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Approaches to oximidines, lobatamides and related natural products: the coupling reactions of 3-iodoacrolein *O*-methyl oximes

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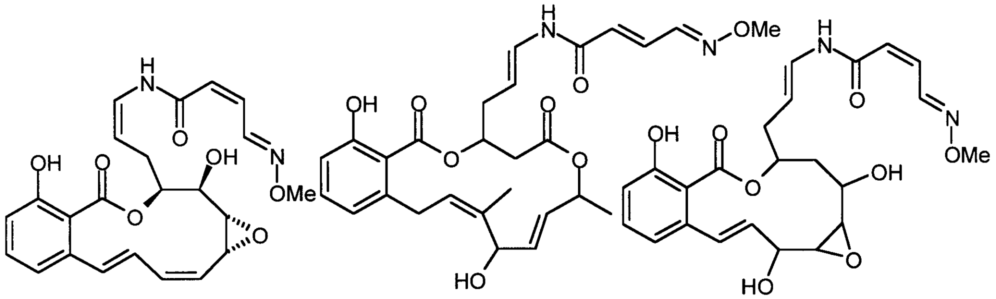
Abstract

Both 2*E*- and 2*Z*-3-iodoacrolein *O*-methyl oximes are prepared in two steps from ethyl propiolate. Lithium–iodine exchange is effected and the resulting organolithium reagents added to several electrophiles, including styryl isocyanate which gives a conjugated *O*-methyl oxime enamide of the type found in the side chains of the oximidine, lobatamide and CJ-12950 natural products. The Pd(0) catalysed cross-coupling of these iodoalkenes is also explored. © 2000 Elsevier Science Ltd. All rights reserved.

The oximidines (e.g. oximidine I, **1**),[1] the lobatamides (e.g. lobatamide C, **2**)[2] and CJ-12950, **3**,[3] all contain the unusual conjugated *O*-methyl oxime enamide side chain, in contrast to the other members of the salicylate family of antitumour natural products.[4]



Oximidine I **1** Lobatamide C **2** CJ-12950 **3**

As part of a programme to prepare salicylate natural products and their analogues for anti-cancer screening,[5] we investigated routes to conjugated *O*-methyl oxime systems. The recent publications in this area by Kitahara et al.[6] and Porco et al.[7] prompt us to reveal our preliminary results.

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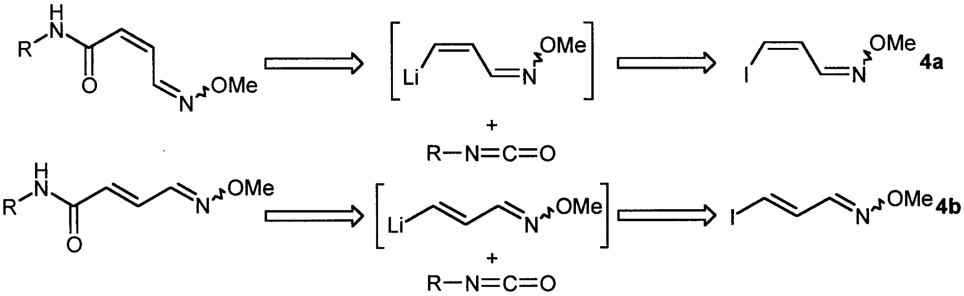
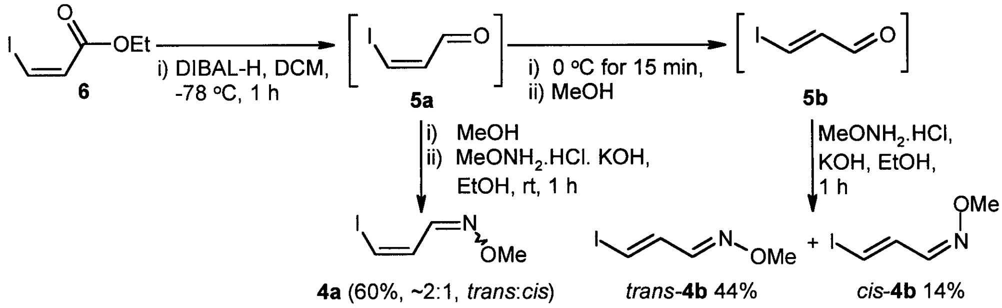
Following our approach to the lansamides and lansiumamides,[5] which we are currently applying to the synthesis of the apicularens, we envisaged the construction of the conjugated *O*-methyl oxime enamide side chain by organometallic addition to isocyanates, as shown in Scheme 1. Kitahara's group used the same approach.[6]



Scheme 1.

Synthesis of the precursor iodides **4a** and **4b** was achieved by the treatment of corresponding iodoacroleins **5a** and **5b**, readily derived from ethyl (2*Z*)-3-iodoacrylate **6**,[8] with a mixture of methoxylamine hydrochloride and potassium hydroxide (Scheme 2). Oxime **4a** could only be isolated as an inseparable mixture of oxime isomers (~2:1 *trans*:*cis* by ^{1}H NMR spectroscopy) but **4b** was isolated as separable *trans*- and *cis*-oxime isomers (~3:1).[9]

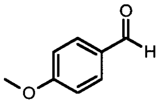
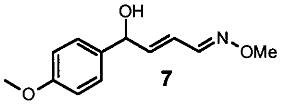
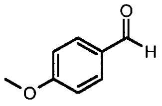
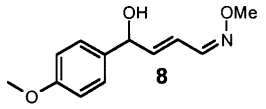
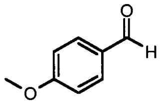
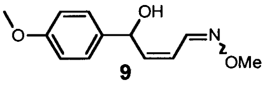
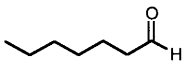
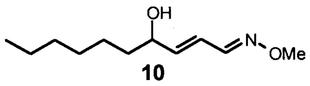
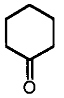
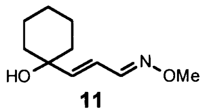
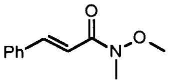
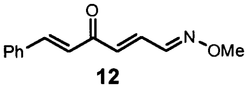
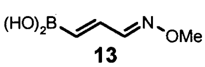
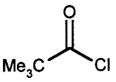
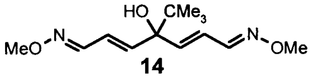
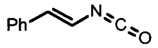
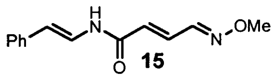
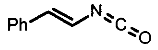
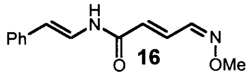
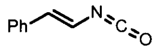
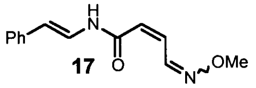


Scheme 2.

With the iodides **4a** and **4b** in hand, their chemistry was investigated. First, the lithium–iodine exchange reaction and the addition of the resulting organolithium reagents to a variety of electrophiles was examined in order to establish the general applicability of *O*-methyl oxime containing organometallic reagents. The organolithium species derived from **4a**,**b** proved to be unstable, resulting in extensive decomposition when the reaction was attempted at temperatures above −78°C. Even at −78°C reaction times had to be limited to ≤10 minutes. Longer reaction times, or the use of a more coordinating solvent such as THF, led to significant decomposition. The results are summarised in Table 1.

As can be seen, the organolithium reagents derived from *trans*-**4b** and *cis*-**4b** underwent addition to anisaldehyde to give adducts **7** and **8** in ca. 70% yield (Table 1, entries i and ii). The corresponding reagent derived from *cis*-/*trans*-**4a** also gave the expected adduct **9**, albeit in slightly lower yield (entry iii). These results confirmed the viability of *O*-alkyl oxime containing organolithium reagents. Further reactions were carried out to establish that aldehydes, ketones, amides and trialkoxyboranes were also suitable electrophiles (Table 1, entries iv–vii). Attempted

Table 1
Addition reactions of lithiated **4a**,**b** to various electrophiles

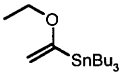
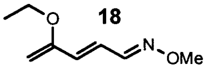
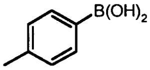
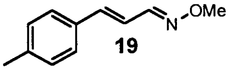
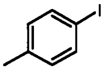
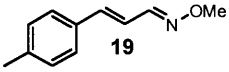
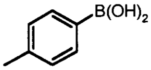
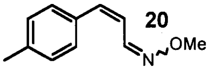
Entry	Substrate	Electrophile	Adduct	Yield (%)
(i)	*trans*-**4b**[10]		 **7**	70
(ii)	*cis*-**4b**		 **8**	69
(iii)	**4a**		 **9**	*trans*: 32, *cis*: 15[a]
(iv)	*trans*-**4b**		 **10**	64
(v)	*trans*-**4b**		 **11**	61
(vi)	*trans*-**4b**		 **12**	62
(vii)	*trans*-**4b**	$B(O^iPr)_3$	 **13**	59
(viii)	*trans*-**4b**		 **14**	17
(ix)	*trans*-**4b**		 **15**	64
(x)	*cis*-**4b**		 **16**	59
(xi)	**4a**		 **17**	*trans*: 34, *cis*: 3[a]

[a] The oxime isomers of adducts **9** and **17** are separable by column chromatography.

alkylations using allyl iodide, benzyl bromide and styrene oxide were unsuccessful; pivaloyl chloride underwent double addition, giving **14** (entry viii). Additions to styryl isocyanate[11] were investigated next (Table 1, entries ix–xi). Again, *trans*-**4b** and *cis*-**4b** gave the expected adducts **15** and **16** in reasonable yield, whereas **4a** gave a lower yield of **17**. In the latter example, it appears that lithiated *trans*-**4a** undergoes isocyanate addition with reasonable efficiency (confirming the results of Kitahara et al.[6]) whereas lithiated *cis*-**4a** appears to give only 3% of the expected adduct *cis*-**17**. It seems likely that *cis*-**17** is unstable under basic conditions.

We also investigated the palladium(0) catalysed cross-coupling reactions of iodides **4a** and **4b** and boronic acid **13** (Table 2). The results shown were obtained using standard conditions[12–14] and are unoptimised.

Table 2
Pd(0) catalysed cross-coupling reactions of **4a**, **4b** and **13**

Entry	Substrate	Conditions	Coupling Partner	Adduct	Yield (%)
(i)	*trans*-**4b**	5% $Pd(PPh_3)_4$, THF, 60 °C, 4 h		 **18**	74
(ii)	*trans*-**4b**	5% $Pd(PPh_3)_4$, K_3PO_4, dioxane, 60 °C, 10 h		 **19**	59
(iii)	**13**	5% $PdCl_2$(dppf), dioxane, 3 M KOH 60 °C, 10 h		 **19**	50
(iv)	**4a**	5% $PdCl_2$(dppf), dioxane, 3 M KOH, 60 °C, 10 h		 **20**	45[a]

[a]*ca.* 1.25:1 *trans*:*cis* by ^{1}H-NMR spectroscopy

Thus, *trans*-**4b** underwent efficient Stille and Suzuki coupling to give adducts **18** and **19** respectively (Table 2, entries i and ii). Adduct **19** was also obtained from the Suzuki coupling of vinyl boronic acid **13** (entry iii). Finally, the mixture of *cis*- and *trans*-**4a** proved to be acceptable Suzuki coupling substrates, giving **20** in reasonable yield (entry iv).

In summary, we have developed both organolithium and palladium-catalysed coupling routes for the preparation of a range of conjugated *O*-methyl oximes, including enamide analogues. We are currently applying this methodology to the synthesis of natural products **1**–**3** and related analogues.

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9. All new compounds were fully characterised by high field NMR spectroscopy and elemental analysis or HRMS.
10. Typical procedure: A stirred solution of *n*-BuLi (1.50 mmol, 2.5 M in hexanes, 0.60 mL) in pentane:ether (3:2, 10 mL) was cooled to −78°C. To this was added a solution of *trans*-**4b** (1.00 mmol, 0.211 g) in pentane:ether (3:2, 2.5 mL) over ~6 min. 10 min after start of addition, a solution of *para*-anisaldehyde (1.55 mmol, 0.268 g) in pentane:ether (3:2, 1.5 mL) was added over 30 sec. After 10 min at −78°C, the mixture was warmed to ambient temperature. Extractive work up and column chromatography gave the product **7** (0.154 g, 70%) as a pale yellow oil; R_f 0.26 (petrol ether:ether, 1:1); ν_{max} (film) 3403 (br), 3000, 2938, 2901, 2837, 1611, 1586, 1513, 1463, 1249, 1175, 1087, 1044, 981, 898, 833 cm^{-1}; δ_H ($CDCl_3$, 270 MHz) 2.50 (1 H, br s, OH), 3.79 (3 H, s, CH_3), 3.85 (3 H, s, CH_3), 5.23 (1 H, br d, *J* 5.5 Hz, C**H**OH), 6.12 (1 H, dd, *J* 5.5, 15.5 Hz, =C**H**–COH), 6.35 (1 H, dd, *J* 10, 15.5 Hz, =CH), 6.88 (2 H, d, *J* 8.5 Hz, ArH), 7.25 (2 H, d, *J* 8.5 Hz, ArH), 7.68 (1 H, d, *J* 10 Hz, HC=N); δ_C ($CDCl_3$, 67.9 MHz) 55.3 (CH_3), 61.8 (CH_3), 73.7 (CH–OH), 114.1 (CH), 123.3 (CH), 127.8 (CH), 134.0 (Ar–C), 142.3 (Ar–CH), 149.6 (Ar–CH), 159.4 (Ar–C); *m*/*z* (CI) 222 (MH^+) [HRMS (CI) calcd. for $C_{12}H_{16}NO_3$, 222.1130. Found: MH^+ 222.1131 (0.2 ppm error)] [Found: C, 65.19; H, 7.12; N 6.14%. $C_{12}H_{15}NO_3$ requires C, 65.14; H, 6.83; N, 6.33%].
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