COMMUNICATION

ChemComm
www.rsc.org/chemcomm

Use of allene in 1,3-dipolar addition to a carbonyl ylide: syntheses of 3-hydroxy-*cis*-nemorensic acid and nemorensic acid

David M. Hodgson* and Frédéric Le Strat

Department of Chemistry, University of Oxford, Chemistry Research Laboratory, Mansfield Road, Oxford, UK OX1 3TA. E-mail: david.hodgson@chem.ox.ac.uk

Received (in Cambridge, UK) 23rd December 2003, Accepted 10th February 2004
First published as an Advance Article on the web 24th February 2004

1,3-Dipolar addition of allene to the carbonyl ylide derived from 6-diazoheptane-2,5-dione is the key step in syntheses of 3-hydroxy-*cis*-nemorensic acid and nemorensic acid.

The stereoselective preparation of polysubstituted saturated oxygen heterocycles, especially structurally complex tetrahydrofurans, has attracted considerable attention in recent years.[1] Previously, we described the first syntheses of *cis*-nemorensic acid **1** and 4-hydroxy-*cis*-nemorensic acid **2**,[2] which are the dicarboxylic (necic) acids obtained from the pyrrolizidine alkaloids mulgediifoline **5**, retroisosenine **6** and 13-hydroxyretroisosenine **7** (Fig. 1).[3] Our approach to these necic acids used $Rh_2(OAc)_4$-catalysed tandem carbonyl ylide formation–1,3-dipolar cycloaddition[4] of 6-diazoheptane-2,5-dione **10** with propyne or propargyl bromide, followed by oxidative cleavage of the ring originally derived from the cyclic carbonyl ylide **11** (Scheme 1). We now report related studies which have led to the syntheses of the necic acids 3-hydroxy-*cis*-nemorensic acid **3**[3b] and nemorensic acid **4**[5] (relative stereochemistry shown), which are obtained from 12-hydroxyretroisosenine **8** and nemorensine **9**, respectively.

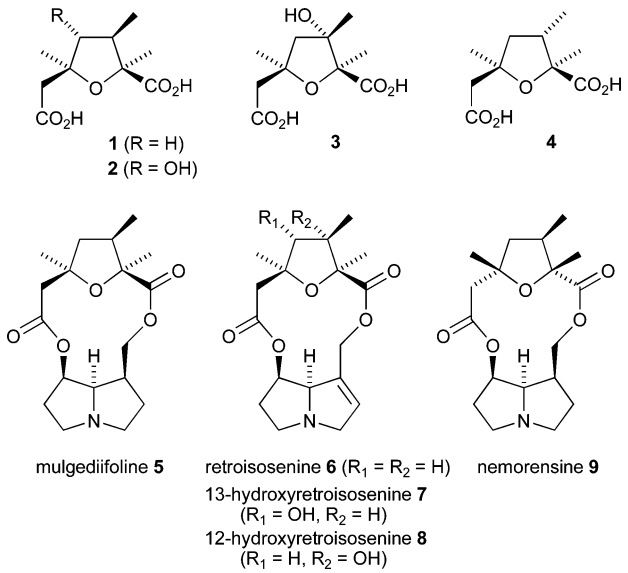
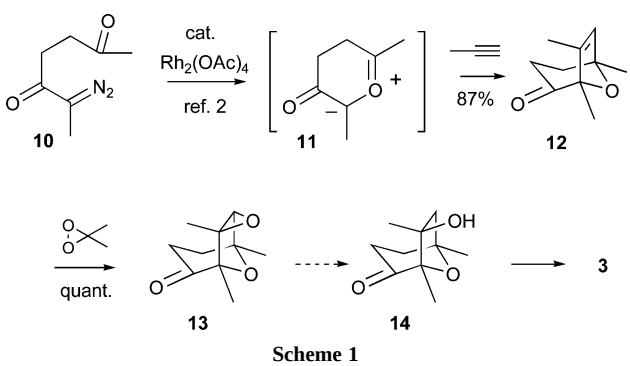
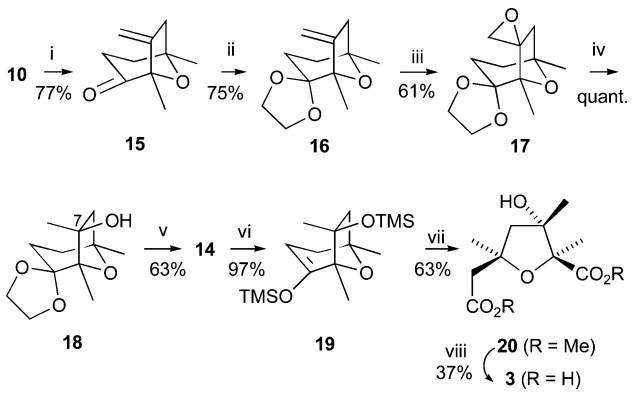


Fig. 1



Scheme 1

The synthesis of 3-hydroxy-*cis*-nemorensic acid **3** was first investigated using the previously described cycloadduct **12** (Scheme 1). However, attempts to convert cycloadduct **12** into the desired *exo*-tertiary alcohol **14** proved fruitless. For example, the *exo*-epoxide **13**, prepared with complete *exo*-stereoselectivity from cycloadduct **12** using dimethyldioxirane (DMDO), was found to be inert to ring opening under a variety of conditions. In order to obtain a less hindered epoxide, we envisaged epoxidation of an exocyclic double bond in a cycloadduct which could potentially be prepared from cycloaddition using allene as the dipolarophile (Scheme 2). Allenes have been used as dipolarophiles with other 1,3-dipoles[6] (DFT studies indicate a stepwise process with allene),[7] and phenoxy-, methoxy- and methoxycarbonyl-allene have been shown to undergo [3 + 2] cycloaddition to symmetrical non-stabilised carbonyl ylides generated using samarium reagents.[8] However, although diazocarbonyl compounds have been extensively examined in tandem carbonyl ylide formation–1,3-dipolar cycloadditions,[4] to the best of our knowledge allenes have not been reported as dipolarophiles in such processes. In the event, we were pleased to observe that reaction of diazodione **10** with allene[9] catalysed by $Rh_2(OAc)_4$ gave the desired cycloadduct **15** (77% yield) as a single regioisomer.†



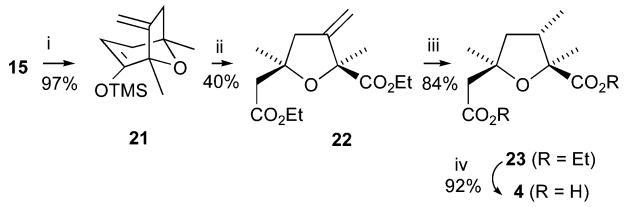
Scheme 2 *Reagents and conditions*: i, allene (~30 equiv.), cat. $Rh_2(OAc)_4$ (0.02 equiv.), CH_2Cl_2, 0 °C, 30 min; ii, ethylene glycol (40 equiv.), CSA (0.1 equiv.), CH_2Cl_2, 25 °C, 48 h; iii, MCPBA (1.3 equiv.), CH_2Cl_2, 25 °C, 18 h; iv, $LiAlH_4$ (2.8 equiv.), THF, 25 °C, 24 h; v, 2 M HCl, THF, 25 °C, 2 h; vi, LDA (3 equiv.), THF, −78°C, 1 h then TMSCl (3.5 equiv.), 25 °C, 2 h; vii, (*a*) O_2/O_3, CH_2Cl_2, −78 °C, 5 min, then 88% HCO_2H (92 equiv.), 35% H_2O_2 (24 equiv.), reflux, 30 min, (*b*) $TMSCHN_2$ (10 equiv.), hexane–MeOH (4 : 1), 25 °C, 3 h; viii, KOH (80 equiv.), H_2O, 25 °C, 3 h.

Cycloadduct **15** could be successfully converted into the *exo*-tertiary alcohol **14** by ketalisation,[10] epoxidation,[11] reductive epoxide ring-opening using $LiAlH_4$[12] and deprotection (Scheme 2). The epoxidation of ketal **16** occurred with good selectivity (5 : 1) in favour of the desired stereochemistry. The structure of the chromatographically separable minor epoxide isomer was determined by X-ray crystallographic analysis;‡ this also established the earlier cycloaddition regiochemistry. Deprotection of hydroxyketal **18** to give the *exo*-tertiary alcohol **14** (63%, 68% based on recovered **18**) was carried out with minimal exposure to aqueous hydrochloric acid in order to reduce epimerisation at C-7. *exo*-Tertiary alcohol **14** was then converted to 3-hydroxy-*cis*-nemor-

DOI: 10.1039/b316908a

ensic acid **3** *via* ozonolysis of the derived disilyl ether **19**. After oxidative work-up, crude **3** was best purified as the dimethyl ester[13] **20**; saponification of the latter gave 3-hydroxy-*cis*-nemorensic acid **3** possessing spectral data consistent with the natural material.[3b]

We also investigated the preparation of nemorensic acid **4** starting from the cycloadduct **15**. As direct hydrogenation of **15** using activated palladium on carbon occurred mainly from the *exo*-face to give a known precursor of *cis*-nemorensic acid **1**,[2] we envisaged cleavage of the bicyclic system before hydrogenation. Thus, **15** was efficiently transformed into the unsaturated silyl enol ether **21** (Scheme 3). Epoxidation of the more activated double bond with DMDO[14] provided an α-hydroxyketone which was not isolated but directly treated with sodium periodate to perform ring cleavage.[15] The resulting oxoacid was further oxidised[16] to give a diacid which was then esterified with diazoethane providing the unsaturated diester **22** in 40% yield over 4 steps from unsaturated silyl enol ether **21**. Nemorensic acid **4**[5] was obtained from unsaturated diester **22** by ester-directed[17] homogeneous hydrogenation in the presence of Crabtree's catalyst which gave saturated diester **23** in good yield (84%) and de (97%), followed by hydrolysis.



Scheme 3 *Reagents and conditions*: i, LDA (1.2 equiv.), THF, −78 °C, 1 h, then TMSCl (2 equiv.), 25 °C, 1 h; ii, (*a*) DMDO (1.1 equiv.), acetone, CH_2Cl_2, 0 °C, 30 min, (*b*) $NaIO_4$ (2 equiv.), THF, H_2O, 25 °C, 30 min, (*c*) $AgNO_3$ (1.2 equiv.), NaOH (3.4 equiv.), EtOH, 25 °C, 15 min, (*d*) CH_3CHN_2 (~3 equiv.), Et_2O, 0 °C, 18 h; iii, H_2 (60 psi), [Ir(cod)py(P-Cy_3)]PF_6 (0.05 equiv.), CH_2Cl_2, 25 °C, 18 h; iv, KOH (17 equiv.), H_2O, 25 °C, 18 h.

In summary, using a tandem carbonyl ylide formation–1,3-addition, we have developed the first synthesis of 3-hydroxy-*cis*-nemorensic acid **3** and a concise (7-step) and highly stereoselective synthesis of nemorensic acid **4** from a common cycloadduct **15**. The successful use of allene as dipolarophile provides encouragement to examine such cumulenes with other stabilised carbonyl ylides, and the application of ester-directed hydrogenation provides a straightforward way to install the C-3 stereocentre in nemorensic acid. While the syntheses reported herein are racemic, the 1,3-dipolar addition with allene could be performed using chiral catalysts.[18] A preliminary screen of representative catalysts gave cycloadduct **15** in 76% yield and 45% ee {$[\alpha]^{25}_D$ +42 (c = 0.5 in $CHCl_3$)}, using Rh_2(*S*-DOSP)$_4$ in CH_2Cl_2 at 0 °C.

We thank the Leverhulme Trust for support of this work, the EPSRC National Mass Spectrometry Service Centre for mass spectra and Dr. Romo de Vivar for providing spectra of **3**.

Notes and references

† Using a dry-ice condenser, allene[9] (~6.4 g, ~160 mmol) was distilled directly into a degassed solution of diazodione **10** (771 mg, 5.00 mmol) in CH_2Cl_2 (50 mL) at −50 °C under argon. After 5 min at −50 °C, $Rh_2(OAc)_4$ (48 mg, 0.11 mmol) was added and the mixture was then placed in a ice bath at 0 °C for 30 min. The reaction mixture was then purged with argon and concentrated under reduced pressure. Purification of the residue by column chromatography (9 : 1, petrol–ether) gave cycloadduct **15** as a colourless oil (640 mg, 77%); R_f 0.42 (petrol–ether, 4 : 1); ν_{max}/cm^{-1} 2974, 1726, 1660, 1449, 1374 and 1080; δ_H(400 MHz; $CDCl_3$) 5.07 (1H, dd, *J* 2.4 and 2.0, =CH), 4.95 (1H, dd, *J* 2.4 and 2.0, =CH), 2.80 (1H, dt, *J* 16.4 and 2.0, allylic CH), 2.68–2.62 (1H, m, allylic CH), 2.56 (1H, ddd, *J* 16.9, 11.2 and 8.4, CH), 2.37 (1H, ddd, *J* 16.9, 7.6 and 2.0, CH), 2.21–2.12 (1H, m, CH), 1.99 (1H, ddd, *J* = 13.2, 8.4 and 2.0, CH), 1.46 (3H, s, Me) and 1.40 (3H, s, Me); δ_C(100 MHz, $CDCl_3$) 205.2 (C=O), 151.5 (=C), 107.4 (=CH_2), 88.0 and 78.8 (COC), 43.0, 38.4 and 33.2 (3 × CH_2), 25.9 and 17.0 (2 × Me); *m/z* (CI+) 184 (M + NH_4, 35%), 167 (M + H, 100), 77 (45); Found M + H, 167.1067. $C_{10}H_{15}O_2$ requires *M* 167.1067.

‡ $C_{12}H_{18}O_4$, *M* = 226.27, monoclinic, *a* = 12.7237(3), *b* = 8.2796(2), *c* = 10.8451(2) Å, *β* = 99.5173(11)°, *U* = 1126.77(4) Å^3, *T* = 150 K, space group $P2_1/c$, *Z* = 4, *μ*(Mo–Kα) = 0.099 mm^{-1}, 11736 reflections measured, 2728 unique (R_{int} = 0.025), 1914 observed with $I > 3\sigma(I)$ used in refinement. The final *Rw* (*F*, observed data) was 0.0549. CCDC 225241. See http://www.rsc.org/suppdata/cc/b3/b316908a/ for crystallographic data in CIF or other electronic format.

1 (*a*) W. Friedrichsen in *Comprehensive Heterocyclic Chemistry II*, ed., C. W. Bird, Pergamon Press, Oxford, 1996, **vol. 2**, pp. 351; (*b*) M. C. Elliot and E. Williams, *J. Chem. Soc., Perkin Trans. 1*, 2001, 2303.
2 D. M. Hodgson, T. D. Avery and A. C. Donohue, *Org. Lett.*, 2002, **4**, 1809.
3 (*a*) A. Romo de Vivar, A.-L. Pérez, A. Arciniegas, P. Vidales, R. Gaviño and J. L. Villaseñor, *Tetrahedron*, 1995, **51**, 12521; (*b*) A.-L. Pérez-Castorena, A. Arciniegas, A. Castro, J. L. Villaseñor, R. A. Toscano and A. Romo de Vivar, *J. Nat. Prod.*, 1997, **60**, 1322.
4 G. Mehta and S. Muthusamy, *Tetrahedron*, 2002, **58**, 9477.
5 For syntheses of nemorensic acid, see: (*a*) L. L. Klein, *J. Am. Chem. Soc.*, 1985, **107**, 2573; (*b*) M. P. Dillon, N. C. Lee, F. Stappenbeck and J. D. White, *J. Chem. Soc., Chem. Commun.*, 1995, 1645; (*c*) J. R. Rodriguez, A. Rumbo, L. Castedo and J. L. Mascareñas, *J. Org. Chem.*, 1999, **64**, 4560; F. López, L. Castedo and J. L. Mascareñas, *Chem. Eur. J.*, 2002, **8**, 884; (*d*) T. Honda and F. Ishikawa, *J. Org. Chem.*, 1999, **64**, 5542; (*e*) T. J. Donohoe, J.-B. Guillermin, C. Frampton and D. S. Walter, *Chem. Commun.*, 2000, 465; T. J. Donohoe, J.-B. Guillermin and D. S. Walter, *J. Chem. Soc., Perkin Trans. 1*, 2002, 1369; (*f*) B. Liu and K. D. Moeller, *Tetrahedron Lett.*, 2001, **42**, 7163; B. Liu, S. Duan, A. C. Sutterer and K. D. Moeller, *J. Am. Chem. Soc.*, 2002, **124**, 10101.
6 *1,3-Dipolar Cycloaddition Chemistry*, ed. A. Padwa, Wiley-Interscience, New York, 1984.
7 K. Kavitha and P. Venuvanalingam, *J. Chem. Soc., Perkin Trans. 2*, 2002, 2130.
8 (*a*) M. Hojo, H. Aihara and A. Hosomi, *J. Am. Chem. Soc.*, 1996, **118**, 3533; (*b*) M. Hojo, N. Ishibashi and A. Hosomi, *Synlett*, 1996, 234; (*c*) M. Hojo, H. Aihara, H. Ito and A. Hosomi, *Tetrahedron Lett.*, 1996, **37**, 9241.
9 H. N. Cripps and E. F. Kiefer, *Org. Synth.*, 1973, **Coll. Vol. V**, 22.
10 T. Flessner, V. Ludwig, H. Siebeneicher and E. Winterfeldt, *Synthesis*, 2002, 1373.
11 H. Flörke and E. Schaumann, *Synthesis*, 1996, 647.
12 E. J. Corey and K. Liu, *J. Am. Chem. Soc.*, 1997, **119**, 9929.
13 P. Yuan, R. Plourde, M. R. Shoemaker, C. L. Moore and D. E. Hansen, *J. Org. Chem.*, 1995, **60**, 5360.
14 W. Adam, L. Hadjiarapoglou, V. Jäger, J. Klicic, B. Seidel and X. Wang, *Chem. Ber.*, 1991, **124**, 2361.
15 R. Floresca, M. Kurihara, D. S. Watt and A. Demir, *J. Org. Chem.*, 1993, **58**, 2196.
16 J. E. McMurry and R. G. Dushin, *J. Am. Chem. Soc.*, 1990, **112**, 6942.
17 A. H. Hoveyda, D. A. Evans and G. C. Fu, *Chem. Rev.*, 1993, **93**, 1307.
18 For some recent examples of asymmetric carbonyl ylide cycloadditions, see: (*a*) D. M. Hodgson, P. A. Stupple, F. Y. T. M. Pierard, A. H. Labande and C. Johnstone, *Chem. Eur. J.*, 2001, **7**, 4465; (*b*) D. M. Hodgson, R. Glen, G. H. Grant and A. J. Redgrave, *J. Org. Chem.*, 2003, **68**, 581; (*c*) D. M. Hodgson, A. H. Labande, R. Glen and A. J. Redgrave, *Tetrahedron: Asymmetry*, 2003, **14**, 921; (*d*) D. M. Hodgson, A. H. Labande, F. Y. T. M. Pierard and M. A. Exposito Castro, *J. Org. Chem.*, 2003, **68**, 6153.