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Unsaturated enamides via organometallic addition to isocyanates: the synthesis of Lansamide-I, Lansiumamides A–C and SB-204900

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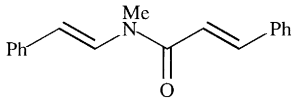
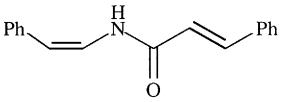
Abstract

Styryl Grignard addition to vinyl isocyanates is employed to prepare the naturally occurring enamides Lansamide-I, Lansiumamides A and B, and SB-204900; the synthesis of Lansiumamide C is also reported.

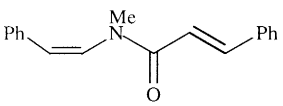
The leaves and fruit of *Clausena lansium* have been used in Southern China to treat a range of ailments including asthma and viral hepatitis.[1] Several novel natural products have been extracted from the plant including the unsaturated enamides Lansamide-I (**1**), Lansiumamide A (**2**) and Lansiumamide B (**3**), and the dihydro-analogue Lansiumamide C (**4**).[2] In a later study, the related epoxide SB-204900 (**5**) was isolated and its structure determined unambiguously by X-ray crystallography.[3]



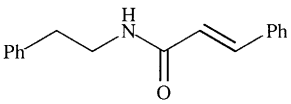
Lansamide-I (**1**)



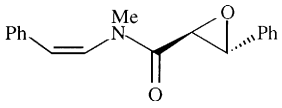
Lansiumamide A (**2**)



Lansiumamide B (**3**)



Lansiumamide C (**4**)



SB-204900 (**5**)

We have a long-standing interest in the development of stereoselective routes to naturally occurring polyenes.[4] As part of this programme we are developing syntheses for macrolides containing unsaturated enamide side chains. Examples include Salicylihalamide A,[5] Apicularen,[6] CJ-12950,[7] the Oximidines,[8]

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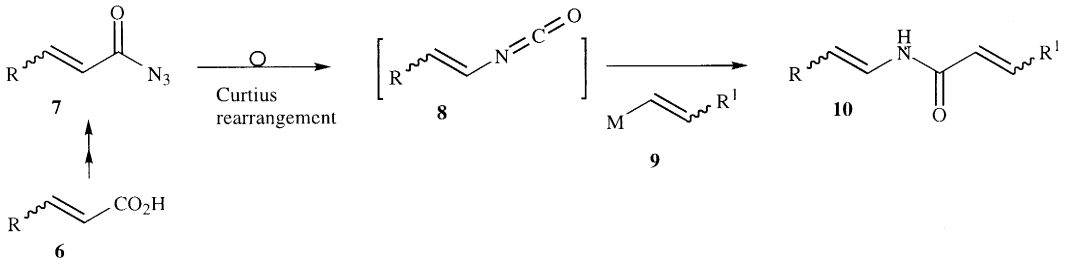
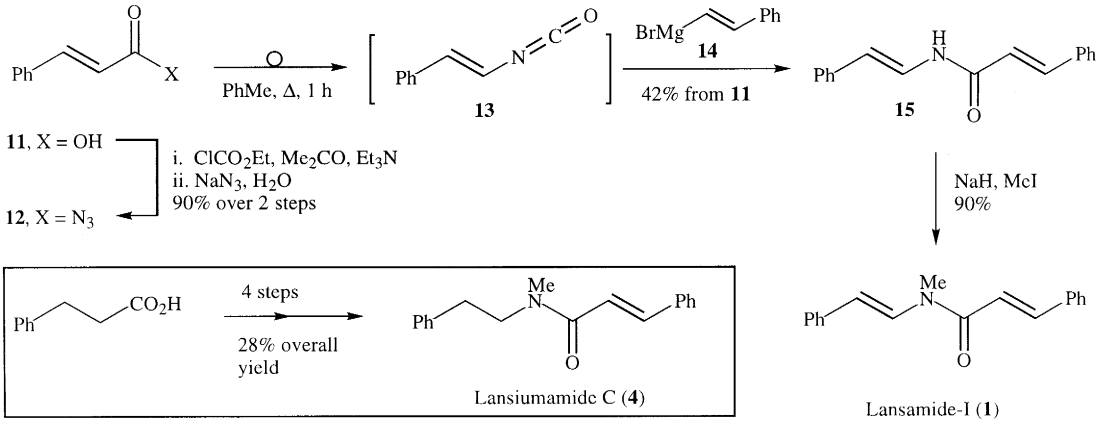
and the Lobatamides.[9] In order to establish methodology suitable for these more complex targets, we set out to prepare compounds **1**–**5**. As far as we are aware, the only previous synthetic publication in this area concerns a synthesis of Lansamide-1 from styrene oxide;[2b] and no-one has reported the synthesis of Lansiumamides or SB-204900.

A number of routes have been employed for the preparation of simple enamides.[10,11] The procedure involving organometallic addition to isocyanates[11] was attractive in view of the ease of preparing vinyl isocyanates **8** using the Curtius rearrangement of acyl azides **7**, readily obtained from α,β-unsaturated acids **6** (Scheme 1). However, very few examples of this procedure have been reported and, to date, only methylmagnesium halides have been employed as organometallic trapping agents with vinyl isocyanates **8**.[11,12] In addition, only *E*-enamides have been prepared using this methodology. We decided to study this procedure to determine whether vinyl organometallic reagents **9** could be employed in order to prepare unsaturated enamides **10**: we also planned to establish the degree of stereocontrol available using this methodology. This Letter outlines the results of this study and describes the successful syntheses of the title compounds.[13]



Scheme 1.

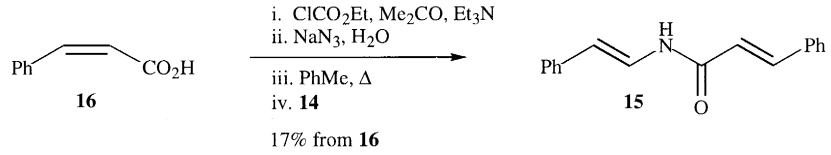
The synthesis of Lansamide-I (**1**) using this methodology was straightforward (Scheme 2). Thus, conversion of cinnamic acid **11** into acyl azide **12** proceeded in excellent yield and thermolysis of **12** to give isocyanate **13**, followed by addition of styryl Grignard **14**, gave adduct **15**[14] in 42% unoptimised, overall yield. It should be noted that other organometallic reagents (e.g. styryllithium, styrylcuprate) proved less satisfactory in this transformation. Finally, methylation proceeded efficiently to give Lansamide-I (**1**) with consistent m.p. (119–120°C; lit.[2a] 119–120°C) and ^{1}H NMR spectral data. This methodology was also employed to prepare Lansiumamide C (**4**) from 3-phenylpropanoic acid as shown in Scheme 2.



Scheme 2.

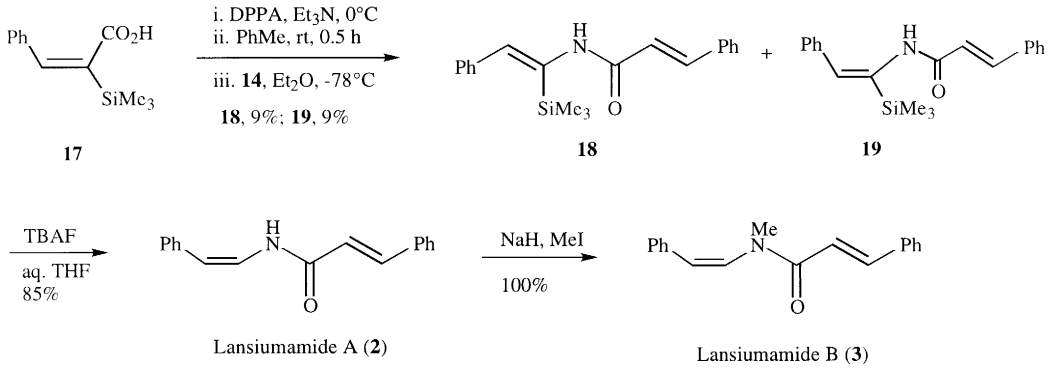
We turned next to the preparation of Lansiumamide A and Lansiumamide B (Scheme 3). It has been reported that *Z*-arylethenyl isocyanates are available from the corresponding unsaturated acids via

the Curtius procedure.[10c] When *Z*-cinnamic acid **16** was treated under the same conditions as before, however, the only product that was observed was the isomerised *E*-adduct **15**, which had been obtained in the earlier study. Different procedures were explored for the formation of the acyl azide,[10c] and a range of conditions investigated for the Curtius rearrangement–Grignard sequence, but without success.



Scheme 3.

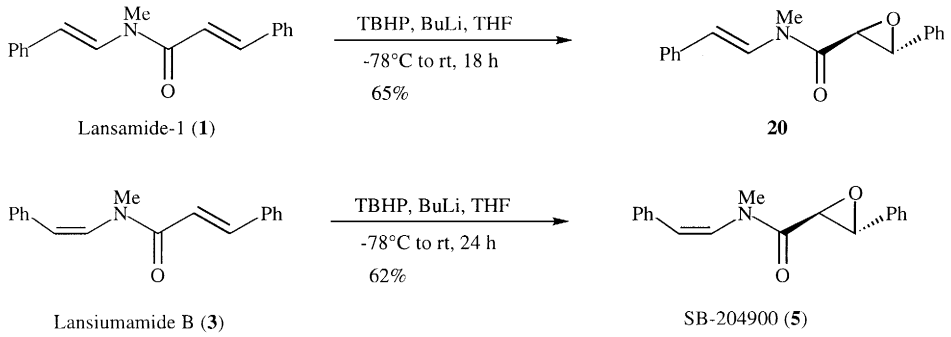
We therefore explored the novel sequence shown in Scheme 4 which commenced with silyl acid **17**[15] in an attempt to prevent or minimise vinyl isocyanate isomerisation. Acyl azide formation proved inefficient using the chloroformate procedure but was successfully carried out using diphenylphosphoryl azide (DPPA).[10c] Conversion of the azide into the vinyl isocyanate proceeded at room temperature (monitored by IR spectroscopy). Addition of the styryl Grignard reagent **14** gave a 1:1 mixture of the required vinylsilane **19** and its isomer **18** which were separable by chromatography. Thus, the silyl modification was successful and, despite the disappointing yield of **19**, sufficient material was available to complete the synthesis. Desilylation without isomerisation was accomplished by treating **19** with tetrabutylammonium fluoride (TBAF) in aqueous THF giving Lansiumamide A (**2**, m.p. 122–125°C; lit.[2a] 121–123°C) and its methylation proceeded quantitatively to produce Lansiumamide B (**3**, m.p. 71–73°C; lit.[2a] 72–73°C). In both cases spectral data were consistent with those published and with assigned structures.



Scheme 4.

We also investigated the epoxidation reactions of Lansamide-I (**1**) and Lansiumamide B (**3**) as shown in Scheme 5. The use of *t*-butyl hydroperoxide (TBHP) and an organic base[16] was unsuccessful but the Meth-Cohn conditions (TBHP, BuLi)[17] gave efficient conversion into the corresponding epoxides. Epoxide **20** has not been isolated from *Clausena lansium* but epoxide **5** is SB-204900 and this constitutes the first synthesis of this compound.[18]

In summary, we have established that vinyl Grignard reagent **14** is an efficient organometallic trapping agent with *E*-vinyl isocyanate **13**, and that this methodology can be employed to prepare Lansamide-I (**1**). We have also shown that the corresponding *Z*-vinyl isocyanate undergoes isomerisation during this elaboration process but that this problem can be partly overcome using silicon technology. As part of this study we have completed the first syntheses of Lansiumamides A–C and SB-204900. We are currently utilising this methodology in the preparation of more complex macrolide natural products.



Scheme 5.

Acknowledgements

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18. Data for **5**: δ_H (500 MHz, $CDCl_3$) 3.13 (3H, s, NMe), 3.76 (1H, d, *J*=2), 3.80 (1H, d, *J*=2), 6.22 (1H, d, *J*=8.6), 6.34 (1H, d, *J*=8.6), 6.96–7.28 (rem.); lit.[3] δ_H (400 MHz, $CDCl_3$) 3.13 (3H, s, NMe), 3.77 (1H, d, *J*=1.8), 3.80 (1H, d, *J*=1.8), 6.22 (1H, d, *J*=8.5), 6.34 (1H, d, *J*=8.5), 6.98–7.27 (rem.); HRMS (CI): found: MH^+, 280.1337. $C_{18}H_{18}NO_2$ requires: 280.1338 (0.2 ppm error).