Enantiospecific Synthesis of (+)-Byssochlamic Acid, a Nonadride from the Ascomycete *Byssochlamys fulva*

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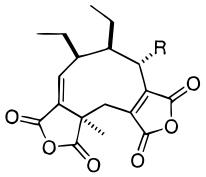
Abstract: A photoaddition−cycloreversion strategy applicable to enantiospecific synthesis of natural byssochlamic acid and its enantiomer was developed in which porcine liver esterase (PLE) catalyzed hydrolysis of **24** was used to desymmetrize this dimethyl ester to give (*R*)-**25**. Analogous PLE catalyzed hydrolysis of dimethyl ester **32** and bis(methylthio)methyl ester **48**, while highly regioselective, gave racemic half acids **33** and **49**, respectively. Stepwise coupling of (±)-**49** and (*R*)-**46**, the latter derived from **25**, afforded diolide **52**, which upon irradiation gave *exo,exo* and *exo,endo* [2 + 2] photoadducts **53** and **54**, respectively. The photoadducts underwent thermal cycloreversion to produce nine-membered bislactones **55** and **56**. Conversion of these lactones via 1,5-cyclononadienes **57** and **58** to (+)-byssochlamic acid (**3**) was accompanied by acid-catalyzed epimerization of the *n*-propyl substituent. Stepwise coupling of *(S)*-**60** (the enantiomer of **46**) with (±)-**49** led to diolide **63**, which upon photoaddition−cycloreversion gave bis-γ-lactones **66** and **67**. These 1,5-cyclononadienes were transformed into (−)-**68**, the enantiomer of natural byssochlamic acid.

Introduction

The natural products known collectively as nonadrides comprise a small structural class in which the core unit is a nine-membered carbocyclic ring.[1] Two five-membered anhydrides or an anhydride and a lactol are fused to the core, which also bears a pair of *n*-alkyl chains and, in some cases, one or more hydroxyl substituents. Glaucanic and glauconic acids, **1** and **2**, respectively, were the first members of the class to be discovered,[2] and soon thereafter a "symmetrical" variant, byssochlamic acid (**3**), was isolated by Raistrick from the ascomycete *Byssochlamys fulva*.[3] Subsequently, two hepatotoxic



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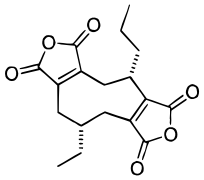
2, R = OH



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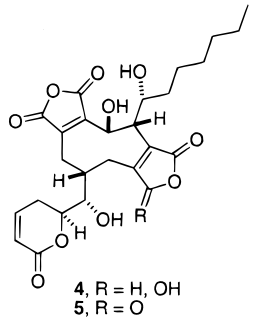
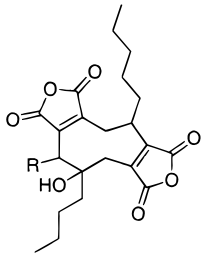
substances, rubratoxins A (**4**) and B (**5**), were obtained from extracts of the fungus *Penicillium rubrum*,[4] and more recently the nonadrides scytalidin (**6**),[5] heveadride (**7**),[6] and castaneiolide (**8**)[7] have been found in nature. The latest examples of this

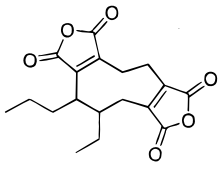


4, R = H, OH
5, R = O



6, R = H
8, R =OH

family of structures are CP-225,917 (**9**) and CP-263,114 (**10**), two metabolites isolated by a research group at Pfizer from an unidentified fungus which also produces zaragozic acid.[8] The



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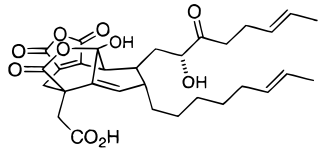

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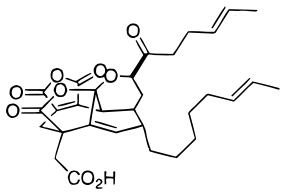

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powerful inhibition of ras farnesyl transferase by **9** and **10**[9] has

(1) Sutherland, J. K. *Fortschr. Chem. Org. Naturst.* **1967**, *25*, 131.
(2) Wijkman, N. *Liebigs Ann. Chem.* **1931**, *485*, 61.
(3) Raistrick, H.; Smith, G. *Biochem. J.* **1933**, *27*, 1814.
(4) (a) Wilson, B. J.; Wilson, C. H. *J. Bacteriol.* **1962**, *83*, 693. (b) Büchi, G.; Snader, K. M.; White, J. D.; Gougoutas, J. Z.; Singh, S. *J. Am. Chem. Soc.* **1970**, *92*, 6638.
(5) Overeem, J. C.; Mackor, A. *Recl. Trav. Chim. Pays-Bas* **1973**, *92*, 349.
(6) Crane, R. I.; Hedden, P.; MacMillan, J.; Turner, W. B. *J. Chem. Soc., Perkin Trans. 1* **1973**, 194.
(7) Arai, K.; Shimizu, S.; Miyajima, H.; Yamamoto, Y. *Chem. Pharm. Bull.* **1989**, *37*, 2870.
(8) Dabrah, T. T.; Kaneko, T.; Massefski, W. Jr.; Whipple, E. B. *J. Am. Chem. Soc.* **1997**, *119*, 1594.
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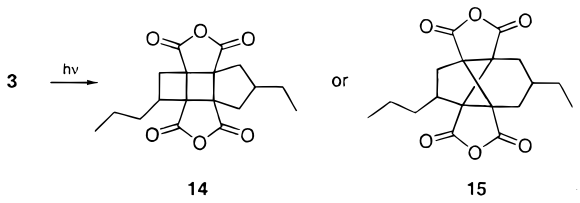
made these nonadrides the objects of much interest,[10] and a synthesis of (±)-**9** and (±)-**10** was completed in 1999 by Nicolaou.[11] A unifying biogenetic hypothesis has been proposed which accommodates the nonadrides, including **9** and **10**, within a matrix of head-to-head and head-to-tail dimers of a putative dialkylmaleic anhydride intermediate.[12]

Structural elucidation of **1**, **2**, and **3** by the Barton group[13] at Imperial College built upon earlier degradative work addressed at **1** and **2** by Sutter[14] and Kraft[15] and led to the proposal **3**, exclusive of stereochemistry, for byssochlamic acid. Confirmation of this assignment and designation of the cis relative configuration was obtained through X-ray crystallographic analysis of the bis-*p*-bromophenylhydrazide of **3**.[16] The absolute configuration of byssochlamic acid was determined by degradative experiments which caused fission of the nine-membered ring and gave products of known stereochemistry.[17] Unfortunately, these degradative studies gave no hint of the relative stability of cis and trans isomers of **3**, a detail which proved to be significant in our synthetic endeavors.

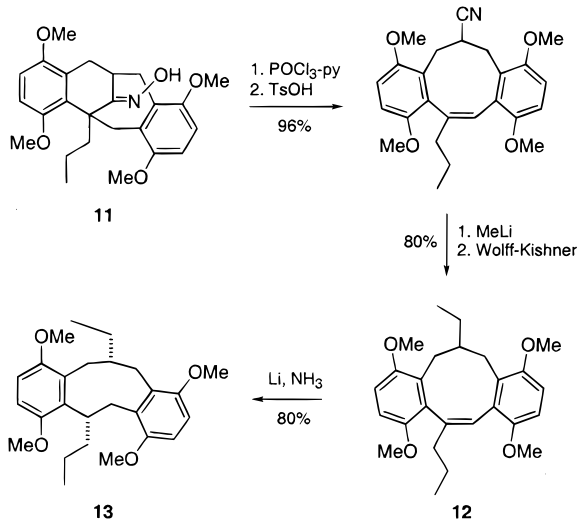
The first synthesis of a member of the nonadride family was that of (±)-**3** by Stork.[18] This pioneering accomplishment, which created the nine-membered ring of **3** through Beckmann fragmentation of oxime **11**, provided the initial indication that a cis orientation of ethyl and *n*-propyl substituents was more stable. Reduction of **12** under thermodynamic conditions afforded **13** in high yield, a result which can be readily understood if **13** adopts a U-shaped conformation similar to that seen in the X-ray crystal structure of the bis-*p*-bromophenylhydrazide of byssochlamic acid. Before beginning our own synthesis of **3**, the anticipated preference for the cis configuration of side chains was substantiated through a conformational analysis in which energy minimization using a PM3 algorithm predicted a difference of ~2.6 kcal/mol between cis (**3c**) and trans (**3t**) isomers in favor of the former. The factor which destabilizes



3t relative to **3c** is the pseudoaxial orientation of the propyl chain, which creates a transannular steric interaction with an endo hydrogen of the methylene adjacent to the ethyl substituent (Figure 1). Interestingly, the nine-membered rings of both **3c** and **3t** adopt a chairlike conformation, according to this computation, and are, therefore, quite different in shape from the ring conformation seen in the crystal structure of byssochlamic acid bis-*p*-bromophenylhydrazide.[16] An important consequence of this conformational analysis of **3** is that, if the center bearing the propyl group is stereomutable, the absolute sense of an asymmetric synthesis of byssochlamic acid can be controlled through correct orientation of the remote ethyl substituent. This point is addressed in more detail below.

A seemingly inconsequential addendum to the Imperial College structural elucidation of byssochlamic acid[17] was the disclosure that the natural product undergoes a reaction to give a saturated isomer when irradiated in tetrahydrofuran. Two structures were considered for "photobyssochlamic acid," one (**14**) derived from intramolecular, parallel [2 + 2] cycloaddition and the other (**15**) corresponding to a crossed photoaddition. Since pyrolysis of the photoisomer of byssochlamic acid failed to regenerate **3**, the conclusion was drawn that its structure was **15**. The implication that **14** should have reverted to byssochlamic acid upon thermolysis was a proposition which played an important role in guiding our synthesis plan for **3**.

The concept of a [2 + 2] photoaddition−cycloreversion strategy for assembling carbocyclic structures has long been recognized as a powerful paradigm in medium-ring synthesis.[19] It was first exemplified in the context of natural product synthesis by Lange[20] and Wender[21] in their approaches to germacranolide sesquiterpenes, and others soon followed their lead.[22] Our own plan for constructing the 1,5-cyclononadiene nucleus of **3** (Scheme 1) hinged upon connection of two



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(14) (a) Sutter, H.; Wijkman, N. *Lieb. Ann. Chem.* **1933**, *505*, 248. (b) Sutter, H.; Wijkman, N. *Lieb. Ann. Chem.* **1935**, *519*, 97. (c) Sutter, H.; Rottmayr, F.; Porsch H. *Lieb. Ann. Chem.* **1936**, *521*, 189.

(15) (a) Kraft, K.; Porsch, H. *Lieb. Ann. Chem.* **1937**, *527*, 168. (b) Kraft, K. *Lieb. Ann. Chem.* **1937**, *530*, 20.

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(17) Baldwin, J. E.; Barton, D. H. R.; Sutherland, J. K. *J. Chem. Soc.* **1965**, 1787.

(18) Stork, G.; Tabak, J. M.; Blount, J. F. *J. Am. Chem. Soc.* **1972**, *94*, 4735.

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(20) (a) Lange, G. L.; Huggins, M.-A.; Neidert, E. *Tetrahedron Lett.* **1976**, 4409. (b) Lange, G. L.; McCarthy, F. C. *Tetrahedron Lett.* **1978**, 4749.

(21) (a) Wender, P. A.; Lechleiter, J. C. *J. Am. Chem. Soc.* **1977**, *99*, 267. (b) Wender, P. A.; Hubbs, J. C. *J. Org. Chem.* **1980**, *45*, 365. (c) Wender, P. A.; Letendre, L. J. *J. Org. Chem.* **1980**, *45*, 367.

(22) (a) Wilson, S. R.; Phillips, L. R.; Pelister, Y.; Huffman, J. C. *J. Am. Chem. Soc.* **1979**, *101*, 7373. (b) Williams, J. R.; Callahan, J. F. *J. Chem. Soc., Chem. Commun.* **1979**, 405. (c) Williams, J. R.; Callahan, J. F. *J. Org. Chem.* **1980**, *45*, 4475, 4479. (d) Randall, M. L.; Lo, P. C.-K.; Bonitatebus, P. J. Jr.; Snapper, M. L. *J. Am. Chem. Soc.* **1999**, *121*, 4534 and ref 5 cited.

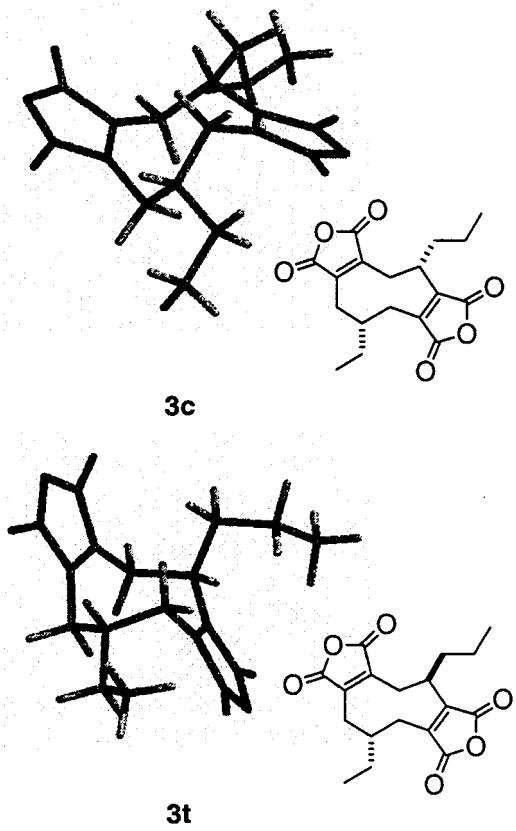
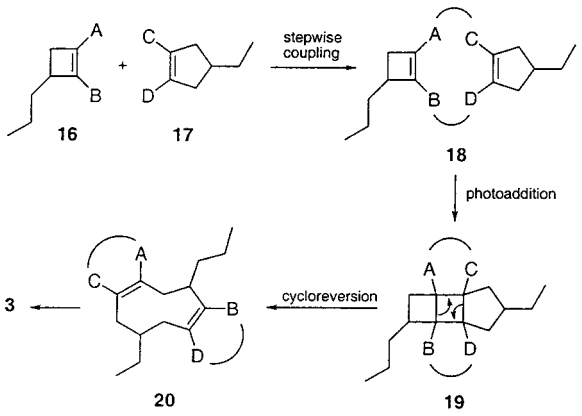


Figure 1. Energy-minimized (PM3) conformations of byssochlamic acid (**3c**) and its trans isomer (**3t**).

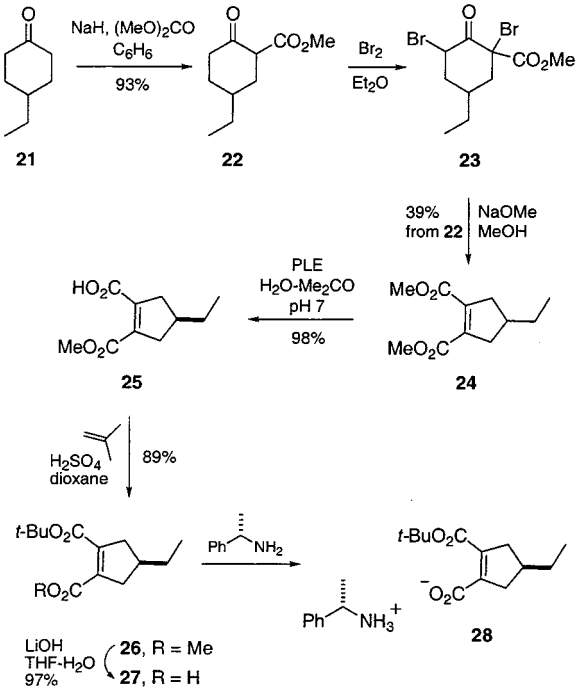
Scheme 1



photopartners, cyclobutene **16** and cyclopentene **17**, to produce a substrate **18** which upon irradiation would be expected to yield **19**. Ideally, the structure of this pentacycle should permit a defined stereochemical relationship between ethyl and propyl substituents which could be translated into the desired cis configuration in **20**. The constraints applied by the braces linking A to C and B to D in **18** should forestall an undesired cycloreversion pathway from **19** leading to a divinylcyclopentane rather than **20**. The general validity of these ideas was demonstrated in a preliminary report describing a synthesis of racemic **3**.[23] We have now extended the photoaddition−cycloreversion approach to embrace an asymmetric variant of the plan shown in Scheme 1 which leads to natural (+)-byssochlamic acid as well as its (−) enantiomer. A subtle element of stereocontrol is revealed in this work which enables our strategy to accommodate synthesis of either enantiomer of byssochlamic acid with only minor modification.

Results and Discussion

The cyclopentene component **17** required for coupling with **16** was prepared from 4-ethylcyclohexanone (**21**) via bromination of the derived β-keto ester **22** and subsequent base-mediated Favorskii rearrangement−elimination of dibromo keto ester **23**.[24]



Desymmetrization of dimethyl ester **24** with buffered (pH 7) porcine liver esterase[25] gave a half acid **25** (>99% ee) in virtually quantitative yield. The absolute configuration of **25** was determined as (*R*) by X-ray crystallographic analysis of the (*S*)-(−)-α-methylbenzylamine salt **28** of carboxylic acid **27**, prepared via *tert*-butyl ester **26**.

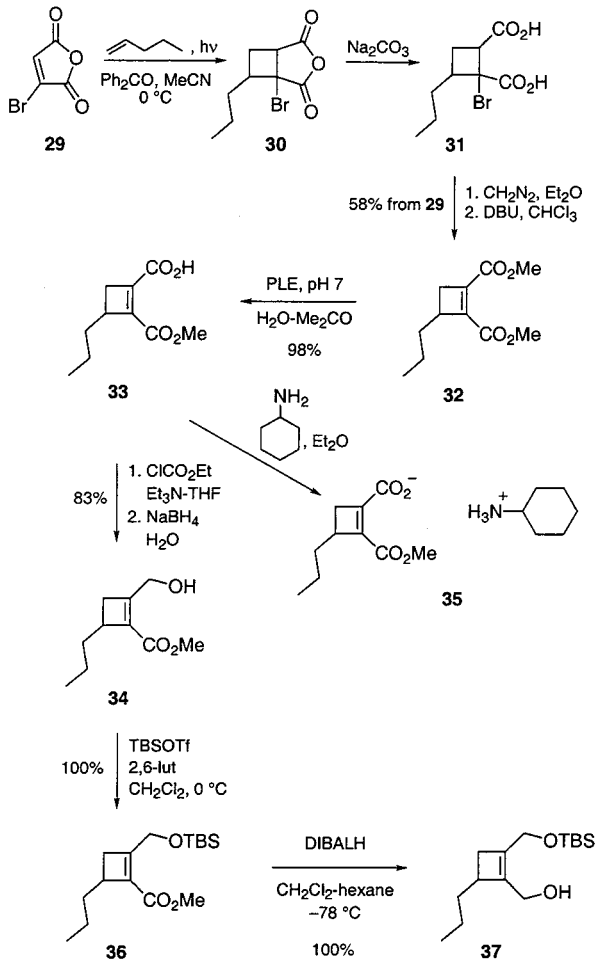
The cyclobutene partner **16** envisioned for coupling to **17** was prepared by photoaddition of bromomaleic anhydride **29** to 1-pentene. The resultant mixture of bromocyclobutanes **30** was hydrolyzed to give the dicarboxylic acid **31** as a mixture of stereoisomers, and esterification with diazomethane followed by elimination of hydrogen bromide then afforded cyclobutene **32** as a single product. Treatment of this dimethyl ester with buffered porcine liver esterase furnished a carboxylic acid which X-ray crystallographic analysis of its cyclohexylammonium salt showed to be **33**. The nearly quantitative yield of **33** implied that the esterase had failed to distinguish enantiomers in the racemate **32** while effecting a completely regioselective ester hydrolysis. Optical rotation values for **33** and the derived alcohol **34** were zero, confirming that both compounds were indeed racemic.

The failure of porcine liver esterase to distinguish stereoisomers of **32** while effecting highly regioselective hydrolysis of this diester is presumably a reflection of the fact that the rate of hydrolysis for each enantiomer is essentially the same, thus precluding kinetic resolution. Although we must conclude that the esterase, while recognizing the location of the propyl substituent in relation to the two esters, makes no distinction

(23) White, J. D.; Dillon, M. P.; Butlin, R. J. *J. Am. Chem. Soc.* **1992**, *114*, 9673.

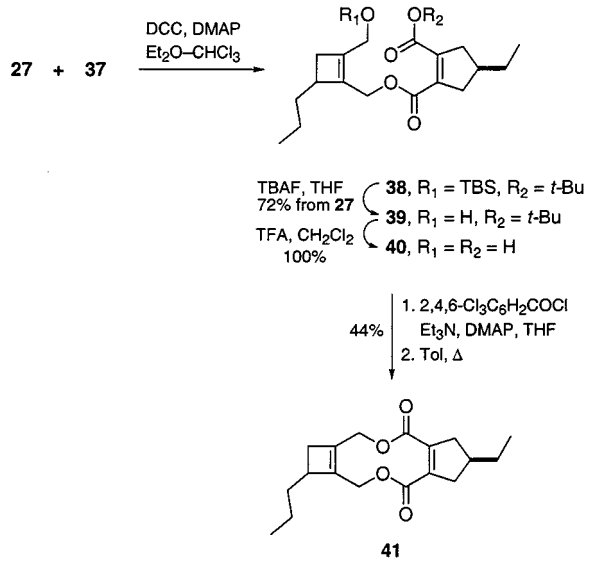
(24) Cf.: Schorno, K. S.; Adolphen, G. H.; Eisenbraun, E. J. *J. Org. Chem.* **1969**, *34*, 2801.

(25) Sabbioni, G.; Shea, M. L.; Jones, J. B. *J. Chem. Soc., Chem. Commun.* **1984**, 236.

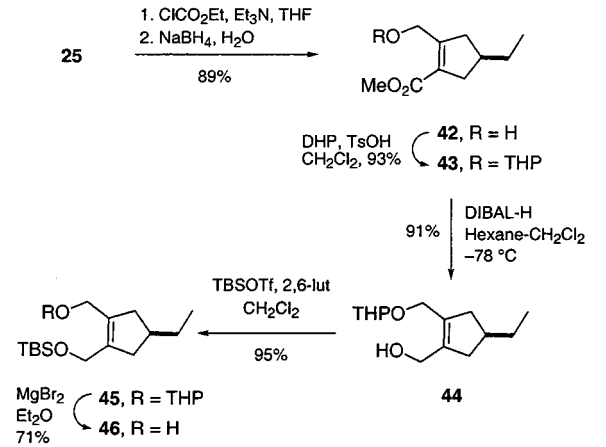


between the orientations of the propyl group relative to the plane of the cyclobutene, this type of observation is not unique.[26] Fortunately, the racemic nature of **33** is of no consequence to the synthesis, because it was already known from our previous work[23] that the propyl group can be epimerized in favor of the natural configuration at a late stage of the route to **3**.

Our previous route to racemic byssochlamic acid[23] did not require a specific orientation of cyclobutene and cyclopentene partners in the coupling process which led to **18**, and in that case, the two subunits were linked in a single step. However, to transmute the chirality of **25** into an asymmetric pathway to **3**, it was necessary to connect the partners stepwise in a predetermined manner. Our initial goal was to couple carboxylic acid **25** with a monoprotected diol derived from **34** so that a second coupling to yield a diolide could be accomplished in sequential fashion. For this purpose, **34** was protected as its silyl ether **36** and the methyl ester was reduced to alcohol **37**. Unfortunately, although **25** could be esterified cleanly with **37**, no means could be found for cleavage of the resulting methyl ester while avoiding scission of the allylic ester linkage between cyclobutene and cyclopentene. This forced us to consider an alternative coupling of **37** with *tert*-butyl ester **27**, an esterification which proceeded efficiently to yield **38**. Removal of the silyl ether from **38** followed by acidic cleavage of the *tert*-butyl ester from **39** afforded hydroxy acid **40**, which underwent Yamaguchi lactonization[27] to produce diolide **41**. To our disappointment, all attempts to effect intramolecular photoaddition of **41** by irradiation through Pyrex resulted only in recovered starting material, and after measurement of the UV spectrum of **41**, which showed an extinction coefficient (ϵ) of 500 at 313 nm, it became clear that insufficient light absorption by **41** was responsible for this lack of reactivity. Irradiation of **41** at shorter wavelengths resulted in significant destruction of the diolide, indicating that the synthesis plan outlined in Scheme 1 would not be implemented with this substrate.



Conformational analysis of **41** revealed that the two carbonyl groups are able to twist out of coplanarity with the cyclopentene to a degree which would disrupt conjugation, and it is this factor which is believed to be responsible for the unexpectedly poor light absorption properties associated with this diolide. On the other hand, conformational analysis suggested that an alternative diolide in which the pair of lactone carbonyls is attached to the cyclobutene would be more likely to have enforced coplanarity and, therefore, enhanced UV absorption. A revised scheme was therefore considered in which the cyclobutene and cyclopentene functionality was reversed. This required reduction of the carboxyl groups of **25** to differentiated primary alcohols without passing through a meso intermediate, a sequence which was accomplished by first reducing the carboxylic acid of **25** via its mixed anhydride to the primary alcohol **42**.[28] The latter was protected as THP ether **43** before the methyl ester was reduced to furnish **44**. Protection of this alcohol as silyl ether **45** was



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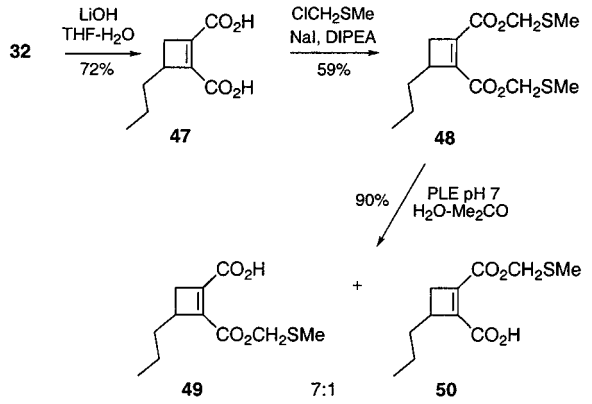
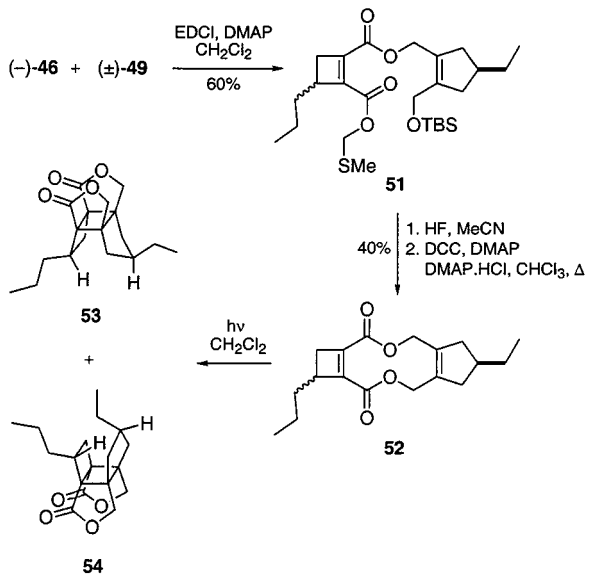
followed by selective removal of the THP protection with magnesium bromide in ether to give **46**.[29]

The selection of a suitable cyclobutene derivative for coupling with **46** was made with the goal of acquiring a diolide precursor in which the silyl ether from **46** and the cyclobutene ester would be cleaved in a single step that would not perturb the connecting ester linkage between cyclobutene and cyclopentene subunits. This reasoning led us to prepare the bismethylthiomethyl ester **48** from dicarboxylic acid **47**, itself obtained by exhaustive saponification of **32**, in the hope that porcine liver esterase hydrolysis of **48** would parallel the esterase catalyzed reaction of **32**.[30] Our expectation was fulfilled with isolation of the



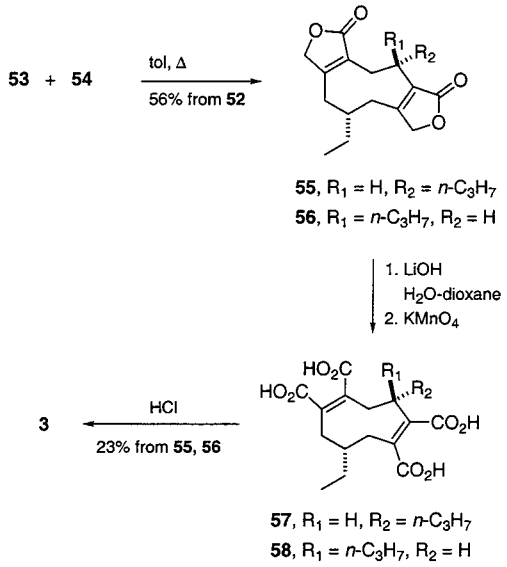
desired monocarboxylic acid **49**, although a small quantity of regioisomer **50** was also produced in this reaction. As with **33**, carboxylic acid **49** was found to be racemic. Methylthiomethyl ester **51**, obtained by coupling **49** with **46**, was exposed to HF which, as expected, removed both the silyl and methylthiomethyl groups without compromising the cyclopentenylmethyl ester.



The hydroxy acid generated in this reaction was not isolated but was subjected directly to Keck−Steglich lactonization conditions[31] to produce dilactone **52**. The remote stereocenters in **51** provide no basis for stereoselection, and none was observed in the coupling of racemic **49** with **46**; diester **51** was produced as an inseparable 1:1 mixture of stereoisomers at the center bearing the propyl substituent, and a similar inseparable mixture of stereoisomers was seen in **52**. In contrast to **41**, diolide **52** exhibited significant absorption in its UV spectrum above 300 nm ($\epsilon \sim 16\,000$ at 313 nm), supporting the rationale based upon comparison of the conformations of the two diolides and suggesting a more productive outcome for the irradiation of **52**.

In the event, irradiation of **52** (1:1 mixture) through Pyrex glass yielded two stereoisomeric photoproducts in approximately equal amount. One of these products, resulting from the cis isomer of **52**, is assigned the *exo*,*exo* structure **53**, in which both the ethyl and propyl substituents are directed away from the interior of the cage. The second photoproduct, derived from the trans isomer of **52**, is believed to be *exo*,*endo* adduct **54**, in which the ethyl substituent rather than the propyl group occupies the interior space. Puckering of the cyclopentane ring of **54** moves the ethyl group away from the congested cage interior, whereas the alternative photoadduct in which the propyl group is endo would create severe compression between the propyl substituent and a methylene group of the cyclopentane ring.

It was apparent during the photolysis of **52** that, even under the irradiation conditions, cycloreversion was taking place, and the facility of this fragmentation was confirmed when the mixture of **53** and **54** was heated in toluene. A quantitative yield

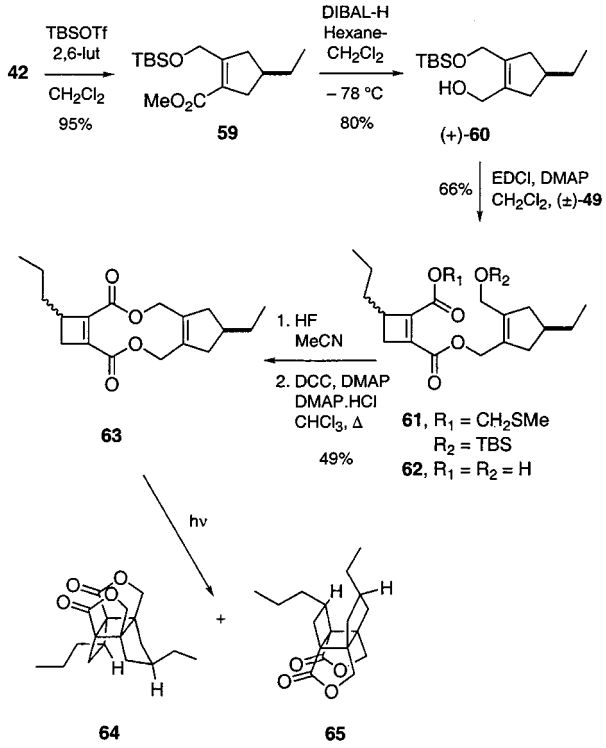


of **55** and **56** resulted from this reaction, the former arising from **53** and the latter from **54.** The steps from **55** and **56** to (+)-byssochlamic acid entailed hydrolysis of the pair of γ-lactones, oxidation of the resultant diol to tetracarboxylic acids **57** and **58**, and final treatment with hydrochloric acid to effect dehydration to give the bisanhydride (+)-**3**. As expected, the last step was also accompanied by epimerization of the propyl substituent in **58**, probably via a maleic−itaconic anhydride equilibrium, since only byssochlamic acid (**3**) and none of its trans isomer was produced in this sequence. The identity of our synthesized (+)-**3** with natural byssochlamic acid was confirmed by direct comparison (IR, ^{1}H and ^{13}C NMR, mass spectra, mp, optical rotation) of the two samples.

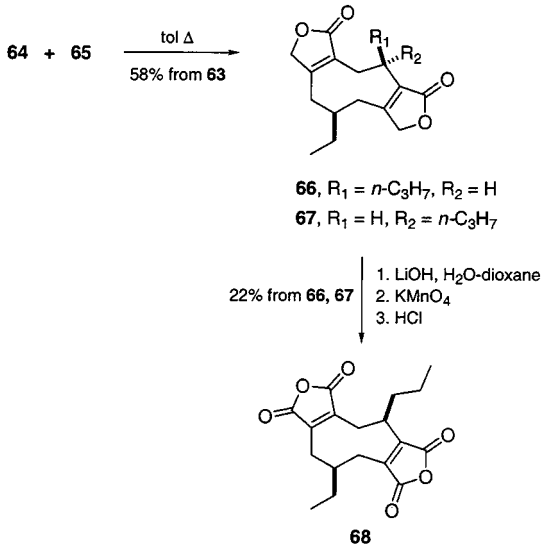
With the recognition that the cis relationship of ethyl and propyl substituents of **3** can be controlled through equilibration, the opportunity presented by the strategy outlined in Scheme 1 for synthesis of the nonnatural enantiomer of byssochlamic acid could be implemented in straightforward fashion by reversing the configuration of the ethyl group in the cyclopentene **17**. In

(29) Kim, S.; Park, J. H. *Tetrahedron Lett.* **1987**, *28*, 439.
(30) Ladner, W. E.; Whitesides, G. M. *J. Am. Chem. Soc.* **1984**, *106*, 7250.
(31) Boden, E. P.; Keck, G. E. *J. Org. Chem.* **1985**, *50*, 2394.

principle, there are two options for accomplishing this. A different esterase could perhaps be employed to effect desymmetrization of **24** in the opposite sense to **25**.[32] Alternatively, **25** can be adapted to our goal by stepwise coupling with **49** in the reverse sequence. This approach only requires interchange of the primary alcohol and silyl ether substituents in **46**, a transformation which was easily achieved by silylation of **42** and reduction of methyl ester **59**. The alcohol **60**, enantiomeric



with **46**, was used to esterify **49**, and the resultant diester **61** was deprotected to **62** and lactonized as before to give a 1:1 mixture of inseparable diolides **63**. Irradiation of this stereoisomeric mixture gave *exo,exo* and *exo,endo* cage photoadducts **64** and **65** in equal quantity, the assumption again being made that in **65** the ethyl substituent rather than the propyl chain is more easily accommodated in an endo orientation. As with **53**/**54**, thermal cycloreversion of **64** and **65** was a quantitative reaction, resulting in a 1:1 mixture of dilactones **66** and **67**.



The same hydrolysis, oxidation, and acidification sequence used with **55** and **56** was applied to this mixture to give (−)-**68**, enantiomeric with natural byssochlamic acid.

In conclusion, we have shown that a [2 + 2] photoaddition−cycloreversion pathway can be employed for asymmetric synthesis of both enantiomers of the nonadride byssochlamic acid. The possibility of extending this approach to more complex members of the nonadride family (e.g. **5**) can be foreseen, and efforts along these lines will be described in due course.

Experimental Section

Esterase Hydrolysis of 24. To a rapidly stirred mixture of **24** (1.70 g, 8.0 mmol) in acetone (20 mL) and pH 7 phosphate buffer (180 mL, sodium phosphate dibasic and potassium phosphate dibasic) at room temperature was added porcine liver esterase (200 mg, 4005 units). After the mixture was stirred for 3 h at room temperature, it was diluted with brine and ethyl acetate and was acidified to pH 1 with 2 N HCl at 0 °C. The resulting emulsion was filtered through a pad of Celite, and the filtrate was extracted with ethyl acetate (3 × 100 mL). The combined organic extracts were washed with saturated aqueous NaCl, dried over anhydrous $MgSO_4$, and concentrated under reduced pressure to yield 1.55 g (98%) of **25**: $[\alpha]_D^{23}$ −7.8 (*c* 1.00, $CHCl_3$); IR (neat) 3400−2400 (br), 2952, 2921, 2664, 1735, 1730, 1650, 1458, 1350, 1293 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.9 (3H, t, J = 7 Hz), 1.42 (2H, dq, J = 7, 7 Hz), 2.18 (1H, m), 2.48−2.63 (2H, m), 2.95−3.12 (2H, m), 3.9 (3H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.1, 28.3, 36.2, 41.2, 42.3, 53.5, 137.8, 147.3, 163.8, 168.6; MS(CI) *m*/*z* 199 (M^+ + H), 181, 167, 151, 137; HRMS (CI) *m*/*z* 199.0969 (calcd for $C_{10}H_{15}O_4$: 199.0970).

Esterase Hydrolysis of 48. To a rapidly stirred mixture of **48** (0.155 g, 0.51 mmol) in acetone (2 mL) and pH 7 phosphate buffer (10 mL, sodium phosphate dibasic and potassium phosphate dibasic) at room temperature was added porcine liver esterase (5 mg, 100 units). After the mixture was stirred for 3 h at room temperature, it was diluted with brine (10 mL) and ethyl acetate (10 mL), and the resulting emulsion was filtered through a pad of Celite. The filtrate was extracted with ethyl acetate (4 × 30 mL), and the combined organic extracts were washed with saturated aqueous NaCl, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to yield 0.11 g (90%) of a 7:1 mixture of **49** and **50** (determined by ^1H NMR analysis) as racemates. Chromatography of the mixture on silica, using 50% ether in hexane as eluent, afforded 0.076 g of pure **49** as a colorless oil: IR (neat) 3300−2800 (br), 2959, 2930, 1738, 1673, 1631, 1421, 1349, 1266, 1210 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.95 (3H, t, J = 7 Hz), 1.43 (3H, m), 1.89 (1H, m), 2.31 (3H, s), 2.37 (1H, dd, J = 2, 16 Hz), 2.89 (1H, dd, J = 4, 16 Hz), 3.03 (1H, m), 5.36 (1H, d, J = 12 Hz), 5.39 (1H, d, J = 12 Hz), 12.03 (1H, br s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 15.7, 20.4, 33.7, 34.1, 39.7, 71.0, 144.9, 150.2, 160.3, 164.3; MS(CI) *m*/*z* 245 (M^+ + H), 195, 183, 167, 139, 123, 93; HRMS (CI) *m*/*z* 245.0846 (calcd for $C_{11}H_{17}O_4S$: 245.0848).

Irradiation and Thermolysis of 52. A photolysis apparatus, equipped with a dry ice condenser and an argon inlet, was charged with a solution of **52** (0.040 mg, 0.13 mmol) in CH_2Cl_2 (100 mL). The solution was purged with argon for 1 h and was irradiated with a 450-W Hanovia medium-pressure mercury lamp using a Pyrex filter for 6 h. The solvent was evaporated under reduced pressure, and the residue was chromatographed on silica, using 5% ethyl acetate in hexane and 70% ethyl acetate in hexane as eluent, to give 7 mg of **52** and 19 mg of a mixture of **53**, **54**, **55**, and **56**. The mixture was taken up into toluene (3 mL) and heated to reflux for 7 h. After removal of the solvent, the residue was chromatographed on silica, using 50% ethyl acetate in hexane as eluent, to give 17.5 mg (44%, 56% based on recovered **52**) of **55** and **56** as a colorless oil: IR (neat) 2958, 2930, 1750, 1653, 1457, 1060, 1033 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.88 (m, 3H), 1.03 (m, 3H), 1.10−1.40 (m, 2H), 1.41−1.72 (m, 4H), 1.72−2.00 (m, 1H), 2.25−2.58 (m, 5H), 2.70 (m, 1H), 2.96−3.28 (m, 1H), 4.43−

(32) (a) Wang, Y.-F.; Chen, C.-S.; Girdaukas, G.; Sih, C. *J. Am. Chem. Soc.* **1984**, *106*, 3695. (b) Laumen, K.; Schneider, M. P. *J. Chem. Soc., Chem. Commun.* **1986**, 1248.

4.75 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 12.0, 12.3, 13.9, 14.0, 20.7, 21.1, 27.7, 27.8, 29.0, 29.8, 30.3, 31.2, 32.1, 33.2, 34.5, 35.3, 41.6, 42.2, 70.8, 71.5, 71.8, 72.3, 127.4, 128.1, 130.1, 131.6, 158.2, 158.8, 159.2, 159.8, 173.9, 174.3, 174.8, 174.9; MS(CI) *m*/*z* 304 (M^+), 286, 257, 224, 193, 167, 153, 143, 119, 99; HRMS (CI) *m*/*z* 304.1681 (calcd for $C_{18}H_{24}O_4$: 304.1675).

(+)-Byssochlamic Acid (3). To a solution of **55** and **56** (11 mg, 0.036 mmol) in dioxane (2 mL) and water (2 mL) was added lithium hydroxide monohydrate (15 mg, 0.36 mmol), and the mixture was stirred for 1.5 h at 50 °C. The mixture was cooled to 0 °C, and $KMnO_4$ (40 mg, 0.252 mmol) was added. After 1 h at room temperature, the solution was heated at 40 °C for 1 h, cooled to 0 °C, and acidified to pH 1 with 2 N HCl. The mixture was extracted with CH_2Cl_2 (5 × 20 mL), and the combined organic extracts were washed with saturated aqueous NaCl and dried over anhydrous $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica, using 30% ethyl acetate in hexane as eluent, to give 2.8 mg (23%) of (+)-**3**: mp 164−165 °C; $[\alpha]_D^{23}$ +101 (*c* 0.24, $CHCl_3$); IR (neat) 2966, 2934, 1829, 1766, 1260, 927 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.96 (3H, t, J = 7 Hz), 1.12 (3H, t, J = 7 Hz), 1.28−1.50 (2H, m), 1.50−1.75 (4H, m), 1.90 (1H, m), 2.25−2.43 (2H, m), 2.65 (1H, m), 2.72 (1H, dd, J = 2, 14 Hz), 2.77−2.98 (2H, m), 3.41 (1H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 11.6, 13.7, 20.6, 28.1, 29.2, 29.7, 30.0, 34.7, 36.0, 40.4, 143.2, 143.4, 144.1, 144.7, 164.9, 165.4 (2), 165.7; MS(CI) *m*/*z* 332 (M^+), 260, 208, 166, 125; HRMS (CI) *m*/*z* 332.1263 (calcd for $C_{18}H_{20}O_6$: 332.1259).

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Supporting Information Available: Experimental procedures for **3**, **22**, **24**, **26**, **27**, **32**−**37**, **39**−**56**, **59**−**61**, **63**−**68** (PDF); ^{1}H and ^{13}C NMR spectra of **3**, **22**, **24**−**27**, **32**-**37**, **39**-**49**, **51**, **52**, **55**, **56**, **59**−**61**, **63**, **66**−**68**; X-ray crystallographic data for **28** and **35**. This material is available free of charge via the Internet at http://pubs.acs.org.

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