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Nitrile oxide cycloadditions to olefinated sugars

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Abstract—Carbohydrate derivatives with a spiro-isoxazoline moiety as present in psammaplysins and ceratinamides (metabolites isolated from marine sponges) were prepared in good yields and excellent regio- and diastereoselectivity by a route involving Wittig olefination and 1,3-dipolar cycloaddition as key steps. © 2003 Published by Elsevier Science Ltd.

1. Introduction

The psammaplysins and ceratinamides **1** are a unique small family of bromostyrene metabolites isolated from marine sponges of the order Verongida; they feature the most unusual spiroketal ring system found in nature so far.[1] The psammaplysins were reported to exhibit potent cytotoxicity against P388 murine leukemia cells and anti-HIV activity against the Haitian RF strain of HIV-1, while the ceratinamides display anti-fouling activity.[2]

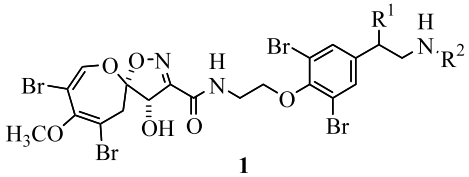
In the last years we have developed the synthesis of enol ethers derived from 2-deoxypentoses[3a] and hexoses.[4] Further interest is in the reactions of the 'enol ether' function which offers numerous possibilities for transformations and which can be regarded as a valuable intermediate in the synthesis of various new C-glycosides.[4] To the best of our knowledge, only one example of nitrile oxide cycloaddition to 1-methylene sugars is known, with few experimental details given.[5] We wish to report a method for the synthesis of spiro-isoxazolines derived from carbohydrates by a sequence involving the Wittig reaction and 1,3-dipolar cycloaddition as key steps (Scheme 1).

2. Synthesis of the D-*lyxo*-enitols

Wittig reactions of the phosphonium salt[4] **2** and several aldehydes using *n*-BuLi in THF gave the exocyclic enol ethers **3**, which after filtration through silica gel, were obtained spectroscopically pure in good yield (Scheme 2). The *E* and *Z* isomers could be separated by MPLC on silica gel.[6]

3. Nitrile oxide cycloadditions

The cycloadditions of the olefinated sugars **3** were performed with two nitrile oxides: mesitonitrile oxide (stable monomer) and ethoxycarbonylnitrile oxide (unstable; generated in situ using Huisgen's method).



1

	R^1	R^2
Psammaplysin A	H	H
Psammaplysin B	OH	H
Psammaplysin C	OH	CH_3
Psammaplysin D	OH	$CO(CH_2)_{11}CH(CH_3)_2$
Ceratinamide A	H	CHO
Ceratinamide B	H	$CO(CH_2)_{11}CH(CH_3)_2$

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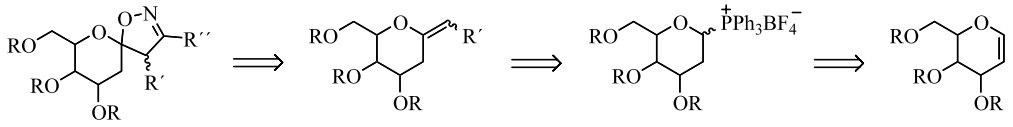
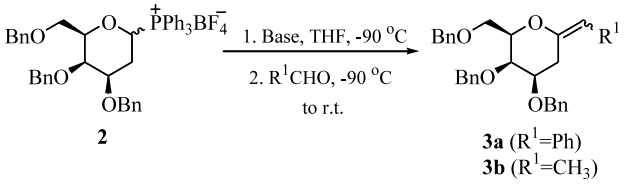


Scheme 1.



R^1CHO	Ratio E/Z	Yield (%)
PhCHO	55:45	68
CH_3CHO	82:18	65

Scheme 2.

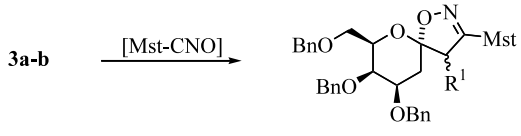
3.1. Mesitonitrile oxide cycloadditions

The enol ether **3** and mesitonitrile oxide were dissolved in dichloromethane and allowed to react under the conditions (temperature, time) indicated in Table 1. The products were easily purified using chromatography on silica gel.[7] In all cases the d.r. determined from the crude reaction mixtures was >95:5. The ^1H NMR, ^{13}C NMR, 2D-COSY (H–H, H–C) and NOESY experiments supported the proposed structures for compounds **4**. The lack of NOE between the H-4 (isoxazoline) and the H-7 (pyranosyl C-5 hydrogen) confirms the configuration of the spiro-isoxazolines. Also this configuration is in agreement with the attack of the nitrile oxide to the less hindered α-face of the *exo*-glycal.

3.2. Ethoxycarbonylnitrile oxide cycloadditions

The enol ether and triethylamine were dissolved in dichloromethane and the hydroximoyl chloride **5** was very slowly added at room temperature.[3c,8] The normal method involving the addition of triethylamine to the solution could not be used due to very fast reaction between the enol ether and the nitrile oxide precursor, which afforded the addition product **7**, probably catalyzed by small quantities of HCl. The method reported in the literature,[5] involving the mixing of all reactants at 0°C, was also employed but only led to a low yield of the cycloadduct **6**. Under these conditions the cycloadditions of the enol ethers (*E*)- and (*Z*)-**3a** were unsuccessful and only the furoxan was obtained (Table 2).

Table 1. Reactions of **3** with mesitonitrile oxide[a]



4a-b

a R^1=Ph

b R^1=CH_3

Olefin	Product	Temp.	Time	Yield (%)
(*E*)-**3a**	*trans*-**4a**	rt	20 d	85
		reflux	36 h	80
(*Z*)-**3a**	*cis*-**4a**	rt	20 d	86
		reflux	30 h	78
(*E*)-**3b**	*trans*-**4b**	rt	12 h	76

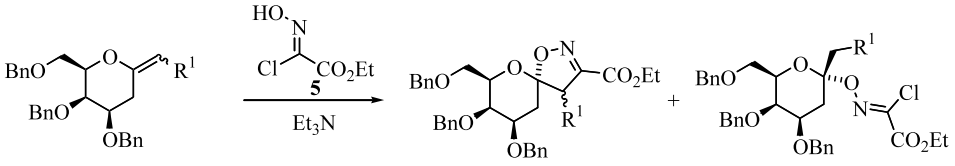
[a] Dipole:dipolarophile 1:1.

In some cases, solvent-free conditions coupled with microwave irradiation have proven useful for the generation of nitrile oxides and good yields were found with sluggish dipolarophiles.[9,10] Due to the low reactivity of the 1-phenylenitols (*E*)- and (*Z*)-**3a**, we applied these conditions to the reaction with the ethoxycarbonylnitrile oxide, which was generated in situ using Al_2O_3 as base (Table 3).[11] Also the methyl derivate (*E*)-**3b** was used for comparison.

The reaction of trisubstituted alkenes with nitrile oxides was accelerated under high pressure (10 kbar) using potassium carbonate as base.[12] Unfortunately, the reactions of the *exo*-glycals **3a**–**b** with the ethoxycarbonylnitrile oxide did not proceed in reasonable yields under these conditions.

The high stereoselectivity observed is in accord with the steric approach control, which favors the attack to the less hindered α-face of the enol ethers **3** leading to products with a β-oriented C-substituent at the anomeric center (Fig. 1). This stereochemical outcome was also found in other additions to *exo*-glycals (like hydrogenation, hydroboration, etc.).[4,5] The regioselectivity, with the preference for the more substituted carbon atom to end up at the 5-position of the heterocycle, corresponds to the mode normally found in nitrile oxide cycloadditions to trisubstituted alkenes.[12] In conclusion, the method described here allows for the regio- and diastereoselective preparation of such spiro-

Table 2. Reactions with ethoxycarbonylnitrile oxide[a]



3a-b **6a-b** **7a-b**

a R^1 = Ph
b R^1 = CH_3

Reactants	Reagent added	Temperature	Yield (%)		
			6	**7**	Furoxan
(*E*)-**3b**+**5**	Et_3N	rt 18 h	–	92	–
(*E*)-**3b**+**5**+Et_3N	–	0°C, rt 18 h	30[b,e] (*trans*)	8	30
(*E*)-**3b**+Et_3N	**5**	rt 18 h	76[e] (*trans*)	-	10
(*E*)-**3a**+Et_3N	**5**	rt 18 h	–	–	70[c]
(*Z*)-**3a**+Et_3N	**5**	rt 18 h	–	–	78[d]

[a] Dipole:dipolarophile 1:1.
[b] 50% of (*E*)-**3b** recovered.
[c] 80% of (*E*)-**3a** recovered.
[d] 76% of (*Z*)-**3a** recovered.
[e] d.r. >95:5 (determined by ^{1}H NMR).

Table 3. Cycloadditions with microwave irradiation[a,b]

Olefin	Product	Power (W)	Time (min)	Yield (%)
(*E*)-**3a**	*trans*-**6a**	400	15	42
		400	30	40
		700	15	35
(*Z*)-**3a**	*cis*-**6a**	400	15	45
(*E*)-**3b**	*trans*-**6b**	400	15	70

[a] Dipole:dipolarophile 1:1.
[b] d.r. >95:5.

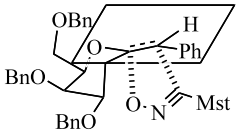


Figure 1.

isoxazolines. The reactions with the phenyl-substituted enol ethers afforded lower yields than the ones with the methyl substituent, but the yields and/or reaction times could be improved by using higher temperature (Table 1) or with the aid of microwave irradiation (Table 3).

Various transformations of the spiro-isoxazolines are meanwhile in progress and will be presented in due course.

Acknowledgements

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6. The *E* and *Z* configurations were assigned on the basis of the chemical shifts of the vinyl protons, according to increment calculations done for related olefins: Pascual, C.; Meier, J.; Simon, W. *Helv. Chim. Acta* **1969**, *49*, 164–168; Pretsch, E.; Clerc, T.; Seibl, J.; Simon, W. *Strukturauflklärung organischer Verbindungen*, 3rd ed.;

Springer: Berlin-Heidelberg-New York, 1986. Also the assignment was confirmed by comparison with earlier *exo*-glycals prepared by us: Refs. 3a and 4.

7. Preparation of **4a**: A solution of 0.1 mmol of the enol ether (*E*)- or (*Z*)-**3a**, (*E*)-**3b** and 0.1 mmol of the mesitonitrile oxide in 1 mL of dry methylenchloride, under nitrogen, was stirred at the temperature and time indicated. The solution was concentrated in vacuo to afford an oil, which was purified by chromatography on silica gel (eluent: hexane/ethyl acetate 9:1) to give the products **4**. Trans **4a**: colorless syrup, IR (neat): 3062.4, 3030, 2918.2, 2360.1, 1495.4, 1454.1, 1364.1, 1104.0 1067.1, 1027.4, 812.8, 737.0, 698.1 ^{1}H NMR (500 MHz) $\delta=1.94$ (dd, 1H, $J=4.4$, $J=12.6$, H-10), 2.04 (t, 1H, $J=12.6$, H-10), 2.18 (s, 9H, 3×CH_3 (Mst)), 3.55 (dd, 1H, $J=5.4$, $J=8.7$, H-11), 3.71 (t, 1H, $J=8.7$, H-11), 4.03 (s, 1H, H-7), 4.06 (m, 1H, H-9), 4.35 (t, 1H, $J=6.4$, H-8), 4.38 (s, 1H, H-4), 4.45 (AB, 1H, $J=11.6$, PhC$\underline{H}_2$), 4.49 (AB, 1H, $J=11.6$, PhC$\underline{H}_2$), 4.50 (AB, 1H, $J=11.6$, PhC$\underline{H}_2$), 4.57 (AB, 1H, $J=11.6$, PhC$\underline{H}_2$), 4.64 (AB, 1H, $J=11.5$, PhC$\underline{H}_2$), 4.87 (AB, 1H, $J=11.5$, PhC$\underline{H}_2$), 6.73 (s, 2H, Mst), 7.16–7.37 (m, 20H, Ph). ^{13}C NMR (125 MHz) $\delta=20.3$, 20.9 (CH_3, Mst), 30.0 (C-10), 67.0 (C-4), 68.9 (C-11), 70.8 (Ph-$\underline{C}H_2$), 71.4 (C-8) 71.9 (C-7), 72.2 (Ph-$\underline{C}H_2$), 73.3 (Ph-$\underline{C}H_2$), 74.4 (C-9), 109.9 (C-5), 125.1–131.9, 137.3–138.7(Ph), 163.4 (C-3). Anal. calcd for $C_{44}H_{45}NO_5$: C, 79.13; H, 6.79; N, 2.10. Found: C, 79.03; H, 6.80; N, 2.06.
cis-**4a**: colorless oil, IR (neat): 3087.6, 2921.5, 2360.3, 2349.8, 2288.6, 1454.4, 1256.1, 1210.9, 1169.5, 1069.3, 736.6, 697.9 ^{1}H NMR (500 MHz) $\delta=2.18$ (s, 3H, 1×CH_3 (Mst)), 2.24 (s, 6H, 2×CH_3 (Mst)), 2.38 (dd, 1H, $J=4.6$, $J=12.5$, H-10), 2.52 (t, 1H, $J=12.5$, H-10), 3.47 (dd, 2H, $J=5.4$, $J=3.2$, H-11), 3.92 (s, 1H, H-7), 4.07 (m, 1H, H-9), 4.27 (t, 1H, $J=6.6$, H-8), 4.37 (AB, 1H, $J=11.8$, PhC$\underline{H}_2$), 4.43 (AB, 1H, $J=11.8$, PhC$\underline{H}_2$), 4.48 (AB, 1H, $J=12.2$, PhC$\underline{H}_2$), 4.60 (s, 1H, H-4), 4.62 (AB, 2H, $J=11.8$, 2×PhC$\underline{H}_2$), 4.85 (AB, $J=11.5$, PhC$\underline{H}_2$), 6.74 (s, 2H, Mst), 6.94–7.33 (m, 20 H, Ph). ^{13}C NMR (125 MHz) $\delta=20.7$, 21.0 (CH_3, Mst), 31.8 (C-10), 65.2 (C-4), 68.9 (C-11), 70.5 (Ph-$\underline{C}H_2$), 71.6 (C-8), 71.9 (C-7), 73.1 (Ph-$\underline{C}H_2$), 73.2 (Ph-$\underline{C}H_2$), 75.7 (C-9), 107.6(C-5), 125.6–131.4, 138.1–139.3(Ph), 162.7(C-3). Anal. calcd for $C_{44}H_{45}NO_5$: C, 79.13; H, 6.79; N, 2.10. Found: C, 79.10; H, 6.75; N, 2.05.
trans-**4b**: colorless oil, $[\alpha]_D^{20}$ +135.2 (*c* 1.1, $CHCl_3$) IR (neat): 3029.9, 2918.3, 2361.2, 1610.1, 1496.5, 1454.4, 1365.3, 1211.3, 1166.4, 1111.2, 1069.6, 1027.9, 850.7, 823.9, 734.8, 696.6. ^{1}H NMR (500 MHz) $\delta=1.03$ (d, 3H, $J=7.6$, CH_3-C4), 2.14 (dd, 1H, $J=4.3$, $J=12.2$, H-10), 2.23 (s, 6H, 2×CH_3(Mst)), 2.27 (s, 3H, 1×CH_3(Mst)), 2.42 (t, 1H, $J=12.2$, H-10), 3.31 (c, 1H, $J=7.6$, H-4), 3.50 (dd, 1H, $J=5.5$, H=9.0, H-11), 3.66 (t, 1H, $J=9.0$, H-11), 4.04 (s, 1H, H-7), 4.11 (m, 1H, H-9), 4.30 (t, 1H, $J=6.6$, H-8), 4.44 (AB, 2H, $J=11.7$, PhC$\underline{H}_2$), 4.64 (AB, 2H, $J=11.8$, PhC$\underline{H}_2$), 4.69 (AB, 1H, $J=11.5$, PhC$\underline{H}_2$), 4.93 (AB, 1H, $J=11.5$, PhC$\underline{H}_2$), 6.86 (s, 2H, Mst), 7.23–7.36 (m, 20 H, Ph). ^{13}C NMR (125 MHz) $\delta=11.4$ (CH_3-C4), 19.9, 21.1 (CH_3 (Mst)), 29.7 (C-10), 55.3 (C-4), 69.0 (C-11), 70.8 (Ph-$\underline{C}H_2$), 71.4 (C-8), 72.4 (C-7), 73.3 (Ph-$\underline{C}H_2$), 74.5 (Ph-$\underline{C}H_2$), 76.3 (C-9), 108.9 (C-5), 122.3–128.6, 137.3–138.8 (Ph), 164.1 (C-3). Anal. calcd for $C_{39}H_{43}NO_5$: C, 77.33; H, 7.15; N, 2.31. Found: C, 77.20; H, 7.04; N, 2.25.

8. Preparation of *trans*-**6b**: To a solution of 0.1 mmol of (*E*)-**3b** and 0.15 mmol of triethylamine in 2 mL of dry methylenchloride was added, under argon and at room temperature, 0.1 mmol of the hydroximoyl chloride **5** dissolved in 10 mL of methylenchloride during 18 h. The reaction mixture was filtrated, washed with brine and dried. The residue, after removal of the solvent in vacuo, was chromatographed on silica gel (eluent: hexane/ethyl acetate 8:2) to give the product *trans*-**6b** as a colorless oil in 76% yield. $[\alpha]_D^{20}$: +99.5 (*c* 0.8, $CHCl_3$) IR (neat) 2871.8, 2359.9, 1720.7, 1586.1, 1496.5, 1454.3, 1372.2, 1254.2, 1060.9, 860.3, 822.4, 738.7, 697.0. ^{1}H NMR (500 MHz) $\delta=1.17$ (d, 3G, $J=7.5$, CH_3-C4), 1.35 (t, 3H, $J=7.2$, C$\underline{H}_3$CH$_2$), 2.06 (dd, 1H, $J=4.2$, $J=12.6$, H-10), 2.36 (t, 1H, $J=12.6$, H-10), 3.27 (c, 1H, $J=7.5$, H-4), 3.45 (dd, 1H, $J=5.3$, $J=9$, H-11), 3.60 (t, 1H, $J=9$, H-11), 4.05 (m, 1H, H-9), 4.17 (dd, 1H, $J=5.8$, $J=7.8$, H-8), 4.32 (m, 2H, CH$_3$C$\underline{H}_2$), 4.42 (s, 2H, Ph-C$\underline{H}_2$), 4.61 (m, 2H, PH-C$\underline{H}_2$), 4.64 (d, 1H, $J=11.4$, Ph-C$\underline{H}_2$), 4.91 (d, 1H, $J=11.4$, Ph-C$\underline{H}_2$), 7.25–7.38 (m, 15H, Ph). ^{13}C NMR (125 MHz) $\delta=11.9$ ($\underline{C}H_3$-C4), 14.1 ($\underline{C}H_3$CH$_2$), 29.4 (C-10), 50.1 (C-4), 62.0 (CH$_3$$\underline{C}H_2$), 68.3 (C-11), 70.6 (Ph$\underline{C}H_2$), 72.0, 72.1 (C-7, C-8), 73.3 (Ph$\underline{C}H_2$), 74.5 (Ph$\underline{C}H_2$), 75.6 (C-9), 111.9 (C-5), 127.3–128.5 (Ph), 137.9–138.7 (Ph), 157.5 (C-3), 160.2 ($\underline{C}$(O)OEt). Anal. calcd for $C_{33}H_{27}NO_7$: C, 72.12; H, 4.95; N, 2.55. Found: C, 71.98; H, 4.86; N, 2.51.

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11. General procedure for the cycloadditions with microwave irradiation: 0.1 mmol of the enol ether and 0.1 mmol of **5** were adsorbed on 1 g of Al_2O_3 previously dried. The mixture was then irradiated for the given time and power. Then the mixture was extracted with methylenchloride, and, after removal of the solvent, the residue was purified by chromatography on silica gel (eluent: hexane/ethyl acetate 9:1).
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