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Asymmetric first total syntheses and assignment of absolute configuration of oxazinin-5, oxazinin-6 and preoxazinin-7†‡

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Asymmetric first total syntheses of the unprecedented toxins oxazinin-5, oxazinin-6 and preoxazinin-7 have been achieved from a common key intermediate 18, derived from a regiocontrolled Sharpless asymmetric aminohydroxylation and oxa-Michael reaction, which in addition to confirming the structure also established the absolute configuration of the natural products. On the way an expeditious synthesis of a metabolite bursatellin was completed in 8 steps.

Oxazinins are a new and intriguing class of cytotoxic compounds which are hazardous to human health and can cause serious loss to shellfish industries.[1] Fattorusso and Ciminiello *et al.* reported the isolation and the structural elucidation of the unprecedented toxins oxazinin-1 (**1**), -2 (**2**) -3 (**3**) and -4 (**4**) (Fig. 1) from the digestive glands of *Mytilus galioprovincialis*,[2,3] marine toxins from edible mussels of the North Adriatic Sea. The absolute stereochemistry of both oxazinin-1 (**1**) and -2 (**2**) was assigned by applying the Riguera's method[4] by the same group.[5] Subsequently in 2007 they reported structures and relative stereochemistries of two more oxazinins (oxazinin-5 (**5**) and -6 (**6**)) and a related linear precursor preoxazinin-7 (**7**)[6] (Fig. 1). Determination of the structure and the relative stereochemistry of all oxazinins was based on spectroscopic evidence including extensive 2D NMR and Molecular Mechanics (MM) calculations. In 1980 a structurally similar metabolite bursatellin **8**[7] whose structure was later revised in 1987[8] was isolated from sea hare *Bursatella leachii pleii*. Structurally bursatellin **8** resembles preoxazinin-7 (**7**) except that the indole glyoxylic amide moiety in preoxazinin is replaced by simple formamide functionality. Oxazinin-l (**1**) was shown to inhibit the growth of WEHI 164 and 1774 cell lines *in vitro*.[2] Preliminary toxicological studies performed on oxazinins bring to light that their cytotoxicities are due to the –CN functionality.[2]

Oxazinins contain three structural units: an indole, a central morpholinone ring containing two or three substituents, and a substituted phenol ring. Scarce availability of the oxazinin compounds limits the evaluation of the extent of threat posed to human health. Synthetic approaches therefore are crucial to obtain a quantity of the pure compounds that is sufficient for comprehensive toxicological studies, indeed synthetic efforts from Couladouros *et al.* culminated in the synthesis of a simple member of this family oxazinin-3 (**3**).[9] Subsequently Baran *et al.* also reported an expedient synthesis of oxazinin-3 (**3**) using the direct coupling of indole to carbonyl compound in 4 steps from a known compound.[10] In 1990 Sodano *et al.* reported the semi-synthesis of bursatellin **8** from chloramphenicol,[11] and later in 1995 Hiroshi IRIE *et al.* reported the total synthesis of bursatellin **8** in 16 steps starting from L-tryptophan,[12] but so far there are no reports in the literature on the synthesis of any other oxazinins. Herein we report expedient and efficient asymmetric first total syntheses of preoxazinin-7 (**7**), oxazinin-5 (**5**) and -6 (**6**) using Sharpless asymmetric aminohydroxylation, oxa-Michael reaction and the intramolecular cyclisation of hydroxyl to form the central morpholine ring as key steps. The key retrosynthetic disconnection of our strategy involves the C(2)–O(1) bond. It was based on the hypothesis that the central morpholinone ring of the oxazinins might be formed through intramolecular diastereoselective addition of an appropriate hydroxyl substituent to a 3-methyleneindolenine (**9**, Scheme 1), which in turn could be generated *in situ* from 3-hydroxymethylindoles **10a,b**. Finally, further disconnection at the amide bond revealed 3-indoleglyoxylic acid chloride **11** and tyrosine derivative **12** as appropriate building blocks. Compound **12** could be obtained from **13**, which in turn could be obtained from *p*-hydroxybenzaldehyde **14** by HWE

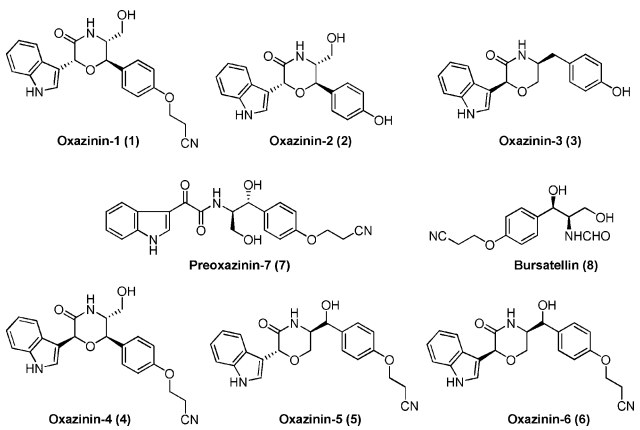

Fig. 1 Structures of oxazinin-1, -2, -3, -4, -5, -6, preoxazinin-7 and bursatellin.

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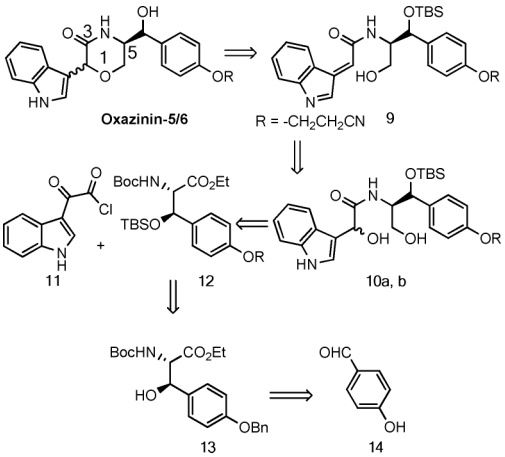
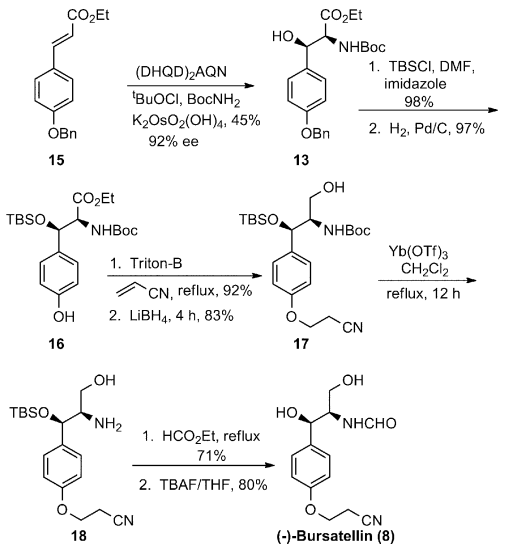
† Dedicated to Prof. S. Chandrasekaran, Indian Institute of Science, Bangalore, on the occasion of his 65th birthday.

‡ Electronic supplementary information (ESI) available: Experimental procedures and copies of ^{1}H NMR, ^{13}C NMR and DEPT spectra of all new compounds. See DOI: 10.1039/c1ob06320k



Scheme 1 Retrosynthetic analysis.

reaction followed by asymmetric aminohydroxylation. An expedient route to building block **12** took advantage of the Sharpless asymmetric aminohydroxylation reaction, as shown in Scheme 2.

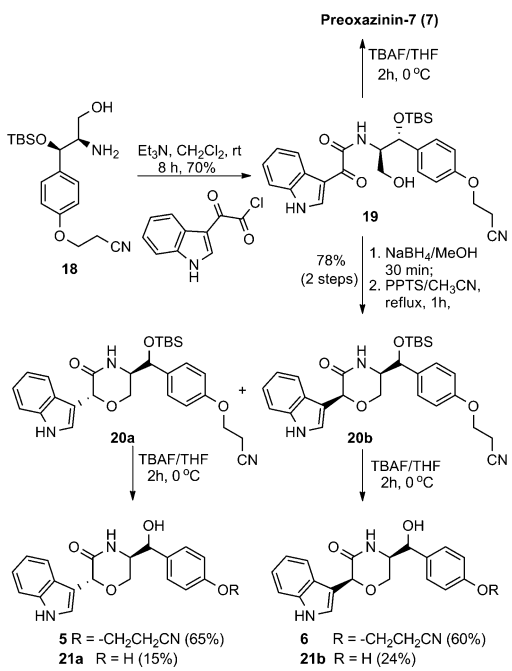


Scheme 2 Completion of the synthesis of (–)-bursatellin.

The required starting material for this reaction, the cinnamate **15**, was obtained from *p*-hydroxybenzaldehyde **14** by benzylation using K_2CO_3, BnBr and a catalytic amount of TBAI (98% yield), followed by reaction with $PPh_3{=}CHCO_2Et$ (95% yield). Substrate **15** was used in the Sharpless asymmetric aminohydroxylation reaction[13] [NaOH, $BocNH_2$, ^{t}BuOCl, $(DHQD)_2AQN$, $K_2OsO_2(OH)_4$, *n*PrOH–H_2O (1 : 1)], affording directly amino alcohol **13** in its Boc-protected form in 45% yield and 92% ee (chiral HPLC). The hydroxy group in **13** was then protected as its TBS ether (TBSCl, imidazole, 98% yield), followed by hydrogenolysis [H_2, 5% Pd/C, 97% yield] to afford Boc-protected amino phenol **16**.

Attempts at cyanoethylation of the phenolic hydroxyl group in the aminophenol **16** with acrylonitrile using several kinds of bases such as $NaHCO_3$, $KHCO_3$, K_2CO_3 and NaH were unsuccessful as a result of the retro-Michael fragmentation reaction, as mentioned by the two independent groups of G. Sodano *et al.* and Hiroshi IRIE *et al.* in their syntheses of bursatellin.[11,12] Ph_3P/acrylonitrile[14] under various reaction conditions also failed to give the expected product. Finally to our delight the oxa-Michael reaction of aminophenol **16** with acrylonitrile using a catalytic amount of Triton-B under reflux conditions gave the desired cyanoethylation product **12** in 92% yield. The ester group in **12** was then reduced using lithium borohydride to afford primary alcohol **17**. Routine and simple Boc-deprotection proved to be more complex and led to multiple products and decomposition under various conditions such as TFA–CH_2Cl_2,[15a] TFA–triethylsilane,[15b] 4*M* HCl in dioxane,[15c] CAN,[15d] TMSOTf,[15e] and 10% H_2SO_4[15f] and TMSI.[15g] Interestingly treatment of **17** with a stoichiometric amount of $Yb(OTf)_3$ under CH_2Cl_2 reflux conditions generated Boc-deprotected amine **18**, which upon *N*-formylation with ethyl formate followed by removal of the TBS group using TBAF gave bursatellin **8** in 80% yield as a mixture of rotamers due to restricted rotation around the *N*-formyl bond. Its spectroscopic properties (^{1}H, ^{13}C, mass) and $[\alpha]_D^{25}$ value ($[\alpha]_D^{25}$ –8.6° (*c* = 0.6, MeOH) were in good agreement with that of the natural (–)-bursatellin ($[\alpha]_D^{25}$ –8.8° (*c* = 2.4, MeOH), indicating the accomplishment of the synthesis of **8** starting from *p*-hydroxybenzaldehyde.

Alternatively coupling of compound **18** with indole glyoxylic chloride using Et_3N generated the TBS-protected preoxazinin-7 (**19**) in 70% yield (Scheme 3). Deprotection of TBS group generated preoxazinin-7 (**7**) in 78% yield, identical in all respects (CD, IR, Mass, ^{1}H, ^{13}C) to natural preoxazinin-7.[6] For the synthesis of oxazinin-5 (**5**) and -6 (**6**), reduction of the ketone functionality of the 3-indoleglyoxylic amide **19** by employing $NaBH_4$ afforded the diastereomeric mixture of diols **10a,b** that upon subsequent treatment with PPTS in refluxing acetonitrile furnished morpholinones **20a,b** as a 3 : 1 mixture of C-2 diastereomers. The two diastereomers **20a** and **20b** were separated by preparative TLC. Finally individual TBS-deprotection of major **20a** and minor **20b** isomers provided oxazinin-5 (**5**) and -6 (**6**) respectively along with minor amount of cyanoethyl side chain



Scheme 3 Synthesis of preoxazinin-7, oxazinin-5 and -6.

cleaved compounds **21a** and **21b**. The synthetic oxazinin-5 (**5**) and -6 (**6**) exhibited IR, ^{1}H and ^{13}C NMR, and mass spectra, as well as the sign of the CD curves, identical with those of the natural oxazinins-5 and -6,[6] thus confirming the stereostructure of the natural products as well as establishing their absolute configuration.

In conclusion, concise total syntheses of preoxazinin-7 (**7**), oxazinin-5 (**5**), oxazinin-6 (**6**) and bursatellin **8** were achieved. Our synthetic route features four highlights: (1) application of a key intermediate for syntheses of four natural products; (2) application of Sharpless asymmetric aminohydroxylation; (3) oxa-Michael reaction for introduction of cyanoethyl side chain; (4) intramolecular diastereoselective addition of an appropriate hydroxyl substituent to a 3-methyleneindolenine for the construction of morpholine ring. The application of this route paves the way for the total syntheses of other oxazinins and related natural products which are underway in our laboratory and will be reported in due course.

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