Stereoselective Synthesis of a Bicyclic Isoxazolidine Related to the Pyrinodemin Family of Alkaloids via an Intramolecular Asymmetric [2+3] Cycloaddition

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Abstract: Bicyclic isoxazolidine **21**, a synthetic intermediate for pyrinodemins, was synthesized in six steps using an asymmetric intramolecular [2+3] cycloaddition of a new phenylglycinol-derived oxazoline *N*-oxide

Key words: asymmetric synthesis, alkaloids, pyrinodemin, cycloadditions, dipolar

The pyrinodemins are a new family of marine alkaloids that have been extracted from the sponge *Amphimedon Sp.* Pyrinodemin A (**1**) was reported by Kobayashi and coworkers in 1999.[1] Later, three other pyrinodemins B, C and D (**2**–**4**) were also isolated from the same sponge in lower yields[2] (Figure 1). All these natural products contain a *cis*-cyclopent[*c*]isoxazolidine ring system substituted with two fatty chains terminated with a 3-pyridyl moiety; they differ by the nature of the side chain on the nitrogen atom. However, the exact structure of pyrinodemin A (**1**) has been the subject of some controversy, and the accurate position of the *cis* double bond as well as the absolute configuration were recently determined by total synthesis.[3,4]

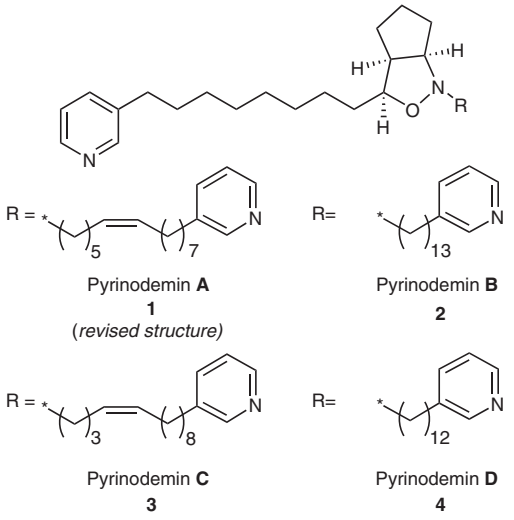

Figure 1

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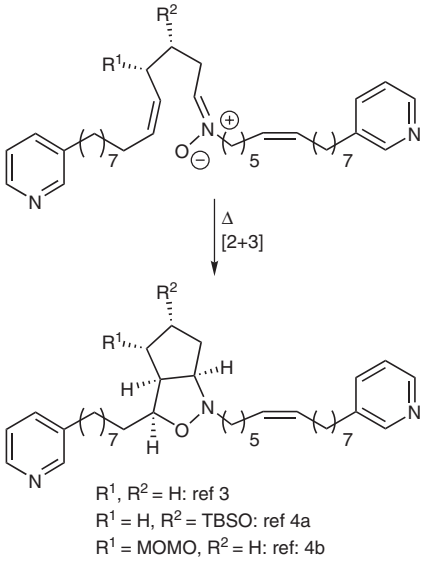
All pyrinodemins show cytotoxic activity against murine leukemia L210 and epidermoid carcinoma KB, pyrinodemin A being the most active compound (IC_{50} = 0.058 μg mL^{-1}, and 0.5 μg mL^{-1}, respectively). Due to this biological activity and unusual structure, pyrinodemin A (**1**) has been the subject of several synthetic studies.[3,4]

Synthesis of the bicyclic core of the molecule involves an intramolecular [2+3] cycloaddition of a nitrone (or nitrone equivalent) with a *Z* double bond (Scheme 1). This strategy was applied by Snider[3a] and Baldwin[3b] in their racemic synthesis of **1**, and by Baldwin[4a] and Morimoto[4b] in their enantioselective synthesis. In the latter case, an additional function (e.g. a protected hydroxyl group) creating a stereogenic center was used to induce diastereoselectivity in the cycloaddition.

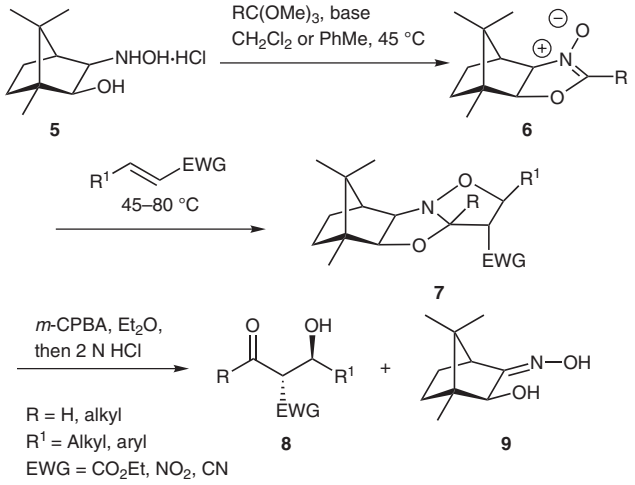


Scheme 1

Our strategy for the synthesis of pyrinodemins involves a flexible approach in which the bicyclic core of pyrinodemins would first be synthesized in an enantioselective fashion, followed by the appendage of the side chains; this approach would allow the preparation of all the pyrinodemins **1**–**4** from a common intermediate.

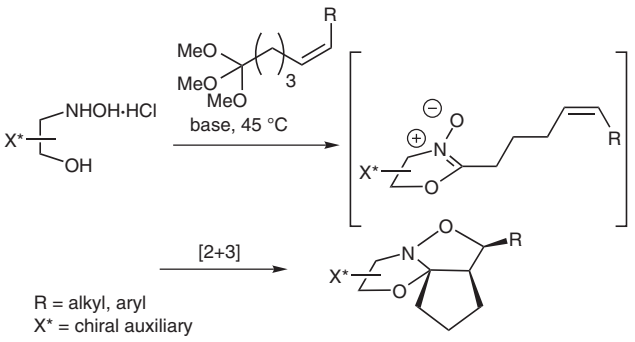
In the recent years, our laboratory has investigated the scope and synthetic applications of asymmetric [2+3] cycloadditions of chiral, camphor-derived oxazoline *N*-

oxides with electron-deficient olefins.[5] These cycloadditions occur in a highly regio- and stereoselective fashion, a single isomer of cycloadducts **7** being often obtained. The chiral dipole **6** is prepared in situ by condensation of the 1,2-hydroxyaminoalcohol hydrochloride **5** with a trimethyl orthoester (Scheme 2). Removal of the chiral auxiliary involves cleavage of the N–O bond under oxidative conditions, followed by acidic hydrolysis. β-Hydroxycarbonyl derivatives **8** are obtained, together with the oxime **9**. In this synthetic sequence, the dipole **6** is equivalent to a chiral nitrile oxide.



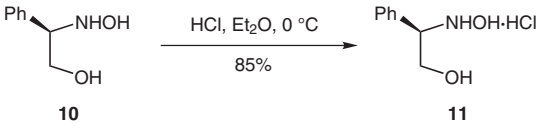
Scheme 2

Since any orthoester can be condensed with the chiral auxiliary **5**, the possibility of condensing unsaturated orthoesters in order to perform intramolecular cycloadditions looked like a promising method for the stereoselective synthesis of functionalized carbocyclic structures (Scheme 3).[6] In this communication we wish to report the application of asymmetric intramolecular [2+3] cycloaddition of chiral oxazoline *N*-oxides to the synthesis of the bicyclic structure of pyrinodemins.



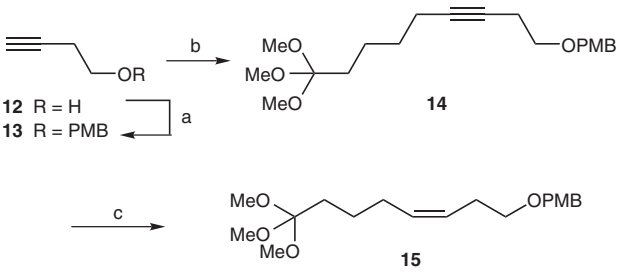
Scheme 3

In order to use the asymmetric intramolecular cycloaddition as the key step for pyrinodemin synthesis, it was necessary to remove the chiral auxiliary without cleaving the N–O bond. Thus, it appeared that camphor-derived chiral auxiliary **5** was not appropriate for such a process. We anticipated that a chiral auxiliary with a benzylic nitrogen atom could be cleaved after cycloaddition using reductive and hydrogenolytic conditions. Consequently, the hydroxyaminoalcohol hydrochloride **11** derived from (*R*)-phenylglycinol was prepared from the known[8] chiral auxiliary **10** (Equation 1).



Equation 1

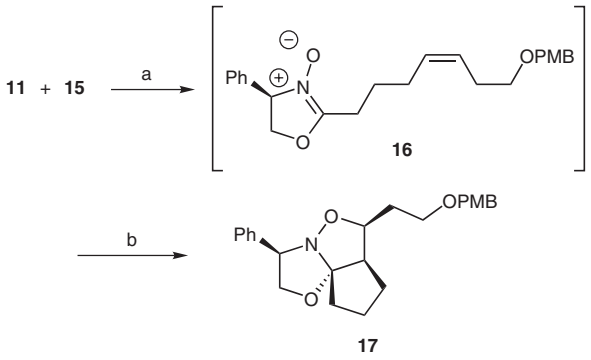
The preparation of the unsaturated trimethylorthoester **15** with a *Z* double bond is reported in Scheme 4: protection of 3-butyn-1-ol (**12**) as its PMB ester gave the alkyne **13** which was deprotonated (2.5 M BuLi, THF–HMPA) and condensed to the commercially available (Aldrich) trimethyl 4-bromoorthobutyrate. The highly labile orthoester **14** was immediately submitted to hydrogenation over Lindlar catalyst in methanol–pyridine to give the crude orthoester **15**, which was used without purification in the cycloaddition reaction.[7]



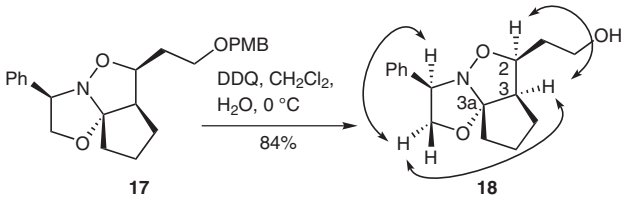
Scheme 4 a) NaH, PMBBr, THF, DMF, 91%; b) *n*-BuLi (2.5 M), THF, HMPA, –78 °C, then $(MeO)_3C(CH_2)_2CH_2Br$, –78 °C to 25 °C; c) H_2 (1 atm), $Pd/BaSO_4$, MeOH, pyridine; 25 °C (82% crude overall yield).

Condensation of orthoester **15** with the chiral auxiliary **11** (1.7 equiv) at 45 °C in toluene gave the intermediate oxazoline *N*-oxide **16**; after addition of triethylamine (to neutralize hydrochloric acid) and raising the temperature to 75 °C, the reaction gave after 18 hours the cycloadduct **17** as a single compound in 56% yield (Scheme 5). The reaction was highly stereoselective since only one stereoisomer was detected by ^1H NMR (400 MHz) of the crude mixture.

This asymmetric intramolecular [2+3] cycloaddition therefore allows the formation of three stereogenic centers in a single operation, and with complete control of the stereoselectivity. For better characterization, the *para*-methoxybenzyl group was removed under standard conditions (DDQ, CH_2Cl_2) and the corresponding free alcohol **18** was submitted to extensive ^1H NMR and ^{13}C NMR analysis.[7] From 2D NOESY data, it appeared that the configurations of the newly created stereogenic centers were 2*S*, 3*R*, 3a*S*, which correspond to those of the natural product.



Scheme 5 a) 45 °C, PhMe, then Et_3N; b) 75 °C, 18 h, 56%.



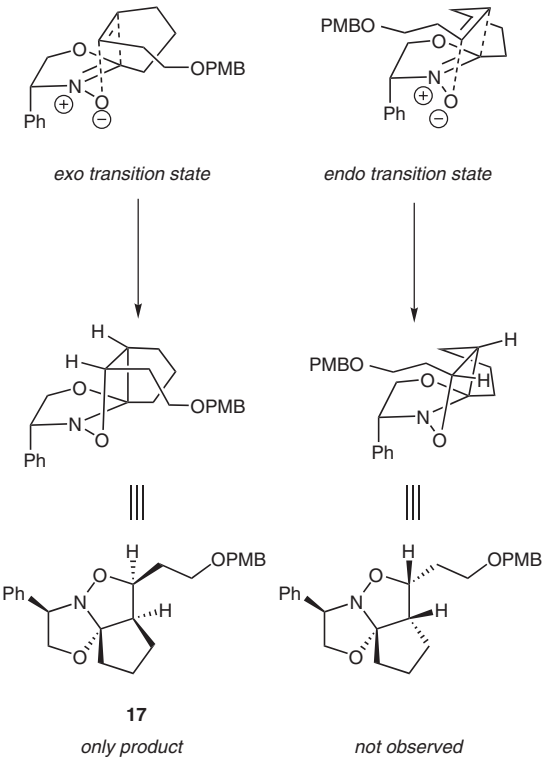
Equation 2

The most representative NOE correlations are shown in Equation 2.[9]

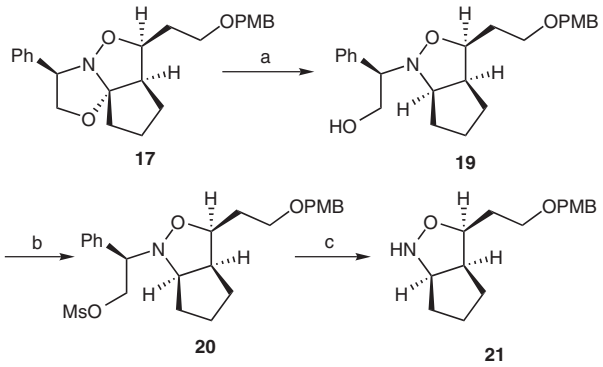
Cycloadduct **17** comes from an *exo* transition state in which the dipolarophile approaches the dipole from the face opposite to the phenyl substituent on the oxazoline ring (*Si* face, Scheme 6). The *endo* transition state is destabilized by torsion of the chain and steric repulsions between the OPMB group and the oxazoline ring hydrogens; this explains the exclusive formation of the cycloadduct **17**. Hence, the phenylglycinol-derived chiral auxiliary **11** shows remarkable efficiency in directing the facial selectivity of the intramolecular [2+3] cycloaddition, the sense of asymmetric induction being identical to the one obtained using (+)-camphor-derived chiral auxiliary **5**.[10]

The use of phenylglycinol-derived oxazoline *N*-oxide as a nitrone equivalent was illustrated by the synthesis of bicyclic isoxazoline **21** (Scheme 7): chemo- and stereoselective reduction of the aminoacetal using zinc borohydride in diethyl ether[11] afforded the N-substituted isoxazolidine **19** as a single isomer. Removal of the chiral auxiliary was performed using slight modification of the Agami–Couty method:[12] mesylation of the primary alcohol **19** (MsCl, Et_3N) followed by treatment of the crude mesylate **20** with potassium cyanide in DMSO with subsequent β-elimination gave the target compound **21**;[13] the use of microwave activation in the second step strongly reduced reaction time and increased both yield and selectivity.[14]

In conclusion, we have prepared an advanced intermediate in pyrinodemin synthesis in 6 steps and in 19% overall yield from 3-butyn-1-ol; the key step for the synthesis is an asymmetric intramolecular [2+3] cycloaddition of a chiral oxazoline *N*-oxide, for which we have developed a new and highly selective chiral auxiliary. Progress towards the total synthesis of pyrinodemins, as well as the development of new nitrone-type chiral cycloaddition with chiral auxiliary **11** are currently underway.



Scheme 6



Scheme 7 a) $Zn(BH_4)_2$, Et_2O, –10 °C to 0 °C, 84%; b) MsCl, Et_3N, CH_2Cl_2, 0 °C, 98%; c) KCN, DMSO, 120 °C, microwave, 55%.

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(7) The crude product consists in essentialy pure orthoester **15** with a trace of pyridine. All attempts to purify the crude product by chromatography resulted in partial hydrolysis of the orthoester to the corresponding methyl ester.
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(9) Data for compound **18**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.49–7.14 (5 H, br s), 4.45 (1 H, m, C_2-H), 4.45 (1 H, t, *J* = 7 Hz), 4.30 (1 H, dd, *J* = 7 and 2 Hz), 3.73 (3 H, m), 2.75 (1 H, m, C_3-H), 2.18 (1 H, m), 1.85–1.62 (7 H, m) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 138.6, 128.4–127.1, 116.0, 77.6, 71.9, 69.7, 60.7, 56.4, 37.0, 31.8, 25.4, 24.6 ppm. IR (liquid film): ν = 3423, 3057, 2959, 1495, 1467, 1452, 1438, 1311, 1266, 1200, 1052 cm^{-1}. MS (ES): *m/z* = 298.2 [M + Na], 276.2 [M + 1]. HRMS: *m/z* calcd for $C_{16}H_{22}NO_3$ [M + 1]: 276.15997; found: 276.16029. $[\alpha]_D^{20}$ –174.4 (*c* 2, $CHCl_3$).
(10) Condensation of camphor-derived chiral auxiliary **5** with orthoester **15** resulted in the formation of a cycloadduct as a single isomer, albeit in lower yield.
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(13) Data for compound **21** (clear oil): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.25 (2 H, d, *J* = 9.0 Hz), 6.85 (2 H, d, *J* = 9.0 Hz), 4.40 (2 H, s), 3.90 (1 H, m), 3.78 (3 H, s), 3.68 (1 H, dd, *J* = 7.6 and 7.0 Hz), 3.55 (2 H, dt, *J* = 7.6 and 3.6 Hz), 2.75 (1 H, m), 1.85 (3 H, m), 1.79–1.40 (4 H, m), 1.35 (1 H, m) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 159.1, 130.4, 129.2, 113.7, 83.6, 72.7, 67.7, 66.5, 55.2, 50.1, 34.9, 29.0, 26.9, 26.5 ppm. IR (liquid film): ν = 3428, 2955–2864, 1613, 1513, 1248, 1091 cm^{-1}. MS (ES): *m/z* = 300.2 [M + Na], 278.2 [M + 1]. HRMS: *m/z* calcd for $C_{16}H_{23}NaNO_3$ [M + Na]: 300.15756; found: 300.15727. $[\alpha]_D^{20}$ +36.4 (*c* 1, $CHCl_3$).
(14) Product arising from elimination of the mesylate was also observed in the crude product. Using microwave activation results in decrease of elimination from 15% to 5%.