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Synthetic studies towards oxazinins. An expedient first total synthesis and proof of the absolute stereochemistry of oxazinin-3

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Abstract—A synthetic strategy, based on intramolecular addition of an appropriate hydroxyl substituent to a 3-methyleneindolenine, towards the naturally occurring marine toxins oxazinin-1, -2 and -3 is presented. The expedient first total synthesis of oxazinin-3, thus accomplished, demonstrated the efficiency of the approach and established the absolute stereochemistry of oxazinin-3 as 2*S*,5*S*.

Notwithstanding the serious threat that harmful algal blooms (red tides) pose to both human health and coastal economic activities, they constitute a rich source of novel bioactive natural products of which brevetoxins, saxitoxin, domoic and ocadaic acid are just a few illustrative examples.[1] Oxazinin-1, -2 and -3 (**1**, **2** and **3**, respectively, Fig. 1), isolated from edible mussels from the North Adriatic Sea during such an incident, are but a recent addition to the list.[2,3] A central morpholinone ring containing two or three substituents, including an indole and a phenol ring, dominates their structure. This structural motif, while being reminiscent of the well-known pharmacophoric structure of morpholine, is unprecedented in natural products and can be viewed as a promising scaffold for new bioactive molecule prospecting through combinatorial chemistry.[4] This possibility prompted us to develop and report herein an expedient and efficient synthetic strategy towards this class of compounds exemplified by the first total synthesis of oxazinin-3.

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 oxazinines might be formed through intramolecular diastereoselective addition of an appropriate hydroxyl substituent to a 3-methyleneindolenine (**4a** or **4b**, Fig. 1). However, since 3-methyleneindolenines are reactive species, postulated as intermediates either in the oxidation of 3-alkyl-indoles[5] or the reduction of 3-hydroxymethylindoles,[6] diols **5a** and **5b** were designed as convenient progenitors. Finally, further disconnection at the amide bond revealed 3-indoleglyoxylic acid **6**[7] and tyrosine derivatives **7a**[8] and **7b** as appropriate building blocks.

The diol **5b** required to test our hypothesis was easily obtained upon coupling of 3-indoleglyoxylic acid **6** with tyrosine methyl ester **7b** and subsequent concomitant reduction of the keto and ester functionalities of **8** (Scheme 1). Both diastereomers of diol **5b** upon treatment with PPTS in refluxing acetonitrile furnished morpholinone **3**, as a 1:1 mixture of diastereomers. The two isomers were easily separated by flash column chromatography (8:2 CH_2Cl_2:acetone, silica gel). One of them had an identical ^1H NMR spectrum to that reported for oxazinin-3 **3** and was thus assigned as the *cis*-isomer. The undesired diastereomer could be equilibrated with the desired one upon exposure to the

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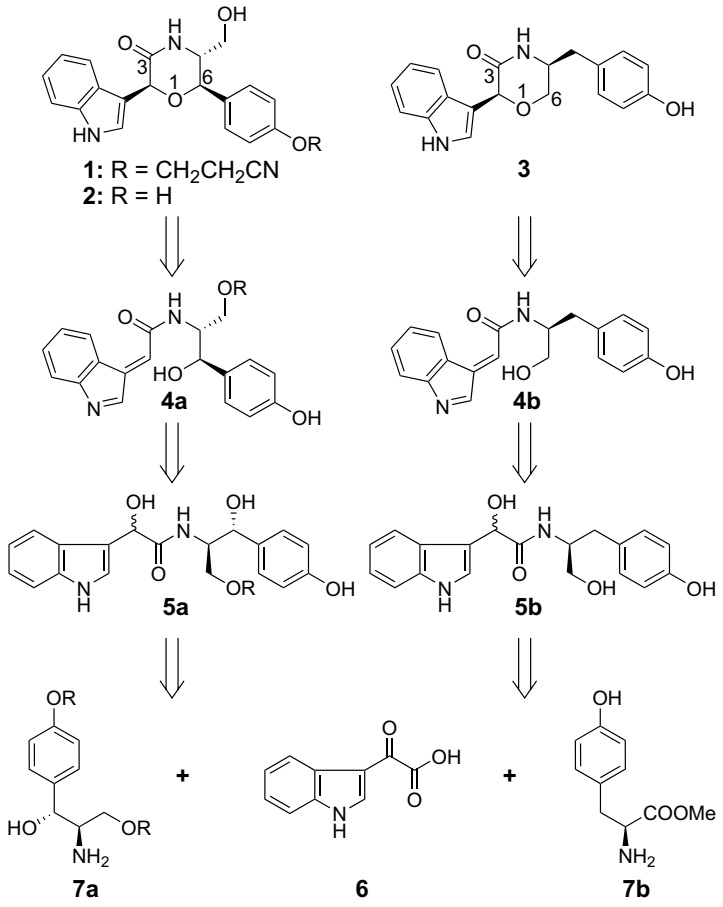
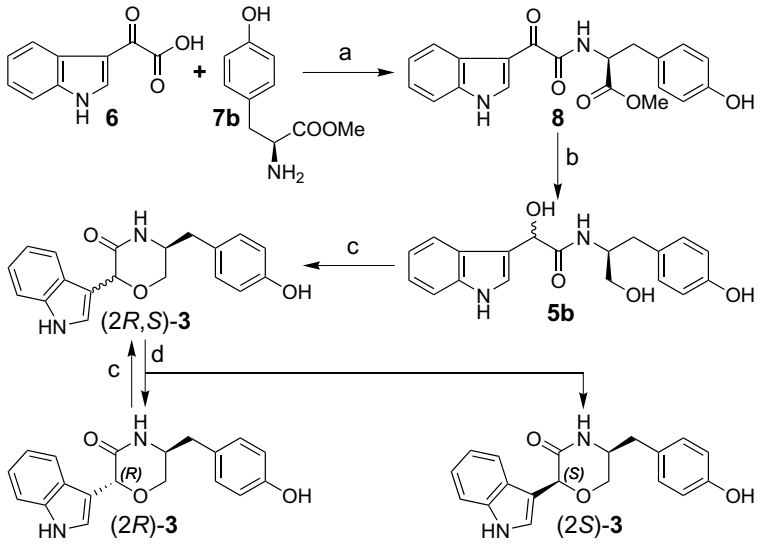


Figure 1. Synthetic strategy towards oxazinin-1 **1**, -2 **2** and -3 **3**.



Scheme 1. Preparation of oxazinin-3. Reagents and conditions: (a) EDC, HOBt, *N*,*N*-diisopropylethylamine, CH_2Cl_2:DMF 20:1, 0 °C→2 h, rt→22 h, 95%; (b) $LiBH_4$, MeOH:Et_2O 1:2, rt, 12 h 96%; (c) PPTS, CH_3CN, reflux, 1 h, 67%; (d) flash column chromatography (8:2 CH_2Cl_2:acetone, silica gel).

reaction conditions of its formation. Thus, after two cycles, oxazinin-3 could be obtained in three steps and 61% overall chemical yield.

At this point it should be noted that, although the absolute stereochemistry of oxazinin-1 has been unambiguously assigned,[3] the same was not possible in the case of oxazinin-3 due to the very small amount of material isolated.[2] Thus, the above synthesis established, by comparison of the specific optical rotations of synthetic and natural material, the absolute stereochemistry of oxazinin-3 as 2*S*,5*S*.[9]

The observed lack of diastereoselectivity of the anulation reaction may be attributed to the low stereochemical demand of the primary hydroxyl involved and the distant 1,4-arrangement of the ring substituents. Whether addition of a more sterically demanding secondary hydroxyl to 3-methyleneindolenine **4a** in conjunction with a more intimate substituent arrangement around the morpholinone ring of oxazinin-1 and -2 would lead to higher diastereoselectivity remains to be investigated. In this context, preparation of oxazinin-1 and -2 as well as of a library of related analogues is underway.

Acknowledgements

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9. Selected spectroscopic data:
   Compound **8**: $[\alpha]_D^{25}$ −18 (*c* = 0.65 in MeOH). ^{1}H NMR (250 MHz, acetone-d_6): δ 11.32 (br s, 1H), 8.99 (s, 1H), 8.52–8.09 (m, 2H), 7.57 (m, 1H), 7.29 (m, 2H), 7.12 (d, *J* = 8.4 Hz, 2H), 6.80 (d, *J* = 8.4 Hz, 2H), 4.95–4.75 (m, 1H), 3.72 (s, 3H), 3.30–3.10 (m, 2H). ^{13}C NMR (62.5 MHz, acetone-d_6) δ: 182.0, 173.1, 164.1, 158.1, 140.6, 138.2, 132.1, 129.0, 128.5, 125.5, 124.6, 123.6, 117.1, 114.0, 55.5, 53.5, 38.1. Mass: ESI pos. *m*/*z*: 367.2 [(M+H)$^+$].
   Compound **5b** (1:1 mixture of diastereomers): ^{1}H NMR (500 MHz, MeOH-d_4): δ 7.73/7.48 (two d, *J* = 8.2/7.8 Hz, 1/1 H; Ar*H*), 7.39/7.35 (two d, *J* = 8.1/9.3 Hz, 1/1H; Ar*H*), 7.22–6.95 (m, 5+5H; Ar*H*), 6.75/6.70 (two d, *J* = 8.5/8.2 Hz, 2/2H; Ar*H*), 5.35/5.33 (two s, 1/1H; C*H*OH), 4.25–4.13 (m, 1+1H; NHC*H*), 3.62/3.60 (two br d, *J* = 3.4/4.8 Hz, 2/2H; CH_2OH), 2.94/2.84 (two dd, *J* = 13.9/13.8, 6.1/6.5 Hz, 1/1H; ArC*H*H), 2.79–2.72 (m, 1+1H; ArCH*H*). ^{13}C NMR (125 MHz, MeOH-d_4) δ: 175.7, 175.6, 156.9, 156.8, 138.2, 138.1, 131.4, 130.4, 130.1, 127.2, 125.3, 122.7, 122.7, 120.3, 116.4, 116.2, 115.2, 115.0, 112.4, 112.3, 69.6, 69.4, 64.1, 63.7, 54.1, 53.9, 49.4, 49.2, 49.0, 48.9, 48.7, 37.1, 37.0. Mass: ESI pos. *m*/*z*: 341.3 [(M+H)$^+$].
   Compound (2*R*)-**3**: $[\alpha]_D^{25}$ −23 (*c* 0.65 in MeOH). ^{1}H NMR (500 MHz, CD_3CN): δ 9.35 (br s, 1H), 7.63 (d, *J* = 7.9 Hz, 1H), 7.40 (d, *J* = 8.3 Hz, 1H), 7.17–7.01 (m, 4H), 6.73 (d, *J* = 8.4 Hz, 2H), 6.62 (br s, 1H), 5.36 (s, 1H), 3.76 (dd, *J* = 13.4, 5.4 Hz 1H), 3.71–3.67 (m, 2H), 2.87 (d, *J* = 6.5 Hz, 2H). ^{13}C NMR (125 MHz, CD_3CN) δ: 170.4, 156.6, 131.5, 129.3, 126.3, 122.8, 120.4, 120.2, 116.2, 112.5, 74.4, 64.7, 54.2, 39.5. Mass: ESI pos. *m*/*z*: 323.3 [(M+H)$^+$].
   Compound (2*S*)-**3**: $[\alpha]_D^{25}$ +40 (*c* 0.66 in MeOH). ^{1}H NMR (500 MHz, CD_3CN): δ 9.27 (br s, 1H), 7.58 (br d, *J* = 7.7 Hz, 1H), 7.39 (br d, *J* = 8.2 Hz, 1H), 7.23 (d, *J* = 2.6 Hz, 1H), 7.13 (ddd, *J* = 8.2, 7.2, 1.0 Hz, 1H), 7.09 (d, *J* = 8.4 Hz, 2H), 7.04 (ddd, *J* = 7.7, 7.2, 0.9 Hz, 1H), 6.92 (br s, 1 H), 6.76 (d, *J* = 8.4 Hz, 2H), 6.45 (br s, 1H), 5.30 (s, 1H), 3.91–3.83 (m, 3H), 3.52 (dd, *J* = 11.3, 6.7 Hz, 1H), 2.78 (d,*J* = 6.9 Hz, 2H). ^{13}C NMR (125 MHz, CD_3CN) δ: 156.6, 137.4, 131.3, 129.2, 126.1, 122.7, 120.2, 116.3, 112.4, 74.5, 66.2, 54.3, 39.0. Mass: ESI pos. *m*/*z*: 323.3 [(M+H)$^+$].