ORGANIC
LETTERS

2002
Vol. 4, No. 10
1809−1811

Concise, Stereoselective Syntheses of *cis*-Nemorensic Acid and 4-Hydroxy-*cis*-nemorensic Acid via Tandem Carbonyl Ylide Formation–Cycloaddition

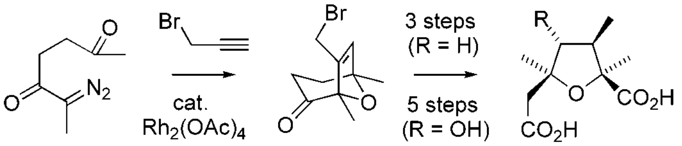
David M. Hodgson,* Thomas D. Avery, and Andrew C. Donohue

*Dyson Perrins Laboratory, Department of Chemistry, University of Oxford,
South Parks Road, Oxford OX1 3QY, U.K.*

david.hodgson@chem.ox.ac.uk

Received March 22, 2002

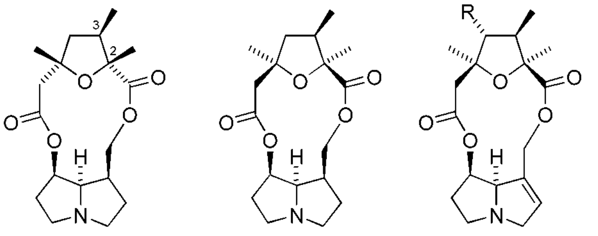
ABSTRACT



1,3-Dipolar cycloaddition of propargyl bromide with the carbonyl ylide derived from 6-diazoheptane-2,5-dione is the key step in concise syntheses of *cis*-nemorensic acid and 4-hydroxy-*cis*-nemorensic acid.

The stereoselective preparation of highly substituted oxygen heterocycles, especially structurally complex tetrahydrofurans, has attracted considerable attention in recent years.[1] A rich source of such synthetically challenging tetrahydrofurans is the *Senecio* class of pyrrolizidine alkaloids, (e.g., Figure 1).[2] These natural products show diverse biological activity ranging from potent hepatotoxicity to antitumour activity.[3]

The synthesis of nemorensic acid (the dicarboxylic (necic) acid obtained from nemorensine) has been accomplished by a number of inventive approaches.[4] However, these strategies are not directly applicable to the tetrahydrofuran stereochemistry found in mulgediifoline and (hydroxy)retroisosenine. For example, the two cycloaddition approaches to nemorensic acid both used alkenes which are tethered to a furan[4a] or oxidopyrylium[4g] via a sulfur atom; these intramolecular cycloadditions nicely ensure complete control of both the tetrahydrofuran substitution pattern and, following reductive removal of sulfur, the *cis*-orientation between the C-2 and C-3 Me groups (Figure 1).


nemorensine

mulgediifoline

retroisosenine (R = H)
12-hydroxyretroisosenine
(R = OH)

Figure 1. Pyrrolizidine alkaloids from the *Senecio* genus.

---

(1) (a) Friedrichsen, W. In *Comprehensive Heterocyclic Chemistry II*; Bird, C. W., Ed.; Pergamon Press: Oxford, 1996; Vol. 2, pp 351−393. (b) Elliott, M. C.; Williams, E. *J. Chem. Soc., Perkin, Trans. 1* **2001**, 2303−2340.

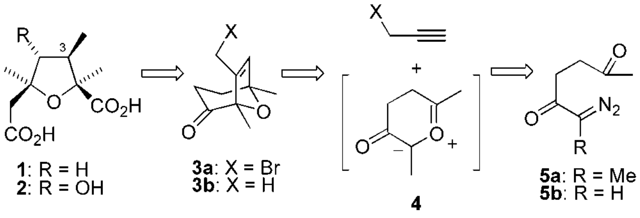
(2) (a) Romo de Vivar, A.; Pérez, A.-L.; Arciniegas, A.; Vidales, P.; Gaviño, R.; Villaseñor, J. L. *Tetrahedron* **1995**, *51*, 12521−12528. (b) Pérez-Castorena, A.-L.; Arciniegas, A.; Castro, A.; Villaseñor, J. L.; Toscano, R. A.; Romo de Vivar, A. *J. Nat. Prod.* **1997**, *60*, 1322−1325.

(3) Liddell, J. R. *Nat. Prod. Rep.* **2001**, *18*, 441−447.

10.1021/ol025917c CCC: $22.00

In connection with our interest in tandem carbonyl ylide formation−1,3-dipolar cycloaddition of diazocarbonyl compounds in natural product synthesis,[5] we considered that oxidative cleavage of the ring originally derived from a cyclic carbonyl ylide (e.g., **4**, Scheme 1) could provide a straightforward synthesis of polysubstituted tetrahydrofurans, and in particular an efficient entry to the previously unsynthesized *cis*-nemorensic acids **1** and **2**.[6]

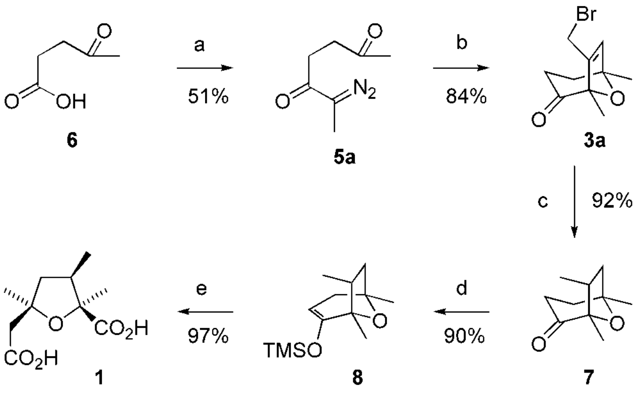
Scheme 1. Retrosynthetic Analysis of Necic Acids



Pioneering studies by Padwa et al. have established Rh(II)-catalyzed tandem carbonyl ylide formation−1,3-dipolar cycloaddition of diazocarbonyl compounds as an excellent method for the synthesis of oxapolycycles.[7] Indeed, Padwa has shown that diazodione **5b** undergoes intermolecular cycloaddition with propargyl chloride (in our desired regiochemical sense, and in 60% yield),[8] thus providing encouraging precedent for the approach we wished to investigate. Nevertheless, it was not clear at the outset of our studies if an α-alkyl (e.g., methyl) α-diazoketone would successfully undergo carbonyl ylide formation and 1,3-dipolar cycloaddition,[9] or if the additional Me substituent would affect cycloaddition regioselectivity.

In the event diazodione **5a** (readily available from levulinic acid **6** and diazoethane[10]) underwent $Rh_2(OAc)_4$-catalyzed tandem carbonyl ylide formation−cycloaddition with propargyl bromide to give cycloadduct **3a** in good yield (84%, Scheme 2).[11] That cycloaddition had occurred with the desired regioselectivity was initially indicated by NOE studies (and ultimately confirmed by X-ray crystallographic analysis, vide infra).

Scheme 2. Synthesis of *cis*-Nemorensic Acid **1**[a]



[a] (a) Et_3N (1 equiv), $ClCO_2CH_2CHMe_2$ (1 equiv), Et_2O, 0 → 25 °C, 2 h, then $MeCHN_2$ (4 equiv), Et_2O, 0 °C, 18 h; (b) $BrCH_2C{\equiv}CH$ (3 equiv), $Rh_2(OAc)_4$ (cat.), CH_2Cl_2, 25 °C, 3 h; (c) H_2 (1 atm), Pd/C (10%), MeOH, 25 °C, 48 h; (d) LDA (1.1 equiv), THF, −78 °C, 2 h, then TMSCl (2 equiv), −78 → 25 °C, 1 h; (e) O_2/O_3, CH_2Cl_2, −78 °C, 5 min, then 35% H_2O_2 (12 equiv), 88% HCO_2H (46 equiv), 100 °C, 30 min.

Reaction of cycloadduct **3a** with H_2−Pd/C in MeOH effected both hydrogenolysis of the C−Br bond and *exo* selective alkene hydrogenation to give a single saturated ketone **7** (92%), with the correct relative stereochemistry at all three stereocenters for *cis*-nemorensic acid synthesis. Thus, propargyl bromide functions as a convenient equivalent of propene in this two-step cycloaddition reduction sequence. Propene itself proved unreactive in the cycloaddition step. This is not surprising, given the lack of success with other unstrained alkenes in attempted related intermolecular cycloadditions.[8] Propyne (present in excess) did undergo successful cycloaddition to give a single cycloadduct, **3b** and in good yield (87%). Interestingly, addition of trace amounts of HBr (conditions otherwise as in Scheme 2) was found to be necessary to effect hydrogenation of cycloadduct **3b** to give ketone **7** (91%). Formation of the silyl enol ether **8** (90%) under standard conditions[12] was followed by oxidative cleavage to give *cis*-nemorensic acid **1**. This latter step was efficiently carried out (97% from silyl enol ether **8**) by ozonolysis and reaction of the crude ozonide with aqueous formic acid and hydrogen peroxide. Spectral data for synthetic *cis*-nemorensic acid **1** were in accord with those of the natural isolate;[2a] X-ray crystallographic analysis of our synthetic material (Figure 2) provided unequivocal confirmation.[13]

It was envisaged (Scheme 1) that cycloadduct **3** might also be used to access more highly functionalized tetrahydro-

---

(4) (a) Klein, L. L. *J. Am. Chem. Soc.* **1985**, *107*, 2573−2574. (b) Dillon, M. P.; Lee, N. C.; Stappenbeck, F.; White, J. D. *J. Chem. Soc., Chem. Commun.* **1995**, 1645−1646. (c) Rodríguez, J. R.; Rumbo, A.; Castedo, L.; Mascareñas, J. L. *J. Org. Chem.* **1999**, *64*, 4560−4563. (d) Honda, T.; Ishikawa, F. *J. Org. Chem.* **1999**, *64*, 5542−5546. (e) Donohoe, T. J.; Guillermin, J.-B.; Frampton, C.; Walter, D. S. *Chem. Commun.* **2000**, 465−466. (f) Liu, B.; Moeller, K. D. *Tetrahedron Lett.* **2001**, *42*, 7163−7165. (g) López, F.; Castedo, L.; Mascareñas, J. L. *Chem. Eur. J.* **2002**, *8*, 884−899.

(5) Hodgson, D. M.; Bailey, J. M.; Villalonga-Barber, C.; Drew, M. G. B.; Harrison, T. *J. Chem. Soc., Perkin Trans. 1* **2000**, 3432−3443.

(6) The "*cis*" terminology refers to the *cis* relationship of the C-3 Me and the two carboxylic acid groups.

(7) (a) Padwa, A.; Weingarten, M. D. *Chem. Rev.* **1996**, *96*, 223−269. (b) Doyle, M. P.; McKervey, M. A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*; John Wiley & Sons: New York, 1998; Chapter 7.

(8) Padwa, A.; Fryxell, G. E.; Zhi, L. *J. Am. Chem. Soc.* **1990**, *112*, 3100−3109.

(9) During the course of our work, α-methyl α-diazoketones were shown to undergo tandem ylide formation−cycloaddition: (a) Muthusamy, S.; Babu, S. A.; Gunanathan, C.; Suresh, E.; Dastidar, P.; Jasra, R. V. *Tetrahedron* **2000**, *56*, 6307−6318. (b) Wood, J. L.; Thompson, B. D.; Yusuff, N.; Pflum, D. A.; Matthäus, M. S. P. *J. Am. Chem. Soc.* **2001**, *123*, 2097−2098.

(10) Marshall, J. A.; Partridge, J. J. *J. Org. Chem.* **1968**, *33*, 4090−4095.

(11) A small amount (<5% by ^1H NMR) of the regioisomeric cycloadduct was generated which was easily removed by column chromatography.

(12) Fleming, I.; Paterson, I. *Synthesis* **1979**, 736−738.

(13) CCDC 181801 available at http://www.ccdc.cam.ac.uk.

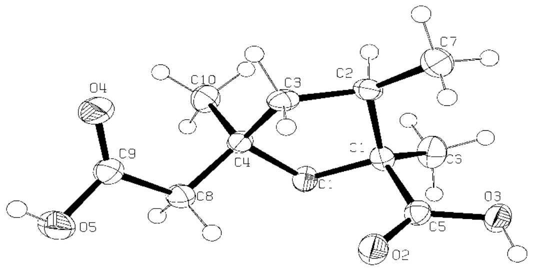
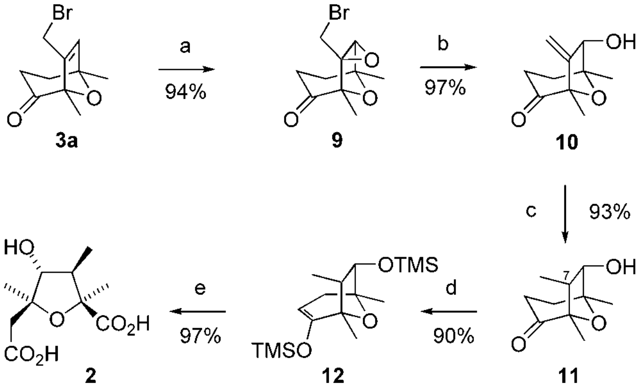


Figure 2. X-ray structure of *cis*-nemorensic acid **1**.

Scheme 3. Synthesis of 4-Hydroxy-*cis*-nemorensic Acid **2**[a]



[a] (a) DMDO (0.1 M in acetone, 5 equiv) CH_2Cl_2, 25 °C, 24 h; (b) Zn (3 equiv), NaI (2.5 equiv), MeOH, 65 °C, 3.5 h; (c) H_2 (1 atm), [Ir(cod)py(PCy_3)]PF_6 (0.05 equiv), CH_2Cl_2, 25 °C, 1 h; (d) LDA (2.1 equiv), THF, −78 °C, 2 h, then TMSCl (3 equiv), −78 → 25 °C, 1 h; (e) O_2/O_3, CH_2Cl_2, −78 °C, 5 min, then 35% H_2O_2 (12 equiv), 88% HCO_2H (46 equiv), 100 °C, 30 min.

furans, in particular 4-hydroxy-*cis*-nemorensic acid **2** (the necic acid obtained from recently reported 12-hydroxy-retroisosenine)[2b] by (formal) *exo*-selective anti-Markovnikov hydration of the embedded dihydrofuran, prior to oxidative cleavage as before. This was achieved starting with epoxidation of cycloadduct **3a** (Scheme 3). Epoxidation to give a single epoxide, **9** (94%), was best carried out using preformed dimethyldioxirane (DMDO),[14] which avoided a competing Baeyer−Villiger reaction observed using per acids.

Attempted formation of alcohol **11** directly from epoxide **9** using H_2−Pd/C in MeOH proceeded in modest yield to generate an inseparable mixture of **11** and 7-*epi*-**11** (45% total yield; **11**:7-*epi* **11**, 3:2). Higher stereoselectivity (**11**: 7-*epi* **11**, 9:1) was achieved if epoxide **9** was converted[15] to allylic alcohol **10** (97%) prior to hydrogenation, but the overall yield remained low (36%). Hydroxyl-directed homogeneous hydrogenation of allylic alcohol **10** in the presence of Crabtree's catalyst generated alcohol **11** in excellent yield (93%) as a single stereoisomer. The relative stereochemistry of alcohol **11** was established to be that required for 4-hydroxy-*cis*-nemorensic acid **2** by X-ray crystallographic analysis.[16] Silyl enol ether **12** formation was effected (with concomitant silyation of the secondary alcohol) to give disilyl ether **12** (90%). Ozonolysis of disilyl ether **12** followed by oxidative workup, as in our *cis*-nemorensic acid synthesis, gave 4-hydroxy-*cis*-nemorensic acid **2** in excellent yield (97%), and with spectral data consistent with the natural material.[2b]

In summary, using cycloadduct **3a** as a pivotal intermediate, we have developed truly concise, sterecontrolled syntheses of previously unsynthesized *cis*-nemorensic acids, demonstrating the power of tandem carbonyl ylide formation−cycloaddition in natural product synthesis. While the syntheses reported herein are racemic, the strategy offers the attractive prospect of an enantioselective entry using a chiral catalyst in the ylide formation−cycloaddition.[17] Efforts along these lines are underway.[18]

Acknowledgment. We thank the Leverhulme Trust and the EPSRC (GL/L98022) for support of this work, the EPSRC National Mass Spectrometry Service Centre for mass spectra, and Dr. Romo de Vivar for providing spectra of **1** and **2**.

Supporting Information Available: ^{13}C NMR spectra for previously unreported compounds (**3a**, **5a**, **7**, **8**, **9**, **10**, **11**, and **12**). This material is available free of charge via the Internet at http://pubs.acs.org.

OL025917C

---

[14] (a) Adam, W.; Bialas, J.; Hadjiarapoglou, L. *Chem. Ber*. **1991**, *124*, 2377. (b) Lusinchi, X.; Harquet, G. *Tetrahedron* **1997**, *53*, 13727−13738.

[15] Nicolaou, K. C.; Duggan, M. E.; Ladduwahetty, T. *Tetrahedron Lett*. **1984**, *25*, 2069−2072.

[16] CCDC 181906 available at http://www.ccdc.cam.ac.uk.

[17] Hodgson, D. M.; Stupple, P. A.; Pierard, F. Y. T. M.; Labande, A. H.; Johnstone, C. *Chem. Eur. J.* **2001**, *7*, 4465−4476.

[18] A preliminary screen of representative chiral catalysts[17] gave cycloadduct **3a** in up to 34% ee ($[\alpha]^{25}_{D} = +129$ (c 1.0, $CHCl_3$)), using Rh_2(S-DOSP)$_4$ in CH_2Cl_2 at −10 °C. Full details of this study will be reported in due course.