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ARTICLE TYPE

Enantioselective total Syntheses and determination of absolute configuration of marine toxins, oxazinins.

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The enantioselective total syntheses of natural marine toxins, oxazinin-1, -2, -4, -5, -6 and linear precursor preoxazinin-7 are described. The synthetic highlights include Sharpless asymmetric aminohydroxylation and dihydroxylation, Oxa-Michael reaction and intramolecular diastereoselective addition of an appropriate hydroxyl substituent to a 3-methyleneindolenine for the construction of morpholine ring as key steps. The synthetic route also allowed the synthesis of the epi-preoxazinin and a structurally related secondary metabolite bursatellin isolated in 1980 from sea hare Bursatella leachii pleii and its epimer.

Introduction

The Marine biotoxins pose serious threats to both human health and fishery resources throughout the world[1]. The problem has aggrevated in last two decades, earlier only few regions were affected in scattered locations, now in essence every costal region is affected, not only fish and shellfish but life of marine mammals, seabirds and other animal is also in danger due to the toxic algal species[2]. In order to prevent or minimize such damage, lot of efforts are directed towards structure elucidation and synthetic confirmation of these toxins[3]. These marine biotoxins are found to be polyether compounds such as okadaic acid[4], yessotoxin[5] etc. During their investigation of toxic Adriatic mussels, Ciminiello *et al* have also isolated new type of toxins, which are completely different from polyether biotoxins isolated so for, but can raise further alarm for Sea life and public health.

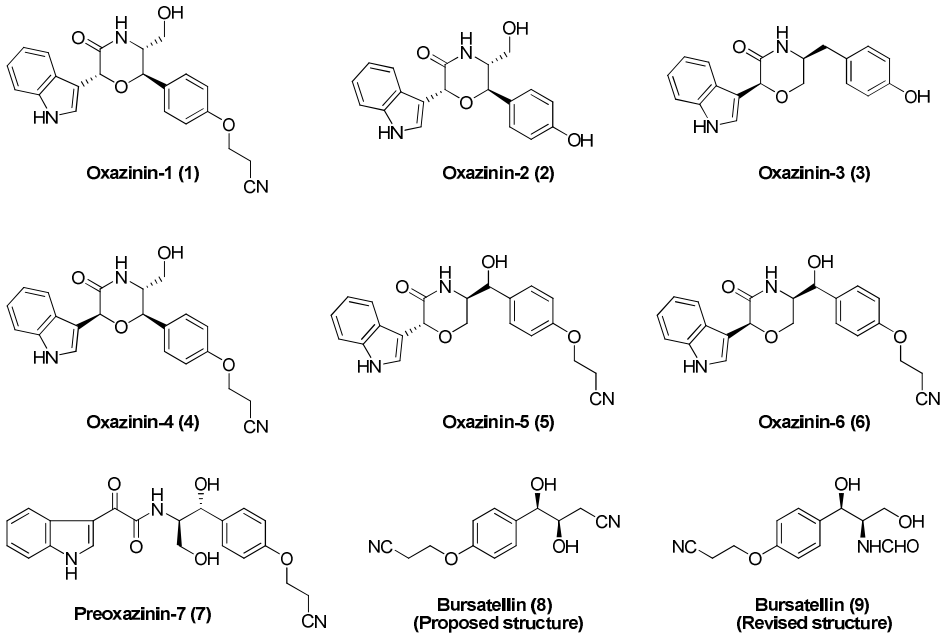

Figure 1. Structures of Oxazinin-1, -2, -3, -4, -5, -6, Preoxazinin-7 and Bursatellin

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In 2001, Fattorusso and Ciminiello *et al* reported the isolation of Oxazinin-1 (**1**), -2 (**2**), and -3 (**3**)[6] from the digestive glands of *Mytilus galioprovincialis* from northern Andriatic Sea. Subsequentaly in 2006 cimminello *et al* reported isolation of another natural product Oxazinin-4 (**4**)[7] from toxic mussels collected along the Emilia Romagna coasts, Italy. Again in 2007 same group reported isolation of three new natural products, namely, oxazinin-5 (**5**), -6 (**6**), and a linear precursor preoxazinin-7 (7)[8]. The structural elucidation of these oxazinins has been determined by extensive 2D NMR analysis and Molecular Mechanics and dynamics calculations. The absolute configuration of oxazinin-1 was established by application of the 9-AMA shift correlation method for β-chiral primary alcohols[9]. Possible biogenetic pathway was proposed by Ciminiello *et al* leading to these novel class of cytotoxic marine natural products[8].

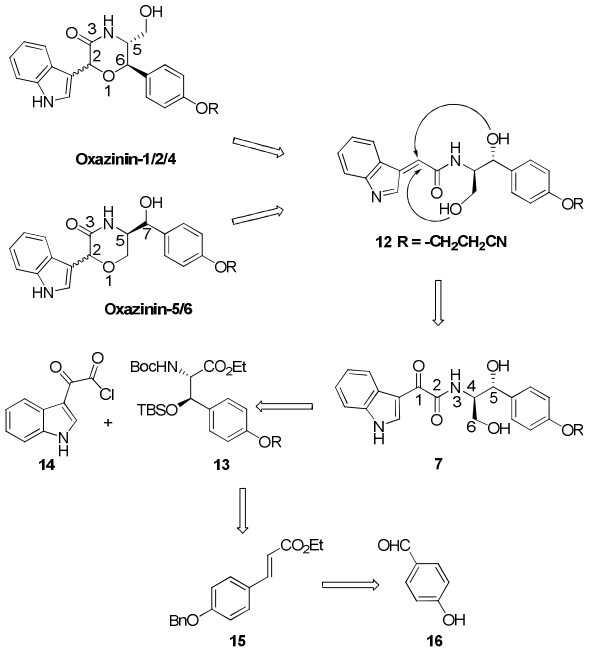
Oxazinin-1 (**1**) was shown to inhibit the proliferation of fibrosarcoma cell (WEHI-164) and J774 macrophages in vitro[6]. The originally assigned *cis*-stereochemistry at C-2 and C-6 centre in oxazinin-1 (**1**) and oxazinin-2 (**2**) was latter corrected as *trans* by Ciminiello *et al*. in 2006[7]. Because of their potential risk, these novel class of cytotoxic natural products could represent for human health and fish industries, comprehensive toxicological studies are needed. However their evaluation is hampered by the limited availability of oxazinins from isolation, therefore efficient total synthesis of these natural products and their analogues are necessary.

In this direction, Couladouros has reported total synthesis of a simple member of this family, oxazinin-3 (**3**) containing two stereocentres[10]. Subsequently in 2007, Baran group[11] also reported a 4 step synthesis of oxazinin-3 (**3**) using the direct coupling of indole to carbonyl compound under basic condition as key step. In 1980 Schmitz *et al* isolated a metabolite bursatellin[12] from the sea hare Bursatella leachii pleii. Initially Schmitz *et al* proposed structure **8**[12] for bursatellin, later in 1987 research group of G. Sodano[13] collected two Mediterranean sea hares, *Bursatella leachii leachii and Bursatella leachii savignyana***,** and isolated from them a compound that exhibited ^{1}H NMR spectral data nearly identical with that reported for bursatellin except for one additional low-field singlet observed at 8.20 ppm, this eventually lead to the revision of originally proposed structure of bursatellin **8** to structure **9**. Structurally bursatellin **9** is similar to preoxazinin-7 (**7**) except that the indole glyoxylic amide functionality in preoxazinin-7 (**7**) is replaced by formamide group. In 1990 Sodano *et al*[14] reported the semisynthesis of bursatellin **9** from chloramphenicol, and later in 1991 Hiroshi *et al*[15] reported the total synthesis of bursatellin **9** in 16 steps starting from L-tryptophan, both these syntheses are tedious and very low yielding.

We recently initiated a research program directed towards the total synthesis of oxazinins. In preliminary communication[16] we have reported the first total synthesis of oxazinin-5 (**5**), -6 (**6**), and their biogenetic precursor preoxazinin-7 **(7)**. Prior to our report there were no reports of synthesis of oxazinins except for oxazinin-2 as described earlier. In this article we describe further studies in this area that include enantioselective total synthesis of oxazinin-1 (1) -2 (2), -4 (4) as well as epi-preoxazinin-7 (**10**) and *epi*-bursatellin **11**.

Results and discussion.

Retrosynthetic analysis of oxazinins is depicted in *scheme 1*. It was envisaged that oxazinin-1 (**1**), -2 (**2**), and -4 (**4**) could be obtained from intermediate **12** by intramolecular regioselective addition of secondary hydroxyl group at –C-X position to 3-methyleneindolene moiety while oxazinin-5 (**5**) and -6 (**6**) could be prepared from same intermediate **12** by regioselective intramolecular addition of primary alcohol to 3-methyleneindolene. Key intermediate **12** in turn could be generated in situ from chemoselective reduction of preoxazinin-7 **(7)** via 3-hydroxymethylindole intermediate. Preoxazinin-7 **(7)** could be easily obtained by coupling of 3-indoleglyoxylic acid chloride **14** and tyrosine derivative **13**. To unambiguously establish the relative as well as absolute configuration of all oxazinin natural products, both (R, R) and (R, S) diastereomers of unnatural amino acid derivative could be synthesized from ethyl cinnamate **15** by Sharpless asymmetric dihydroxylation[17] and Sharpless asymmetric aminohydroxylation[18] respectively.



Scheme 1. Retrosynthetic Analysis

To begin with the cinnamate **15** was prepared in two step from p-hydroxybenzaldehyde **16** by first protection of hydroxyl group as its benzyl ether followed by treatment of resultant aldehyde with PPh_3=$CHCO_2Et$. As discussed in retrosynthetic analysis cinnamate **15** was subjected to Sharpless asymmetric hydroxylation and Sharpless asymmetric aminohydroxylation, independently. Treatment of cinnamate **15** with AD mix-β gave diol **17** in 94% yield and 98% ee. Nosylation (Nscl, Et_3N, 92% Yield) of the diol **17** followed by treatment with sodium azide furnished hydroxyl azide **19** in 90% yield via nosylate **18**. $SnCl_2$ mediated reduction of the azido group within **19**, followed by in

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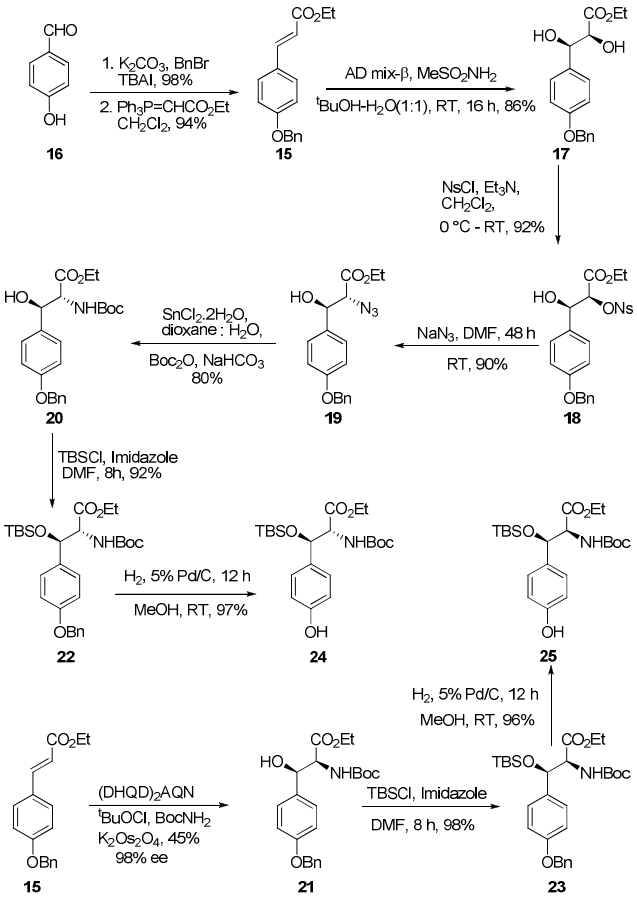
situ trapping of the resulting amine with $(Boc)_2O$ furnished amino derivative **20** in 80% overall yield. On the other hand Sharpless



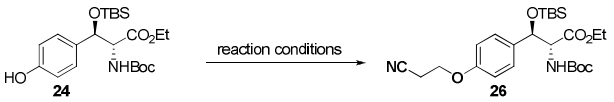
Scheme 2. Synthesis of diastereomers of tyrosine derivative

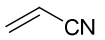
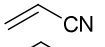
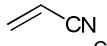
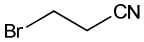
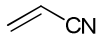
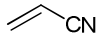
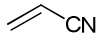
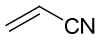
asymmetric aminohydroxylation[18] [NaOH, $BocNH_2$, ^tBuOCl, $(DHQD)_2AQN$, $K_2OsO_2(OH)_4$, nPrOH/H_2O (1:1)], of substrate **15** afforded directly boc protected amino alcohol **21** in 45% yield and 98% ee. Finally silylation of **20** and **21** (TBSCl, imidazole, 98% yield) gave the targeted (*R, R*) **22** and (*R, S*) **23** phenyl alanine derivatives respectively. Hydrogenolysis of benzyl ether in **22** and **23** using Pd/C afforded phenols **24** and **25** respectively (*Scheme 2*).

Next we turned our attention towards the cyanoethylation of the phenolic hydroxyl group in compound **24** using oxa-Michael reaction, our initial efforts using several standard bases failed to facilitate this reaction possibly due to retro-Michael fragmentation, as mentioned by the two independent groups of Sodano *et al*[14] and Hiroshi *et al*[15] in their synthesis of bursatellin **9**, a metabolite isolated in 1980[12]. Sodano *et al.*[14] have also shown that bursatellin **9** on treatment with dil. aq. Na_2CO_3 undergoes retro-Michael fragmentation reaction to generate the corresponding phenol derivative. After trying several different conditions (**table 1**), finally to our delight treatment of aminophenol **24** with acrylonitrile using 20 mol% of triton-B under reflux condition generated the desired oxa-Michael product **26** in 92% yield.

After having fully functionalized amino ester derivative **26** in hand the stage was set for coupling reaction using indoleglyoxylic chloride. Accordingly reduction of ester in compound **26** using $LiBH_4$ followed by deprotection of boc group using TFA/CH_2Cl_2 afforded the amine 27. Coupling of amine 27

Table 1 : Optimization of oxa-Michael reaction



Base	Reagent	solvent	Temp (°C)	Product
$NaHCO_3$		MeOH/THF	60	No reaction
NaH		THF	RT	No reaction
K_2CO_3		MeOH/THF	60	No reaction
NaH		THF	RT	No reaction
Ph_3P		CH_3CN	reflux	Complex mixture
Ph_3P		-	reflux	Complex mixture
Triton-B		CH_3CN/THF	reflux	30%
Triton-B		-	reflux	92%

with indoleglyoxylic chloride [prepared in one step by treatment of indole with oxalyl chloride] followed by TBS-deprotection using TBAF afforded epi-preoxazinin (**10**). On the other hand amine **27** on refluxing with ethyl formate followed by TBS-deprotection generated epi-bursatellin (**11**) in 80% over all yield (*Scheme 3*).

After making epimers **10** and **11**, we next turned our attention towards syntheses of preoxazinin-7 (**7**) and bursatellin **9**. Oxa-Michael reaction of phenol **25** with acrylonitrile using 20 mol% of triton-B under reflux condition as described earlier for diastereomer **24** generated the desired oxa-Michael product **13** in 92% yield. Reduction of ester **13** generated the primary alcohol **28** in 83% yield. Unlike the diastereomer **24**, boc deprotection of compound **28** proved to be more complex and led to multiple products and decomposition under various conditions such as TFA/CH_2Cl_2[19a], TFA-Triethylsilane[19b], 4M HCl in dioxane[19c], CAN[19d], TMSOTf[19e], and 10% H_2SO_4[19f] and TMSI[19g]. Interestingly treatment of **28** with stoichiometric amount of $Yb(OTf)_3$ under CH_2Cl_2 reflux conditions generated boc-deprotected amine **29** in excellent yield. Amine **29** on treatment with ethyl formate under reflux condition followed by TBS deprotection afforded the natural product bursatellin **9** in 80% yield (*Scheme 4*).

It was envisioned that amine **29** on coupling with indoleglyoxalic chloride **14** would generate the key intermediate **30**, which will eventually lead to synthesis of oxazinin 5 (**5**), -6 (**6**) and preoxazinin-7 (**7**). On the other hand, boc-deprotection of amino group in compound **13** followed by coupling with indoleglyoxylic acid and further functional group transformation would generate oxazinin-1 (**1**), -2 (**2**) and -4 (**4**). Accordingly coupling of amine **29** with indoleglyoxylic acid afforded ketoamide **30** in 70% yield. TBS-deprotection of compound **30** generated the natural product preoxazinin-7 (**7**) in excellent yield (*Scheme 5*).

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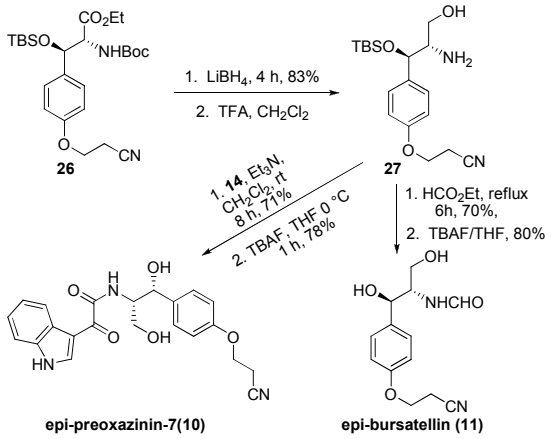
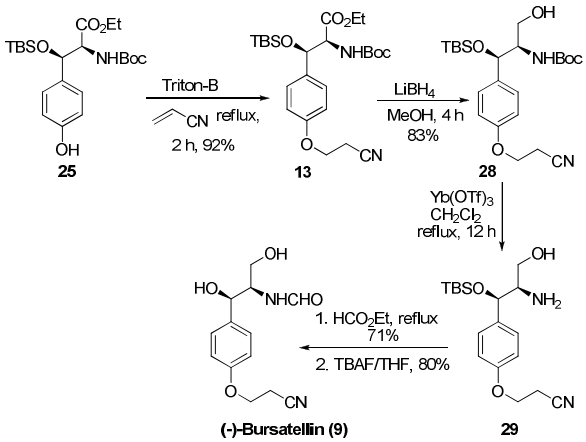
Reduction of ketone functionality in 3-indoleglyoxylic amide **30** using sodium borohydride generated the diastereomeric mixture of diols **31a,b** Which was then further treated with 10 mol% of PPTS in refluxing acetonitrile without further purification to furnish morpholinones **32a** and **32b** as a 3:1 mixture of C-2 diastereomers. The two diastereomers **32a** and **32b** were separated by careful silica gel column chromatography. The treatment of oxazinin-1**(1)** with 1.0 *N* aq. NaOH solution generated another natural product oxazinin-2 (**2**) by retro-Michael fragmentation reaction in 85% yield (*Scheme 7*). All the synthetic oxazinins exhibited IR, ^{1}H and ^{13}C NMR, mass as well as sign of

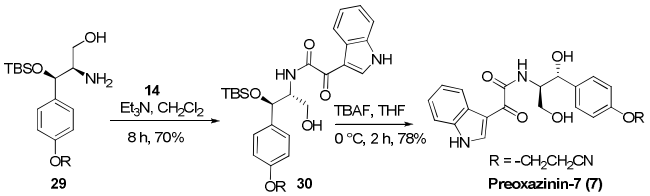


Scheme 3. Synthesis of epi-preoxazinin-7 and (+)-epi-bursatellin

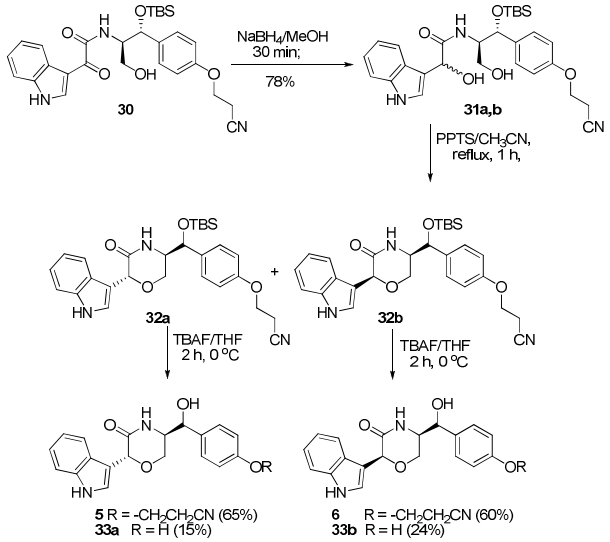


Scheme 4. Synthesis of (-) bursatellin

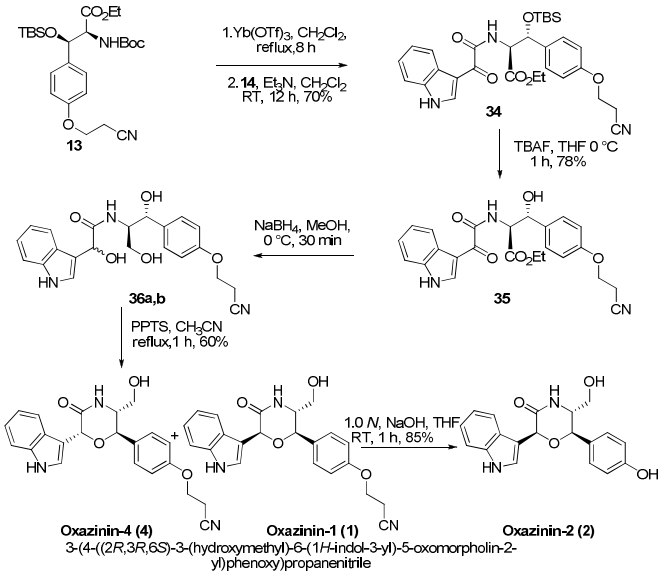
separated by preparative TLC. Finally TBS-deprotection of major **32a** and minor **32b** diastereomers provided natural products oxazinin-5 (**5**) and oxazinin-6 (**6**) respectively along with minor amount of cyanoethyl side chain cleaved compound **33a** and **33b** (*Scheme 6*). On the other hand, for the syntheses of oxazinin-1 (**1**), -2 (**2**) and -4 (**4**), boc group in compound **13** was deprotected using $Yb(OTf)_3$ under CH_2Cl_2 reflux conditions. The resultant amine was then coupled with indoleglyoxylic chloride using Et_3N to generate the intermediate **34** in excellent yield. TBS-deprodection of compound **34** using TBAF/THF afforded the alcohol **35** in 78% yield. To our surprise $NaBH_4$ reduction of indoleglyoxylic amide **35** not only reduced the ketone functionality but also the ester group to afford diastereomeric mixture of diols **36a,b**. This is one of the rare example of ester reduction using $NaBH_4$. The mixture of diols **36a,b** on treatment with 10 mol% PPTS in refluxing acetonitrile furnished the natural products oxazinin-1 **(1)** and -4 **(4)** along with small amount of oxazinin-5 **(5)** (3%) and oxazinin-6 **(6)** (2%) which were



Scheme 5. Synthesis of preoxazinin-7



Scheme 6. synthesis of Oxazinin-5 and -6



Scheme 7. Synthesis of Oxazinin-1 (**1**),-2 (**2**) and -4 (**4**)

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CD curves (for oxazinin-5,-6 and preoxazinin-7) identical with the natural oxazinin-1 **(1),** -2 **(2)**, -4 **(4)**, -5 **(5)**, -6 **(6)** and preoxazinin-7 **(7)** reported in literature, thus confirming the structure of the natural products as well as their relative and absolute stereochemistry.

Conclusions

In summary, we have completed the first enantioselective total syntheses of oxazinin-1, -2, -4, -5, -6 and their biogenetic linear precursor preoxazinin-7 along with structurally related metabolite bursatelline and its epimer using, aminohydroxylation and oxa-Michael reaction as the key steps, in a longest linear sequence of 8 steps, from the cinnamate **15** with excellent overall yields. In addition, the absolute configuration of stereogenic center were firmly established by the total synthesis to be (2*S*, 5*R*, 6*R*) for oxazinin-1 and -2, (2*R*, 5*R*, 6*R*) and for oxazinin-4, (2*R*, 5*R*, 7*R*) for oxazinin-5, (2*S*, 5*R*, 7*R*) for oxazinin-6 and (4*R*, 5*R*) for preoxazinin-7. The synthetic route developed here is general and efficient and could also be applied to the syntheses of other substituted morpholine related natural products.

Experimental section

General Information

All reactions were carried out under nitrogen or argon atmosphere with dry solvents under anhydrous conditions, unless otherwise mentioned. Anhydrous THF and diethyl ether were distilled from sodium-benzophenone and dichloromethane was distilled from calcium hydride. Yields refer to chromatographically pure material, unless otherwise stated. Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm Merck silica gel plates (60F-254) using UV light as a visualizing agent and an p-anisaldehyde or ninhydrin stain, and heat as developing agents. Merck silica gel (particle size 100-200 and 230-400 mesh) was used for flash column chromatography. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. NMR spectra were recorded on either a Bruker Avance 200 (^{1}H: 200 MHz, ^{13}C: 50MHz), Bruker Avance 400 (^{1}H: 400 MHz, ^{13}C: 100MHz), Bruker Avance 500 (^{1}H: 500 MHz, ^{13}C: 125 MHz), JEOL ECX 400 (^{1}H: 400 MHz, ^{13}C: 100 MHz) JEOL ECX 500 (^{1}H: 500 MHz, ^{13}C: 125 MHz). Mass spectrometric data were obtained using WATERS-Q-Tof Premier-ESI-MS. Optical rotations were measured on a Rudolph and JASCO using a 6.0 ml and 1.0 ml cell with a 100 and 50 mm path length are reported as $[\alpha]_D^{25}$ (c in g per ml solvent) at 25 °C. Enantiomeric ratios (er) were determined by HPLC using grace denali RP-18 250 x 4.6 and kromasil 5- cellucoat 0.46cm x 25cm (detection at 230 nm). Diastereomeric ratios (dr) were determined by crude ^{1}H NMR. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublet, dt = doublet of triplet, ddd = doublet of a doublet of a doublet, dm = doublet of a multiplet, m = multiplet, br = broad.

Experimental procedures

(*E*)-ethyl 3-(4-(benzyloxy)phenyl)acrylate (15): To a solution of the aldehyde **16a** (8.0 g, 37.7 mmol) in water (150 ml) was added PPh_3=$CHCO_2Et$ salt (19.7 g, 56.5 mmol) and heated it to 90 °C for 2h. The reaction mixture was cooled to RT and extracted with CH_2Cl_2 (3 x 80 ml), washed with brine and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on a silica gel column using EtOAc-petroleum ether (1:9) as eluent furnished the ester **15** (*E/Z*-ratio : 95/5, 10.0 g, 94%), *Rf* = 0.30 (EtOAc-petroleum ether, 1:9). IR (neat): νmax/cm^{-1} 3282, 1682 (C=O), 1632, 1603, 1585, 1515, 1439, 1371, 1279, 1189, 1033, 830; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.64 (d, *J* 16.0 Hz, 1H) 7.53-7.29 (m, 7H), 6.97 (dt, *J* 8.7 and 2.0 Hz, 2H) , 6.31 (d, *J* 16.0 Hz, 1H), 5.10 (s, 2H), 4.25 (q, *J* 14.3 and 7.1 Hz, 2H), 1.33 (t, *J* 7.1 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 167.3, 160.5, 144.2, 136.5, 129.7, 128.6, 128.1, 127.4, 115.9, 115.2, 70.1, 60.3, 14.3; HRMS (ESI): *m/z* calcd for $C_{18}H_{19}O_3$ (M+H) 283.1334; found 283.1330.

(2*R*,3*R*)-ethyl 3-(4-benzyloxy)phenyl)-2,3-dihydroxypropanoate (17): To a solution of AD-mix β (86.6 g) in *t*-BuOH/H_2O (1:1, 800.0 ml) was added $MeSO_2NH_2$ (5.9 g, 61.9 mmol) at RT. The mixture was cooled to 0 °C, and ethyl cinnamate **15** (17.5 g, 61.9 mmol) was added dropwise. The resulting mixture was warmed to RT over a period of 16 h before it was quenched with Na_2SO_3 (200 ml, sat. aq. solution), extracted with EtOAc (3 × 200 ml). The combined organic layers were washed with brine (200 ml), dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on silica gel column using ethyl acetate-petroleum ether (1:2) as eluent furnished the diol **17** (16.9 g, 86%)**;** *Rf* = 0.40 (EtOAc-petroleum ether, 1:2). $[\alpha]_D^{25}$ = -10.6 (*c* 4.7, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3438, 3019, 1727, 1613, 1585, 1513, 1455, 1216, 1106, 1026, 747, 697; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.44-7.30 (m, 7H), 6.98 (d, *J* 8.7 Hz, 2H), 5.06 (s, 2H), 4.95 (dd, *J* 5.8 and 3.0 Hz, 1H), 4.33–4.29 (m, 1H), 4.25 (q, *J* 12.1 and 4.9 Hz, 2H), 3.17 (d, *J* 6.0 Hz, 1H), 2.75 (d, *J* 6.7 Hz, 1H), 1.25 (t, *J* 7.0 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 172.7, 158.6, 136.9, 132.3, 128.6, 127.9, 127.6, 127.4, 114.7, 74.7, 74.2, 70.0, 62.1, 14.1; HRMS (ESI): *m/z* calcd for $C_{18}H_{20}O_5Na$ (M+Na) 339.1208; found 339.1204.

(2*S*,3*R*)-ethyl-(4-(benzyloxy)phenyl)-3-hydroxy-2-(4nitrophenylsulf onyloxy)propanoate (18): To a solution of diol **17** (11.2 g, 35.4 mmol) in CH_2Cl_2 (85 ml) were added NsCl (8.7g, 35.4 mmol) and Et_3N (7.4 ml, 53.1 mmol) at 0 °C. The reaction mixture was stirred for 6 h before it was quenched with HCl (20.0 ml, 5 % aq). Water was added to the reaction mixture, extracted with CH_2Cl_2 (3 x 100 ml), washed with brine and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate-petroleum ether (1:4) furnished the nosylate **18** (16.3 g, 92%); *Rf*= 0.40 (EtOAc-petroleum ether 1:4). $[\alpha]_D^{25}$ = -40.0 (*c* 0.9, $CHCl_3$); IR (neat)**:** ν_{max}/cm^{-1} 3437, 2926, 1760, 1610, 1532, 1455, 1378, 1350, 1188, 1094, 1026, 744, 617; ^{1}H NMR (200 MHz, $CDCl_3$): δ 8.23 (dt, *J* 9.1 and 4.3 Hz, 2H), 7.85 (dt, *J* 9.2 and 4.3 Hz, 2H) , 7.45-7.32 (m, 5H), 7.13 (d, *J* 8.7 Hz, 2H), 6.80 (dt, *J* 8.8 and 4.8 Hz, 2H), 5.14 (d, *J* 4.2 Hz, 1H), 5.00 (s, 2H), 4.95 (d, *J* 4.0 Hz, 1H), 4.15 (q, *J* 14.3 and 7.2 Hz, 2H), 2.60 (s, 1H), 1.17 (t, *J* 7.2 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 166.4, 158.9, 150.5, 141.4, 136.4, 129.5, 129.1, 128.6, 128.1, 127.5, 127.4, 124.0, 114.7, 82.4, 73.0, 69.9, 62.5, 13.8; HRMS (ESI): *m/z* calcd for $C_{24}H_{23}NO_9SNa$

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(M+Na) 524.0991; found 524.1001.

(2*S*,3*R*)-ethyl-2-azido-3-(4-(benzyloxy)phenyl)-3-hydroxypropanoate (19): To a solution of nosylate **18** (15.0 g, 29.8 mmol) in DMF (80.0 ml) was added sodium azide (11.6 g, 179.7 mmol) at RT. The resulting reaction mixture was heated at 50 °C for 38h. After cooled to RT, the reaction mixture was concentrated in vacuo, extracted with ethyl acetate (3 x 100 ml), washed with brine and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate-petroleum ether (2:3) furnished azide **19** (9.2 g, 90%), *Rf* = 0.40 (EtOAc-petroleum ether 2:3). $[\alpha]_D^{25}$ = +63.8 (*c* 6.0, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3443, 2112, 1574, 1397, 1115, 618, 536; ^1H NMR (200 MHz, $CDCl_3$): δ 7.43-7.30 (m, 8H), 7.00 (dt, *J* 8.8 and 5.1 Hz, 2H), 4.98 (dd, *J* 7.0 and 4.4 Hz, 1H), 4.26 (q, *J* 14.3 and 7.0 Hz, 2H), 4.10 (d, *J* 7.0 Hz, 1H), 2.78 (d, *J* 4.4 Hz, 1H), 1.58 (s, 1H), 1.28 (t, *J* 7.1 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.0, 159.0, 136.7, 131.3, 128.6, 128.0, 127.9, 127.4, 114.9, 73.6, 69.9, 66.8, 62.1, 14.0; HRMS (ESI): *m/z* calcd for $C_{18}H_{19}N_3O_4Na$ (M+Na) 364.1273; found 364.1282.

(2*S*,3*R*)-ethyl 3-(4-(benzyloxy)phenyl)-2-(*tert*-butoxycarbonylamino)-3-proxypropanoate (20): To a solution of azide **19** (4.0 g, 11.7 mmol) in dioxane (60.0 ml) was added a solution of $SnCl_2 \cdot 2H_2O$ (13.2 g, 58.5 mmol) in H_2O/dioxane (4:1, 100.0 ml) at 0 °C. The resulting mixture was warmed to RT over a period of 5 h before it was cooled to 0 °C. Solid $NaHCO_3$ was slowly added until pH 8-9 was reached. Boc_2O (3.8 g, 17.6 mmol) was added at 0 °C and the reaction mixture was warmed to RT over a period of 15 h before it was acidified by slow addition of HCl (2 N) until pH 5-6 was reached. The reaction mixture was filtered through a mixture of silica gel and celite, and the filtrate was extracted with EtOAc (4 × 30 ml). The combined organic layers were dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on silica gel column using ethyl acetate-petroleum ether (1:3) as eluent furnished the Boc-carbamate **20** (3.1 g, 80%). *Rf* = 0.40 (EtOAc-petroleum ether, 1:3). $[\alpha]_D^{25}$ = -50.2 (*c* 9.6, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3436, 2979, 2932, 1715, 1612, 1586, 1511, 1455, 1369, 1243, 1170, 1114, 1025, 864, 752; ^1H NMR (200 MHz, $CDCl_3$): δ 7.43-7.30 (m, 5H), 7.20 (d, *J* 8.6 Hz, 2H), 6.94 (dt, *J* 8.7 and 2.8 Hz, 2H) , 5.32 (br d, *J* 7.5 Hz, 1H), 5.12 (br s, 1H), 5.04 (s, 2H), 4.65 (dd, *J* 7.6 and 3.9 Hz, 1H), 4.13 (q, *J* 14.3 and 7.2 Hz, 2H), 4.04 (br s, 1H), 1.43 (s, 9H), 1.19 (t, *J* 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.8, 158.5, 156.3, 136.8, 131.6, 128.5, 127.9, 127.4, 127.3, 114.5, 80.5, 74.6, 69.9, 61.6, 59.7, 28.2, 14.0 HRMS (ESI): *m/z* calcd for $C_{23}H_{30}NO_6$ (M+H) 416.2073; found 416.2065.

(2*S*,3*R*)-ethyl 3-(4-(benzyloxy)phenyl)-2-((*tert*-butoxycarbonyl)amino)-3-(*tert*-butyldimethylsilyloxy)propanoate (22): To a solution of the alcohol **20** (2.0 g, 4.8 mmol) in DMF (15.0 ml) were added TBSCl (1.0 g, 6.2 mmol), imidazole (0.5 g, 7.2 mmol) and stirred magnetically at RT for 12 h. Water was added to the reaction mixture, extracted with ethyl acetate (3 x 20 ml), washed with brine and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate-petroleum ether (1:9) furnished the TBS ether **22** (2.3 g, 92%) as colorless oil, *Rf* = 0.40 (EtOAc-petroleum ether 1:9). $[\alpha]_D^{25}$ = -57.9 (*c* 11.8, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3446, 2931, 2858, 1718, 1611, 1511, 1367, 1250, 1170, 1094, 1050, 939, 837; ^1H NMR (200 MHz, $CDCl_3$): δ 7.36-7.18 (m, 7H), 6.85 (d, *J* 8.7 Hz, 2H), 5.22 (d, *J* 8.3 Hz, 1H), 4.94 (s, 3H), 4.43 (dd, *J* 8.3 and 4.2 Hz, 1H), 3.98 (q, *J* 14.2 and 7.1 Hz, 2H), 1.35 (s, 9H), 1.05 (t, *J* 7.1 Hz, 3H), 0.84 (s, 9H), 0.00 (s, 3H), -0.19 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 169.7, 158.1, 154.6, 136.8, 132.7, 128.3, 127.7, 127.2, 114.0, 79.3, 74.9, 69.7, 60.8, 60.6, 28.1, 25.5, 17.9, 13.8, -5.0, -5.5; HRMS (ESI): *m/z* calcd for $C_{29}H_{44}NO_6$ (M+H) 530.2938; found 530.2944.

(2*R*,3*R*)-ethyl 2-(*tert*-butoxycarbonylamino)-3-(*tert*-butyldimethylsilyloxy)-3-(4-hydroxyphenyl)propanoate (24): To a solution of the ester **22** (2.0 g, 3.8 mmol) in methanol was added 5% Pd/C (40.0 mg) and shaken in hydrogenation atmosphere at RT for 12 h. The reaction mixture was filtered on celite using ethyl acetate. Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate-petroleum ether (1:4) as eluent furnished hydroxy ester **24** (1.6 g, 97%) as a colorless oil, *Rf* = 0.30 (EtOAc-petroleum ether 1:4). $[\alpha]_D^{25}$ = -50.3 (*c* 9.7, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3434, 3020, 2859, 1694, 1616, 1516, 1369, 1169, 1084, 834; ^1H NMR (200 MHz, $CDCl_3$): δ 7.49 (br s, 1H), 7.11 (d, *J* 8.6 Hz, 2H), 6.73 (d, *J* 8.5 Hz, 2H), 5.26 (d, *J* 8.6 Hz, 1H), 4.91 (d, *J* 4.2 Hz, 1H), 4.44 (dd, *J* 8.5 and 4.4 Hz, 1H), 4.05 (q, *J* 14.2 and 7.0 Hz, 2H), 1.37 (s, 9H), 1.12 (t, *J* 7.0 Hz, 3H), 0.84 (s, 9H), 0.00 (s, 3H), -0.19 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.4, 156.0, 155.1, 131.3, 127.4, 114.9, 80.1, 75.1, 61.2, 60.3, 28.2, 25.5, 17.9, 13.8, -4.9, -5.5; HRMS (ESI): *m/z* calcd for $C_{22}H_{38}NO_6Si$ (M+H) 440.2468; found 440.2475.

(2*R*,3*R*)-ethyl 2-(*tert*-butoxycarbonylamino)-3-(*tert*-butyldimethylsilyloxy)-3-(4-(2-cyanoethoxy)phenyl)propanoate (26): To a solution of the phenol **24** (1.0 g, 2.3 mmol) in acrylonitrile (10.0 ml) was added catalytic amount of triton B and refluxed for 8 h. Excess acrylonitrile was removed under reduced pressure and the reaction mixture was diluted with water, extracted with CH_2Cl_2, washed with brine and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on silica gel column using ethyl acetate-petroleum ether (1:4) as eluent furnished the cyanoester **26** (1.0 g, 92%). *Rf* = 0.40 (EtOAc-petroleum ether, 1:4). $[\alpha]_D^{25}$ = -53.3 (*c* 10.7, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3444, 3020, 2931, 2240, 1712, 1612, 1510, 1250, 1170, 1115, 1080, 1056, 930, 757, 669; ^1H NMR (200 MHz, $CDCl_3$): δ 7.23 (d, *J* 8.6 Hz, 2H), 6.80 (d, *J* 8.7 Hz, 2H), 5.20 (d, *J* 8.3 Hz, 2H), 4.95 (d, *J* 3.8 Hz, 1H), 4.40 (dd, *J* 8.3 and 4.0 Hz, 1H), 4.13 (t, *J* 6.3 Hz, 2H), 4.03 (q, *J* 14.4 and 7.3 Hz), 2.77 (t, *J* 6.3 Hz, 2H), 1.36 (s, 9H), 1.10 (t, *J* 7.2 Hz, 3H), 0.84 (s, 9H), 0.00 (s, 3H), -0.19 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 169.6, 157.0, 154.7, 133.9, 127.5, 117.1, 113.9, 79.6, 75.0, 62.5, 61.0, 60.7, 28.2, 25.5, 18.5, 18.5, 17.9, 13.9, -4.9, -5.4; HRMS (ESI): *m/z* calcd for $C_{25}H_{41}N_2O_6Si$ (M+H) 493.2734; found 493.2735.

***tert*-butyl (1*R*,2*S*)-1-(*tert*-butyldimethylsilyloxy)-1-(4-(2-cyanoethoxy)phenyl)-3-hydroxypropan-2-ylcarbamate (26a):** To a magnetically stirred solution of the cyanoester **26** (2.0 g, 4.1

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mmol) in ether/methanol (20:10 ml) was added $LiBH_4$ (0.45 g, 20.5 mmol) and stirred for 4 h at RT. Solvent was evaporated under reduced pressure, water (15.0 ml) was added to the residue and extracted with ether (3 x 20 ml). The combined extract was washed with brine (15.0 ml) and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate-petroleum ether (1:2) as eluent furnished the alcohol **26a** (1.5 g, 83%), *Rf* = 0.30 (EtOAc-petroleum ether, 1:2). $[\alpha]_D^{25}$ = -17.9 (*c* 4.3, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3445, 2930, 2260, 1701, 1510, 1392, 1367, 1246, 1170, 1086, 868, 557; ^1H NMR (200 MHz, $CDCl_3$): δ 7.25 (d, *J* 8.5 Hz, 2H), 6.81 (d, *J* 8.6 Hz, 2H), 5.39 (d, *J* 7.8 Hz, 1H), 5.06 (br s, 1H), 4.12 (t, *J* 6.3 Hz, 2H), 3.75 (dd, *J* 11.5 and 2.5 Hz, 1H),3.48-3.34 (m, 2H), 2.76 (t, *J* 6.3, Hz, 2H), 1.38 (s, 9H), 0.84 (s, 9H), 0.00 (s, 3H), -0.18 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 156.9, 155.5, 134.3, 127.1, 117.1, 114.3, 79.4, 76.8, 62.5, 60.9, 56.5, 28.3, 25.7, 18.5, 18.0, -5.0, -5.5; HRMS (ESI): *m/z* calcd for $C_{23}H_{39}N_2O_5Si$ (M+H) 451.2628; found 451.2628.

***N*-((1*R*,2*R*)-1-(4-(2-cyanoethoxy)phenyl)-3-hydroxy-1-((trimethylsilyl) oxy) propan-2-yl)formamide (27a) :** To a solution of boc-amine **26a** (90.0 mg, 0.20 mmol) in CH_2Cl_2 (4.0 ml) was added TFA (0.19 ml, 2.00 mmol) at 0 °C and stirred for 8 h at RT. It was quenched with $NaHCO_3$ and concentrated on vacuo. The residue was dissolved in ethyl formate (6.0 ml) and refluxed for 6 h. Evaporation of the solvent and purification of the residue on a silica gel column using MeOH-CH_2Cl_2 (1:19) furnished TBS-protected bursatellin **27a** (50.0 mg, 70%, 2 steps) as colorless oil, *Rf* = 0.30 (MeOH-CH_2Cl_2 1:19). $[\alpha]_D^{25}$ = +13.0 (c 1.1, $CHCl_3$); IR (neat): νmax/cm^{-1} 3357, 2928, 2856, 2280,1746, 1670, 1512, 1381, 1245, 1080, 1040, 837; ^1H NMR (200 MHz, $CDCl_3$, peaks due to major rotamer): δ 8.21 (s, 1H), 7.26 (d, *J* 8.6 Hz, 2H), 6.84 (d, *J* 8.7 Hz, 2H), 6.44 (d, *J* 7.6 Hz, 1H), 5.05 (d, *J* 2.7 Hz, 1H), 4.14 (t, *J* 6.3 Hz, 2H), 3.93-3.82 (m, 2H), 3.45-3.36 (m, 1H), 2.78 (t, *J* 6.3 Hz, 2H), 0.85 (s, 9H), 0.00 (s, 3H), -0.20 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.0, 157.3, 134.0, 128.0, 127.3, 117.1, 114.5, 62.6, 60.7, 54.6, 25.8, 18.6, 17.9, -4.9, -5.3; HRMS (ESI): *m/z* calcd for $C_{19}H_{30}N_2O_4SiNa$ (M+Na) 401.1873; found 401.1867;

Synthesis of *epi*-bursatellin (11): To a magnetically stirred solution of the TBS protected bursatellin **27a** (30.0 mg, 0.08 mmol) in THF (2.0 ml) was added 1 M solution of TBAF in THF (0.08 ml, 0.08 mmol) and stirred for 1 h at 0 °C. Solvent was evaporated under reduced pressure, water (3.0 ml) was added to the residue and extracted with CH_2Cl_2 (3 x 10 ml). The combined extract was washed with brine (6.0 ml) and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on a silica gel column using MeOH-CH_2Cl_2 (1:9) as eluent furnished the (+)-bursatellin **11** (16.8 mg, 80%), *Rf* = 0.40 (MeOH:CH_2Cl_2, 1:9). $[\alpha]_D^{25}$ = +7.1 (c 0.4, MeOH); IR (neat): νmax/cm^{-1} 3362, 2977, 2243, 1660, 1450, 1377, 1174, 1099; ^1H NMR (400 MHz, $CDCl_3$): δ 8.27 (s, 1H), 7.37 (d, *J* 8.3 Hz, 2H), 6.94 (d, *J* 8.5 Hz, 2H), 6.42 (br d, *J* 6.8 Hz, 1 H), 5.06 (d, *J* 3.3 Hz, 1H), 4.22 (t, *J* 6.5 Hz, 2H), 4.14 (dd, *J* 7.5 and 3.8 Hz,1H), 3.90 (dd, *J* 10.8 and 2.8 Hz, 1H), 3.66 (d, *J* 11.0 Hz, 1H), 3.06 (br s, 1H) 2.85 (t, *J* 6.3 Hz, 2H), 2.57 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 161.3, 157.5, 133.9, 127.2, 117.1, 114.8, 75.4, 62.7, 61.4, 54.2, 29.7, 18.7;

***N*-((1*R*,2*R*)-1-((*tert*-butyldimethylsilyl)oxy)-1-(4-(2-cyanoethoxy)phenyl)-3-hydroxypropan-2-yl)-2-(1H-indol-3-yl)-2-oxoacetamide (27b):** To a solution of indole (1.0 g, 8.6 mmol) in anhydrous diethyl ether (15.0 ml) at 0 °C, freshly distilled oxalyl chloride (0.8 ml, 9.5 mmol) was added dropwise. The reaction mixture was stirred at 0 °C for 0.5 h and then allowed to warm to RT. The resulting yellow crystals of indoleglyoxylic chloride **14** were collected by filtration, washed with cold anhydrous diethyl ether and dried under vacuum (1.6 g, 15.7 mmol). The compound **14** was used without further purification in next step. To a solution of boc-amine **26a** (100 mg, 0.2 mmol) in CH_2Cl_2 (5.0 ml) was added TFA (0.15 ml, 2.0 mmol) and stirred for 2 h. aq. $NaHCO_3$ was added to the reaction mixture and extracted with CH_2Cl_2 (3 x 10 ml). The organic layer was washed with brine and dried over Na_2SO_4. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2, cooled to 0 °C. To the cold solution was added Et_3N (17.0 mg, 0.16 mmol) followed by 3-indoleglyoxalyl chloride **14** (40.0 mg, 0.14 mmol) and stirred magnetically at RT for 12 h. Water (10.0 ml) was added to the reaction mixture and extracted with CH_2Cl_2 (3 x 10 ml). Combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent and purification of the residue on a silica gel column using MeOH:CH_2Cl_2 (1:19) furnished the TBS-protected preoxazinin **27b** (73 mg, 70%). $[\alpha]_D^{25}$ = +24.3 (c 1.4, $CHCl_3$); IR (neat): νmax/cm^{-1} 3436, 3010, 2930, 2400, 2280, 1611, 1511, 1438, 1214, 1124, 1045, 929, 756, 618; ^1H NMR (200 MHz, $CDCl_3$): δ 9.27 (s, 1H), 8.88 (d, *J* 3.3 Hz, 1H), 8.41-8.45 (m, 1H), 8.13 (d, *J* 8.6 Hz, 1H), 7.45-7.29 (m, 5H), 6.86 (d, *J* 8.7 Hz, 2H), 5.05 (d, *J* 4.0 Hz, 1H), 4.16 (t, *J* 6.3 Hz, 2H), 4.07-3.94 (m, 2H), 3.71-3.60 (m, 1H), 3.04 (d, *J* 7.2 Hz, 1H), 2.82 (t, *J* 6.2 Hz, 2H), 1.75 (s, 1H), 0.92 (s, 9H), 0.07 (s, 3H), -0.15 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 180.4, 162.5, 157.2, 138.1, 135.7, 134.2, 127.5, 126.5, 124.2, 123.3, 122.4, 117.4, 144.4, 113.2, 111.7, 75.8, 62.5, 61.0, 56.2, 25.7, 18.6, 18.0, -4.9, -5.3; HRMS (ESI): *m/z* calcd for $C_{28}H_{36}N_3O_5Si$ (M+H) 522.2424; found 522.2424.

Synthesis of *epi*-preoxazinin-7 (10): To the solution of **27b** (60.0 mg, 0.15 mmol) in THF (4.0 ml) was added TBAF (1.0 M in THF, 0.15 ml, 0.15 mmol). The resulting mixture was stirred for 1 h at 0 °C, before it was concentrated in *vacuo*. Water (5.0 ml) was added to the residue and extracted with ether (3 x 20 ml). The combined extract was washed with brine (13.0 ml) and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate-petroleum ether (9:1) as eluent furnished the epi-preoxazinin-7 **10** (27.0 mg, 80 %). *Rf* = 0.30 (EtOAc-petroleum ether, 9:1). $[\alpha]_D^{25}$ = +40.4 (c 0.25, MeOH); IR (neat): νmax/cm^{-1} 3434, 3340, 3162, 2977, 2270, 1662, 1622, 1450, 1377, 1113, 1089, 929, 757; ^1H NMR (400 MHz, CD_3CN): δ 10.19 (br s, 1H), 8.78 (d, *J* 3.3 Hz, 1H), 8.27 (dd, *J* 5.8 and 2.0 Hz, 1H), 7.71 (d, *J* 9.5 Hz, 1H), 7.54 (dd, *J* 7.5 and 4.0 Hz, 1H), 7.36-7.25 (m, 4H), 6.87 (dt, *J* 8.7 and 2.0 Hz, 2H), 4.82 (dd, *J* 6.4 and 5.0 Hz, 1H), 4.19-4.07 (m, 3H), 3.92 (d, *J* 4.8 Hz, 1H), 3.84-3.60 (m, 2H), 3.23 (t, *J* 5.8 Hz, 1H), 2.81 (t, *J* 6.1 Hz, 2H); ^{13}C NMR (100 MHz, CD_3CN): δ 182.4, 163.7, 158.7, 140.1, 137.5, 136.3, 129.3, 127.8, 125.1, 124.2, 122.9,

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119.6, 115.5, 113.6, 74.3, 64.3, 62.2, 57.5, 19.5; HRMS (ESI): *m/z* calcd for $C_{22}H_{21}N_3O_5Na$ (M+Na) 430.1379; found 430.1370.

(2*S*,3*R*)-ethyl 3-(4-(benzyloxy)phenyl)-2-((*tert*-butoxycarbonyl)amino)-3-hydroxypropanoate (21): A round bottom flask was charged with sodium hydroxide (30.5 ml of 1 N solution) and diluted with water (45.0 ml) in a dark fume hood. Part of this alkaline solution (5.0 ml) was transferred into a vial to dissolve $K_2[OsO_2(OH)_4]$ (147 mg, 0.4 mmol). With vigorous stirring, n-propanol (40.0 ml) and *tert*-butylcarbamate (3.6 g, 31.0 mmol) were added to the flask, followed by dropwise addition of freshly prepared *tert*-butyl hypochlorite (3.5 ml, 3.05 mmol). After five minutes, n-propanol solution (35.0 ml) of $(DHQD)_2AQN$ (343 mg, 0.4 mmol) and ethyl cinnamate **15** (2.82 g, 1.0 mmol), and the aqueous $K_2[OsO_2(OH)_4]$ solution were added. After 2 h, the solution was quenched with 5.0 g sodium bisulfite, added water and extracted with ethyl acetate (3 x 50 ml), washed with brine and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on a flash silica gel column using ethyl acetate-petroleum ether (1:4) furnished the hydroxy ester **21** (2.14 g, 45%, 98% ee), *Rf* = 0.30 (EtOAc-petroleum ether 1:4). $[\alpha]_D^{25}$ = -12.8 (c 4.0, $CHCl_3$); IR (neat): νmax/cm^{-1} 3421, 2930, 1716, 1690, 1512, 1392, 1244, 1162, 1025; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.50-7.20 (m, 7H), 6.94 (td, *J* 8.7 and 2.0 Hz, 2H) , 5.35 (d, *J* 8.8 Hz, 1H), 5.12 (t, *J* 3.4 Hz, 1H), 5.04 (s, 2H), 4.45 (br d, *J* 7.4 Hz, 1H), 4.18 (q, *J* 14.3 and 7.2 Hz, 2H), 2.9 (br s, 1H), 1.35 (s, 9H), 1.22 (t, *J* 7.1 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 171.0, 158.6, 155.8, 136.9, 132.4, 128.6, 128.0, 127.5, 127.4, 114.7, 80.1, 73.7, 70.0, 61.7, 59.7, 28.2, 14.1; HRMS (ESI): *m/z* calcd for $C_{23}H_{30}NO_6$ (M+H) 416.2073; found 416.2086.

(2*S*,3*R*)-ethyl 3-(4-(benzyloxy)phenyl)-2-((*tert*-butoxycarbonyl)amino)-3-((*tert*-butyldimethylsilyl)oxy)propanoate (23): To a solution of the alcohol **21** (4.0 g, 9.6 mmol) in DMF (25.0 ml) were added TBSCl (1.9 g, 12.5 mmol), imidazole (0.9 g, 14.4 mmol) and stirred magnetically at RT for 12 h. Water was added to the reaction mixture, extracted with ethyl acetate (3 x 20 ml), washed with brine and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate-petroleum ether (1:9) furnished the TBS ether **23** (4.9 g, 98%) as colorless oil, *Rf* = 0.40 (EtOAc-petroleum ether 1:9). $[\alpha]_D^{25}$ = -16.5 (*c* 5.4, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 2930, 1720, 1643, 1510, 1367, 1250, 830, 778; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.50-7.20 (m, 7H), 6.94 (dt, *J* 8.7 and 2.0 Hz, 2H), 5.30-5.10 (m, 2H), 5.05 (s, 2H), 4.38 (dd, *J* 7.5 and 2.5 Hz, 1H), 4.30-4.10 (m, 2H), 1.35 (s, 9H), 1.31 (t, *J* 7.1 Hz, 3H), 0.89 (s, 9H), 0.00 (s, 3H), -0.15 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.0, 158.3, 154.9, 137.1, 133.0, 128.6, 127.9, 127.5, 114.3, 79.6, 75.2, 69.9, 61.0, 60.9, 53.5, 28.4, 25.8, 18.2, 14.1, -4.8, -5.3; HRMS (ESI): *m/z* calcd for $C_{29}H_{44}NO_6Si$ (M+H) 530.2938; found 530.2941.

(2*S*,3*R*)-ethyl 2-(*tert*-butoxycarbonylamino)-3-(*tert*-butyldimethylsilyloxy)-3-(4-hydroxyphenyl)propanoate (25): To a solution of the ester **23** (2.0 g, 3.8 mmol) in methanol was added 5% Pd/C (40.0 mg) and shaken in hydrogenation atmosphere at RT for 12 h. The reaction mixture was filtered on celite using ethyl acetate. Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate-petroleum ether (1:4) as eluent furnished hydroxy ester **25** (1.6 g, 97%) as a colorless oil, *Rf* = 0.30 (EtOAc-petroleum ether 1:4). $[\alpha]_D^{25}$ = -17.8 (*c* 2.3, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3434, 3020, 2859, 1694, 1616, 1516, 1369, 1169, 1084, 834; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.22 (d, *J* 8.5 Hz, 2H), 6.97 (s, 1H), 6.79 (d, *J* 8.5 Hz, 2H), 5.50 (br d, *J* 9.3 Hz, 1H), 5.22 (s, 1H), 4.30-4.05 (m, 3H), 1.36 (s, 9H), 1.27 (t, *J* 7.0 Hz, 3H), 0.89 (s, 9H), 0.01 (s, 3H), -0.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 172, 157.9, 156.9, 133.7, 129.1, 116.0, 80.4, 75.6, 62.6, 62.3, 28.9, 26.4, 19.0, 14.8, -4.0, -4.8; HRMS (ESI): *m/z* calcd for $C_{22}H_{38}NO_6Si$ (M+H) 440.2468; found 440.2467.

(2*S*,3*R*)-ethyl 2-(*tert*-butoxycarbonylamino)-3-(*tert*-butyldimethylsilyloxy)-3-(4-(2-cyanoethoxy)phenyl)propanoate (13) : To a solution of the phenol **25** (1.0 g, 2.3 mmol) in acrylonitrile (10.0 ml) was added catalytic amount of triton B and refluxed for 8 h. Excess acrylonitrile was removed under reduced pressure and the reaction mixture was diluted with water, extracted with CH_2Cl_2, washed with brine and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on silica gel column using ethyl acetate-petroleum ether (1:4) as eluent furnished the ester **13** (1.0 g, 92%). *Rf* = 0.40 (EtOAc-petroleum ether, 1:4). $[\alpha]_D^{25}$ = -15.6 (*c* 2.0, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3447, 3020, 2931, 2240, 1712, 1612, 1510, 1215, 1171, 1086, 757, 669; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.30 (d, *J* 8.3 Hz, 2H), 6.87 (d, *J* 8.4 Hz, 2H), 5.35-5.00 (m, 2H), 4.40-4.05 (m, 5H), 2.82 (t, *J* 6.3 Hz, 2H), 1.35 (s, 9H), 1.32 (t, *J* 7.2 Hz, 3H), 0.89 (s, 9H), 0.00 (s, 3H), -0.15 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 170.5, 157.1., 155.3, 133.9, 127.5, 117.1, 114.1, 79.5, 74.2, 62.5, 61.3, 60.5, 28.1, 25.5, 18.4, 17.9, 13.9, -4.8, -5.7; HRMS (ESI): *m/z* calcd for $C_{25}H_{41}N_2O_6Si$ (M+H) 493.2734; found 493.2727.

***tert*-butyl (1*R*,2*R*)-1-(*tert*-butyldimethylsilyloxy)-1-(4-(2-cyanoethoxy)phenyl)-3-hydroxypropan-2-ylcarbamate (28)**: To a magnetically stirred solution of the cyano ester **13** (2.0 g, 4.1 mmol) in ether/methanol (20:10 ml) was added $LiBH_4$ (0.5 g, 20.5 mmol) and stirred for 4 h at RT. Solvent was evaporated under reduced pressure, water (15.0 ml) was added to the residue and extracted with ether (3 x 20 ml). The combined extract was washed with brine (15.0 ml) and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate-petroleum ether (1:2) as eluent furnished the alcohol **28** (1.5 g, 83%), *Rf* = 0.30 (EtOAc-petroleum ether, 1:2). $[\alpha]_D^{25}$ = -22.2 (*c* 4.2, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3442, 3020, 2931, 2255, 1700, 1510, 1392, 1367, 1216, 1172, 1086, 838; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.25 (d, *J* 8.6 Hz, 2H), 6.86 (d, *J* 8.6 Hz, 2H), 5.0-4.8 (m, 2H), 4.18 (t, *J* 6.3 Hz, 2H), 3.75-3.50 (m, 3H), 2.83 (t, *J* 6.3, Hz, 2H), 1.37 (s, 9H), 0.90 (s, 9H), 0.06 (s, 3H), -0.16 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 156.9, 156.1, 135.0, 127.6, 117.2, 114.2, 79.5, 72.9, 62.7, 62.5, 58.5, 28.2, 25.7, 18.5, 18.0, -4.7, -5.3; HRMS (ESI): *m/z* calcd for $C_{23}H_{39}N_2O_5Si$ (M+H) 451.2628; found 451.2620.

***N*-((1*R*,2*R*)-1-(*tert*-butyldimethylsilyloxy)-1-(4-(2-cyanoethoxy)phenyl)-3-hydroxypropan-2-yl)formamide (28a)**: To a solution of boc-amine **28** (80.0 mg, 0.2 mmol) in CH_2Cl_2

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(8.0 ml) was added $Yb(OTf)_3$ (110.0 mg, 0.2 mmol) and refluxed for 8 h. It was quenched with $NaHCO_3$ and concentrated on vacuo. The residue was dissolved in ethyl formate (6.0 ml) and refluxed for 6 h. Evaporation of the solvent and purification of the residue on a silica gel column using MeOH-CH_2Cl_2 (1:19) furnished TBS-protected bursatellin **28a** (47.6 mg, 71%, 2 steps) as colorless oil, *Rf* = 0.30 (MeOH-CH_2Cl_2 1:19). $[\alpha]_D^{25}$ = -15.1 (*c* 4.4, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3358, 2928, 2856, 2280, 1746, 1672, 1512, 1389, 1245, 1080, 1047, 837; ^1H NMR (500 MHz, $CDCl_3$, peaks due to major rotamer): δ 8.14 (s, 1H), 7.25 (d, *J* 15.0 Hz, 2H), 6.86 (d, *J* 8.8 Hz, 1H), 6.10 (d, *J* 7.3 Hz, 1H), 4.97 (d, *J* 3.3 Hz, 1H), 4.19 (t, *J* 6.5 Hz, 2H), 4.07-4.01 (m, 1H), 3.68 (d, *J* 5.8 Hz, 2H), 2.84 (t, *J* 6.0 Hz, 2H), 0.91 (s, 9H), 0.08 (s, 3H), -0.14 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.0, 161.6, 157.3, 134.7, 127.8, 127.4, 117.2, 114.5, 114.5, 73.5, 72.3, 63.0, 62.6, 60.8, 57.2, 25.8, 25.8, 18.7, 18.2, -4.6, -5.2; HRMS (ESI): m/z calcd for $C_{19}H_{30}N_2O_4SiNa$ (M+Na) 401.1873; found 401.1869.

Synthesis of (-)-bursatellin (9): To a magnetically stirred solution of the TBS protected bursatellin **28a** (20.0 mg, 0.05 mmol) in THF (2.0 ml) was added 1 M solution of TBAF in THF (0.05 ml, 0.05 mmol) and stirred for 1 h at 0 °C. Solvent was evaporated under reduced pressure, water (3.0 ml) was added to the residue and extracted with CH_2Cl_2 (3 x 8 ml). The combined extract was washed with brine (6.0 ml) and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on a silica gel column using MeOH-CH_2Cl_2 (1:9) as eluent furnished the (-)-bursatellin **9** (11.2 mg, 80%), *Rf* = 0.40 (MeOH:CH_2Cl_2, 1:9). $[\alpha]_D^{25}$ = -8.6 (*c* 0.6, MeOH); IR (neat): ν_{max}/cm^{-1} 3360, 2977, 2240, 1660, 1450, 1377, 1174, 1089; ^1H NMR (400 MHz, CD_3OD): δ 7.90 (s, 1H), 7.23 (d, *J* 8.5 Hz, 2H), 6.82 (d, *J* 8.5 Hz, 2H), 4.80 (d, *J* 3.6 Hz, 1H), 4.07 (t, *J* 6.0 Hz, 2H), 4.01-3.96 (m, 1H), 3.54 (dd, *J* 10.8 and 6.2 Hz, 1H), 3.38 (dd, *J* 10.8 and 6.0 Hz, 1H), 2.80 (t, *J* 6.0 Hz, 2H); ^{13}C NMR (100 MHz, CD_3OD): δ 164.0, 159.0, 136.7, 128.6, 119.0, 115.4, 71.9, 64.2, 62.5, 57.1, 19.0;

***N*-((1*R*,2*R*)-1-((*tert*-butyldimethylsilyl)oxy)-1-(4-(2-cyanoethoxy)phenyl)-3-hydroxypropan-2-yl)-2-(1H-indol-3-yl)-2-oxoacetamide (30):** To a solution of boc-amine **28** (100 mg, 0.2 mmol) in CH_2Cl_2 (10.0 ml) was added $Yb(OTf)_3$ (138 mg, 0.2 mmol) and refluxed for 8 h. Aq. $NaHCO_3$ was added to the reaction mixture and extracted with CH_2Cl_2 (3 x 10 ml). The organic layer was washed with brine and dried over Na_2SO_4. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2, cooled to 0 °C. To the cold solution was added Et_3N (17.0 mg, 0.16 mmol) followed by 3-indoleglyoxalyl chloride **14** (40.0 mg, 0.14 mmol) and stirred magnetically at RT for 12 h. Water (10.0 ml) was added to the reaction mixture and extracted with CH_2Cl_2 (3 x 10 ml). Combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent and purification of the residue on a silica gel column using MeOH:CH_2Cl_2 (1:19) furnished the TBS-protected preoxazinin-7 **30** (73.0 mg, 70%). $[\alpha]_D^{25}$ = -24.0 (*c* 0.9, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3392, 3020, 2930, 2400, 2280, 1635, 1511, 1423, 1215, 1045, 929, 758, 669; ^1H NMR (400 MHz, $CDCl_3$): δ 9.58 (s, 1H), 8.71 (dd, *J* 5.1 and 3.4 Hz, 1H), 8.39 (d, *J* 7.5 Hz, 1H), 7.92 (d, *J* 9.0 Hz, 1H), 7.40-7.20 (m, 5H), 6.73 (d, *J* 8.7 Hz, 2H), 5.00 (d, *J* 3.1 Hz, 1H), 4.15-4.05 (m, 1H), 4.02 (t, *J* 6.2 Hz, 2H), 3.85-3.70 (m, 2H), 2.72 (t, *J* 6.2 Hz, 2H), 0.92 (s, 9H), 0.07 (s, 3H), -0.15 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 180.3, 163.0, 157.0, 138.5, 135.8, 134.7, 127.4, 126.5, 124.1, 123.3, 122.2, 117.4, 114.2, 112.9, 111.9, 72.73, 62.73, 62.36, 58.1, 25.8, 18.6, 18.1, -4.61, -5.25; HRMS (ESI): *m/z* calcd for $C_{28}H_{36}N_3O_5S_i$ (M+H) 522.2424; found 522.2424.

Synthesis of preoxazinin-7 (7): To the solution of **30** (80.0 mg, 0.2 mmol) in THF (5.0 ml) was added TBAF (1.0 M in THF, 0.2 ml, 0.2 mmol). The resulting mixture was stirred for 1 h at 0 °C, before it was concentrated in vacuo. Water (5.0 ml) was added to the residue and extracted with ether (3 x 20 ml). The combined extract was washed with brine (15.0 ml) and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate-petroleum ether (9:1) as eluent furnished the preoxazinin-7 **7** (48.7 mg, 78 %). *Rf* = 0.30 (EtOAc-petroleum ether, 9:1). $[\alpha]_D^{25}$ = -11.0 (*c* 0.6, MeOH); IR (neat): ν_{max}/cm^{-1} 3480, 3340, 3162, 2977, 2270, 1660, 1622, 1450, 1377, 1174, 1089, 929; ^1H NMR (400 MHz, CD_3CN): δ 10.12 (br s , 1H), 8.81 (s, 1H), 8.31 (d, *J* 9.1 Hz, 1H), 7.79 (br s, 1H), 7.54 (d, *J* 9.1 Hz, 1H), 7.30 (dd, *J* 9.1 and 7.3 Hz, 2H), 7.29 (dd, *J* 9.1 and 7.3 Hz, 2H), 6.88 (d, *J* 8.9 Hz, 2H), 5.00 (t, *J* 3.6 Hz, 1H), 4.14 (t, *J* 6.2 Hz, 2H), 4.10-4.00 (m, 1H), 3.86 (d, *J* 4.0 Hz, 1H), 3.70 (dd, *J* 11.4 and 5.6 Hz, 1H), 3.63 (dd, *J* 11.4 and 5.6 Hz, 2H), 2.81 (t, *J* 6.2 Hz, 2H); ^{13}C NMR (100 MHz, CD_3CN): δ 181.8, 163.6, 158.4, 139.9, 137.2, 136.5, 128.5, 127.6, 124.9, 124.0, 122.7, 119.3, 115.3, 113.5, 113.3, 72.5, 64.0, 63.1, 57.8, 19.2, HRMS (ESI): *m/z* calcd for $C_{22}H_{21}N_3O_5Na$ (M+Na) 430.1379; found 430.1382.

3-(4-((*S*)-((3*S*,6*R*)-6-(1H-indol-3-yl)-5-oxomorpholin-3-yl)(*tert*-butyldimethylsilyloxy)methyl)phenoxy)propanenitrile (32a) & 3-(4-((S)-((3S,6S)-6-(1H-indol-3-yl)-5-oxomorpholin-3-yl)(*tert*-butyldimethylsilyloxy)methyl)phenoxy)propanenitrile (32b): To a cold solution (0 °C) of **30** (104.0 mg, 0.2 mmol) in MeOH was added $NaBH_4$ (40.0 mg, 1 mmol) and stirred vigorously at the same temperature for 30 min. Excess MeOH was removed from reaction mixture under reduced pressure. Added water (10.0 ml), extracted with ethyl acetate (3 x 8 ml), washed with brine (10.0 ml) and dried over Na_2SO_4 and concentrated. To the crude alcohol was added acetonitrile (50.0 ml), catalytic (10.0 mg) pyridine para-toluene sulfonate (PPTS) and refluxed for 1 h. The reaction mixture was quenched with aq. $NaHCO_3$ (20.0 ml), extracted with ethyl acetate (3 x 8 ml), washed with brine and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue using preparative thin layer chromatography furnished the diastereomers **32a** (23.0 mg) and **32b** (58.0 mg) (yield 78% for two steps).

TBS-protected oxazinin-5 (32a): $[\alpha]_D^{25}$ = +19.1 (*c* 2.0 $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3396, 3269, 2928, 2856, 1668(C=O), 1612, 1512, 1462, 1238, 1105, 858, 839, 780, 744, 618; ^1H NMR ($CDCl_3$, 400 MHz): δ 8.35 (br s, 1H), 7.68 (d, *J* 7.8 Hz, 1H), 7.35-7.00 (m, 6H), 6.89 (d, *J* 8.6 Hz, 1H), 6.55 (br s, 1H), 5.51 (s, 1H), 4.63 (d, *J* 8.3 Hz, 1H), 4.18 (t, *J* 6.3 Hz, 2H), 3.70-3.55 (m,

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2H), 3.41 (dd, *J* 11.5 and 5.0 Hz, 1H), 2.83 (t, *J* 6.3 Hz, 2H), 1.64 (br s, 1H), 0.91 (s, 9H), 0.10 (s, 3H), -0.19 (s, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.4, 157.8, 136.4, 133.7, 128.2, 126.1, 124.6, 122.4, 120.0, 119.5, 117.1, 114.7, 111.3, 76.2, 73.8, 62.6, 61.5, 58.6, 25.8, 18.6, 18.1, -4.5, -5.0; HRMS (ESI): *m/z* calcd for $C_{28}H_{36}N_3O_4Si$ (M+H) 506.2475; found 506.2486.

Synthesis of TBS-protected oxazinin-6 (32b): $[\alpha]_D^{25}$ = -28.4 (*c* 4.5, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3398, 2927, 2856, 1668 (C=O), 1611, 1511, 1459, 1248, 1097, 859, 838, 779, 743, 617**;** ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.65 (br s, 1H), 7.71 (d, *J* 7.6 Hz, 1H), 7.35-7.00 (m, 6H), 6.81 (d, *J* 8.6 Hz, 2H), 6.62 (s, 1H), 5.51 (s, 1H), 4.61 (d, *J* 8.5 Hz, 1H), 4.12 (t, *J* 6.1 Hz, 2H), 3.70-3.50 (m, 2H), 3.50-3.40 (m, 1H), 2.79 (t, *J* 6.1 Hz, 2H), 0.90 (s, 9H), 0.09 (s, 3H), -0.21 (s, 3H).^{13}C NMR ($CDCl_3$, 125 MHz): δ 169.7, 157.7, 136.5, 133.5, 128.2, 126.2, 124.9, 122.3, 119.9, 119.4, 117.1, 114.6, 111.5, 110.9, 76.1, 73.8, 62.5, 61.1, 58.6, 25.8, 18.6, 18.1, -4.5, -5.0; HRMS (ESI): *m/z* calcd for $C_{28}H_{36}N_3O_4Si$(M+H) 506.2475; found 506.2463.

Oxazinin-5 (5) and (2*R*,5*S*)-5-((*S*)-hydroxy(4-hydroxyphenyl)methyl)-2-(1H-indol-3-yl)morpholin-3-one (33a): To an ice cold (0 °C) solution of the compound **32a** (22.0 mg, 0.043 mmol) in anhydrous THF (2.0 ml) was added dropwise 1 M solution of TBAF in THF (0.08 ml, 0.08 mmol) and stirred magnetically for 1 h. The reaction mixture was quenched with aq. $NaHCO_3$ (5.0 ml), extracted with ethyl acetate (5 ml x 3), washed with brine and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue using preparative TLC furnished oxazinin-5 **5** (11.0 mg, 65%) and the diol **33a** (2.5 mg, 15%). $[\alpha]_D^{25}$ = + 6.9 (*c* 0.4, MeOH); IR (neat): ν_{max}/cm^{-1} 3360, 3302, 2924, 2853, 2257, 1660, 1609, 1513, 1456, 1306, 1240, 1177, 1106, 1049, 838, 749, 618; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.29 (br s, 1H), 7.58 (d, *J* 8.1 Hz, 1H), 7.40 (d, *J* 8.3 Hz, 1H), 7.34 (d, *J* 8.5 Hz, 2H), 7.27 (d, *J* 2.7 Hz, 1H), 7.15 (dd, *J* 8.1 and 7.1 Hz, 1H), 7.05 (dd, *J* 8.1 and 7.1 Hz, 1H), 6.96 (d, *J* 8.8 Hz, 1H), 5.29 (s, 1H), 4.58 (dd, *J* 8.1 and 4.2 Hz, 1H), 4.19 (t, *J* 6.1 Hz, 2H), 3.86 (d, *J* 4.1 Hz, 1H), 3.85-3.70 (m, 1H), 3.59 (dd, *J* 12.0 and 3.9 Hz, 1H), 3.50 (dd, *J* 12.0 and 7.6 Hz, 1H), 2.85 (t, *J* 6.1 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.2, 158.0, 136.5, 134.1, 128.1, 126.1, 125.3, 121.8, 119.4, 118.2, 114.6, 112.0, 111.5, 73.9, 73.6, 63.1, 63.0, 57.5, 18.1; HRMS (ESI): *m/z* calcd for $C_{22}H_{21}N_3O_4Na$ (M+Na) 414.1430; found 414.1418.

(2*R*,5*S*)-5-((*S*)-hydroxy(4-hydroxyphenyl)methyl)-2-(1H-indol-3-yl)morpholin-3-one (33a): $[\alpha]_D^{25}$ = +5.3 (*c* 0.6, MeOH); IR (neat): ν_{max}/cm^{-1} 3362, 3169, 2923, 2853, 1653, 1612, 1463, 1186, 1108, 967, 838, 745, 618; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.30 (br s, 1H), 7.58 (d, *J* 8.0 Hz, 1H), 7.39 (d, *J* 8.0 Hz, 1H), 7.25 (s, 1H), 7.20 (d, *J* 7.3 Hz, 2H), 7.18-7.00 (m, 3H), 6.85-6.75 (m, 2H), 5.28 (s, 1H), 4.49 (dd, *J* 8.1 and 3.9 Hz, 1H), 3.85-3.75 (m, 2H), 3.56 (dd, *J* 12.0 and 3.9 Hz, 1H), 3.47 (dd, *J* 11.7 and 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 169.3, 156.9, 136.4, 132.2, 128.0 (2C), 126.2, 125.3, 121.8, 119.4 (2C), 115.2 (2C), 111.9, 74.1, 73.6, 63.2, 57.6; HRMS (ESI): *m/z* calcd for $C_{19}H_{18}N_2O_4Na$ (M+Na) 361.1164; found 361.1181.

Oxazinin-6 (6) and (2*S*,5*S*)-5-((*S*)-hydroxy(4-hydroxyphenyl)methyl)-2-(1H-indol-3-yl)morpholin-3-one (33b): To an ice cold (0 °C) solution of the compound **32b** (20.0 mg, 0.04 mmol) in anhydrous THF (2.0 ml) was added dropwise 1 M solution of TBAF in THF (0.08 ml, 0.08 mmol) and stirred magnetically for 1 h. The reaction mixture was quenched with aq. $NaHCO_3$ (5.0 ml), extracted with ethyl acetate (5 ml x 3), washed with brine and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue using preparative TLC furnished oxazinin-6 **6** (9.3 mg, 60%) and the diol **33b** (3.7 mg, 24%). $[\alpha]_D^{25}$ = +9.0 (*c* 0.5, MeOH); IR (neat): ν_{max}/cm^{-1} 3360 (OH), 3163, 2924, 2857, 2256 (CN), 1661 (C=O), 1618, 1513, 1456, 1306, 1241, 1177, 1107, 1051, 838, 749, 618; ^{1}H NMR (CD_3CN, 400 MHz): δ 9.37 (br s, 1H), 7.62 (d, *J* 7.8 Hz, 1H), 7.43 (d, *J* 8.0 Hz, 1H), 7.35-7.26 (m, 2H), 7.25-7.20 (m, 1H), 7.18-7.14 (m, 1H), 7.09-7.05 (m, 1H), 6.92 (d, *J* 8.3 Hz, 2H), 6.86 (br s, 1H), 5.38 (s, 1H), 4.71 (dd, *J* 7.8 and 3.9 Hz, 1H), 4.17 (t, *J* 6.1 Hz, 2H), 3.91 (d, *J* 3.9 Hz, 1H), 3.68-3.52 (m, 3H), 2.84 (t, *J* 6.1 Hz, 2H); ^{13}C NMR (CD_3CN, 100 MHz): δ 170.1, 158.8, 137.3, 135.4, 129.3, 127.3, 126.3, 122.7, 120.6, 120.2, 119.2, 115.6, 112.7, 112.5, 75.3, 74.5, 64.2, 62.7, 58.2, 19.0.

(2*S*,5*S*)-5-((*S*)-hydroxy(4-hydroxyphenyl)methyl)-2-(1H-indol-3-yl)morpholin-3-one (33b): $[\alpha]_D^{25}$ = +7.0 (*c* 0.6, MeOH); IR (neat): ν_{max}/cm^{-1} 3360 (OH), 2923, 2853, 1652 (C=O), 1613, 1457, 1182, 1108, 966, 838, 745, 618; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 9.38 (br s, 1H), 7.63 (d, *J* 7.6 Hz, 1H), 7.43 (d, *J* 8.1 Hz, 1H), 7.30-7.00 (m, 6H), 6.87 (br s, 1H), 6.85-9.70 (m, 2H), 5.38 (s, 1H), 4.70-4.60 (m, 1H),3.83 (br s, 1H), 3.65-3.50 (m, 3H).^{13}C NMR ($CDCl_3$, 100 MHz): δ 170.2, 157.8, 137.5, 133.4, 129.2, 127.5, 126.4, 122.9, 120.5, 120.4, 116.2, 112.7, 112.6, 75.6, 74.5, 62.8, 58.6; HRMS (ESI): *m/z* calcd for $C_{19}H_{18}N_2O_4Na$ (M+Na) 361.1164; found 361.1158.

(2*S*,3*R*)-ethyl 2-(2-(1H-indol-3-yl)-2-oxoacetamido)-3-(*tert*-butyldimethylsilyloxy)-3-(4-(2-cyanoethoxy)phenyl)propaneate (34): To a solution of boc-amine **13** (100 mg, 0.2 mmol) in CH_2Cl_2 (10.0 ml) was added $Yb(OTf)_3$ (138 mg, 0.2 mmol) and refluxed for 8 h. aq. $NaHCO_3$ was added to the reaction mixture and extracted with CH_2Cl_2 (3 x 10 ml). The organic layer was washed with brine and dried over Na_2SO_4. After evaporation of the solvent, the residue was dissolved in CH_2Cl_2, cooled to 0 °C. To the cold solution was added Et_3N (17.0 mg, 0.16 mmol) followed by 3-indoleglyoxalyl chloride **14** (40.0 mg, 0.14 mmol) and stirred magnetically at RT for 12 h. Water (10.0 ml) was added to the reaction mixture and extracted with CH_2Cl_2 (3 x 10 ml). Combined organic layers were washed with brine and dried over anhydrous Na_2SO_4. Evaporation of the solvent and purification of the residue on a silica gel column using (EtOAc-petroleum ether, 1:1) furnished the TBS-protected compound **34** (114 mg, 80%). $[\alpha]_D^{25}$ = -50.0 (*c* 1.5, $CHCl_3$); IR (neat): ν_{max}/cm^{-1} 3393, 3313, 3060, 2954, 2929, 2856, 2255, 1738, 1686, 1511, 1472, 1340, 1052, 939, 780, 651; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.43 (s, 1H), 8.54 (d, *J* 3.4 Hz, 1H), 8.11 (d, *J* 8.1 Hz, 1H), 7.34 (d, *J* 7.9 Hz, 1H), 7.31-7.24 (m, 4H), 6.74 (d, *J* 8.8 Hz, 2H), 5.39 (d, *J* 2.0 Hz, 1H), 4.69 (dd, *J* 9.8 and 2.1 Hz, 1H), 4.31-4.17 (m, 2 H), 4.07-4.00 (m, 2H), 2.73 (t, *J* 6.1 Hz, 2H), 0.91 (s, 9H), 0.02 (s, 3H), -0.15 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 179.9, 169.5, 162.3, 157.2, 138.2, 135.8, 133.7, 127.5, 126.4, 124.0,

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123.2, 122.2, 117.5; 114.2, 112.9, 11.8, 74.3, 62.4, 61.9, 59.4, 29.7, 25.7, 18.6, 18.0, 14.1, -4.6, -5.5; HRMS (ESI): *m/z* calcd for $C_{30}H_{37}N_3O_6S_iNa$ (M+Na) 586.2349; found 586.2345.

(2*S*,3*R*)-ethyl 2-(2-(1H-indol-3-yl)-2-oxoacetamido)-3-(4-(2-cyanoethoxy)phenyl)-3-hydroxypropanoate (35): To the solution of **34** (80.0 mg, 0.14 mmol) in THF (5.0 ml) was added TBAF (1.0 M in THF, 0.20 ml, 0.2 mmol). The resulting mixture was stirred for 1 h at 0 °C, before it was concentrated in vacuo. Water (5.0 ml) was added to the residue and extracted with ether (3 x 20 ml). The combined extract was washed with brine (15.0 ml) and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate-petroleum ether (7:3) as eluent furnished the **35** (49.7 mg, 78 %). *Rf* = 0.40 (EtOAc-petroleum ether, 7:3). $[\alpha]_D^{25}$ = -59.0 (*c* 0.25, MeOH); IR (neat): ν_{max}/cm^{-1} 3377, 2926, 2854, 2255, 1736, 1680, 1632, 1458, 1371, 1157, 1050, 751; ^{1}H NMR (500 MHz, CD_3CN): δ 10.14 (s, 1H), 8.68 (d, *J* 3.4 Hz, 1H), 8.27-8.25 (m, 1H), 7.95 (d, *J* 8.8 Hz, 1H), 7.52-7.49 (m, 1H), 7.32-7.26 (m, 4H), 6.85-6.83 (m, 2H), 5.27 (s, 1H), 4.67 (dd, *J* 9.1 and 3.4 Hz, 1H), 4.20-4.08 (m, 5H), 2.78 (t, *J* 6.0 Hz, 2H), 1.21 (t, *J* 7.1 Hz, 3H); ^{13}C NMR (125 MHz, CD_3CN): δ 181.6, 171.0, 163.7, 159.0, 140.2, 137.5, 135.1, 128.8, 127.8, 125.3, 124.4, 123.1, 119.6, 115.6, 113.7, 73.6, 64.3, 62.8, 59.9, 19.5, 14.8; HRMS (ESI): *m/z* calcd for $C_{24}H_{23}N_3O_6Na$ (M+Na) 472.1485; found 472.1489;

Synthesis of oxazinin 1 and 4: To a cold solution (0 °C) of **35** (110 mg, 0.25 mmol) in MeOH was added $NaBH_4$ (80.0 mg, 2 mmol) and stirred vigorously at the same temperature for 30 min. Excess MeOH was removed from reaction mixture under reduced pressure. Added water (10.0 ml), extracted with ethyl acetate (3 x 8 ml), washed with brine (10.0 ml) and dried over Na_2SO_4 and concentrated. To the crude alcohol was added acetonitrile (50.0 ml), catalytic (15.0 mg) pyridine para-toluene sulfonate (PPTS) and refluxed for 1 h. The reaction mixture was quenched with aq. $NaHCO_3$ (20.0 ml), extracted with ethyl acetate (3 x 8 ml), washed with brine and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue using preparative thin layer chromatography furnished the diastereomers **1** (23 mg) and **4** (57 mg) (yield 60% for two steps).

Oxazinin-1 (1): $[\alpha]_D^{25}$ = +28.6 (*c* 0.28 MeOH); IR (neat): ν_{max}/cm^{-1} 3421, 2923, 2852, 2253(CN), 1660(C=O), 1614, 1540, 1514, 1458, 1384, 1177, 1050, 830, 839, 780, 746; ^{1}H NMR (CD_3CN, 500 MHz): δ 9.39 (br s, 1H), 7.59 (d, *J* 7.9 Hz, 1H), 7.43 (d, *J* 7.9 Hz, 1H), 7.30 (d, *J* 2.1 Hz, 1H) 7.21 (d, *J* 8.8 Hz, 2H), 7.14 (t, *J* 7.3, 1H), 7.00 (t, *J* 7.3 Hz, 1H), 6.88 (d, *J* 8.8 Hz, 2H), 6.69 (s, 1H), 5.59 (s, 1H), 4.62 (d, *J* 8.3 Hz, 1H), 4.15 (t, *J* 6.1 Hz, 2H), 3.74-3.71 (m, 1H), 3.41 (dd, *J* 11.3 and 3.0 Hz, 1H), 3.28 (dd *J* 11.3 and 5.8 Hz, 1H), 2.82 (t, *J* 6.1 Hz, 2H); ^{13}C NMR (CD_3CN, 125 MHz): δ 170.2, 159.0, 137.4, 131.8, 130.0, 127.5, 126.1, 122.8, 120.4, 120.0, 119.1, 115.4, 112.4, 112.3, 72.9, 71.0, 63.9, 61.9, 59.9, 19.0; HRMS (ESI): *m/z* calcd for $C_{22}H_{21}N_3O_4Na$ (M+Na) 414.1430 found 414.1439.

Oxazinin-4 (4): $[\alpha]_D^{25}$ = +34.0 (*c* 1.0 MeOH); IR (neat): ν_{max}/cm^{-1} 3410, 2921, 2850, 2253(CN), 1736, 1661(C=O), 1613, 1513, 1462, 1238, 1353, 1177, 1045, 831, 746; ^{1}H NMR (CD_3CN, 500 MHz): δ 9.28 (br s, 1H), 7.68 (d, *J* 7.2 Hz, 1H), 7.41 (d *J* 8.0 Hz, 2 H), 7.36 (d, *J* 8.5 Hz, 2H), 7.32 (d, *J* 2.6 Hz, 1H), 7.15 (t, *J* 7.1 Hz, 1H), 7.07 (t, *J* 8.0 Hz, 1H), 6.93 (, *J* 6.3 Hz, 2H), 6.68 (s, 1H), 5.43 (s, 1H), 4.74 (d, *J* 9.7 Hz, 1H), 4.16 (t, *J* 6.3 Hz, 2H), 3.89-3.86 (m, 1H), 3.43 (dd, *J* 11.4 and 2.6 Hz, 1H), 3.31 (dd, *J* 10.8 and 6.1 Hz, 1H), 3.10 (br s, 1H), 2.82 (t, *J* 6.0 Hz, 2H); ^{13}C NMR (CD_3CN, 125 MHz): δ 170.8, 158.3, 137.6, 132.1, 129.9, 127.1, 126.4, 122.9, 120.6, 120.5, 119.3, 115.7, 113.4, 112.6, 78.0, 75.7, 64.1, 62.0, 60.8, 19.2; HRMS (ESI): *m/z* calcd for $C_{22}H_{21}N_3O_4Na$ (M+Na) 414.1430; found 414.1439

Oxazinin-2 (2): To the solution of **1** (35.0 mg, 0.1 mmol) in THF (2.0 ml) was added 1N NaOH solution (1.0 N in H_2O, 0.4 ml, 0.4 mmol). The resulting mixture was stirred for 1 h at RT, before it was quenched with 1N HCl. Water (5.0 ml) was added to the residue and extracted with ethyl acetate (3 x 20 ml). The combined extract was washed with brine (15.0 ml) and dried over Na_2SO_4. Evaporation of the solvent and purification of the residue on a silica gel column using ethyl acetate-petroleum ether (9:1) as eluent furnished the **2** (22 mg, 80 %). $[\alpha]_D^{25}$ = +6.0 (*c* 0.1, MeOH); IR (neat): ν_{max}/cm^{-1} 3318, 2923, 1651, 1613, 1515, 1456, 1377, 1172, 1086, 1057, 976, 754; ^{1}H NMR (CD_3CN, 500 MHz): δ 9.37 (br s, 1H), 7.59 (d, *J* 7.7 Hz, 1H), 7.43 (d *J* 8.3 Hz, 2 H), 7.29 (d, *J* 2.6 Hz, 1H), 7.16 (t, *J* 7.1 Hz, 1H), 7.09 (d, *J* 8.5 Hz, 2H), 7.00 (, *J* 6.8 Hz, 1H), 6.74(d, J 8.5 Hz, 2H), 6.63 (s, 1H), 5.57 (s, 1H) 4.57 (d, *J* 9.2 Hz, 1H), 3.73-3.69 (m, 1H), 3.44 (dd, *J* 11.4 and 2.6 Hz, 1H), 3.26 (br s, 1H), 3.03 (br s, 1H); ^{13}C NMR (125 MHz, CD_3CN): δ 170.2, 158.0, 137.4, 130.0, 129.9, 127.5, 126.1, 122.8, 120.3, 120.1, 116.0, 112.4, 112.4, 72.9, 71.2, 62.1, 59.9; HRMS (ESI): *m/z* calcd for $C_{19}H_{19}N_2O_4$ (M+H) 339.1345; found 339.1343.

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Notes and references

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