5,10,10a-tetrahydro[1,3]oxazolo[3,4-*b*]isoquinolin-3-one (**5i**)*

Yellowish solid foam, yield 50%, $[\alpha]_D$=−325.5. ^{1}H NMR δ: 2.95 (dd, *J*=10.3 and 15.3 Hz, 1H), 3.13 (dd, *J*=4.2 and 15.6 Hz, 1H), 4.15 (dd, *J*=4.1 and 7.9 Hz, 1H), 4.50–4.70 (m, 2H), 5.99 (s, 1H), 6.98 (d, *J*=7.4 Hz, 1H), 7.10–7.30 (m, 4H), 7.48 (d, *J*=7.7 Hz, 1H), 7.70 (td, *J*=1.6 and 7.6 Hz, 1H), 8.53 (d, *J*=4.1 Hz, 1H). ^{13}C NMR δ: 34.2, 48.3, 57.5, 68.6, 122.6, 122.9, 126.7, 127.1, 127.9, 129.4, 132.0, 133.6, 136.6, 149.9, 156.6, 160.5. Anal. calcd for $C_{16}H_{14}N_2O_2$: C, 72.16; H, 5.31; N, 10.52, Found: C, 71.73; H, 5.53; N, 10.55. MS: 221, 180, 167, 144 (100), 115, 102, 91, 77.

*3.12. (5*R*,10a*S*)-5-[4-(Trifluoromethyl)phenyl]-1,5,10,10a-tetrahydro[1,3]oxazolo[3,4-*b*]isoquinolin-3-one (**5j**)*

Colorless solid, mp 188–189°C, yield 89%, $[\alpha]_D$=−190.7. ^{1}H NMR δ: 3.00 (dd, *J*=10.7 and 15.7 Hz, 1H), 3.09 (dd, *J*=4.7 and 15.7 Hz, 1H), 4.00–4.15 (m, 1H), 4.17 (dd, *J*=4.3 and 8.6 Hz, 1H), 4.51 (t, *J*=8.3 Hz, 1H), 6.10 (s, 1H), 6.96 (d, *J*=7.4 Hz, 1H), 7.15–7.30 (m, 3H), 7.41 (d, *J*=8.1 Hz, 2H), 7.59 (d, *J*=8.0 Hz, 2H). ^{13}C NMR δ: 34.2, 48.2, 55.8, 68.5, 123.4 (q, J^1_{C-F}=272.8 Hz) 125.5, 125.55, 127.1, 127.7, 128.6, 129.0, 129.4, 130.2 (q, J^2_{C-F}=32.7 Hz), 132.4, 132.95, 145.75, 156.6. Anal. calcd for $C_{18}H_{14}F_3NO_2$: C, 64.86; H, 4.24; N, 4.20. Found: C, 64.41; H, 4.24; N, 4.21. MS: 333, 314, 288, 260, 188, 179 (100), 144, 117, 91, 77.

*3.13. (5*R*,10a*S*)-5-[4-Nitrophenyl]-1,5,10,10a-tetrahydro[1,3]oxazolo[3,4-*b*]isoquinolin-3-one (**5k**)*

Colorless solid, mp 150–151°C, yield 90%, $[\alpha]_D$=−219.0. ^{1}H NMR δ: 3.01 (dd, *J*=10.8 and 15.6 Hz, 1H), 3.10 (dd, *J*=4.8 and 15.7 Hz, 1H), 4.05–4.15 (m, 1H), 4.19 (dd, *J*=4.3 and 8.7 Hz, 1H), 4.53 (t, *J*=8.4 Hz, 1H), 6.12 (s, 1H), 6.94 (d, *J*=7.4 Hz, 1H), 7.15–7.33 (m, 3H), 7.46 (d, *J*=8.7 Hz, 2H), 8.19 (d, *J*=8.5 Hz, 2H). ^{13}C NMR δ: 34.1, 48.2, 55.5, 68.6, 123.8, 127.2, 127.9, 128.4, 129.45, 129.5, 132.3, 147.4, 148.7, 156.6. Anal. calcd for $C_{17}H_{14}N_2O_4$: C, 65.80; H, 4.56; N, 9.03. Found: C, 65.89; H, 4.64; N, 9.08.

3.14. (5R,10aS)-5-(4-Methoxyphenyl)-1,5,10,10a-tetrahydro[1,3]oxazolo[3,4-b]isoquinolin-3-one (**5l**)

The general procedure for preparation of **2**/**3** was followed using *p*-anisaldehyde. After 65 h, separation of the crude reaction mixture on a silica gel column with hexanes:ethyl acetate, 7:3 to 3:2 gradient elution, afforded 0.93 g of **5l** (31%) along with 0.65 g of *p*-anisaldehyde (48%) and 0.75 g of **1** (42%). **5l**: Colorless solid, mp 126–128°C, $[\alpha]_D$=−241.3. ^{1}H NMR δ: 2.94 (dd, *J*=10.7 and 15.5 Hz, 1H), 3.09 (dd, *J*=4.4 and 15.7 Hz, 1H), 3.78 (s, 3H), 4.00–4.15 (m, 2H), 4.45 (t, *J*=8.0 Hz, 1H), 6.00 (s, 1H), 6.83 (d, *J*=7.7 Hz, 2H), 6.99 (d, *J*=7.4 Hz, 1H), 7.15–7.26 (m, 5H). ^{13}C NMR δ: 34.3, 48.9, 55.2, 55.6, 68.4, 113.8, 126.7, 127.2, 128.7, 129.1, 129.7, 132.25, 134.2, 134.35, 156.4, 159.15. Anal. calcd for $C_{18}H_{17}NO_3$: C, 73.20; H, 5.81; N, 4.74. Found: C, 73.20; H, 5.88; N, 4.75. MS: 295, 264, 250, 234 (100), 209, 178, 165, 144, 116, 102, 91, 77.

3.15. (4S)-4-Benzyl-3-(cyclohexylidenemethyl)-1,3-oxazolan-2-one (**6e**)

The general procedure for the preparation of **2**/**3** was followed. After 24 h, separation of the crude reaction mixture on a silica gel column eluted with hexanes:ethyl acetate, 4:1, afforded 2.34 g of products **2**/**3e** (60%) and 0.73 g of **6e** (27%). **6e**: yellowish oil, $[\alpha]_D$=−30.7. ^{1}H NMR δ: 1.45–1.75 (m, 6H), 2.10–2.30 (m, 4H), 2.66 (dd, *J*=8.8 and 13.5 Hz, 1H), 3.1 (dd, *J*=3.5 and 13.5 Hz, 1H), 4.00–4.15 (m, 2H), 4.20 (t, *J*=7.4 Hz, 1H), 5.62 (s, 1H), 7.14 (d, *J*=6.9 Hz, 2H), 7.15–7.35 (m, 3H). ^{13}C NMR δ: 26.2, 26.8, 27.9, 28.7, 33.3, 38.4, 58.8, 66.5, 113.8, 127.0, 128.7, 129.1, 135.6, 141.0, 156.6. Anal. calcd for $C_{17}H_{21}NO_2$: C, 75.24; H, 7.82; N, 5.16. Found: C, 75.20; H, 8.20; N, 5.88. MS: 271, 180 (100), 154, 117, 100, 91, 88, 77, 67, 54.

3.16. (4S)-4-Benzyl-3-[(E)-2-phenylethenyl]-1,3-oxazolan-2-one (**6f**)

The general procedure for the preparation of **2**/**3** was followed. Separation of the crude product on a silica gel column with hexanes:ethyl acetate, 4:1 gave a main fraction that, after crystallization from ethyl ether, afforded 1.75 g of **6f** (62%): colorless needles, mp 111–112°C, $[\alpha]_D$=+2.5. ^{1}H NMR δ: 2.88 (dd, *J*=8.7 and 13.9 Hz, 1H), 3.30 (dd, *J*=3.0 and 13.9 Hz, 1H), 4.25 (dd, *J*=3.0 and 8.8 Hz, 1H), 4.31 (t, *J*=8.3 Hz, 1H), 4.38–4.48 (m, 1H), 6.03 (d, *J*=15.1 Hz, 1H), 7.15–7.40 (m, 11H). ^{13}C NMR δ: 36.3, 54.9, 66.6, 111.6, 123.0, 125.5, 126.7, 127.4, 128.7, 129.0, 129.3, 135.1, 135.8, 155.1. Anal. calcd for $C_{18}H_{17}NO_2$: C, 77.39; H, 6.15; N, 5.02. Found: C, 77.59; H, 6.20; N, 5.07. MS: 279, 188, 144 (100), 117, 91, 77, 65.

3.17. (4S)-4-Benzyl-3-(3-methylimidazo[1,5-a]pyridin-1-yl)-1,3-oxazolan-2-one (**7**)

To a solution of **2**/**3i** (1 mmol) in 5 ml of acetonitrile were added dropwise 1.5 equiv. of $TiCl_4$, and the mixture stirred at 60°C for 3 h. Afterwards, the reaction was quenched with water (5 ml), and then mixture extracted with ethyl ether (2×5 ml). The combined organic extracts were washed with aqueous NaOH (2 N, 2×5 ml) and aqueous ammonium chloride (satd, 2×5 ml), and then dried over anhydrous sodium sulfate. After removal of the solvent, 0.26 g of the residue were separated by silica gel column chromatography with ethyl acetate to give 0.24 g of **7** (78%), crystallized from ethyl ether: colorless crystals, mp 122–124°C, $[\alpha]_D$=+106.1. ^{1}H NMR δ: 2.59 (s, 3H), 2.81 (dd, *J*=9.4 and 13.4 Hz, 1H), 3.09 (dd, *J*=3.4 and 13.4 Hz, 1H), 4.24 (dd, *J*=6.0 and 8.5 Hz, 1H), 4.42 (t, *J*=8.5 Hz, 1H), 4.75–4.85 (m, 1H), 6.56 (t, *J*=6.6 Hz, 1H), 6.69 (dd, *J*=6.6 Hz and 9.1 Hz, 1H), 7.10 (d, *J*=6.7 Hz, 2H), 7.15–7.30 (m, 3H), 7.48 (d, *J*=9.2 Hz, 1H), 7.60 (d, *J*=6.7 Hz, 1H). ^{13}C NMR δ: 12.3, 38.6, 58.1, 67.2, 112.7, 118.0, 120.3,

122.5, 123.3, 126.7, 128.5, 129.0, 132.1, 135.4, 156.1. Anal. calcd for $C_{18}H_{17}N_3O_2$: C, 70.33; H, 5.59; N, 13.67 Found: C, 69.58; H, 5.69; N, 13.63. MS: 307, 216, 172, 131 (100), 105, 78, 51.

4. X-Ray crystallography

Data were collected with a Siemens SMART CCD area detector, using graphite monochromatized Mo-Kα radiation (λ=0.71073 Å). The structures were solved by direct methods using SHELXS[10] and refined on F^2 using all data by full-matrix least-squares procedures with SHELXTL Version 5.10.[11] Hydrogen atoms were included in calculated positions with isotropic displacement parameters 1.2 times the isotropic equivalent of their carrier atoms. The minimized functions were $\Sigma w(F_o^2-F_c^2)$, with $w=[\sigma^2(F_o^2)+(aP)^2+bP]^{-1}$, where $P=[\max(F_o)^2+2F_c^2]/3$.

*4.1. Crystal data for **5H** at −115°C*

$C_{17}H_{15}NO_2$, M=265.30, orthorhombic, space group $P2_12_12_1$, a=7.5540(7), b=9.4076(8), c=18.679(2) Å, V=1327.4(2), Z=4, F(000)=560, D_x=1.327 g cm^{-3}, colorless block, 0.73×0.38×0.24 mm, μ, 0.087 mm^{-1}, $2\theta_{max}$ 53°, 2649 unique reflections, 182 parameters, a=0.0499, b=0.013, wR=0.0724 for all data, R=0.0272 for 2414 data with $I>2\sigma(I)$.

*4.2. Crystal data for **7** at −115°C*

$C_{18}H_{17}N_3O_2$, M=307.35, triclinic, space group P1, a=10.7941(9), b=10.8038(9), c=13.5104(12) Å, α=87.916(1), β=85.642(1), γ=82.755(1)°, V=1557.9(2), Z=4, F(000)=648, D_x=1.310 g cm^{-3}, colorless block, 0.67×0.59×0.27 mm, μ, 0.088 mm^{-1}, $2\theta_{max}$ 53°, 6800 unique reflections, 833 parameters, a=0.0483, b=0, wR=0.0690 for all data, R=0.0292 for 6073 data with $I>2\sigma(I)$.

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