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Model studies towards the bistramide D tetrahydropyran

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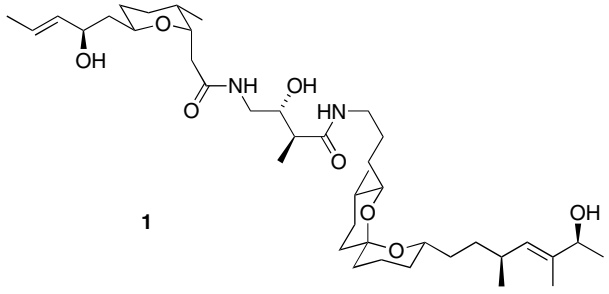
Abstract

The synthesis of a model of the bistramide D tetrahydropyran ring is achieved using a selective cross-metathesis and an intramolecular Michael addition under kinetic control.

Keywords: Tetrahydropyran; Michael addition; Cyclisation; Metathesis

The bistramides are a small family of natural products isolated from an ascidian, *Lissoclinum bistratum*.[1] The molecules are made up of three units, a tetrahydropyran (except in the case of bistramide K), an amino acid and a spiroketal. The bistramides display a range of biological properties, and have been shown to bind to actin.[2] A number of syntheses of bistramides A and C have been reported.[3] On the other hand, bistramide D **1**, reportedly less toxic than A or C, has only been synthesised from bistramide A.[4] We report here our model studies towards the synthesis of the tetrahydropyran moiety of bistramide D, utilising a stereoselective kinetic intramolecular Michael addition.[5]



1

The intramolecular Michael addition is a facile method to construct a heterocyclic ring and has recently been used for the synthesis of Diospongin A.[6] In these syntheses, an alcohol undergoes nucleophilic addition to an enone moiety. The product, the cis and therefore bis-equatorial isomer, is clearly the more stable of the two, and it appears likely that the reaction is under thermodynamic control. On the other hand, Banwell has shown that the corresponding reaction of an alcohol to an α,β-unsaturated ester, under carefully controlled conditions, yields the product of kinetic control, the trans-isomer, as the major product.[7] We report here the use of this strategy in model studies towards the tetrahydropyran moiety **2** of bistramide D (Scheme 1). The only difference between our target and the natural target is the absence of the methyl group at C9 (model **2a**: R = H; natural product **2b**: R = CH_3).

The first challenge was the construction of the *syn*-1,3-diol in an expeditious fashion (Scheme 2). We opted to employ the iodolactonisation procedure of Bartlett[8] and Cardillo.[9] Thus, (*S*)-(+)-epichlorohydrin was first ring-opened with lithiobutyne in the presence of boron trifluoride etherate. Alcohol **4** was then converted to a *t*-butyl carbonate under mild conditions, and the alkyne was reduced to the *cis*-alkene **5**. For reliability, the use of P2-nickel,[10] prepared from nickel acetate and sodium borohydride, was preferred over the use of Lindlar's catalyst. Treatment of this carbonate with iodine in acetonitrile yielded the

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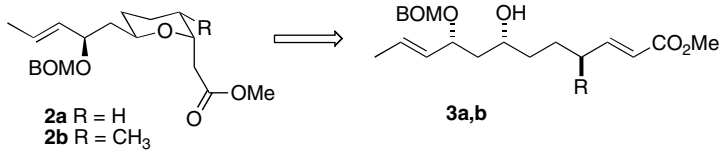
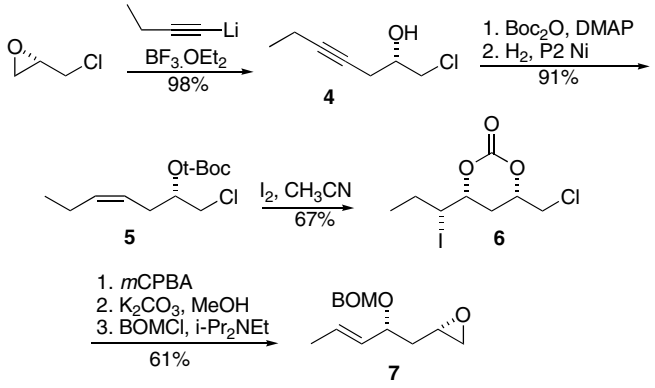
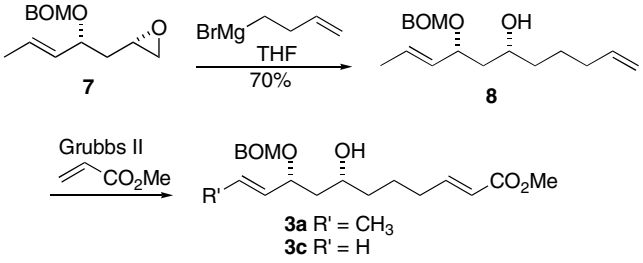


Scheme 1.



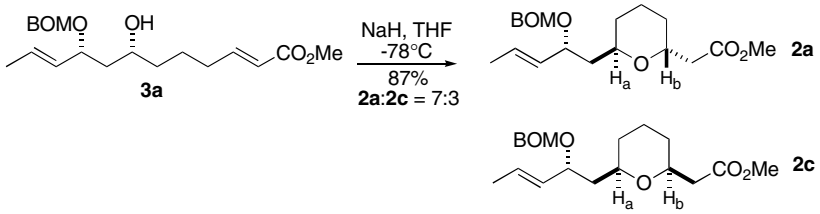
Scheme 2.



Scheme 3. Synthesis of the cyclisation precursor.

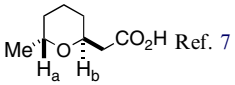
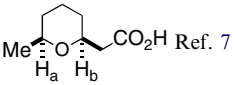
iodocarbonate **6**. The *syn* stereochemistry of the two oxygen atoms was apparent from analysis of the coupling constants. Elimination of the iodine was achieved by treatment with *meta*-chloroperbenzoic acid (*m*CPBA), thus effecting a rarely employed iodoso elimination.[11] The product of the elimination was exclusively the *trans*-alkene. At this point, the carbonate was opened, leading to protected[12] epoxy alcohol **7** as a single diastereoisomer.

As in our synthesis of Diospongin A, it was intended to introduce the Michael acceptor by ring opening with a Grignard reagent, followed by cross-metathesis (Scheme 3). Ring opening proceeded smoothly to give diene **8**, provided that THF was used as the solvent. In ether or ether-THF mixtures products resulting from attack on the BOM group by the Lewis acidic magnesium were isolated. Initially, cross-metathesis with methyl acrylate in the presence of Grubbs' second generation catalyst at room temperature resulted in the formation of an inseparable mixture of compounds. It was determined that these were the desired methyl ester **3a** and the corresponding desmethyl compound **3c**. It was apparent that cross-metathesis with the acrylate had occured exclusively at the terminal alkene, but some cross-metathesis of the internal alkene had occured with the ethylene by-product of the first cross-metathesis, giving rise to **3c**. This illustrates the delicate selectivities that can be achieved.[13] The solution to the problem was found by simply passing a stream of nitrogen over the reaction mixture to sweep away the ethylene as generated. With this trivial modification, the desired Michael precursor **3a** could be obtained in both pure and in good yield (76%). Unsurprisingly, no RCM was observed.



Scheme 4. Intramolecular Michael addition.

Table 1
^{1}H NMR chemical shifts of the THP methyne protons (**2a** and **2c**)

	trans-Isomer **2a**	 Ref. 7	Bistramide D[1]	cis-Isomer **2c**	 Ref. 7
H_a	δ 3.84	δ 3.88	δ 3.87	δ 3.37	δ 3.44
H_b	δ 4.19	δ 4.25	δ 4.22	δ 3.72	δ 3.75

The final critical intramolecular Michael addition was carried out under the conditions described by Banwell: treatment of **3a** with sodium hydride in THF at −78 °C (Scheme 4).[7] It was gratifying to find that the major product of the reaction was the trans-isomer **2a**, accompanied by some of the cis-isomer **2c**, in a ratio of 7:3 and which were separable by column chromatography. A remarkable concordance of NMR data was observed and served to assign the stereochemistry (Table 1).[14]

In conclusion, we have shown that the combination of cross-metathesis and intramolecular Michael addition is a viable pathway to complex tetrahydropyrans, even to produce the less stable isomer, and also in the presence of other alkenes.

Acknowledgements

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14. Compound **2a**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37–7.28 (5H, m, Ar), 5.67 (1H, dq, $J = 15.3$, 6.5 Hz, CH_3–*C*H=CH), 5.27 (1H, ddq, $J = 15.3$, 8.5, 1.3 Hz, CH_3–CH=*C*H–CH), 4.81 (1H, d, $J = 6.9$ Hz, O–C*H*$_2$–O), 4.68 (1H, d, $J = 11.7$ Hz, O–C*H*$_2$–Ar), 4.68 (1H, d, $J = 7.0$ Hz, O–C*H*$_2$–O), 4.54 (1H, d, $J = 11.8$ Hz, O–C*H*$_2$–Ar), 4.22–4.12 (2H, m, CH_2–C*H*$_b$–CH_2, =CH–C*H*–CH_2), 3.84 (1H, m, CH_2–C*H*$_a$–CH_2), 3.66 (3H, s, COOC*H*$_3$), 2.56 (1H, dd, $J = 14.8$, 8.2 Hz, CH–C*H*$_2$–COOMe), 2.44 (1H, dd, $J = 14.8$, 5.7 Hz, CH–C*H*$_2$–COOMe), 2.14 (1H, ddd, $J = 13.8$, 8.8, 5.0 Hz, CH–C*H*$_2$–CH), 1.71 (3H, dd, $J = 6.5$, 1.3 Hz, C*H*$_3$–CH=CH), 1.68–1.57 (4H, m), 1.47 (1H, ddd, $J = 13.6$, 8.8, 4.9 Hz, CH–C*H*$_2$–CH), 1.39–1.31 (2H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 138.2, 130.7, 130.0, 128.3, 127.9, 127.5, 91.6, 74.5, 69.4, 68.4, 67.6, 51.6, 39.5, 38.4, 30.0, 29.5, 18.4, 17.7; $[\alpha]_D^{26}$ 42.6 (*c* 0.6, MeOH) HRMS Found 241.1434 (M^+-BOM, $C_{13}H_{21}O_4$ requires 241.1434); Compound **2c**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35–7.27 (5H, m, Ar), 5.65 (1H, dq, $J = 15.3$, 6.6 Hz, CH_3–C*H*=CH), 5.26 (1H, ddq, $J = 15.4$, 8.6, 1.4 Hz, CH_3–CH=C*H*–CH), 4.79 (1H, d, $J = 6.9$ Hz, O–CH_2–O), 4.66 (1H, d, $J = 11.9$ Hz, O–CH_2–Ar), 4.65 (1H, d, $J = 6.6$ Hz, O–CH_2–O), 4.50 (1H, d, $J = 11.8$ Hz, O–CH_2–Ar), 4.23–4.19 (1H, m, =CH–C*H*–CH_2), 3.74–3.69 (1H, m, CH_2–C*H*$_b$–CH_2), 3.69 (3H, s, COOC*H*$_3$), 3.40–3.34 (1H, m, CH_2–C*H*$_a$–CH_2), 2.53 (1H, dd, $J = 14.9$, 8.3 Hz, CH–C*H*$_2$–COOMe), 2.38 (1H, dd, $J = 14.8$, 5.2 Hz, CH–C*H*$_2$–COOMe), 1.88 (1H, ddd, $J = 13.6$, 8.8, 5.2 Hz, CH–C*H*$_2$–CH), 1.83–1.80 (1H, m), 1.72 (3H, dd, $J = 6.5$, 1.5 Hz, C*H*$_3$–CH=CH), 1.62–1.55 (3H, m), 1.50 (1H, ddd, $J = 13.5$, 8.9, 4.7 Hz, CH–C*H*$_2$–CH), 1.27–1.19 (2H, m). Decoupling experiments revealed that both H_a and H_b of this minor isomer displayed typical axial–axial coupling constants (10.6 and 11.1 Hz, respectively). ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.0, 138.1, 130.7, 130.0, 128.3, 127.9, 127.5, 91.4, 74.6, 74.4, 74.2, 69.3, 51.5, 42.0, 41.6, 31.2 (2C), 23.4, 17.8 HRMS Found 241.1434 (M^+-BOM, $C_{13}H_{21}O_4$ requires 241.1434).