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Stereoselective Synthesis of the Bicyclic Core Structure of the Highly Oxidised Sesquiterpene Neoliacinic Acid

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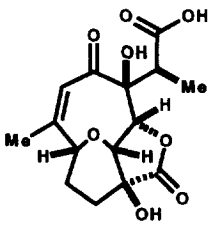
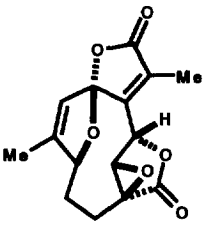
Abstract: The bicyclic core (**3**) of the sesquiterpene neoliacinic acid (**1**) has been constructed in a stereoselective manner by [2,3]-sigmatropic ring-expansion of an oxonium ylide generated catalytically from the α-diazo ketone **4**. Copyright © 1996 Elsevier Science Ltd

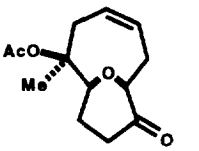
Neoliacinic acid (**1**) is a highly oxidised sesquiterpene which was isolated from leaves of the plant *Neolitsea acciculata* Koidz by Takaoka and co-workers (**Figure 1**).[1] These workers had previously isolated the biosynthetically related cytotoxic sesquiterpene neoliacine (**2**) from the same plant (**Figure 1**).[2] The complex and novel architectural features of neoliacinic acid (**1**), coupled with the potential anti-tumour activity of this natural product,[1] make it an alluring target for synthesis. However, in spite of the unique structure and possible biological activity of this compound, there have been no reports concerning the synthesis of neoliacinic acid (**1**) (**Figure 1**).



1 Neoliacinic acid



2 Neoliacine



3

Figure 1

As part of a programme directed towards the total synthesis of neoliacinic acid, we elected to prepare the ketone **3** as a model for the bicyclic core of the natural product (**Figure 1**). Our synthetic route to the ketone **3** was designed in order to demonstrate the utility of metal carbenoids as reactive intermediates for the construction of complex heterocyclic systems.[3] We planned to prepare the bridged bicycle **3** by tandem oxonium ylide formation and [2,3]-sigmatropic ring-expansion using a metal carbenoid generated catalytically from the α-diazo ketone **4**,[4,5] and to construct the tetrahydrofuran nucleus present in the α-diazo ketone **4** by intramolecular C–H-insertion of a metal carbenoid generated from the acyclic α-diazo ketone **5** (**Figure 2**).[6] Thus, in our synthetic route both reactions utilised for ring construction would involve metal carbenoid intermediates.[7]

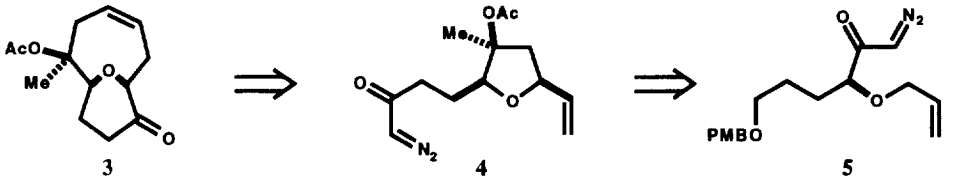
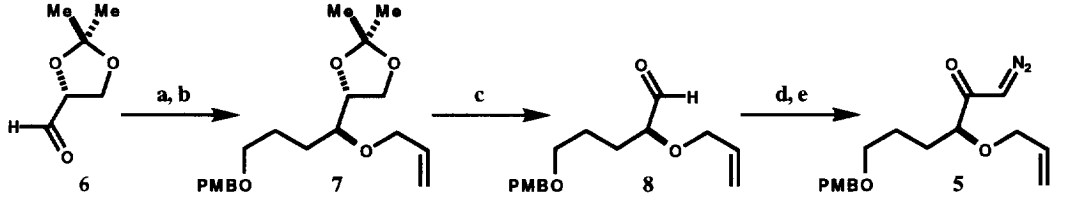


Figure 2

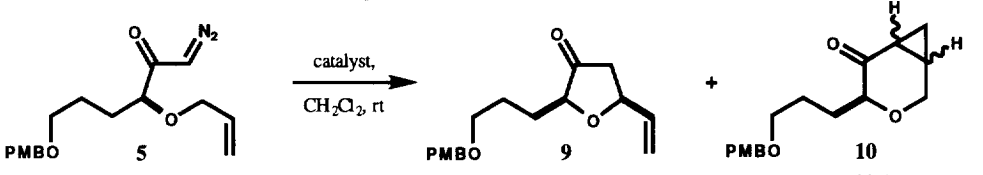
The synthesis of the model system **3** commenced from (*R*)-isopropylideneglyceraldehyde (**6**) (**Scheme 1**). Treatment of the aldehyde **6** with the Grignard reagent prepared from 3-bromopropanol *p*-methoxybenzyl ether,[8] afforded a diastereoisomeric mixture of alcohols (~4:1 ratio) which was then converted into the allyl ether **7**, with the indicated diastereoisomer predominating (**Scheme 1**). Removal of the acetonide protecting group followed by cleavage of the resulting 1,2-diol with $NaIO_4$ afforded the aldehyde **8** in good yield,[9] and this aldehyde was oxidised to the corresponding carboxylic acid using PDC in DMF. The α-diazo ketone **5** was then obtained by conversion of the carboxylic acid into a mixed anhydride by reaction with *i*-BuOCOCl, followed by treatment of this anhydride with excess CH_2N_2.[10]



Reagents: **a** $PMBO(CH_2)_3Br$, Mg, THF, –78°C→rt (87%, 4:1 ratio of isomers); **b** (i) NaH, DMF, rt, (ii) CH_2CHCH_2Br, $Bu_4N^+I^-$, DMF, rt (89%); **c** (i) CF_3CO_2H, THF-H_2O (4:1), reflux, (ii) $NaIO_4$, THF, H_2O, rt (92%); **d** PDC, DMF, rt (89%); **e** (i) *i*-BuOCOCl, Et_3N, Et_2O, rt, (ii) CH_2N_2, Et_2O, 0°C→rt (88%).

Scheme 1

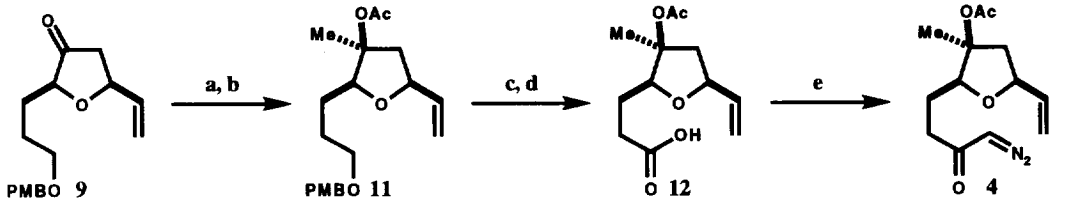
Construction of the furanone **9** by intramolecular C–H-insertion of the carbenoid derived from the α-diazo ketone **5** was then explored (**Scheme 2**).[6] Treatment of the α-diazo ketone **5** with $Rh_2(OAc)_4$ in a variety of solvents afforded varying amounts of the desired product **9** along with a diastereoisomeric mixture of the cyclopropanes **10**. Even under optimum conditions (CH_2Cl_2 at reflux), the yields of the desired C–H-insertion product **9** were modest and substantial amounts of the cyclopropanes **10** were obtained. In an attempt to circumvent this problem, we explored a variety of rhodium(II) complexes as catalysts for carbenoid generation. It transpired that $Rh_2(TPA)_4$ (TPA = O_2CCPh_3) afforded the best results,[11] and the desired furanone **9** was obtained in reasonable yield when this complex was employed as the catalyst.



$Rh_2(OAc)_4$	43%	39%
$Rh_2(TPA)_4$	65%	25%

Scheme 2

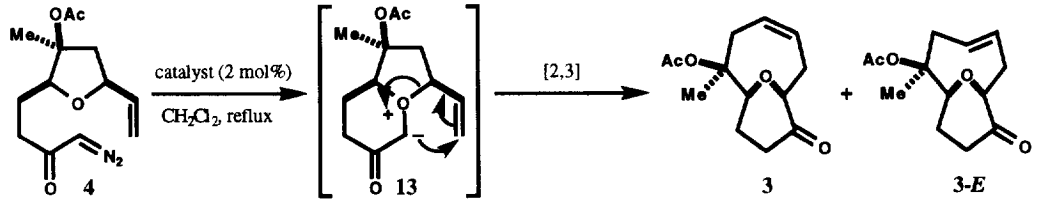
The furanone **9** was elaborated to the cyclisation precursor **4** as shown in **Scheme 3**. Addition of $AlMe_3$ to the ketone **9** followed by acetylation of the resulting tertiary alcohol afforded the acetate **11** in good yield.[12,13] Removal of the PMB protecting group, followed by oxidation with PDC in DMF led directly to the carboxylic acid **12**. Treatment of this carboxylic acid with *i*-BuOCOCl, and reaction of the resulting anhydride with excess CH_2N_2 furnished the required α-diazo ketone **4** in reasonable yield.[10]



Reagents: **a** $AlMe_3$ (3 equiv.), CH_2Cl_2, –78→–10°C (81%); **b** Ac_2O, DMAP, CH_2Cl_2, reflux (83%); **c** DDQ, H_2O, CH_2Cl_2, rt (92%); **d** PDC, DMF, rt (86%); **e** (i) *i*-BuOCOCl, Et_3N, Et_2O, rt, (ii) CH_2N_2, Et_2O (51%).

Scheme 3

The final step in the synthetic route was metal-catalysed tandem oxonium ylide formation and rearrangement reaction of the α-diazo ketone **4**, in order to effect cyclisation with concomitant ring-expansion of the vinyl tetrahydrofuran (**Scheme 4**).[4a] We first explored carbenoid generation using copper catalysis (entries 3–5, **Table**).[5] Treatment of α-diazo ketone **4** with a catalytic amount of $Cu(hfacac)_2$ (hfacac = $CF_3COCHCOCF_3$) in CH_2Cl_2 at reflux afforded a product which appeared to be spectroscopically consistent with the required bicyclic ether **3**.[14] However, when the reaction was performed using $Rh_2(OAc)_4$ as the catalyst under the same conditions (entry 2, **Table**), a product was obtained which was spectroscopically consistent with the bicyclic ether **3**,[14] but which differed from the product isolated from the copper-catalysed reaction. Detailed examination of the ^1H NMR data for both compounds revealed that the product isolated from the copper-catalysed reactions was actually the compound **3-*E***, and that product isolated from the rhodium-catalysed reaction was the expected ketone **3**.[14] When the rhodium-catalysed reaction was performed at 0°C (entry 1, **Table**), equivalent amounts of **3** and **3-*E*** were isolated in a combined yield of 30%. Thus, it appeared that **3-*E*** was formed upon rearrangement of the putative oxonium ylide **13** in both the rhodium- and copper-catalysed reactions, and that isomerisation of **3-*E*** to **3** was occurring in the presence of $Rh_2(OAc)_4$. This hypothesis was confirmed by the finding that **3-*E*** could be converted to **3** in 90% yield by treatment with a catalytic amount of $Rh_2(OAc)_4$ in CH_2Cl_2 at reflux.



Scheme 4

Catalyst[a]	Solvent	Temp.	3,%[b]	3-*E*,%[b]
$Rh_2(OAc)_4$	CH_2Cl_2	0°C	15	15
$Rh_2(OAc)_4$	CH_2Cl_2	reflux	17	0
$Cu(acac)_2$	$(CH_2)_2Cl_2$	reflux	0	34
$Cu(tfacac)_2$	$(CH_2)_2Cl_2$	reflux	0	35
$Cu(hfacac)_2$	CH_2Cl_2	reflux	0	51

a Commercially available catalysts used without further purification
b Isolated yields after flash column chromatography on silica gel

Table

We have prepared the bicyclic core of neoliacinic acid (**1**) in a stereocontrolled fashion, using an efficient route in which carbenoid reactions were used to effect ring construction. We are engaged in a total synthesis of neoliacinic acid (**1**) using this strategy, and results of these endeavours will be reported in due course.

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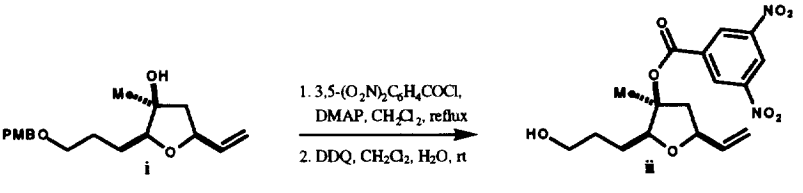
13. The relative configuration of the major product (**i**) obtained by the addition of $AlMe_3$ to the ketone **9** (**Scheme 3**), was established by X-ray analysis of the crystalline derivative **ii** obtained from **i** as shown. The stereochemical outcome of this reaction was contrary to that predicted, based on results reported by Nicolaou for addition of $AlMe_3$ to cyclic ketones [ref. 12(c)].



14. NMR data for **3**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.90 ('dt', *J* = 8.3, 10.0 Hz, 1H), 5.71 ('dt', *J* = 8.1 Hz, 10.0 Hz, 1H), 4.45 (dd, *J* = 6.8, 12.0 Hz, 1H), 4.09 (dd, *J* = 5.1, 10.3 Hz, 1H), 2.64 (dd, *J* = 8.6, 13.6 Hz, 1H), 2.53 (dd, *J* = 7.7, 13.6 Hz, 1H), 2.52–2.48 (m, 2H), 2.45 (ddd, *J* = 5.3, 7.1, 13.9 Hz, 1H), 2.37–2.30 (m, 1H), 2.25–2.16 (m, 1H), 2.15–2.08 (m, 1H), 2.00 (s, 3H), 1.73 (s, 3H). ^{13}C NMR (67.8 MHz, $CDCl_3$) δ 211.6 (s), 170.1 (s), 130.8 (d), 127.6 (d), 87.4 (s), 80.4 (d), 76.5 (d), 34.4 (t), 32.3 (t), 32.0 (t), 23.2 (q), 22. 3 (q), 20.3 (t).
NMR data for **3-*E***: ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.51 (ddd, *J* = 3.2, 12.4, 15.9 Hz, 1H), 5.17 (ddd, *J* = 4.1, 11.6, 15.9 Hz, 1H), 4.43 ('d', *J* = 7.9 Hz, 1H), 4.15 (dd, *J* = 6.1, 12.8 Hz, 1H), 3.23 (dd, *J* = 3.0, 11.5 Hz, 1H), 2.88 (dd, *J* = 4.1, 12.2 Hz, 1H), 2.62 ('t', *J* = 12.0 Hz, 1H), 2.50–2.45 (m, 2H), 2.36 ('dt', *J* = 8.0, 11.7 Hz, 1H), 2.30–2.23 (m, 1H), 1.99 (s, 3H), 1.90–1.81 (m, 1H), 1.82 (s, 3H). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 212.0 (s), 169.4 (s), 135.8 (d), 127.9 (d), 89.7 (s), 81.4 (d), 79.2 (d), 40.6 (t), 39.9 (t), 36.2 (t), 23.1 (q), 22. 4 (q), 20.8 (t).

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