ChemComm

Synthesis of the functionalised core of neoliacinic acid

J. Stephen Clark,*[a] Alexander G. Dossetter,[a] Alexander J. Blake,[a] Wan-Sheung Li[a] and William G. Whittingham[b]

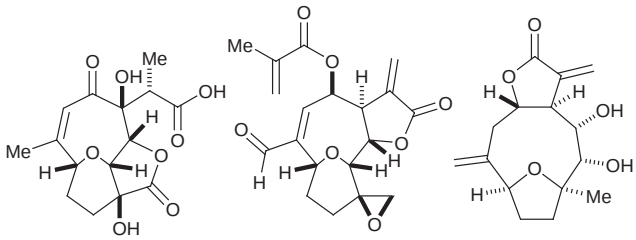
[a] *School of Chemistry, University of Nottingham, University Park, Nottingham, UK NG7 2RD. E-mail: j.s.clark@nottingham.ac.uk*

[b] *ZENECA Agrochemicals, Jealott's Hill Research Station, University Park, Bracknell, Berkshire, UK RG42 6ET*

Received (in Cambridge, UK) 3rd March 1999, Accepted 18th March 1999

An advanced intermediate in the synthesis of neoliacinic acid has been prepared, and the structure and relative stereochemistry have been confirmed by X-ray crystallography.

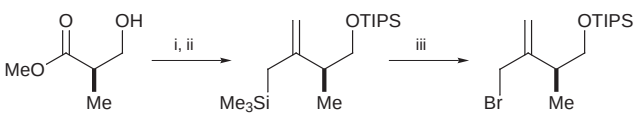
The highly oxidised sesquiterpene neoliacinic acid **1** was isolated from leaves of the plant *Neolitsea acciculata* Koidz in 1987,[1] and is a member of a burgeoning family of bioactive ether-bridged germacranolides. These compounds have been isolated from a variety of plants worldwide; other representative examples are the lactone **2**[2] and the anti-bacterial compound tanargyrolide **3**.[3] Neoliacinic acid **1**[1] is thought to possess cytotoxic activity in common with a structurally related compound, neoliacine, which was isolated from the same plant.[4]



1 neoliacinic acid **2** **3** tanargyrolide

The unusual ether-bridged tricyclic framework of neoliacinic acid **1** coupled with the dense array of oxygen-containing functionality and the number of contiguous stereogenic centres present a formidable challenge to contemporary methods for ring construction and stereocontrol. Recently, we disclosed a powerful new strategy for the synthesis of neoliacinic acid, in which the required ring system was constructed using a carbenoid C–H insertion reaction in conjunction with tandem oxonium ylide generation and rearrangement.[5] We now report the exploitation of this reaction sequence for the construction of an advanced precursor of neoliacinic acid, the structure of which has been confirmed by X-ray crystallography.

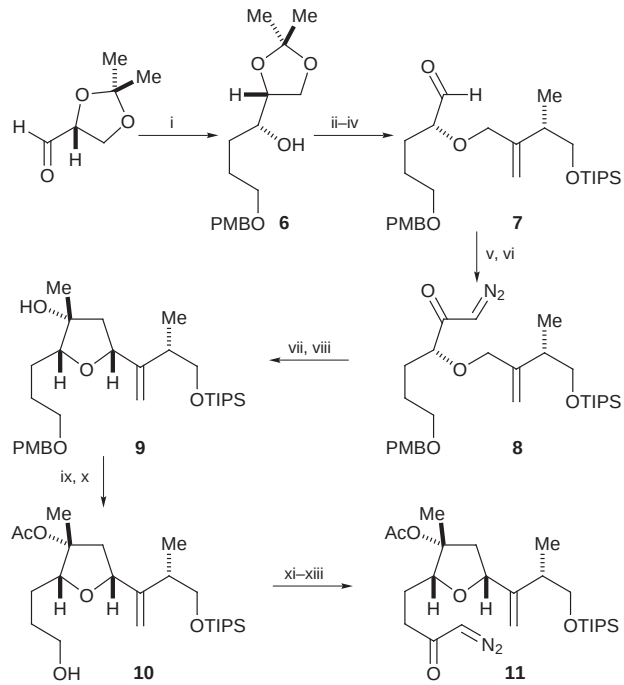
Preparation of the required side chain from commercially available methyl (*R*)-3-hydroxy-2-methylpropionate was undertaken first (Scheme 1). Protection of the hydroxy group as the TIPS ether and reaction of the ester with an excess of the organocerium reagent prepared from $TMSCH_2MgCl$ and $CeCl_3$[6] afforded the allylic silane **4** resulting from double Grignard addition and *in situ* Peterson elimination of the intermediate β-hydroxy disilane.[6,7] The allylic silane **4** was then converted to the allylic bromide **5** by treatment with pyrrolidone hydrotribromide.[8,9] This reagent was used to deliver the precise amount of bromine required, circumventing the problem of over-bromination that was encountered when molecular bromine was employed for the transformation.



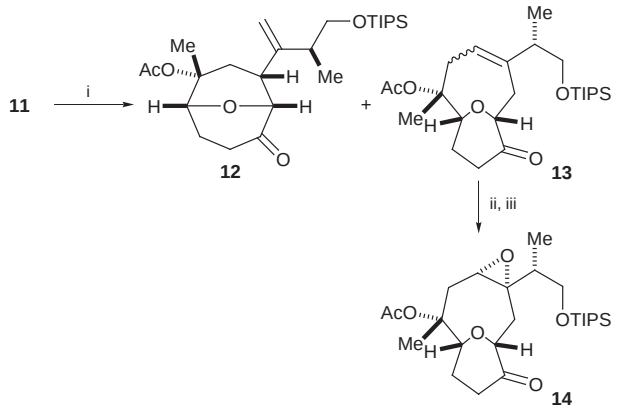
4 **5**

Scheme 1 *Reagents and conditions*: i, Pr^i_3SiCl (1 equiv.), imidazole (2 equiv.), DMF, rt (99%); ii, $TMSCH_2MgCl$ (3 equiv.), $CeCl_3$ (3 equiv.), THF, −70 °C→rt (98%); iii, pyrrolidone hydrotribromide (1 equiv.), pyridine, THF, –10 °C→rt (97%).

Assembly of the cyclisation precursor **11** commenced with (*R*)-isopropylideneglyceraldehyde, which was readily prepared from D-mannitol in two steps using standard literature methods (Scheme 2).[10] Chelation-controlled addition of the organocopper reagent prepared from reaction of CuI with *p*-$MeOC_6H_4CH_2O(CH_2)_3MgBr$ afforded the alcohol **6** in good yield as a 10:1 mixture of diastereoisomers.[11] Alkylation of the alcohol **6** with the allylic bromide **5** under standard ether coupling conditions, followed by acid-promoted removal of the acetonide and periodate cleavage of the resulting 1,2-diol provided the aldehyde **7** in good yield. Subsequent oxidation of



Scheme 2 *Reagents and conditions*: i, *p*-$MeOC_6H_4CH_2O(CH_2)_3MgBr$, CuI, DMS, THF, −78 °C→rt (81%, 10:1 mixture of diastereoisomers); ii,NaH, THF, rt→reflux, then **5**, THF, rt→reflux (90%); iii, PPTS (0.2 equiv.), $HO(CH_2)_2OH$–THF–CH_2Cl_2 (2 : 1 : 1), reflux; iv, $NaIO_4$ (4 equiv.), THF–H_2O (95%, 2 steps); v, PDC (3.5 equiv.), DMF, rt; vi, Bu^iOCOCl (1 equiv.), Et_3N, Et_2O, rt then CH_2N_2, Et_2O, rt (82%, 2 steps); vii, $Rh_2(HNCOCF_3)_4$ (1 mol%), CH_2Cl_2, rt; viii, $AlMe_3$ (3 equiv.), CH_2Cl_2, −78→5 °C (60%, 2 steps); ix, Ac_2O (3 equiv.), DMAP (3 equiv.), CH_2Cl_2, reflux (74%); x, DDQ (1.5 equiv.), CH_2Cl_2–H_2O, rt (94%); xi, PDC (3.5 equiv.), DMF, rt; xii, NaOMe (1 equiv.), MeOH, rt; xiii $(COCl)_2$, C_6H_6, rt, then CH_2N_2, Et_2O, rt (47%, 3 steps).



Scheme 3 *Reagents and conditions*: i, $Cu(hfacac)_2$ (2 mol%), CH_2Cl_2, reflux (**12** 7%, **13** 61%); ii,AIBN, EtSH, C_6H_6, reflux (81%); iii, MCPBA (1.5 equiv.), CH_2Cl_2, reflux (95%).

the aldehyde to afford the carboxylic acid was effected using PDC. The acid was then converted into a mixed anhydride, and this was treated with an excess of CH_2N_2 to give the α-diazo ketone **8**. Exposure of this α-diazo ketone to $Rh_2(HNCOCF_3)_4$[12] in CH_2Cl_2 resulted in formation of a reactive carbenoid that underwent intramolecular C–H insertion adjacent to the ether oxygen[13] to give the required cyclic ether, as a diastereomeric mixture (~7:1, *cis*:*trans*), along with some of the product arising from competitive intramolecular alkene cyclopropanation. Separation of the products was not performed at this stage, and the mixture was treated directly with $AlMe_3$.[5,14] This delivered the required alcohol **9** (60% yield from the α-diazo ketone **8**), which was easily separated from all other products and stereoisomers by chromatography. Standard protocols were then used to acetylate the tertiary hydroxy group and remove the *p*-methoxybenzyl protecting group, and oxidation of the free primary hydroxy group to the carboxylic acid was then performed using PDC. The synthesis of the α-diazo ketone **11** was completed by conversion of the sodium salt of the carboxylic acid to the corresponding acid chloride and treatment of this compound with an excess of CH_2N_2.

The pivotal cyclisation reaction was effected using analogous conditions to those employed in our model study (Scheme 3).[5] Treatment of the α-diazo ketone **11** with copper(II) hexafluoroacetylacetonate [Cu(hfacac)$_2$] in CH_2Cl_2 at reflux afforded the bridged bicyclic ether **13** in 61% yield as a 3:2 mixture of *Z* and *E* isomers along with the compound **12** (7% yield) arising from a [1,2]-shift of the intermediate oxonium ylide.[15] It is noteworthy that a mixture of alkene isomers was obtained upon rearrangement of the putative oxonium ylide intermediate, in contrast with the model reaction which provided the *E* isomer exclusively.[5] Isolation of the [1,2]-shift product[15] was also significant because analogous products were not isolated from model cyclisation reactions.[5]

The mixture of isomers was then subjected to isomerisation under radical conditions[16] to give the thermodynamically favoured *Z* alkene, which was then treated with MCPBA to afford the solid epoxide **14**.† Recrystallisation provided crystals that were suitable for X-ray analysis (Fig. 1),‡ and the structure and relative stereochemistry of the epoxide **14** were confirmed by this method.

We have prepared an advanced intermediate **14** in the synthesis of neoliacinic acid **1**, which possesses the skeleton found in the natural product and most of the oxygen-containing functionality. Completion of the synthesis by elaboration of this highly functionalised intermediate is in progress, and the results of this work will be reported in due course.

We thank the EPSRC for support, and the award of a CASE studentship (to A. G. D.) and a postdoctoral fellowship (to W.-S. L.).

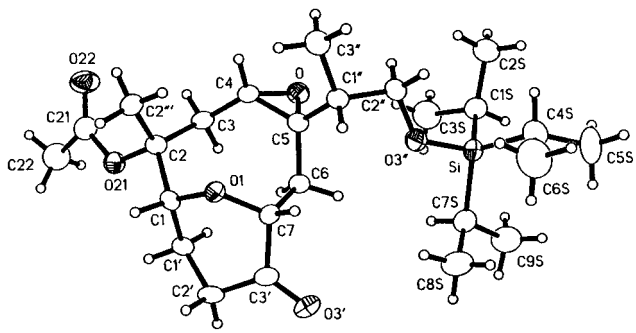


Fig. 1 X-Ray crystal structure of the epoxide **14.**

Notes and references

† *Selected data* for **14**: mp 84–86 °C; $[\alpha]_D^{24}$ −11.9 (*c* 0.426 in $CHCl_3$); $\nu_{max}(CHCl_3)/cm^{-1}$ 2867, 1731, 1459, 1371, 1321, 1085; δ_H(500 MHz; $CDCl_3$) 0.95 (3H, d, *J* 7.0, CHC*H*$_3$), 0.98–1.11 (21H, m, {[C*H*$_3$]$_2$C*H*}$_3$Si), 1.32 (1H, 't', *J* 14.2, O=CCHC*H*$_2$), 1.66 (1H, dd, *J* 9.8, 14.2, C*H*$_2$CH{O}C), 1.82 (3H, s, CC*H*$_3$), 1.84–1.88 (1H, m, C*H*$_2$CH$_2$C=O), 1.90–1.95 (1H, m, C*H*CH$_3$), 1.98 (3H, s, O=CC*H*$_3$), 2.09–2.15 (1H, m, C*H*$_2$CH$_2$C=O), 2.47–2.58 (2H, m, C*H*$_2$C=O), 2.65 (1H, dd, *J* 5.0, 14.4, O=CCHC*H*$_2$), 2.74 (1H, dd, *J* 5.3, 14.2, C*H*$_2$CH{O}C), 3.12 (1H, dd, *J* 5.3, 9.8, CH$_2$C*H*{O}C), 3.51 (1H, dd, *J* 6.7, 9.8, OC*H*$_2$Si), 3.83 (1H, dd, *J* 5.8, 9.8, OC*H*$_2$Si), 4.26 (1H, dd, *J* 5.0, 14.0, O=CC*H*O), 4.46 (1H, dd, *J* 6.1, 12.2, CH$_2$C*H*O); δ_C(126 MHz; $CDCl_3$) 12.3 (d), 13.3 (q), 18.4 (q), 20.3(t), 22.4 (q), 22.7 (q), 33.8 (t), 35.5 (t), 37.1 (t), 39.4 (d), 57.2 (d), 62.7 (s), 66.0 (t), 76.8(d), 77.4 (d), 83.3 (s), 170.0 (s), 210.9 (s); *m*/*z* (FAB) 274 (M^+,100%) (Found: $[M+H]^+$ 469.2966. $C_{25}H_{45}0_6Si$ requires *M*, 469.2985).

‡ *Crystal data* for **14**: $C_{25}H_{44}O_6Si$, *M* = 468.69, orthorhombic, *a* = 8.638(5), *b* = 9.693(9), *c* = 32.149(16)Å, *V* = 2692(3)Å^3, *T* = 150(2)K, space group $P2_12_12_1$ (No. 19), *Z* = 4, μ(Mo-*K*α) = 0.122mm^{-1}, 5535 reflections measured, 5481 unique (R_{int} = 0.023) which were retained in all calculations. The final wR_2 was 0.117 [all data] and R_1 was 0.0506 [4688 $F \geqslant 4\sigma(F)$]. Crystals were grown over a period of 7 d at ambient temperature from a solution in Et_2O into which *n*-hexane had been diffused. The structure was solved by direct methods and refined by full-matrix least-squares on F^2. The Flack absolute structure parameter refined to 0.00(8), confirming the chirality shown. CCDC 182/1200. Crystallographic data are available in CIF format from the RSC web site, see: http://www.rsc.org/suppdata/cc/1999/749/

1 D. Takaoka, H. Nozaki and M. Nakayama, *J. Chem. Soc., Chem. Commun.*, 1987, 1861.
2 J. Jakupovic, V. Castro and F. Bohlmann, *Phytochemistry*, 1987, **26**, 2011.
3 N. Gören, J. Jakupovic and S. Topal, *Phytochemistry*, 1990, **29**, 1467.
4 H. Nozaki, M. Hiroi, D. Takaoka and M. Nakayama, *J. Chem. Soc., Chem. Commun.*, 1983, 1107.
5 J. S. Clark, A. G. Dossetter and W. G. Whittingham, *Tetrahedron Lett.*, 1996, **37**, 5605.
6 B. A. Narayanan and W. H. Bunnelle, *Tetrahedron Lett.*, 1987, **28**, 6261; T. V. Lee, J.A. Channon, C. Cregg, J. R. Porter, F. S. Roden and H. T.-L. Yeoh, *Tetrahedron*, 1989, **45**, 5877.
7 T. J. Mickelson, J. L. Koviach and C. J. Forsyth, *J. Org. Chem.*, 1996, **61**, 9617.
8 D. Grafstein, *J. Am. Chem. Soc.*, 1955, **77**, 6650.
9 D. V. C. Awang and S. Wolfe, *Can. J. Chem.*, 1969, **47**, 706.
10 D. Y. Jackson, *Synth. Commun.*, 1988, **18**, 337.
11 F. Sato, Y. Kobayashi, O. Takahashi, T. Chiba, Y. Takeda and M. Kusakabe, *J. Chem. Soc., Chem. Commun.*, 1985, 1636.
12 A. M. Dennis, J. D. Korp, I. Bernal, R. A. Howard and J. L. Bear, *Inorg. Chem.*, 1983, **22**, 1522.
13 J. Adams, M.-A. Poupart, L. Grenier, C. Schaller, N. Ouimet and R. Frenette, *Tetrahedron Lett.*, 1989, **30**, 1749.
14 For examples of the stereoselective addition of $AlMe_3$ to cyclic ketones, see: E. C. Ashby and J. T. Laemmle, *Chem. Rev.*, 1975, **75**, 521; K. C. Nicolaou, M. E. Duggan and C.-K. Hwang, *J. Am. Chem. Soc.*, 1989, **111**, 6666.
15 For examples of the synthesis of bicyclic ethers by [1,2]-shifts of oxonium ylides generated from carbenoids, see: F. G. West, T. H. Eberlein and R. W. Tester, *J. Chem. Soc., Perkin Trans. 1*, 1993, 2857.
16 R. Annunziata, M. Cinquini, F. Cozzi, C. Gennari and L. Raimondi, *J. Org. Chem.*, 1987, **52**, 4674.

Communication 9/01711I