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Stereocontrolled Syntheses of the Nemorensic Acids Using 6-Diazoheptane-2,5-dione in Carbonyl Ylide Cycloadditions

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Levulinic acid-derived 6-diazoheptane-2,5-dione (**9**) serves as a common precursor in a formal synthesis of frontalin **19**, and in syntheses of *cis*-nemorensic acid **1**, 4-hydroxy-*cis*-nemorensic acid **2**, 3-hydroxy-*cis*-nemorensic acid **3**, and nemorensic acid **4**. The key step in these syntheses is the $Rh_2(OAc)_4$-catalyzed tandem carbonyl ylide formation−intermolecular 1,3-dipolar cycloadditions of diazodione **9** with formaldehyde, alkynes or allene, which occur with high regioselectivity. Subsequent oxidative cleavage of the ring originally derived from the cyclic carbonyl ylide intermediate provides a straightforward access to polysubstituted tetrahydrofurans, and in particular an efficient entry to the nemorensic acids. Enantioselective cycloadditions with diazodione **9**, using chiral rhodium catalysts, gave cycloadducts in up to 51% ee.

Ibata and Padwa developed the use of copper and rhodium complexes as catalysts for the decomposition of diazocarbonyl compounds to produce transient carbonyl ylides, which undergo cycloaddition with a range of dipolarophiles.[1] This is an attractive method for synthesis, because of the relative ease of access of the starting materials combined with the rapid increase in molecular complexity that occurs during the tandem carbonyl ylide formation−cycloaddition process. The strategy has found wide utility in targeted synthesis. We were attracted to the use of 6-diazoheptane-2,5-dione (**9**) as a substrate for this chemistry (Scheme 1). This precursor could potentially allow concise access to nemorensic acids **1**−**4**, following oxidative cleavage of the ring originally derived from the cyclic carbonyl ylide **8**.

The nemorensic acids **1**−**4** are dicarboxylic (necic) acids obtained from certain pyrrolizidine alkaloids **12**−**16** (Figure 1).[2] These natural products have been the focus of considerable attention due to their challenging structure combined with diverse biological activity ranging from potent hepatotoxicity to antitumour activity. The synthesis of nemorensic acid **4** has been accomplished by several approaches;[3] however, we considered our strategy would have the benefit of brevity, and enough flexibility to address the various challenging substitution patterns and stereochemical issues found in all of the nemorensic acids, shown in Scheme 1.[4]

Prior to our work, Padwa had prepared the diazodione **10** from levulinic acid **11** and had examined its cycloaddition chemistry with a range of dipolarophiles;[5] importantly, among these propargyl chloride had been shown to undergo cycloaddition in the regiochemical sense desired for our projected nemorensic acid syntheses. Although during the course of our studies other α-methyl α-diazoketones have been shown to undergo tandem ylide formation−cycloaddition,[6] it was not clear at the outset of our work whether the additional methyl substituent at the diazo-bearing carbon would allow our proposed chemistry to occur, and whether this substituent might affect the regiochemical outcome. Similarly to diazodione **10**, diazodione **9** was prepared from levulinic acid **8**, but with diazoethane[7] instead of diazomethane (Scheme 2). The best yields were obtained if diazoethane (∼3 equiv) was generated and distilled directly into a

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(3) (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) Rodriguez, J. R.; Rumbo, A.; Castedo, L.; Mascareñas, J. L. *J. Org. Chem.* **1985**, *50*, 4560−4563. López, F.; Castedo, L.; Mascareñas, J. L. *Chem. Eur. J.* **2002**, *8*, 884−899. (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. Donohoe, T. J.; Guilermin, J.-B.; Walter, D. S. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1369−1375. (f) Liu, B.; Moeller, K. D. *Tetrahedron Lett.* **2001**, *42*, 7163−7165. Liu, B.; Duan, S.; Sutterer, A. C.; Moeller, K. D. *J. Am. Chem. Soc.* **2002**, *124*, 10101−10111.

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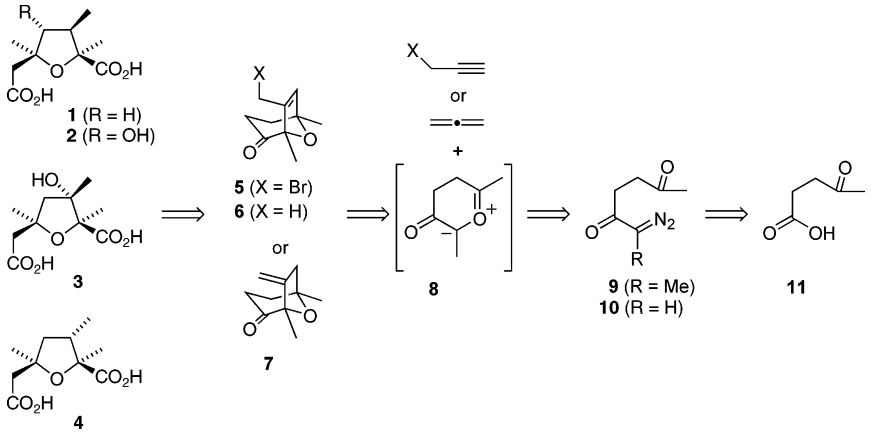
SCHEME 1. Retrosynthetic Analysis of Nemorensic Acids 1−4



solution of the mixed carboxylic carbonic anhydride of levulinic acid and isobutyl chloroformate. It is also important that the receiving flask containing the mixed anhydride is kept cold (−5 °C) to reduce the loss of diazoethane (bp ca. −20 °C) by evaporation, and that the diazodione **9** is purified by rapid chromatography.

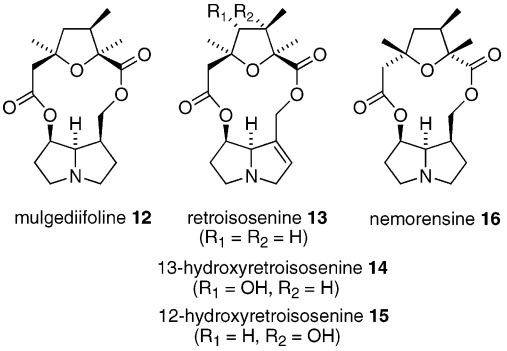
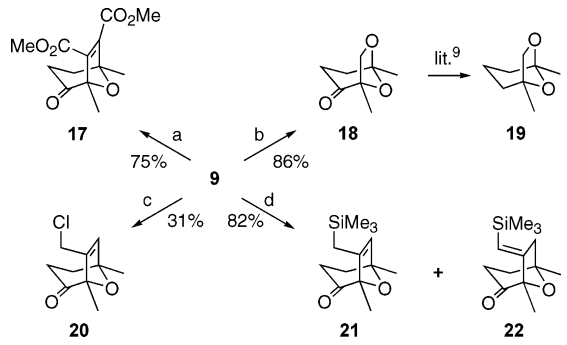


FIGURE 1. Pyrrolizidine alkaloids from the *Senecio* genus.

With diazodione **9** in hand we were pleased to observe that $Rh_2(OAc)_4$-catalyzed reaction with DMAD generated cycloadduct **17** in good yield (75%, Scheme 2). Similarly, reaction with formaldehyde gave dioxabicyclic ketone **18** as a single regioisomer (86% yield), whose structure was

SCHEME 2. Cycloadducts 17, 18, and 20−22 from Diazodione 9[a]



[a] Reagents and conditions: (a) DMAD (2 equiv), $Rh_2(OAc)_4$ (10 mol %), CH_2Cl_2, 25 °C, 1 h; (b) CH_2O (10 equiv), $Rh_2(OAc)_4$ (1 mol %), CH_2Cl_2, −78 to 25 °C, 1 h; (c) propargyl chloride (2 equiv), $Rh_2(OAc)_4$ (10 mol %), CH_2Cl_2, 25 °C, 1 h; (d) propargyltrimethylsilane/allenyltrimethylsilane (9:1, 3 equiv), $Rh_2(OAc)_4$ (5 mol %), CH_2Cl_2, 25 °C, 3 h.

confirmed by X-ray crystallographic analysis.[8] Ketone **18** has been previously converted (by thioketalization then desulfurization) into frontalin **19**, the aggregation pheromone of *Dendroctonus* beetles.[9]

With the reactivity of diazodione **9** as a carbonyl ylide precursor established, we examined dipolarophiles that might generate cycloadducts suitable for nemorensic acid syntheses. Padwa found unstrained alkenes were unreactive in intermolecular carbonyl ylide cycloadditions,[5] and we similarly observed that propene was not a viable dipolarophile in our system. However, propargyl chloride (2 equiv) was found to generate a cycloadduct **20**, albeit in a modest 31% yield (unoptimized); nevertheless and encouragingly, NOE studies indicated cycloaddition had occurred with the desired regiochemistry. Propargyl bromide (3.5 equiv) and propyne were also found to be viable dipolarophiles, generating cycloadducts **5** (84%) and **6** (87%), respectively (Scheme 1). Interestingly, use of propargyltrimethylsilane gave the anticipated cycloadduct **21**, along with (chromatographically inseparable) cycloadduct **22** (combined yield 82%, **21**:**22**, 86:14); **22** probably arises from the ∼10% allenyltrimethylsilane present in the commercial starting silane. The structure of this latter cycloadduct was established on a pure sample, available following treatment of the mixture with TBAF, which selectively desilylated the major cycloadduct **21** to a mixture of alkenes **6** and **7** (combined yield 72%, **6**:**7**, 55:45). The observation that propargyl- and allenyl-trimethylsilane showed similar reactivity in the cycloaddition process prompted us to examine the cycloaddition chemistry with allene[10] itself, which successfully gave cycloadduct **7** (77% yield, Scheme 1). The experiments which involved the volatile unsaturated hydrocarbons propene, propyne, and allene were carried out in a flask equipped with a dry ice condenser, by addition of $Rh_2(OAc)_4$ to a cooled solution of the diazodione **9** in CH_2Cl_2 containing an excess of the dipolarophile, followed by warming to ambient temperature (0

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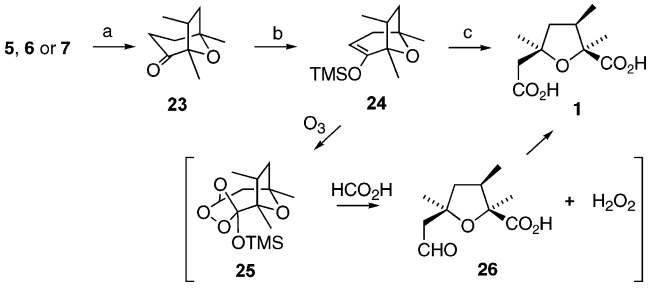
°C with allene).[11] In the absence of a dipolarophile very slow evolution of nitrogen commenced at approximately −60 °C and continued until −10 °C, when the evolution became more vigorous and a color change (pale yellow to green) was observed.

Having several cycloadducts now available as potential precursors to the nemorensic acids, we focused on a synthesis of *cis*-nemorensic acid **1** (Scheme 3). Exo-selective alkene hydrogenation of cycloadducts **5** (with concomitant hydrogenolysis of the C−Br bond), **6** (HBr was found to be beneficial as an additive in this case), and **7** all gave the desired saturated ketone **23** (92%, 91%, and 74% yields, respectively). The procedure starting with cycloadduct **5** is preferred, due to the comparative ease of handling of the precursor dipolarophile (propargyl bromide) and of the cycloadduct **5** (the cycloadducts from allene and propyne are highly volatile).

SCHEME 3. Synthesis of *cis*-Nemorensic Acid 1[a]

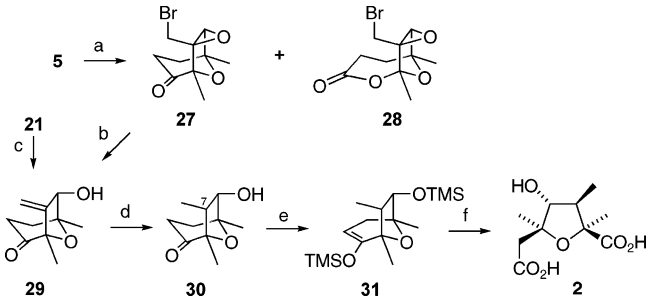


[a] Reagents and conditions: (a) H_2 (1 atm), Pd/C (10%), MeOH, 25 °C, 48 h (92% from **5**, 91% from **6**, 74% from **7**); (b) LDA (1.2 equiv), THF, −78 °C, 2 h then TMSCl (2 equiv), −78 to 25 °C, 1 h (90%); (c) O_2/O_3, CH_2Cl_2, −78 °C, 5 min, then 35% H_2O_2 (6 equiv), 88% HCO_2H (27 equiv), 100 °C, 30 min (96%).

An attempt to transform saturated ketone **23** directly into *cis*-nemorensic acid **1** with use of conditions that are known to convert cyclohexanone into adipic acid (O_2, $Re_2(CO)_{10}$, poly(ethylene glycol) (PEG-400), KOH, and K_2CO_3 in DME, 74%)[12] was not successful. Therefore, a longer sequence proceeding via oxidative cleavage of the corresponding silyl enol ether **24**[13] was examined. The procedure of Kaneda et al. with ($MoO_2(acac)_2$, *t*-BuOOH)[14] gave small amounts of *cis*-nemorensic acid **1** in a complicated product mixture, whereas a sequence involving ozonolysis in CH_2Cl_2, followed by Me_2S workup and oxidation of the resulting oxoacid with Jones' reagent[15] was more successful, generating *cis*-nemorensic acid **1** in 69% yield (structure confirmed by X-ray crystallographic analysis[16]). A more efficient process from the silyl enol ether **24** to *cis*-nemorensic acid **1** (96%) involved reaction with HCO_2H and H_2O_2 following ozonolysis.[17] Consideration of a plausible reaction pathway for the putative silyloxyozonide intermediate **25** under the latter conditions (Scheme 3) led us to examine the necessity of adding H_2O_2 in this process. Indeed, in the absence of H_2O_2 significant (though not complete) conversion to *cis*-nemorensic acid **1** was observed by ^1H NMR analysis (**1**:**26**, 4:1).

Cycloadduct **5** was also examined as a substrate for accessing 4-hydroxy-*cis*-nemorensic acid **2** (Scheme 4). The hydroxyl group in this necic acid could potentially be obtained via (formal) exo-selective anti-Markovnikov hydration of the endocyclic double bond of **5**. As a hydroboration/H_2O_2 protocol would probably be complicated by concomitant reactivity of the ketone, we focused on oxygenation via epoxidation. However, when cycloadduct **5** was treated with *m*-CPBA, the desired epoxide **27** was formed in only modest yield (34%) and epoxylactone **28** arising from a Bayer−Villiger reaction was a significant byproduct (23%). To improve the synthesis of the desired epoxide **27**, epoxidation with dimethyldioxirane (DMDO) generated in situ was attempted.[18] Upon performing this reaction an inseparable mixture of several unidentified compounds was isolated. A possible complication in this reaction could be dioxirane formation at the keto group of **5**. An efficient synthesis of epoxide **27** (94%) was finally achieved by using a pre-prepared solution of DMDO,[19] following precedent with norbornenone.[20]

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



[a] Reagents and conditions: (a) *m*-CPBA (2.5 equiv), CH_2Cl_2, 25 °C, 48 h (34% of **27** and 23% of **28**), or DMDO (0.1 M in acetone, 4 equiv), CH_2Cl_2, 25 °C, 5 d (94% of **27**); (b) Zn (3 equiv), NaI (2.5 equiv), MeOH, 65 °C, 3.5 h (97%); (c) DMDO (0.1 M in acetone, 1.8 equiv), CH_2Cl_2, 25 °C, 6 d (48%); (d) H_2, (1 atm), [Ir(cod)py(PCy_3)]PF_6 (0.03 equiv), CH_2Cl_2, 1 h (93%); (e) LDA (2.2 equiv), THF, −78 °C, 2 h then TMSCl (3 equiv), −78 to 25 °C, 1 h (90%); (f) O_2/O_3, CH_2Cl_2, −78 °C, 5 min, then 35% H_2O_2 (12 equiv), 88% HCO_2H (52 equiv), 100 °C, 30 min (97%).

It was anticipated that hydrogenation of epoxide **27** over Pd/C (10%) would proceed via initial reaction at the C−Br bond, resulting in ring-opening of the epoxide to give the allylic alcohol **29**. Under the reaction conditions hydrogenation was then expected to occur mainly on the exo face of allylic alcohol **29** to give the desired alcohol **30**. Indeed, formation of alcohol **30** directly from epoxide **27** with H_2−Pd/C in methanol did proceed, but only in modest yield to generate an inseparable mixture of **30** and 7-*epi*-**30** (45% total yield; **30**:7-*epi*-**30**, 3:2). Interestingly, synthesis and isolation of the allylic alcohol **29**

(11) See Supporting Information for details.
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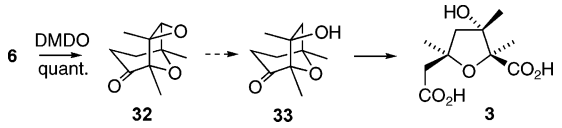
(using Zn and NaI in methanol,[21] 97%), followed by hydrogenation gave alcohol **30** in improved stereoselectivity (**30**:7-*epi*-**30**, 9:1) and yield (62%). The allylic alcohol **29** could also be obtained directly from allylsilane **21**, using DMDO, in fair yield (48%). To circumvent the modest yield and stereoselectivity in the synthesis of alcohol **30**, hydroxyl-directed homogeneous hydrogenation of allylic alcohol **29** in the presence of Crabtree's catalyst was performed;[22] this protocol generated alcohol **30** in excellent yield (93%) as a single isomer whose relative chemistry was confirmed by X-ray crystallographic analysis.[23] With alcohol **30** in hand, simultaneous protection of the alcohol and silyl enol ether formation was effected to give disilyl ether **31** in 90% yield. Ozonolysis of disilyl ether **31** followed by oxidative workup with aqueous HCO_2H and H_2O_2 (as used earlier) gave 4-hydroxy-*cis*-nemorensic acid **2** in excellent yield (97%). Spectral data for synthetic 4-hydroxy-*cis*-nemorensic acid **2** were in accord with those of the natural isolate.[2b]

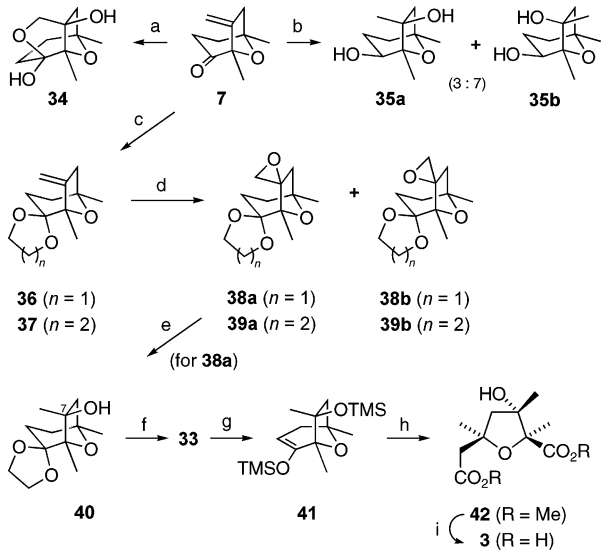
Hydrogenolytic cleavage of the less-substituted epoxy C−O bond in the epoxide **32** (derived from the propyne cycloadduct **6**) was initially considered as a potential entry to 3-hydroxy-*cis*-nemorensic acid **3** (Scheme 5). However, prolonged (2 weeks) reaction of epoxide **32** with Pd/C and H_2 mainly resulted in recovered starting material (52%), with none of the desired tertiary alcohol **33** detected, whereas no reaction was observed with ammonium formate as the hydrogen source.[24] Alternative methods to open the epoxide also met with no success: no reaction was observed with a source of nucleophilic bromide [n-Bu_4NBr in the presence of $Mg(NO_3)_2$];[25] $LiAlH_4$ in THF[26] only reduced the keto group at room temperature after 1 h (77%), whereas a complex mixture was observed at reflux; and $LiEt_3BH$ in THF[27] at room temperature similarly gave ketone reduction (3 h) and prolonged exposure (18 h) led to a multitude of products.

SCHEME 5. Initial Strategy to 3-Hydroxy-*cis*-nemorensic Acid 3



A related strategy to 3-hydroxy-*cis*-nemorensic acid **3**, which ultimately proved successful, involved manipulation of the more accessible exocyclic double bond of the allene-derived cycloadduct **7** (Scheme 6). Direct formation of tertiary alcohol **33** via hydration of cycloadduct **7** with aqueous HCO_2H,[28] TFA,[29] or AcOH in the presence of

SCHEME 6. Synthesis of 3-Hydroxy-*cis*-nemorensic Acid 3[a]



[a] Reagents and conditions: (a) OsO_4 (2.5 mol %), NMO (2 equiv), acetone, H_2O, 25 °C, 5 d (37%); (b) DMDO (0.07 M in acetone, 2 equiv), CH_2Cl_2, 25 °C, 19 h (89%), then $LiAlH_4$, THF, 0−25 °C, 1 h (89%); (c) (for **36**) ethylene glycol (40 equiv), CSA (0.1 equiv),[34] CH_2Cl_2, 25 °C, 44 h (75%); (for **37**) 1,3-propanediol (12 equiv), $(MeO)_3CH$ (3 equiv), PTSA (0.08 equiv),[35] 25 °C, 1 h (83%); (d) *m*-CPBA (1.3 equiv), CH_2Cl_2, 0−25 °C, 18 h [74% for **38** (**38a**:**38b**, 5:1); 59% for **39** (**39a**:**39b**, 1:1.5)]; (e) $LiAlH_4$ (3 equiv), THF, 0−25 °C, 24 h (quant); (f) 2 M HCl, THF, 25 °C, 3 h (57%, 6% of 7-*epi*-**33** also isolated); (g) LDA (3.5 equiv), THF, −78 °C, 1 h then TMSCl (4 equiv), 25 °C, 2 h (97%); (h) (*i*) 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, (*ii*) $TMSCHN_2$ (5 equiv), hexane−MeOH (4:1), 25 °C, 3 h (63%); (i) KOH (80 equiv), H_2O, 25 °C, 3 h (37%).

Ac_2O and PTSA[30] led only to substrate degradation. Dihydroxylation of cycloadduct **7** was expected to lead to a *vic*-diol from which selective deoxygenation of the primary hydroxyl might be possible. In the event, reaction of cycloadduct **7** with OsO_4−NMO[31] proved sluggish and led after 5 days to hemiketal **34** (37%), from which the masked primary hydroxyl could not be coaxed into reactivity (e.g., with thiocarbonyldiimidazole in toluene). Finally, we envisaged the synthesis of alcohol **33** via opening of the epoxide of cycloadduct **7**. Epoxidation of cycloadduct **7** with preformed DMDO (the use DMDO generated in situ led to substrate degradation) gave an inseparable epimeric mixture of epoxides (3:7), which were directly reacted with $LiAlH_4$[32] giving diols **35** (89%, **35a**:**35b**, 3:7). The relative stereochemistry of the major diol **35b** was established by X-ray crystallographic analysis[33] and this indicated that epoxidation had occurred preferentially on the undesired (for 3-hydroxy-*cis*-nemorensic acid **3** synthesis) endo face of cycloadduct **7**. This selectivity contrasts with that observed earlier for hydrogenation and dihydroxylation of cycloadduct **7** (and with epoxidation of cycloadducts **5** and **6**). Thus, DMDO

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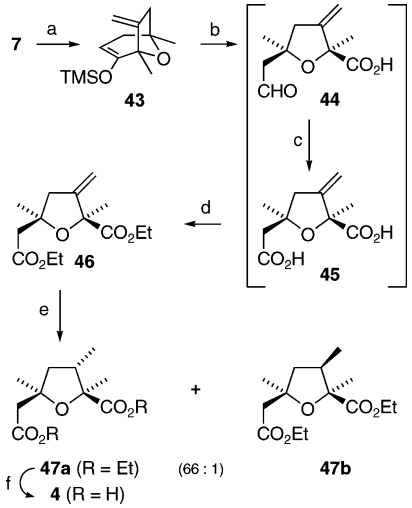
appears to be able to approach both faces of the exocyclic double bond in cycloadduct **7**. Alternatively (or in addition), intramolecular endo epoxidation might occur via dioxirane formation at the keto group of cycloadduct **7**.

To favor exo-selective epoxidation, we examined the epoxidation of ketals **36** and **37** using *m*-CPBA (Scheme 6). The diethyl ketal was also considered; however, this compound could not be synthesized despite several conditions being examined.[36] Pleasingly, epoxidation of ketal **36** gave mainly the desired epoxide **38a** (61%, **38a**:**38b**, 5:1). The stereochemical assignment was supported by NOESY experiments on both isomers, and the structure of the chromatographically separable minor epoxide isomer **38b** was confirmed by X-ray crystallographic analysis.[37] Surprisingly, epoxidation of ketal **37** gave a mixture of epoxides **39** (59%), in favor of the undesired endo-epimer **39b** (**39a**:**39b**, 2:3). The stereochemistry of both epoxides was assigned by NOESY experiments. Epoxide **38a** was therefore used to progress toward 3-hydroxy-*cis*-nemorensic acid **3**. Reduction of epoxide **38a** efficiently provided tertiary alcohol **40**; however, subsequent deprotection to reveal ketone **33** was found not to be straightforward due to the propensity for concomitant epimerization at C-7. Thus, PTSA in acetone containing 1% water at reflux[38] for 24 h, or dilute H_2SO_4 and SiO_2[39] in CH_2Cl_2 for 24 h at room temperature, gave mixtures of ketone **33** and 7-*epi*-**33** (**33**:7-*epi*-**33**, 3:7 and 1:1, respectively). The use of $FeCl_3$ on SiO_2,[40] $CeCl_3$/NaI in MeCN,[41] or $Pd(PhCN)_2Cl_2$ in acetone[42] provided complex mixtures in which **33** was a minor component. An attempt [TMSOTF (2.5 equiv), *i*-Pr_2EtN (2.5 equiv)][43] to convert the ketal present in tertiary alcohol **40** directly into an enol ether suitable for oxidative cleavage only resulted in silylation of the tertiary alcohol. Finally, the simple use of dilute HCl[44] in THF provided, after complete disappearance of **40** (18 h), a 4:1 mixture of **33**:7-*epi*-**33** from which the desired alcohol **33** could be isolated in 41% yield after chromatography. To minimize the epimerization of **33**, minimal exposure to aqueous HCl was studied. After 3 h at room temperature, 92% conversion was observed and epimerization was 10%; ketone **33** was obtained in 57% yield (62% based on recovered **40**). Ketone **33** was then converted to disilyl ether **41** in 97% yield. Ozonolysis of disilyl ether **41** followed by oxidative workup with aqueous HCO_2H and H_2O_2 gave crude 3-hydroxy-*cis*-nemorensic acid **3**. This crude necic acid **3** was best purified as the dimethyl ester **42** (obtained by esterification with $TMSCHN_2$).[45] Saponification of diester **42** gave 3-hydroxy-*cis*-nemorensic acid **9** (37%), possessing spectral data consistent with those of the natural material.[2b]

The approach used above for the synthesis of *cis*-nemorensic acid **1** (and its hydroxylated analogues **2** and **3**) relies on efficient facial discrimination (hydrogenation for **1** and **2)** in unsaturated bicyclic cycloadducts to establish stereochemistry, prior to oxidative cleavage. A strategy to obtain nemorensic acid **4** (Scheme 7, relative, not absolute, stereochemistry of **4** shown) was envisaged in which cleavage of the bicyclic system was carried out before hydrogenation.

SCHEME 7. Synthesis of Nemorensic Acid 4 from Allene-Derived Cycloadduct 7[a]



[a] Reagents and conditions: (a) LDA (1.2 equiv), THF, −78 °C, 1 h, then TMSCl (2 equiv), −78 to 25 °C, 1 h (97%); (b) (*i*) DMDO (1.1 equiv), acetone, CH_2Cl_2, 0−25 °C, 30 min, (*ii*) $NaIO_4$ (1.2 equiv), THF, H_2O, 25 °C, 30 min; (c) $AgNO_3$ (1.2 equiv), NaOH (3.4 equiv), EtOH, 25 °C, 30 min; (d) CH_3CHN_2 (∼3 equiv), Et_2O, 0 °C, 18 h (38% from **43**); (e) H_2 (60 psi), $[Ir(cod)py(PCy_3)]PF_6$ (0.05 equiv), CH_2Cl_2, 25 °C, 18 h (84% of **47a** and 1% of **47b**); (f) KOH (17 equiv), H_2O, 25 °C, 18 h (92%).

Selective ozonolysis of the silyl enol ether **43** of allene-derived cycloadduct **7** could not be achieved, and reaction of **43** under Kaneda and co-workers conditions[14] resulted only in degradation products. However, the more electron rich double bond of **43** could be selectively reacted with preformed DMDO[46] (1.1 equiv) to give an α-hydroxyketone, which was not isolated but directly treated with sodium periodate[47] to give crude oxoacid **44**. Recently, Zhang and co-workers described carboxylate-directed stereoselective hydrogenation of cyclic olefin-containing carboxylic acids in the presence of Wilkinson's catalyst and a base such as Et_3N.[48] Application of this methodology to oxoacid **44** gave a complex mixture, including mainly olefin isomerization (to form endocyclic alkene), and a small amount of hydrogenated product that could

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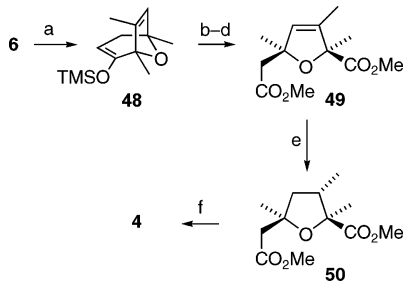
TABLE 1. Cycloadditions with Diazodione 9, Using Chiral Catalysts 51−55

entry	dipolarophile	cycloadduct	catalyst	solvent	temp (°C)	yield (%)	ee (%)[a]	$[\alpha]^{T}_{D}$ [b]
1	DMAD	**17**	Rh_2(*S*-DOSP)$_4$	$CF_3C_6H_5$	20	61	4	
2	DMAD	**17**	Rh_2(*R*-BNP)$_4$	$CF_3C_6H_5$	20	29	17	−71
3	DMAD	**17**	Rh_2(*S*-PTTL)$_4$	$CF_3C_6H_5$	20	63	22	+119
4	DMAD	**17**	Rh_2(*S*-BPTV)$_4$	$CF_3C_6H_5$	20	65	51	+247
5	$H_2C{=}O$	**18**	Rh_2(*S*-DOSP)$_4$	CH_2Cl_2	−78[c]	26	14	+9
6	$H_2C{=}O$	**18**	Rh_2(*S*-BPTV)$_4$	toluene	−78[c]	40	10	+7
7	$BrCH_2C{\equiv}CH$	**5**	Rh_2(*S*-DOSP)$_4$	hexane	20	61	23	+80
8	$BrCH_2C{\equiv}CH$	**5**	Rh_2(*S*-DOSP)$_4$	CH_2Cl_2	20	56	24	+82
9	$BrCH_2C{\equiv}CH$	**5**	Rh_2(*S*-DOSP)$_4$	CH_2Cl_2	−10	42	34	+129
10	$BrCH_2C{\equiv}CH$	**5**	Rh_2(*R*-DDBNP)$_4$	hexane	20	18	10	+33
11	$BrCH_2C{\equiv}CH$	**5**	Rh_2(*R*-DDBNP)$_4$	CH_2Cl_2	20	11	8	+22
12	$BrCH_2C{\equiv}CH$	**5**	Rh_2(*S*-PTTL)$_4$	toluene	20	39	2	−12
13	$BrCH_2C{\equiv}CH$	**5**	Rh_2(*S*-PTTL)$_4$	$CF_3C_6H_5$	20	44	4	−15
14	$BrCH_2C{\equiv}CH$	**5**	Rh_2(*S*-BPTV)$_4$	$CF_3C_6H_5$	0	22	0	−3
15	propyne	**6**	Rh_2(*S*-DOSP)$_4$	CH_2Cl_2	0	30	7	−0.9
16	propyne	**6**	Rh_2(*R*-DDBNP)$_4$	CH_2Cl_2	0	17	6	+0.7
17	propyne	**6**	Rh_2(*S*-BPTV)$_4$	CH_2Cl_2	0	27	7	−0.9
18	allene	**7**	Rh_2(*R*-DDBNP)$_4$	CH_2Cl_2	0	0		
19	allene	**7**	Rh_2(*S*-DOSP)$_4$	CH_2Cl_2	0	76	45	+42
20	allene	**7**	Rh_2(*S*-DOSP)$_4$	Et_2O	0	56	45	+42

[a] Determined by chiral stationary phase chromatography.[11] [b] $c = 0.5-1.0$ in $CHCl_3$, $T = 22-25$ °C. [c] Temperature is −78 to 25 °C over 15 min.

not be cleanly isolated. Tollens-type oxidation of oxoacid **44** with $AgNO_3$ in aqueous ethanolic NaOH[49] provided the corresponding diacid **45**. Attempts to hydrogenate diacid **45** in the presence Wilkinson's catalyst and Et_3N were unsuccessful, possibly due to catalyst coordination at the more accessible (but also more distant from the alkene) primary carboxylate. Diacid **45** was then esterified with diazoethane to give unsaturated diester **46**, which was isolated in 38% yield over 4 steps from silyl enol ether **43**. Hydrogenation of unsaturated diester **46** with Pd/C at atmospheric pressure gave saturated diester **47** (76%) as a separable epimeric mixture, which favored the undesired stereochemistry for nemorensic acid synthesis (**47a**:**47b**, 3:7). The stereochemistry of each isomer was assigned by NOESY experiments. To reverse the hydrogenation selectivity, ester-directed homogeneous hydrogenation with Crabtree's catalyst[22] was investigated. Reaction of unsaturated diester **46** with [Ir(cod)py(PCy_3)]PF_6 in CH_2Cl_2 under hydrogen at atmospheric pressure for 18 h provided a mixture of starting material (40%), the product of isomerization of the double bond into the five-membered ring (35%), and saturated diester **47a** as the single product of hydrogenation (25%). To accelerate the hydrogenation and avoid isomerization of the double bond, the reaction was performed under 60 psi of hydrogen for 18 h; under these conditions **47a** was obtained in good yield (84%) and with high selectivity (**47a**:**47b**, 66:1). Finally, hydrolysis of saturated diester **47a** gave nemorensic acid **4** possessing spectral data in accord with previous syntheses.[3] Nemorensic acid **4** could also be prepared by an essentially identical reaction sequence starting from propyne-derived cycloadduct **6** (Scheme 8). Interestingly, ester-directed hydrogenation of the endocyclic unsaturation in diester **49** was found to be slower (40 h) than that of the exocyclic olefin in diester **46**. However, the hydrogenation of diester **49** provided exclusively the desired saturated diester **50**, in 87% yield.

SCHEME 8. Synthesis of Nemorensic Acid 4 from Propyne-Derived Cycloadduct 6[a]



[a] Reagents and conditions: (a) as Scheme 7 (94%); (b, c) as Scheme 7; (d) $TMSCHN_2$ (10 equiv), hexane−MeOH (3:1), 25 °C, 18 h (37% from **48**); (e) H_2 (60 psi), [Ir(cod)py(PCy_3)]PF_6 (0.05 equiv), CH_2Cl_2, 25 °C, 40 h (87%); (f) KOH (17 equiv), H_2O, 25 °C, 2 h (89%).

With sterecontrolled access to all the nemorensic acids **1**−**4** in a racemic manner demonstrated from a common precursor diazodione **9**, we have conducted some preliminary studies (Table 1) to assess the potential for enantioselective cycloadditions using this precursor with chiral catalysts **51**−**55** (Figure 2). These catalysts were selected because of their previously shown ability to achieve high levels of asymmetric induction in other carbonyl ylide cycloadditions of diazocarbonyl compounds.[50,51]

It should be noted at the outset of the present studies that asymmetric induction in such cycloadditions is very sensitive to the substitution pattern of the dipole, as well

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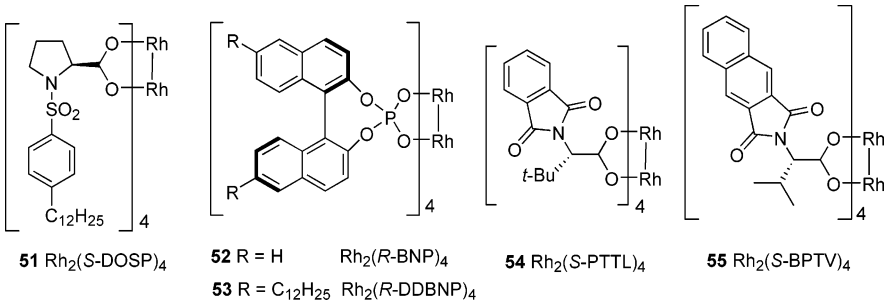

FIGURE 2. Chiral catalysts **51**−**55**.

as the dipolarophile used. An analysis of the limited studies carried out to date indicate that catalysts **51**−**53** work well with electron-deficient carbonyl ylides (derived from α-diazo-*β*-ketoesters) and nonpolarized alkenes and alkynes,[50] whereas **54** and **55** are known to be good catalysts for α-diazoketones and highly electron deficient dipolarophiles (especially DMAD).[51] Initial studies with diazodione **9** and DMAD reinforced the latter generalization (Table 1, entries 1−4): the best asymmetric induction (51%, entry 4) was observed with Hashimoto's catalyst **55**. With formaldehyde as the dipolarophile, the frontalin intermediate **18** was generated in a low yield and asymmetric induction (entries 5 and 6). With use of propargyl bromide as the dipolarophile (entries 7−14), up to 34% ee could be achieved with Davies' catalyst **51** (entry 9); propyne was less effective (entries 15−17). Within the scope of the current study, and for the dipolarophiles investigated which are relevant to the nemorensic acid syntheses, allene provided the most encouraging results (entry 20) with Rh_2(*S*-DOSP)$_4$ **51** generating cycloadduct **7** in 76% yield and 45% ee. This limited investigation of asymmetric cycloadditions with diazodione **9** underlines the need for a greater understanding of the factors which influence enantioselective carbonyl ylide cycloadditions,[52] and especially the development of conditions (and catalysts) which are effective with simple (not electron deficient) carbonyl ylides and nonpolarized alkenes and alkynes.

Experimental Section

General experimental details have been described.[50]

6-Diazoheptane-2,5-dione (9). To a solution of levulinic acid **11** (1.63 g, 14.0 mmol) in Et_2O (30 mL) at 0 °C was added Et_3N (1.43 g, 14.1 mmol). Isobutyl chloroformate (1.92 g, 14.0 mmol) was then added dropwise over 5 min to the vigorously stirred solution. Following addition, the solution was allowed to attain ambient temperature over 15 min and was then stirred for a further 2 h. The solution was then filtered under argon to obtain an ethereal solution of the mixed anhydride, which was placed in the receiving flask of a clear-fit distillation apparatus and cooled to −5 °C. In the reaction flask of the clear-fit distillation apparatus was placed Et_2O (33 mL) and a solution of KOH (8.26 g, 147 mmol) in PrOH (33 mL). The solution was heated in an oil bath at 55 °C with stirring until the Et_2O began to distil. At this time a solution of *N*-nitroso-*N*-ethylurethane[7] (8.26 g, 56.5 mmol) in Et_2O (25 mL) was added dropwise over 5 min to the solution of KOH, such that boiling was not too vigorous, and the yellow ethereal $MeCHN_2$ was allowed to distill under a very slow stream of argon into the stirred solution of the mixed anhydride. Et_2O (∼60 mL) was added dropwise to the reaction flask, until the distillate was coming over colorless (∼1 h) [in a separate experiment the yield of $MeCHN_2$ was determined to be 75% with use of the method of Wilds and Meander[7a]]. At this time the temperature of the receiving flask was maintained between −5 and 0 °C for 5 h, then allowed to attain ambient temperature and stirred for a further 15 h under a slow stream of argon. The remaining volatiles were then removed in vacuo and the residue purified by column chromatography (50% EtOAc in pentane) to give diazodione **9** (1.11 g, 51%) as a yellow oil. R_f 0.40 (50% EtOAc in pentane); IR 2917, 2078, 1719, 1637, 1365, 1281, 1165, 1082, 1032 cm^{-1}; ^{1}H NMR (500 MHz; $CDCl_3$) δ 2.72−2.68 (m, 2H), 2.17 (s, 3H), 1.91 (br s, 3H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 207.6, 193.2, 63.6, 37.7, 31.5, 30.4, 8.4; MS (CI+) *m/z* (%) 155(29) [M + H]$^+$, 146 (65), 129 (25), 128 (100), 118 (39), 111 (67), 77 (20); HRMS calcd for $C_7H_{11}N_2O_2$ 155.0820, found 155.0821 [M + H]$^+$.

7-Bromomethyl-1,5-dimethyl-8-oxabicyclo[3.2.1]oct-6-en-2-one (5). $Rh_2(OAc)_4$ (14 mg, 0.03 mmol) was added in one portion to a solution of diazodione **9** (400 mg, 2.60 mmol) and propargyl bromide (1.10 g, 9.25 mmol, 80% solution in toluene) in degassed CH_2Cl_2 (8 mL) in a 500-mL flask (note: the use of a large reaction vessel is necessary to allow for rapid evolution of N_2) at ambient temperature. The mixture was stirred at ambient temperature for 3 h and the volatiles removed in vacuo. The residue was then purified by column chromatography (20% EtOAc in pentane) to give cycloadduct **5** (539 mg, 84%) as a colorless oil. R_f 0.45 (20% EtOAc in pentane); IR 2981, 2932, 1723, 1449, 1375, 1065, 938, 912, 735 cm^{-1}; ^{1}H NMR (500 MHz; $CDCl_3$) δ 6.20 (X part of ABX, br s, 1H), 4.04 and 3.91 (AB part of ABX, J = 11.5, 1.0 Hz, 2H), 2.80 (ddd, J = 17.6, 8.8, 8.8 Hz, 1H), 2.42 (ddd, J = 17.6, 8.8, 1.3 Hz, 1H), 2.29 (ddd, J = 13.8, 8.8, 8.8 Hz, 1H), 1.99 (ddd, J = 13.8, 8.8, 1.3 Hz, 1H), 1.40 (s, 3H), 1.43 (s, 3H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 203.7, 142.6, 137.1, 90.6, 84.1, 35.1, 33.0, 23.6, 23.5, 15.1; MS (CI+) *m/z* (%) 262(19) [M + NH_4]$^+$, 184-(100), 167(90), 77(13); HRMS calcd for $C_{10}H_{17}BrNO_2$ 262.0443, found 262.0446. Anal. Calcd for $C_{10}H_{13}BrO_2$ (245.1): C, 49.00; H, 5.35. Found: C, 48.79; H, 5.37. Ee determination (Table 1) used chiral GC (Chirasil Dex-CD capillary column, 120 °C, t_R ∼ 70 min) or (for entry 14) chiral HPLC (Chiralcel OD, 99.5% hexane/EtOH, 0.2 mL min^{-1}).

1,5,7-Trimethyl-8-oxabicyclo[3.2.1]octan-2-one (23). To a solution of cycloadduct **5** (539 mg, 2.20 mmol) in MeOH (9 mL) was added 10% Pd/C (130 mg). The reaction vessel was then evacuated and back-filled with hydrogen three times. Hydrogen was then bubbled through the solution for 5 min, the mixture was then allowed to stir at ambient temperature for 24 h. After this time hydrogen was again bubbled through the solution for 5 min and the mixture stirred at ambient temperature for a further 24 h. Upon completion, the reaction mixture was filtered through a pad of silica gel and the pad washed well with CH_2Cl_2, then the solution was made up to 50 mL with CH_2Cl_2 and washed with water (1 × 30 mL) and HCl (2 M, 1 × 30 mL). The solution was then dried ($MgSO_4$) and the volatiles removed by evaporation under argon, and subsequent column chromatography (15% Et_2O in pentane)

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gave saturated ketone **23** (340 mg, 92%) as a colorless oil. R_f 0.3 (15% Et_2O in pentane); IR 2967, 2935, 1720, 1452, 1375, 1103, 1012, 943, 865 cm^{-1}; ^1H NMR (400 MHz; $CDCl_3$) δ 2.51 (ddd, J = 18.0, 7.6, 1.3 Hz, 1H), 2.33−2.15 (m, 3H), 2.08 (ddd, J = 13.2, 8.4, 7.6 Hz, 1H), 1.89 (ddd, J = 13.2, 8.4, 1.3 Hz, 1H), 1.68−163 (m, 1H), 1.41 (s, 3H), 1.27 (s, 3H), 0.91 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz; $CDCl_3$) δ 208.5, 89.6, 79.3, 43.3, 43.1, 38.3, 34.7, 26.6, 18.3, 13.4; MS (EI+) *m/z* (%) 168 (2) $[M]^+$, 140 (7), 97 (13), 84 (33), 49 (76), 43 (100); HMRS calcd for $C_{10}H_{16}O_2$ (M + H) 169.1228, found 169.1229.

Trimethyl(1,5,7-trimethyl-8-oxabicyclo[3.2.1]oct-2-en-2-yloxy)silane (24). Saturated ketone **23** (150 mg, 0.9 mmol) in anhydrous THF (1 mL) was added dropwise over 5 min to a freshly prepared solution of LDA at −78 °C [prepared from a 1.6 M solution of BuLi in hexane (0.7 mL, 1.1 mmol) and *i*-Pr_2NH (0.18 mL, 1.3 mmol)] and stirred for 2 h at this temperature. TMSCl (0.22 mL, 1.8 mmol) was added and the mixture stirred for 5 min before being allowed to attain ambient temperature. The solution was stirred for a further 1 h at this temperature, the volatiles were removed in vacuo, and subsequent column chromatography of the crude material (silica, 10% Et_2O in pentane containing 2% Et_3N) gave silyl enol ether **24** as a colorless oil (194 mg, 90%). R_f 0.5 (10% Et_2O in pentane); IR 2964, 2935, 2892, 2873, 1656, 1453, 1376, 1358, 1252, 1233, 1202, 1177, 1152, 1092, 944, 890, 845 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.59 (dd, J = 4.8, 2.0 Hz, 1H), 2.37 (dd, J = 16.0, 2.0 Hz, 1H), 2.11 (ddq, J = 10.4, 8.0, 6.8 Hz, 1H), 1.95 (ddd, J = 12.0, 10.4, 1.2 (long range to CH_3) Hz, 1H), 1.84 (dd, J = 16.0, 4.8 Hz, 1H), 1.45 (dd, J = 12.0, 8.0 Hz, 1H), 1.34 (s, 3H), 1.27 (s, 3H), 0.97 (d, J = 6.8 Hz, 3H), 0.21 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3, 96.5, 83.6, 76.1, 48.9, 45.8, 40.2, 26.9, 18.6, 14.6, 0.2; MS (EI+) *m/z* (%) 240 (23) $[M]^+$, 197 (20), 157 (17), 84 (56), 73 (83), 49 (100), 43 (84); HRMS calcd for $C_{13}H_{24}O_2Si$ 240.1546, found 240.1547.

***cis*-Nemorensic Acid (1).** A solution of silyl enol ether **24** (100 mg, 0.42 mmol) in CH_2Cl_2 (18 mL) was treated with O_3/O_3 at −78 °C for 15 min. The solution was then purged with O_2 (5 min) and Ar (5 min). The volatiles were then removed in vacuo and the residue refluxed in the presence of HCO_2H (0.5 mL of an 88% solution in water, 11.5 mmol) and H_2O_2 (0.25 mL of a 35% solution in water, 2.6 mmol) for 30 min. Upon cooling the reaction mixture was diluted with brine (1 mL), extracted with EtOAc (3 × 5 mL), and dried ($MgSO_4$) and the volatiles were removed in vacuo to give *cis*-nemorensic acid **1** (82 mg, 96%) as a white solid. Mp 131−133 °C (lit.[2a] mp for (+)-**1** 96−100 °C); IR 1708, 1465, 1375, 1130 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 2.80 (d, J = 15.5 Hz, 1H) and 2.84 (d, J = 15.5 Hz, 1H), 2.49 (ddq, J = 12.4, 6.8, 6.8 Hz, 1H), 2.09 (dd, J = 12.4, 6.8 Hz, 1H), 1.87 (dd, J = 12.4, 6.8 Hz, 1H), 1.55 (s, 3H), 1.39 (s, 3H), 1.13 (d, J = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 178.1, 176.0, 87.1, 81.7, 45.5, 44.7, 44.0, 27.7, 24.9, 14.7; MS (CI+) *m/z* (%) 234 (21) $[M + NH_4]^+$, 217 (4) $[M + H]^+$, 190 (25), 171 (100), 127 (22), 52 (24); HRMS calcd for $C_{10}H_{20}NO_5$ (M + NH_4) 234.1341, found 234.1341. Anal. Calcd for $C_{10}H_{16}O_5$ (206.2): C, 55.55; H, 7.46. Found: C, 55.63; H, 7.56.

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Supporting Information Available: Full experimental details of syntheses and characterization of cycloaddition substrates and cycloadducts not described in the Experimental Section and ^1H and ^{13}C spectra for all compounds (apart from those with satisfactory microanalytical data or spectra already published[4a]). This material is available free of charge via the Internet at http://pubs.acs.org.

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