Photoenolization Diels-Alder Reactions Application to the Total Synthesis of Hybocarpone and Hamigerans

Group Meeting

01/08/04

Vijay

References

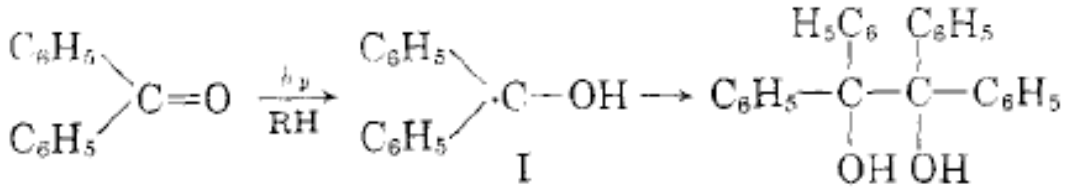
Hybocarpone⇒ Nicolaou,K.C.; Gray, D. L.F. *J.Am,Chem,Soc*.**2004**,*126* ASAP

Nicolaou,K.C.; Gray, D. L.F.*Angew*.*Chem*.*Int*.*Ed*.**2001**,*40*,761

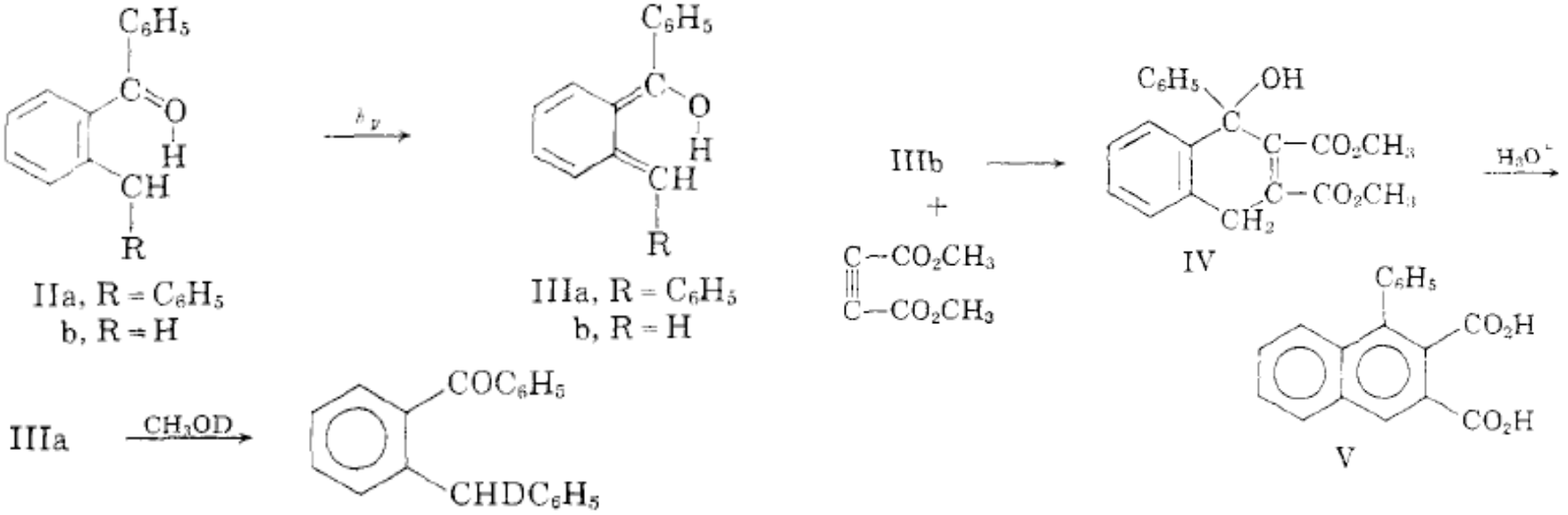
Hamigerans ⇒ Nicolaou,K.C.; Gray, D. L.F.; Tae, Jinsung. *J.Am,Chem,Soc*.**2004**,*126* ASAP

Photoenolization Diels-Alder Reaction: Introduction

Benzophenone to Benzopinacol

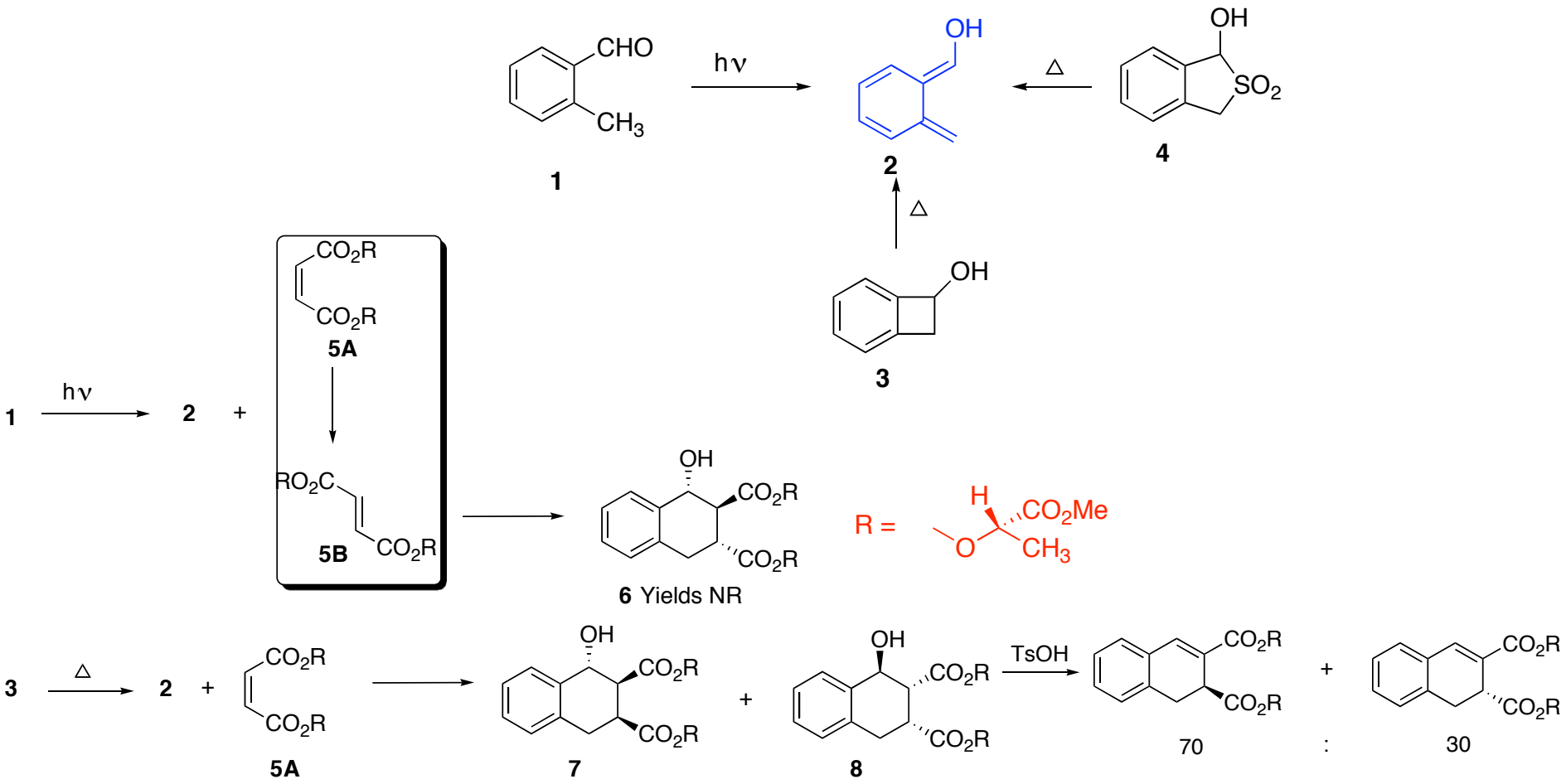


Dienol(α-Hydroxy o-Quninodimethane) Formation via Intramolecular hydrogen transfer



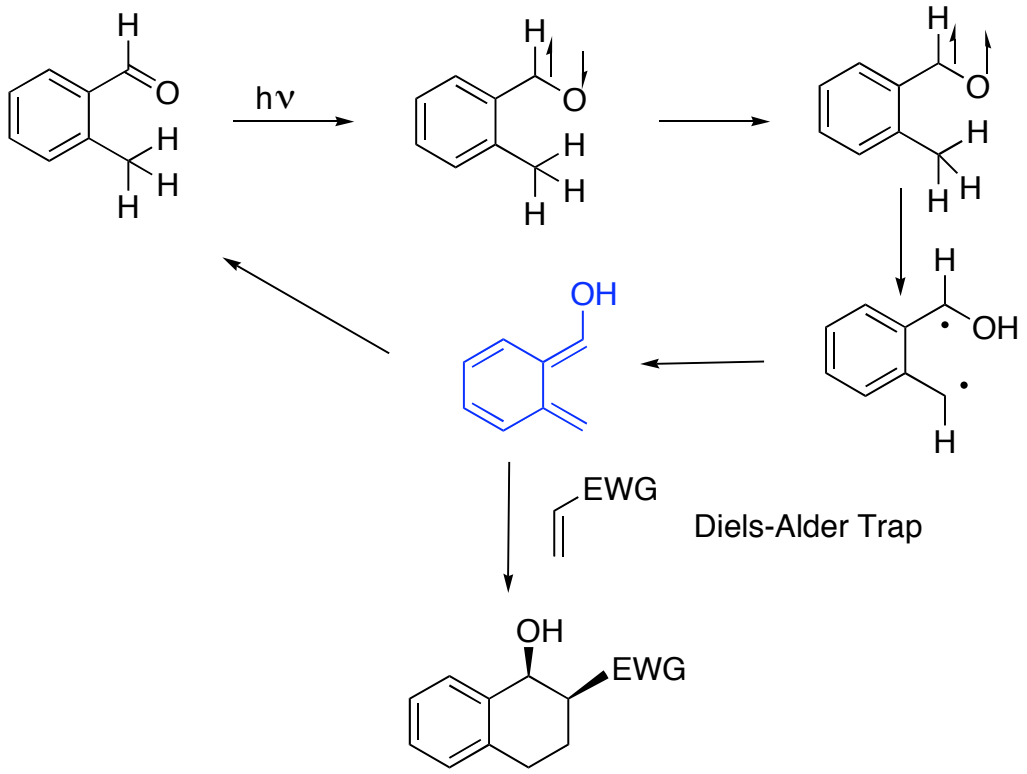
Yang, N.; Rivas, C. *J.Am.Chem.Soc*.**1961**,*83*, 2213

Other methods for Dienol Formation



Charlton, J.; Koh, K.; Plourde, G. *Tet.Lett.***1989**, *30*, 3279

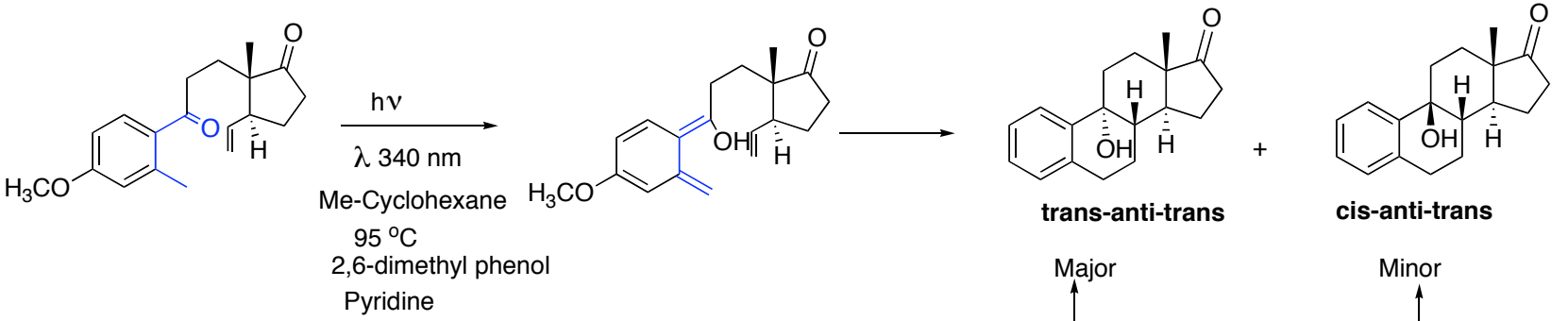
Mechanism



Sammes,P. *Tetrahedron* **1976**, *32*, 405
Charlton, J.; Alauddin, M. *Tetrahedron* **1987**, *43*, 2873

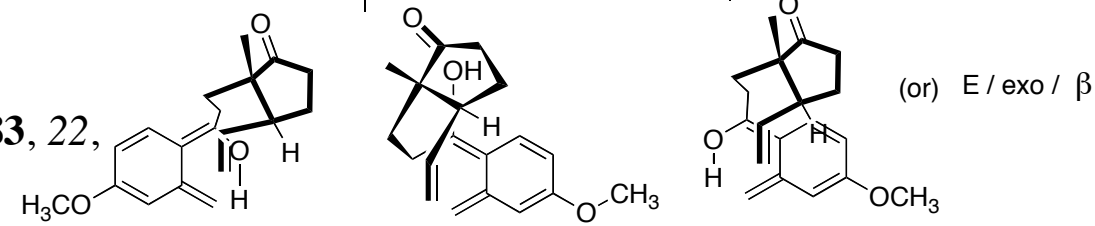
Examples of PEDA and Applications

Photochemical Synthesis of Estrone

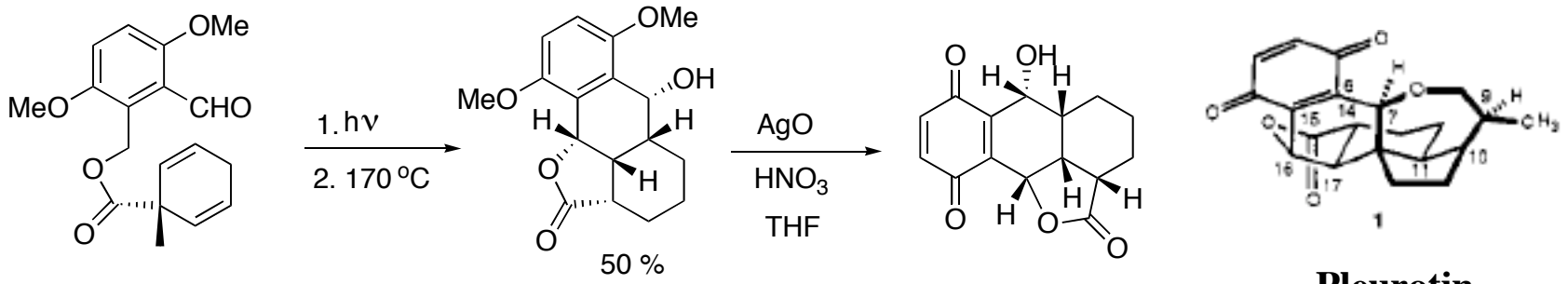


2,6- Dimethyl phenol prevents light induced decomposition of dienol
Pyridine increases the life time of (Z)-Dienol

Quinkert, G.; Stark, H.*Angew Chem.Int.Ed.***1983**, *22*, 637-655



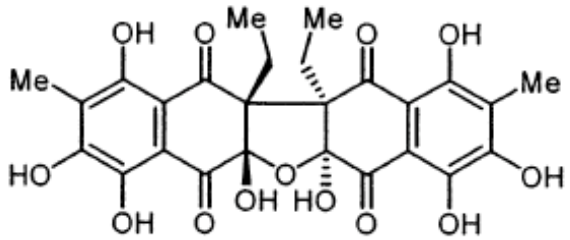
Pleurotin Analog



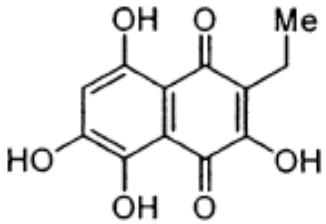
Pleurotin

Kraus,G.A.; Chen,Li. *Synth.Commun.*23, 2041, **1993**

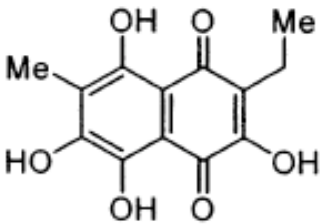
Hybocarpone



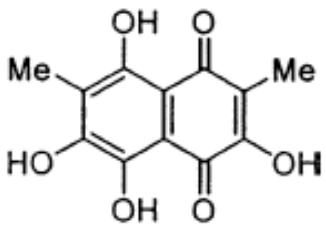
hybocarpone **(1)**



christazarin **(2)**



6-methylchristazarin **(3)**



aureoquinone **(4)**

Figure 1. Molecular structures of **1** and related naphthazarin natural products (**2**−**4**).

- ☞Isolated from lichen species *Lecanora Hybocarpa* in Lousiana woodland
- ☞Cytotoxic against murine mastocytoma P815 transplantable tumor cell line IC_{50} of 150 ng/mL
- ☞Possible DNA intercalation/DNA damage pathway as viable mode of action
- ☞Novel molecular architecture containing dinaphtho furantetraone skeleton possessing element of C_2 symmetry
- ☞Closely structurally related to the naphthazarins

Tetralones as precursors to Hybocarpone and Analogs

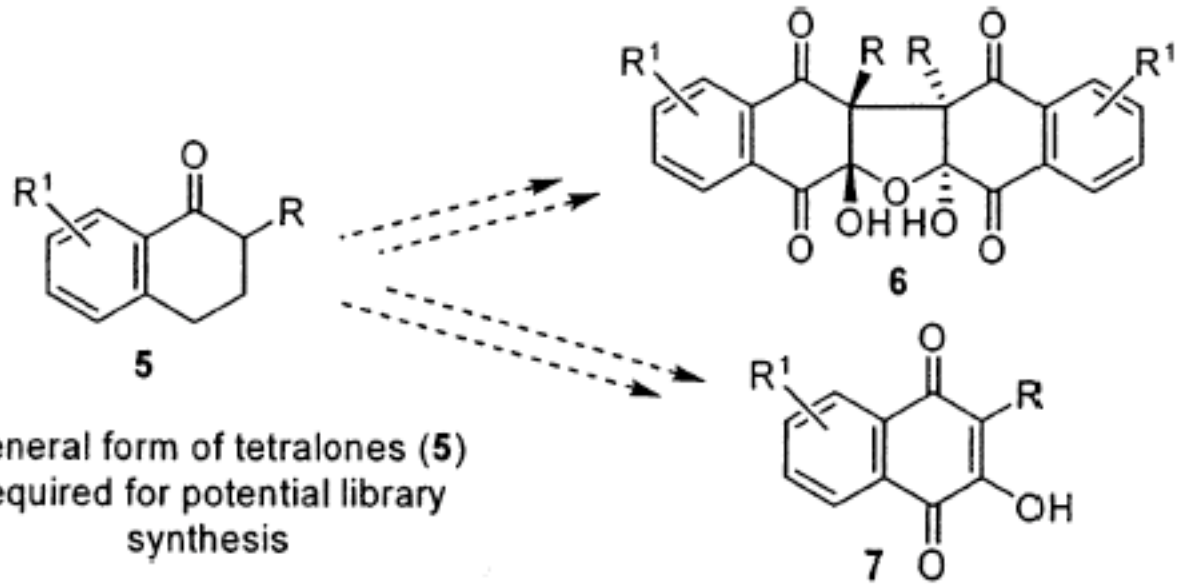


Figure 2. Potential hybocarpone **6** and hydroxynaphthoquinone **7** libraries from tetralones **5**.

PEDA Approach to Tetralones

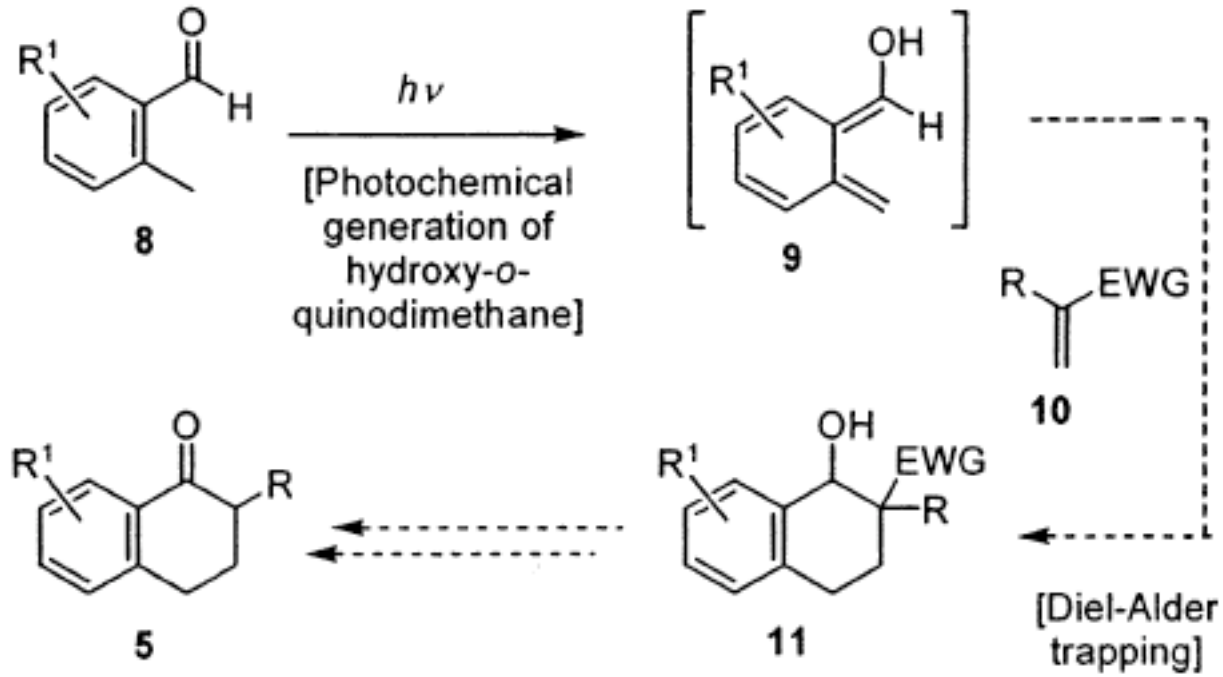
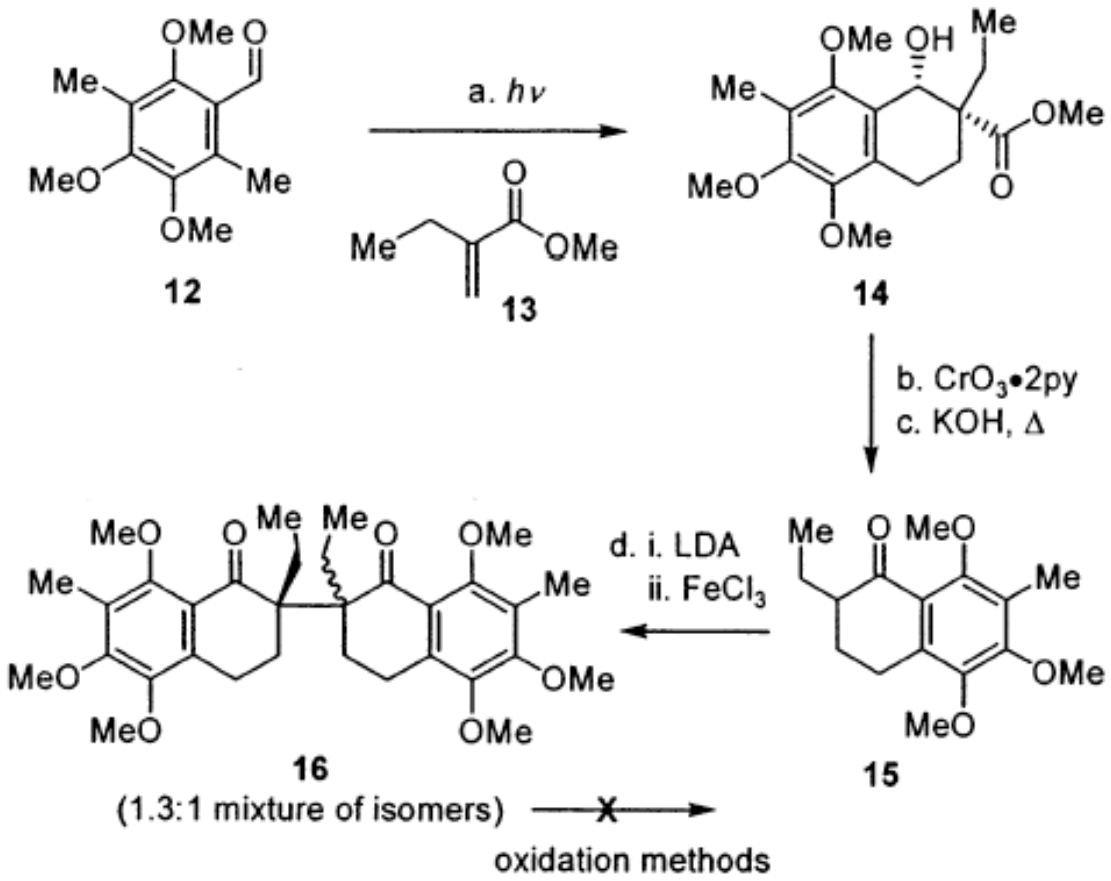


Figure 3. Proposed general synthesis of varied tetralones **5** via photochemically induced benzannulation of *o*-methylbenzaldehydes **8**. EWG = electron-withdrawing group.

Oxidative Dimerization of Ketone Enolate **15**

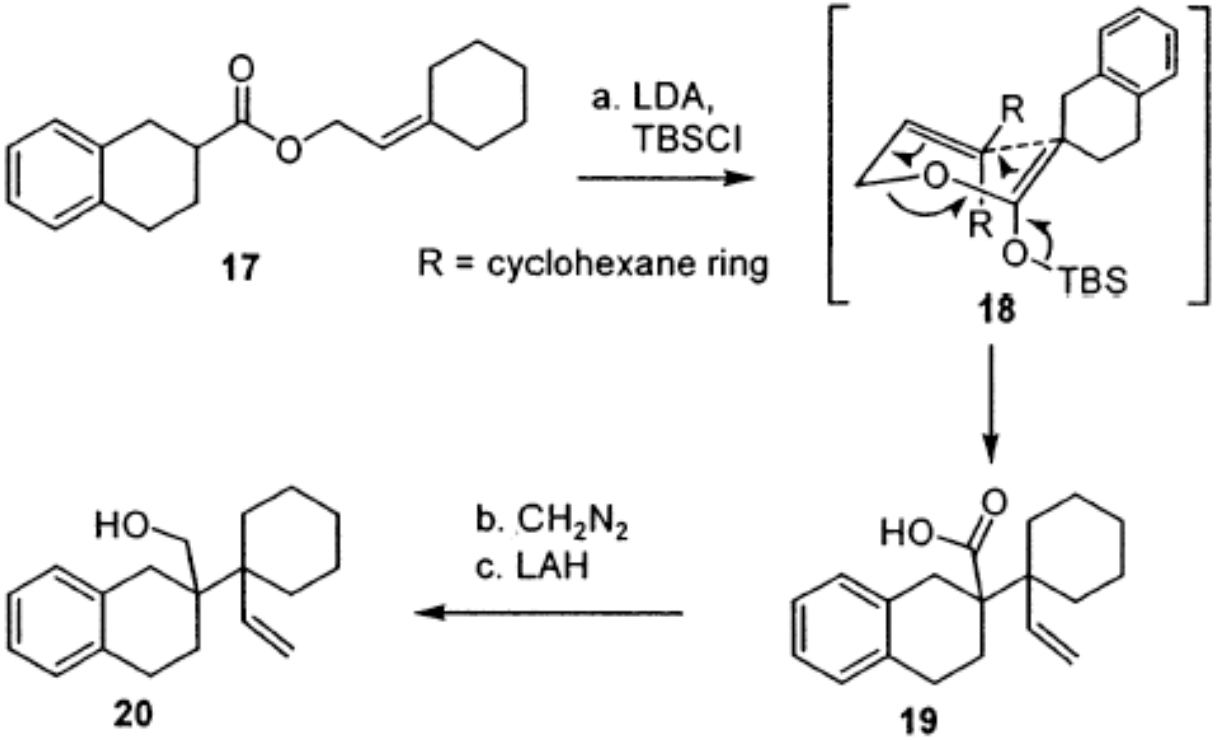
Scheme 1. Construction of Dimer **16** and Unsuccessful Attempts To Elaborate It to **1**[a]



[a] Reagents and conditions: (a) **13** (6.0 equiv), *hν*, toluene, 4 h, 81% (2:1 ratio of diastereoisomers, major isomer shown); (b) CrO_3·2py (6.0 equiv), CH_2Cl_2, 0−25 °C, 1 h, 86%; (c) 1 M aqueous KOH, EtOH, 90 °C, 6 h, 80%; (d) (i) LDA (1.1 equiv), THF, −78 °C, 1 h; (ii) then $FeCl_3$ (1.1 equiv) in DMF, −78 to 0 °C, 4 h, 52%. LDA = lithium diisopropylamide.

Ireland Claisen Rearrangement Approach -A Simple Model System

Scheme 2. Construction of a Hindered Carbon–Carbon Bond via Claisen Rearrangement on a Model System[a]



[a] Reagents and conditions: (a) LDA (1.2 equiv), (TBS)Cl (1.5 equiv), HMPA, THF, −78 °C, 2 h; then warm to 60 °C, 1 h; (b) CH_2N_2, ether, 5 min; (c) LAH (6.0 equiv), THF, 4 h, 48% for three steps.

Biomimetic Approach

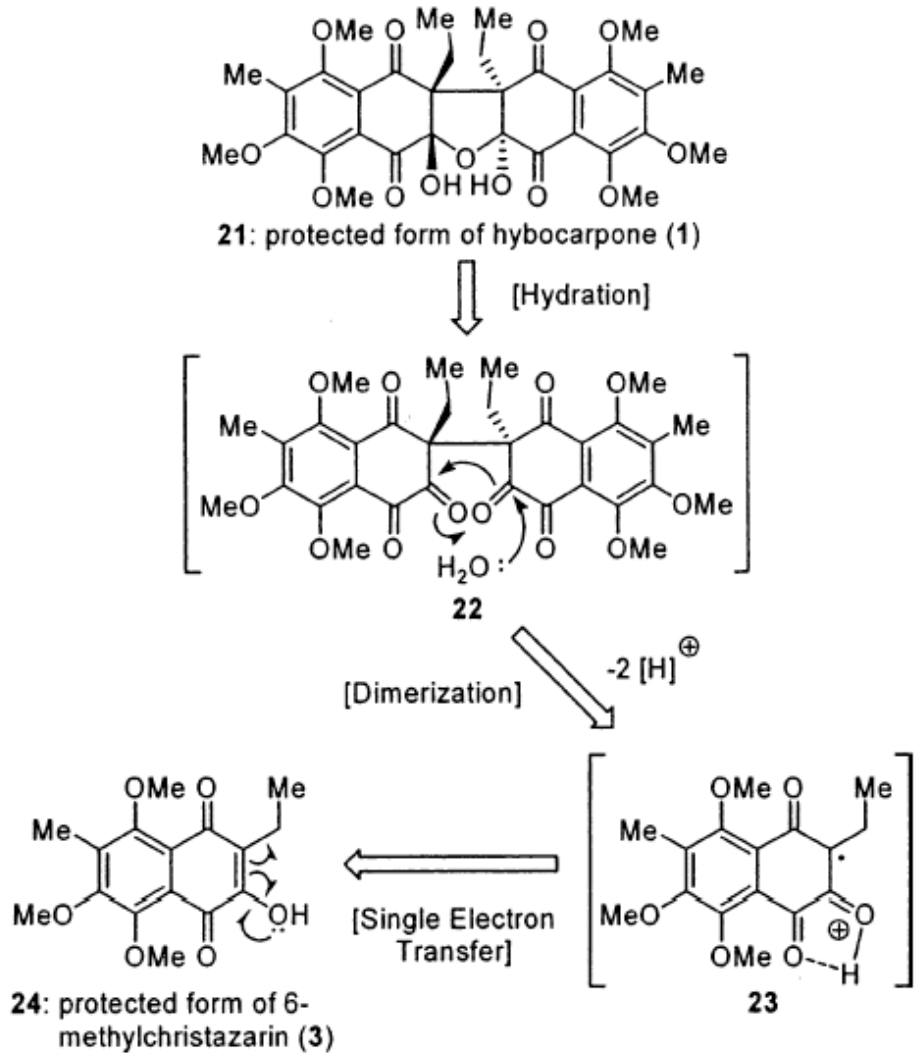


Figure 4. Second-generation retrosynthesis of hybocarpone hexamethyl ether (**21**) bases on the oxidative dimerization of hydroxynaphthoquinone **24**.

Possible diastereomers formed upon hydration/cyclization event

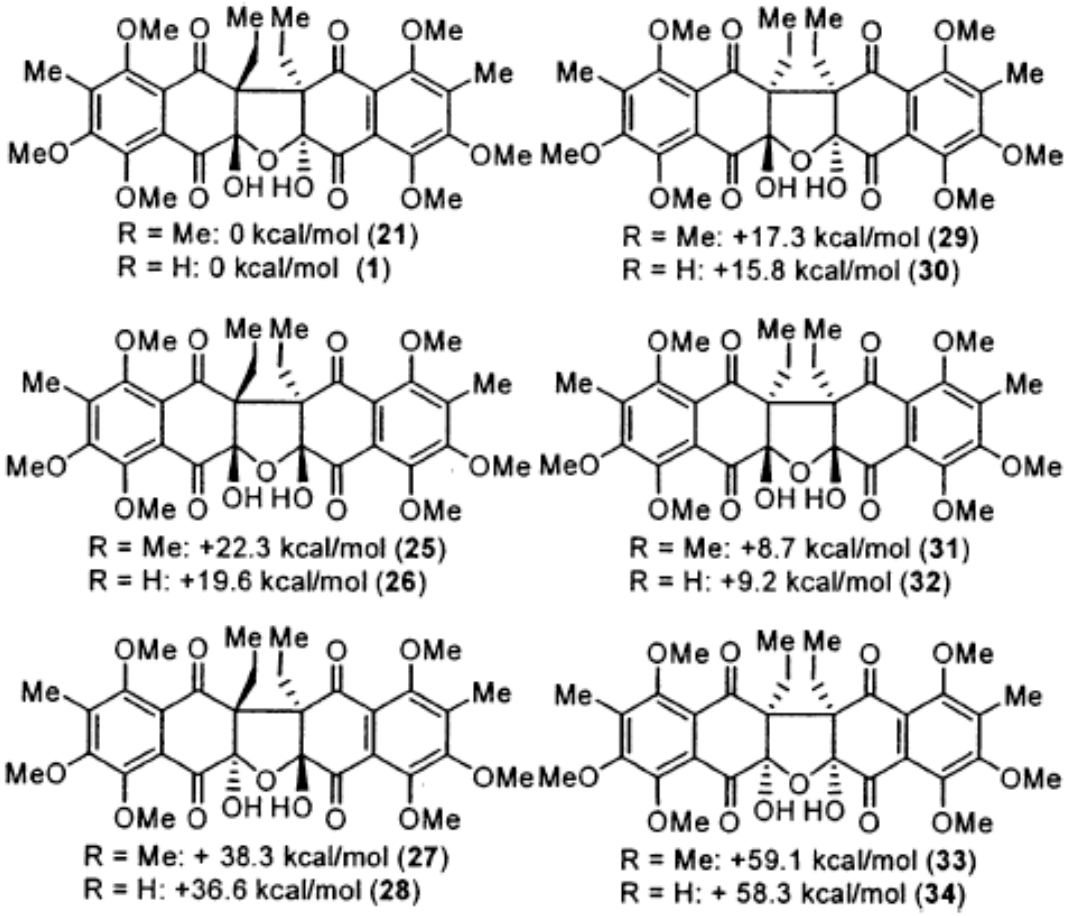
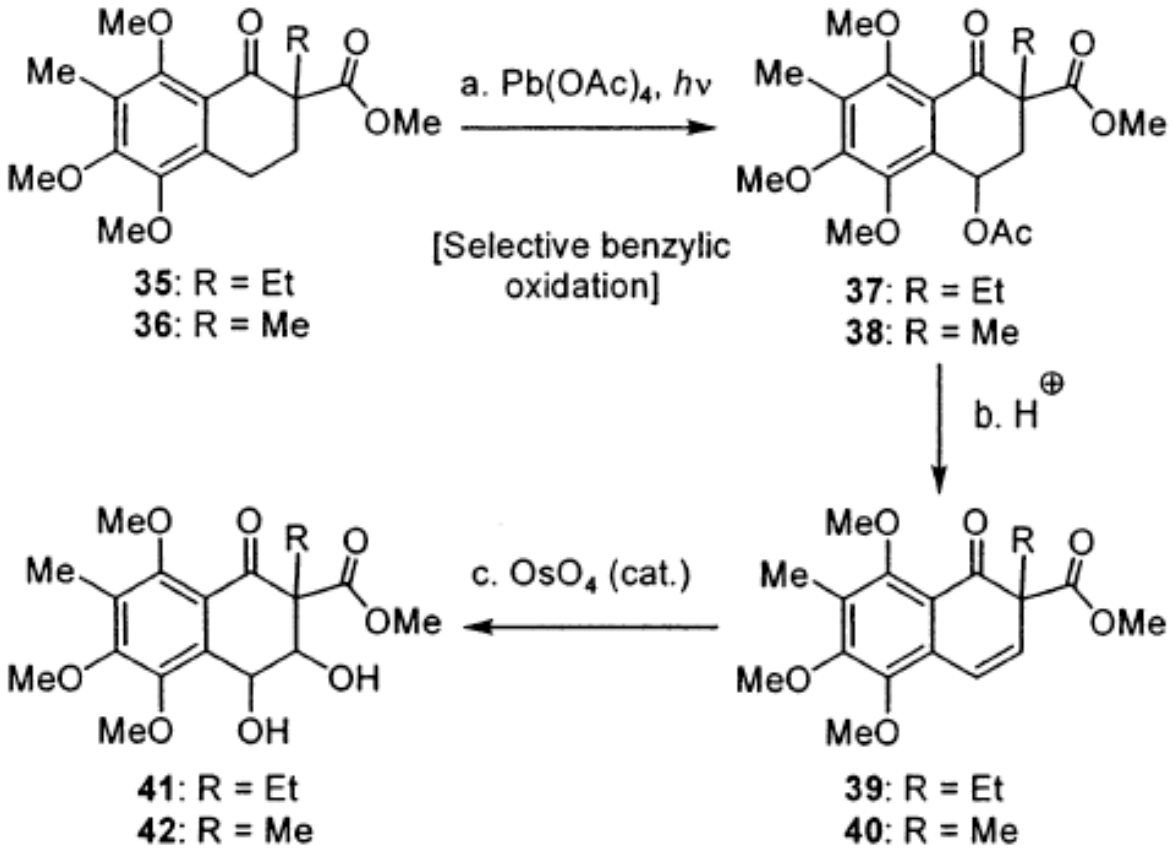


Figure 5. Calculated relative strain energies of the six possible hybocarpone diastereoisomers (R = H) and their corresponding hexamethyl ethers (R = Me) (see ref 21 for computational parameters).

Synthesis of Napthazarins **3,4**

Scheme 3. Synthesis of Naturally Occurring Naphthazarins **3** and **4** via a Series of Selective Oxidation Reactions[a]



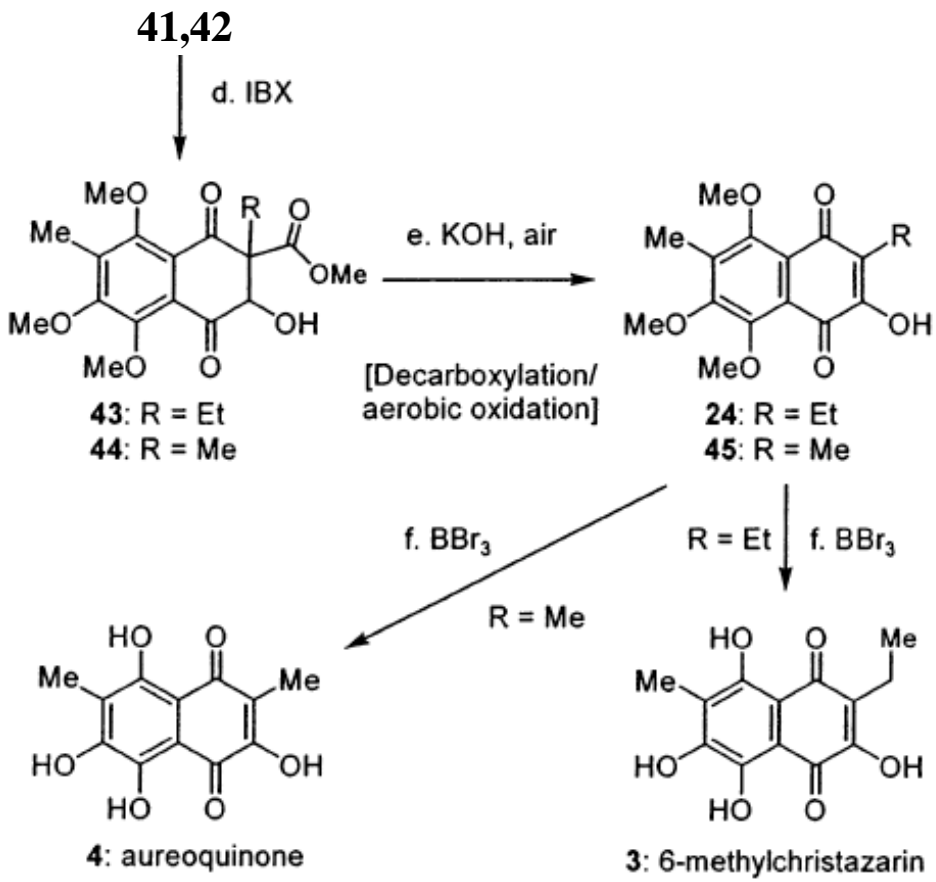
35: R = Et
36: R = Me

37: R = Et
38: R = Me

39: R = Et
40: R = Me

41: R = Et
42: R = Me

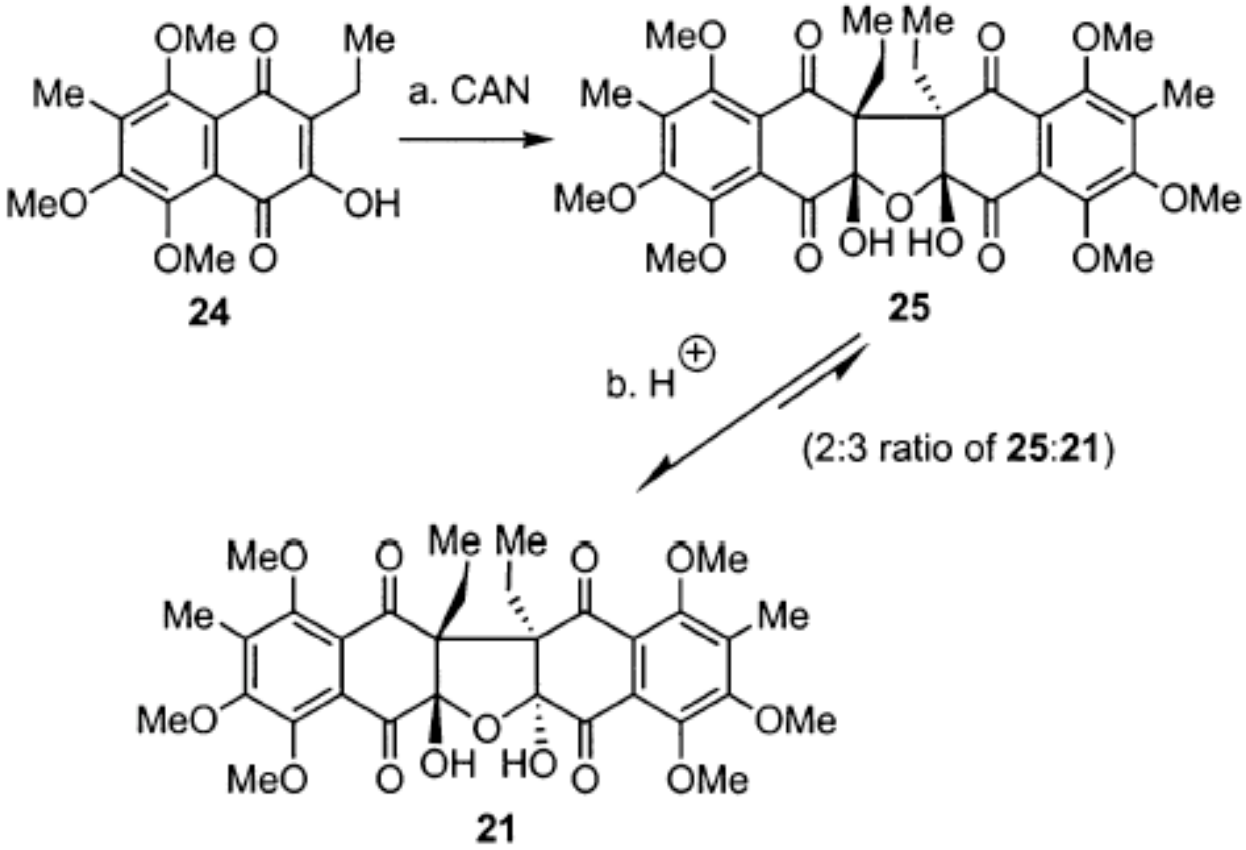
Naphthazarins (Cont'd)



[a] Reagents and conditions: (a) $Pb(OAc)_4$ (1.4 equiv), *hν*, AcOH, 2 h, 71% (3:1 ratio of diastereoisomers); (b) HCl, AcOH, 90 °C, 4 h, 72%; (c) OsO_4 (0.1 equiv), NMO (3.0 equiv), THF−*t*BuOH−H_2O−py (20:20:4:1), 12 h, 92%; (d) IBX (3.0 equiv), DMSO, 25 °C, 0.5 h, 92%; (e) 1.5 M aqueous KOH−THF (1:3.5), air, 1 h, 83%; (f) BBr_3 (10.0 equiv), CH_2Cl_2, −78 to +25 °C, 3 h, 40−50%. NMO = *N*-methylmorpholine *N*-oxide, and IBX = 1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide.

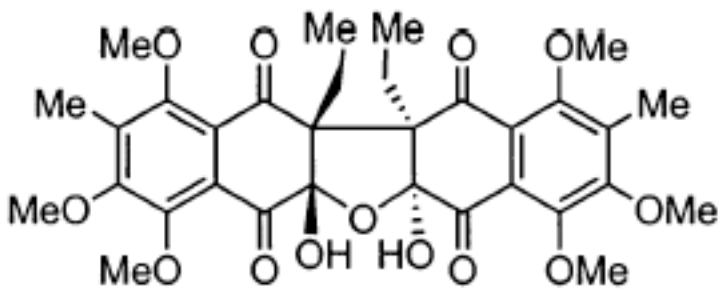
Synthesis of Protected hybocarpone **21**

Scheme 4. Synthesis of **1** via Successful Application of the Oxidative Quinone Coupling Strategy[a]



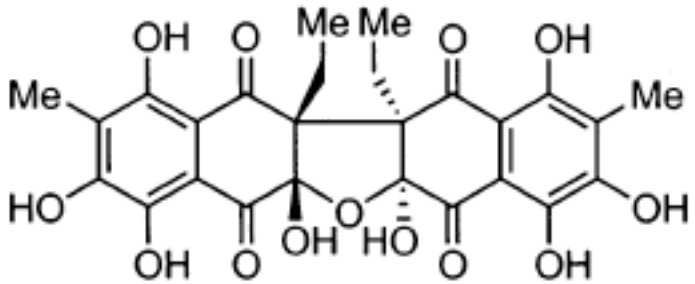
Low yields for dimerization 36 % combined yield of 25&21 after three iterations using recovered starting material.Longer reaction times and other reaction variables did not affect conversion and chemical yields

Completion of synthesis



21

c. $AlBr_3$, EtSH

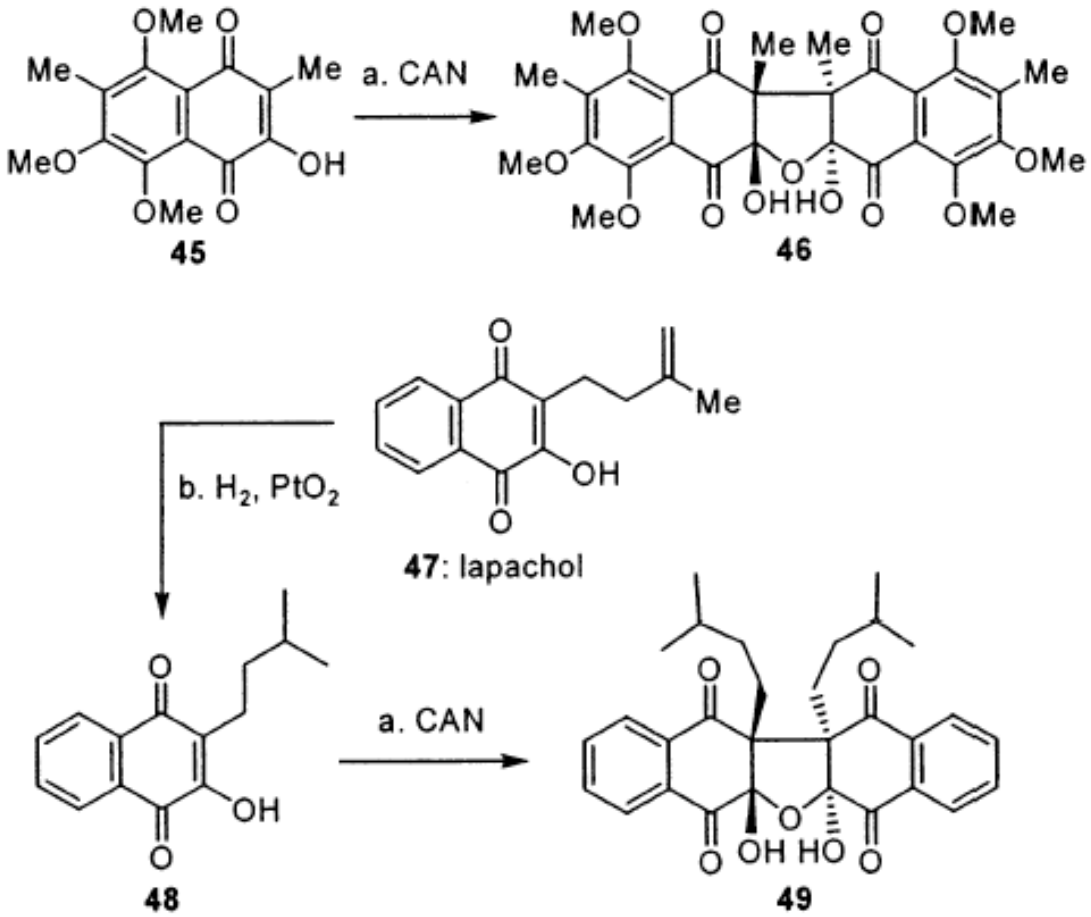


1: hybocarpone

[a] Reagents and conditions: (a) **24** in MeCN; then add CAN (1.0 equiv) in degassed MeCN, −35 to 0 °C, sonication, 2 min; then 5 M aqueous KOH, 0−25 °C, 10 min, 19% plus 60% recovered starting material, **21**:**25** ratio ca. 3:2; (b) AcOH, $CHCl_3$, 5 min, >95%; (c) $AlBr_3$ (1 M in CH_2Br_2, 25 equiv), EtSH−$CHCl_2$ (1:2), 0 °C, 1 h, 60%. CAN = cerium ammonium nitrate.

Synthesis of Hybocarpone Analogs

Scheme 5. Oxidative Dimerization of Hydroxynaphthoquinones **45** and **48**[a]

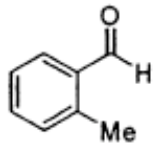
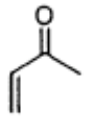
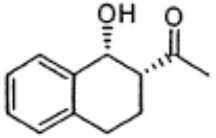
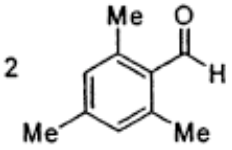
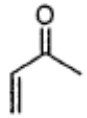
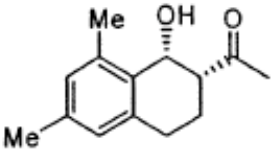
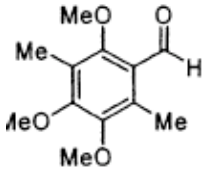
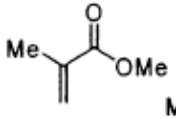
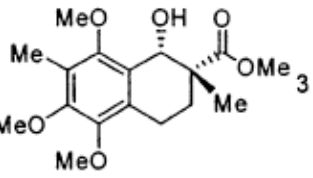
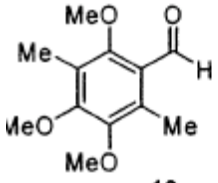
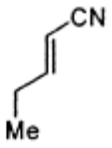
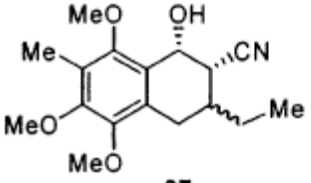


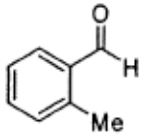
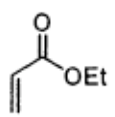
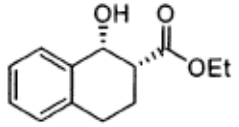
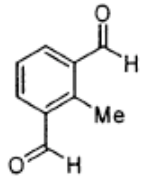
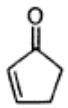
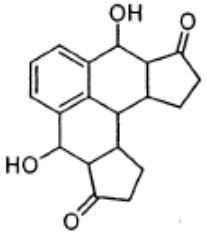
[a] Reagents and conditions: (a) **45** or **48** in MeCN; then add CAN (1.0 equiv) in degassed MeCN, −35 to 0 °C, sonication, 2 min; then 5 M aqueous KOH, 0−25 °C, 10 min, 9% **46** plus 71% recovered starting material; 4% **49** plus 93% recovered starting material; (b) PtO_2(cat.), H_2 (1 atm), EtOAc, 4 h, filter catalyst, then bubble in air, 2 h, 83%.

Two isomeric compounds for 46 were isolated in 1:1 ratio. The other isomer doesn't interconvert in acidic conditions. More prone to decomposition

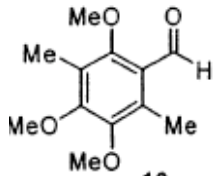
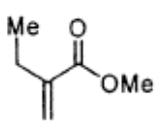
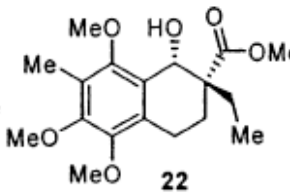
Substrate Scope For Intermolecular PEDA

Table 1. Benzannulation by Intermolecular Diels–Alder Trapping of Hydroxy-*o*-quinodimethanes Generated via Photoenolization

Entry	Aldehyde	Dienophile	Product	*t* [h]	Yield[%]
1	 **12**		 **13**	14	53[b]
2	 **14**		 **15**	8	72[b]
3	 **16**		 **29**	3	82
4	 **16**		 **27**	6	53[b]

Entry	Aldehyde	Dienophile	Product	*t* [h]	Yield[%]
5	 **12**		 **31**	16	53
6	 **32**		 **33**	2	16

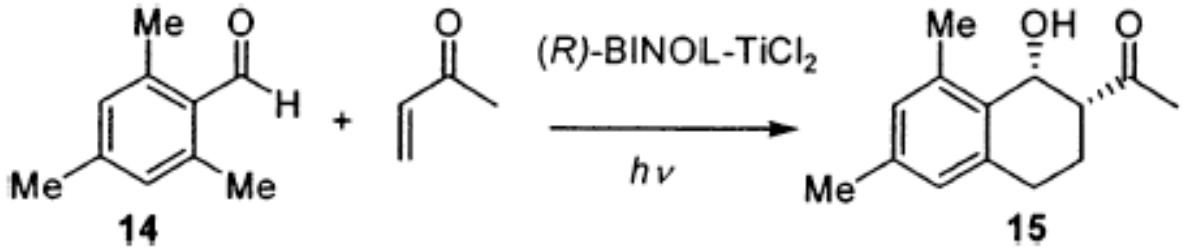
[Products were obtained as separable mixtures of diastereoisomers. Major product shown, all products were racemic. See footnotes for product ratios.]

Entry	Aldehyde	Dienophile	Product	*t* [h]	Yield[%]
7	 **16**		 **22**	4	83

[a] *o*-Alkylbenzaldehyde (0.5–2 mmol) and olefin (4–20 equiv) were dissolved in deoxygenated toluene (0.03 M) in a Pyrex flask and irradiated at ambient temperature (reactions warmed on irradiation) with a 450 W Hanovia lamp at a distance of 5 cm. Product ratios (*endo*:*exo*) as follows by entry number: (1) ca. 4:1, (2) ca. 4:1, (3) ca. 2:1, (4) ca. 6:3:1,5) ca. 1.5:1, (6) ca. 2:1. (7) ca. 8:1, [b] Product ratio determined by NMR spectroscopy.

Asymmetric Induction in PEDA

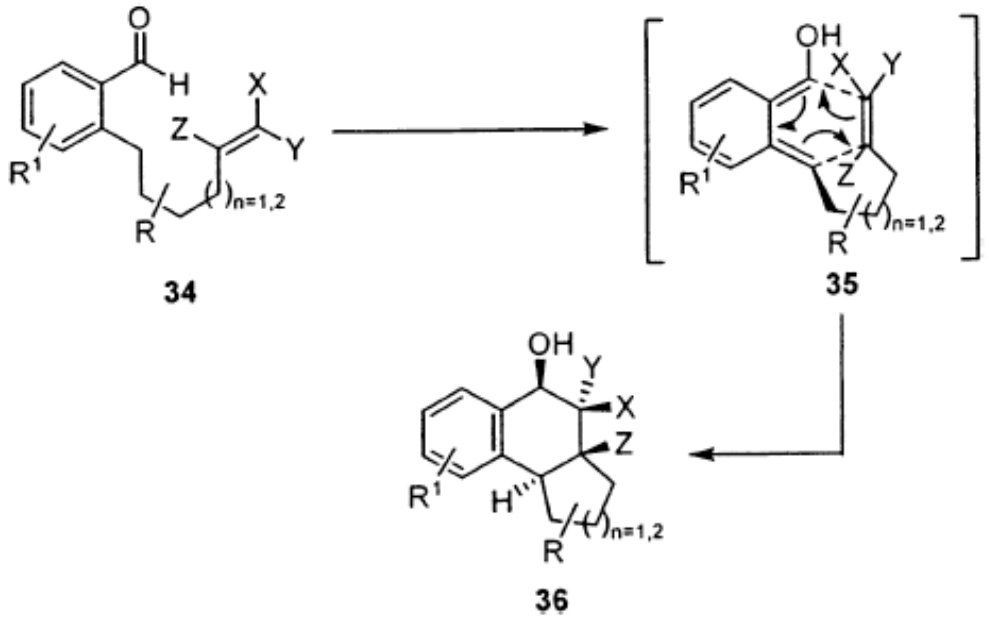
Table 3. Effect of (*R*)-BINOL−$TiCl_2$ on the Diels−Alder Trapping of a Photochemically Generated Hydroxy-*o*-quinodimethane[a]

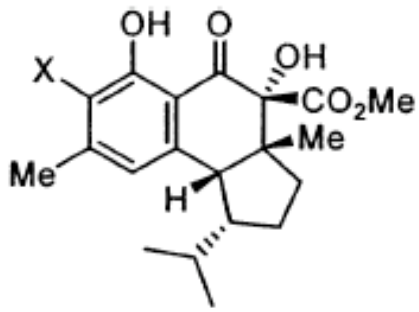


entry	amt of (*R*)-BINOL−$TiCl_2$ (equiv)	temp (°C)	ee[b] (%)	time (h)	yield (%)
1	0.75	−40	25	12	30[c]
2	0.05	−40	0	12	20[d]
3	0.20	25	<5	6	45

[a] A solution of aldehyde **14** (0.2 mmol), methyl vinyl ketone (4.0 equiv), and (*R*)-BINOL−$TiCl_2$ were cooled to the indicated temperature and irradiated (450 W Hanovia lamp) in deoxygentated toluene. Workup and chromatography gave pure **15** along with significant amounts of recovered starting matieral. [b] The enantiomeric excess was measured by chiral HPLC. The absolute configuration was not determined. [c] 30% recovered starting material. [d] 50% recovered starting material.

Intramolecular PEDA Approach to Hamigerans



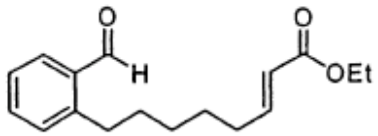
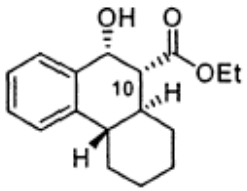
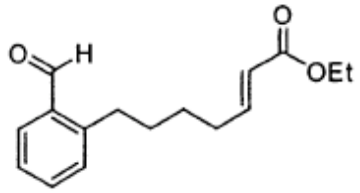
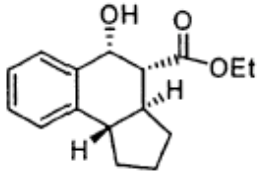
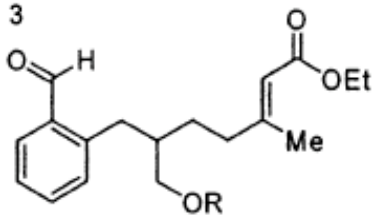
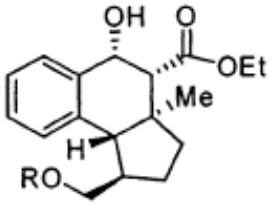
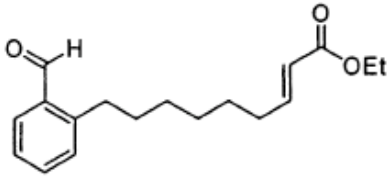
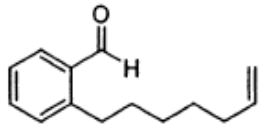
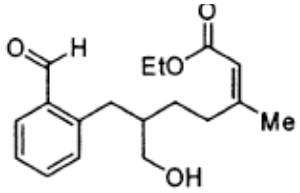
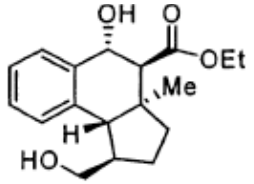
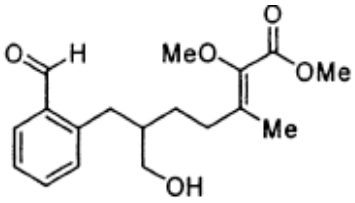
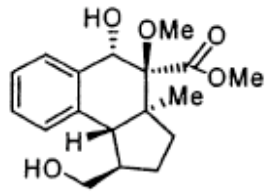


X = H: debromo-hamigeran A (**1**)
X = Br: hamigeran A (**2**)

Figure 3. General scheme for the synthesis of tricycles **36** from substrates **34** via the IMPEDA cascade via hydroxy-*o*-quinodimethanes **35**.

Substrate scope of IMPEDA

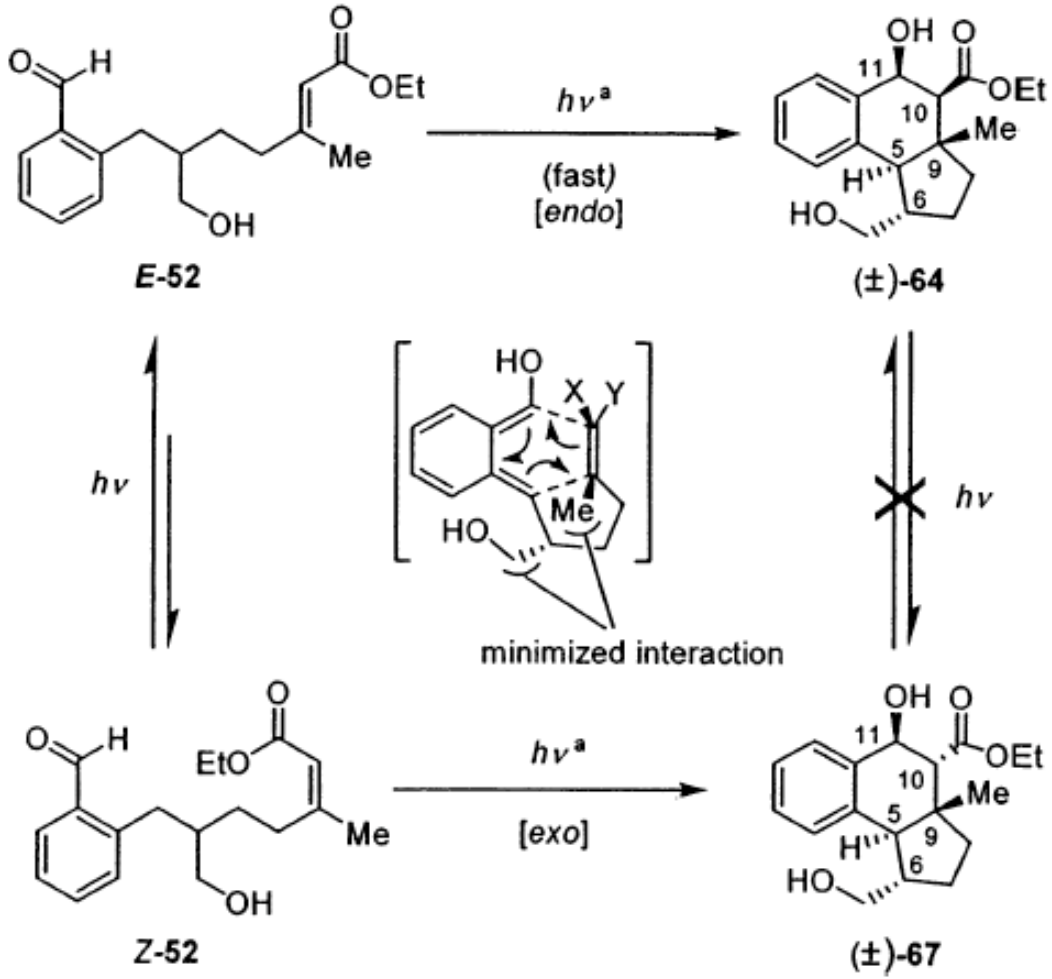
Table 4. Synthesis of Tricycles **36** from Substrates **34** through Intramolecular Photoenolization/Diels–Alder Cascade via Hydroxy-*o*-quinodimethanes **35** (See Figure 3)[a]

Entry	Aldehyde	Product	*t* [min]	Yield[%]
1	 **47a**	 **56**	45	94
2	 **46a**	 **60**	20	91
3	 ***E*-52**: R = H **53**: R = Ac **54**: R = TBS	 **64**: R = H **65**: R = Ac **66**: R = TBS	20 20 20	94[b] 90[b] 93[b]
4	 **48a**	no cyclization product		
5	 **47e**	no cyclization product		
6	 ***Z*-52**	 **67**	40	89[c]
7	 **55**	 **68**	60	75[d]

[a] *o*-Alkylbenzaldehydes (0.1–0.5 mmol) were dissolved in deoxygenated toluene (0.05 M) in a Pyrex flask and irradiated at ambient temperature (reactions warmed slightly upon irradiation) with a 450 W Hanovia lamp at a distance of 5 cm. Products were obtained as separable mixtures of isomers, the ratio of which was related to be the *E*:*Z* ratios of the starting olefins. All products were racemic. Starting aldehydes and products shown are the major isomers. [b] Starting olefin, *E*:*Z* > 25:1; product, C-10 epimers >25:1. [c] Starting olefin, *E*:*Z* > 20:1; product, C-10 epimers ca. 3:1. [d] Starting olefin, *E*:*Z* 1.2:1; product, C-10 epimers 2.5:1.

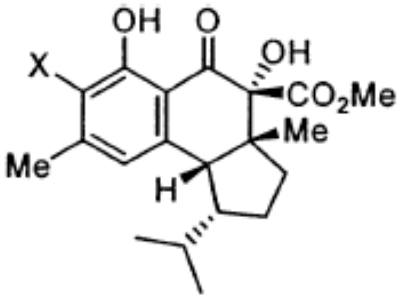
Proposed Model to account for Stereoselectivity in (Z)-Olefin

Scheme 3. Stereochemical Course of the Intramolecular Photocyclization with a Substituent at C-6 and the Observed *cis/trans* Isomerization of Reaction Substrate (*Z*)-**52**

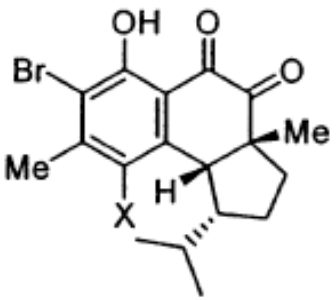


[a] Irradiation of (*E*)-**52** Leads Predominantly to **64** in 94% yield (**64**:**67** > 25:1). Irradiation of (*Z*)-**52** Leads Predominantly to **67** in 89% yield (**67**:**64** = 3:1).

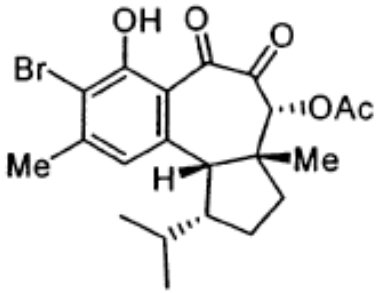
Hamigerans



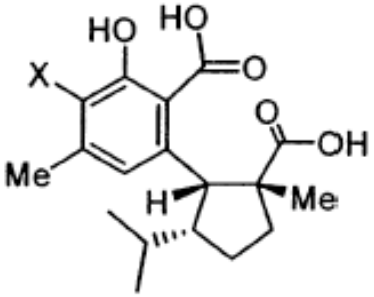
X = H: debromo-
hamigeran A (**1**)
X = Br: hamigeran A (**2**)



X = H: hamigeran B (**3**)
X = Br: 4-bromo-
hamigeran B (**4**)



hamigeran C (**5**)



X = H: debromo-
hamigeran E (**6**)
X = Br: hamigeran E (**7**)

Figure 1. Molecular structures of selected hamigerans (**1**−**7**).[1,2]

☞Isolated from Hamigera Tarangaensis in Newzealand

☞Cytotoxic against P-388 leukemia cells [4-bromo-hamigeran B, IC_{50} = 13.5μM

☞Strong antiviral activity against herpes and polio viruses

☞Substituted benzenoid nucleus fused to [4.3.0] or [5.3.0] bicyclic system

Retrosynthesis of Hamigerans

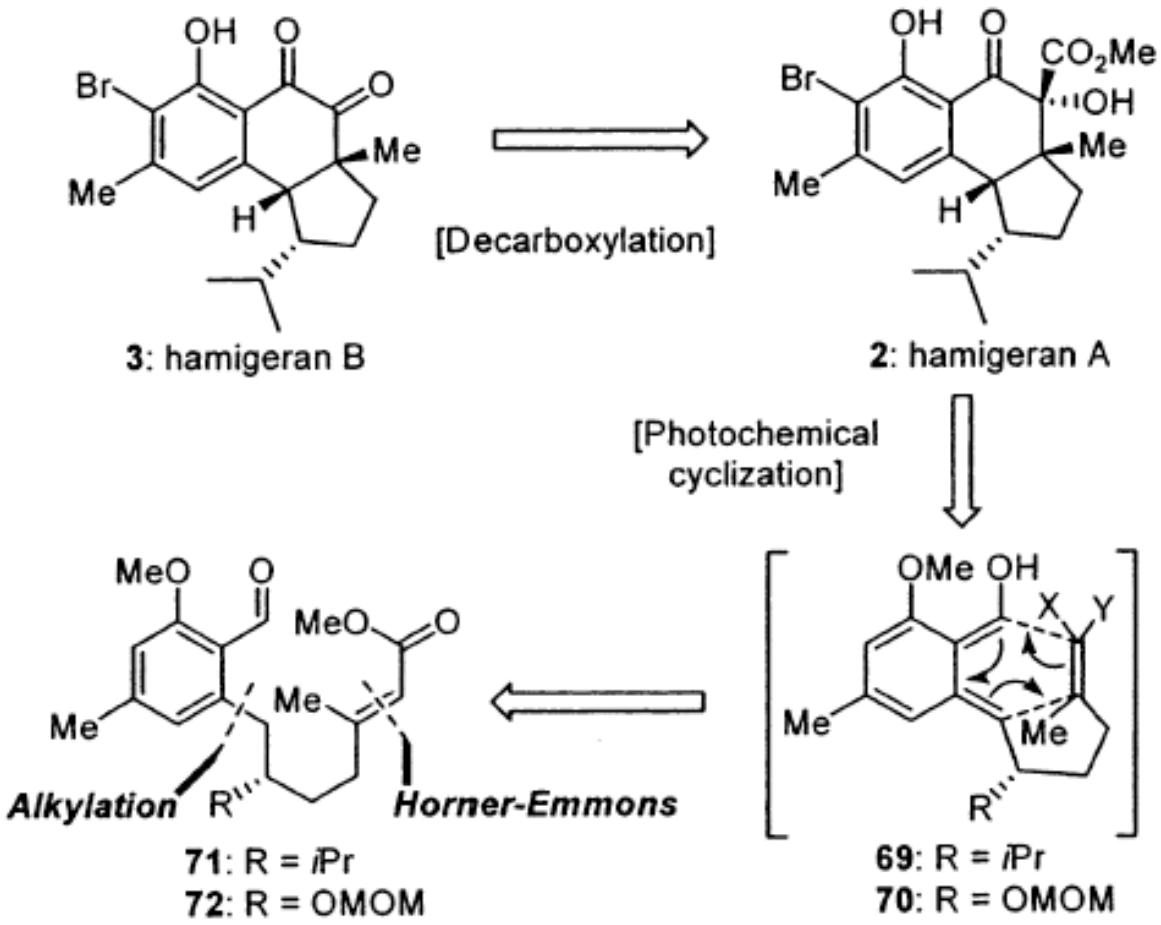
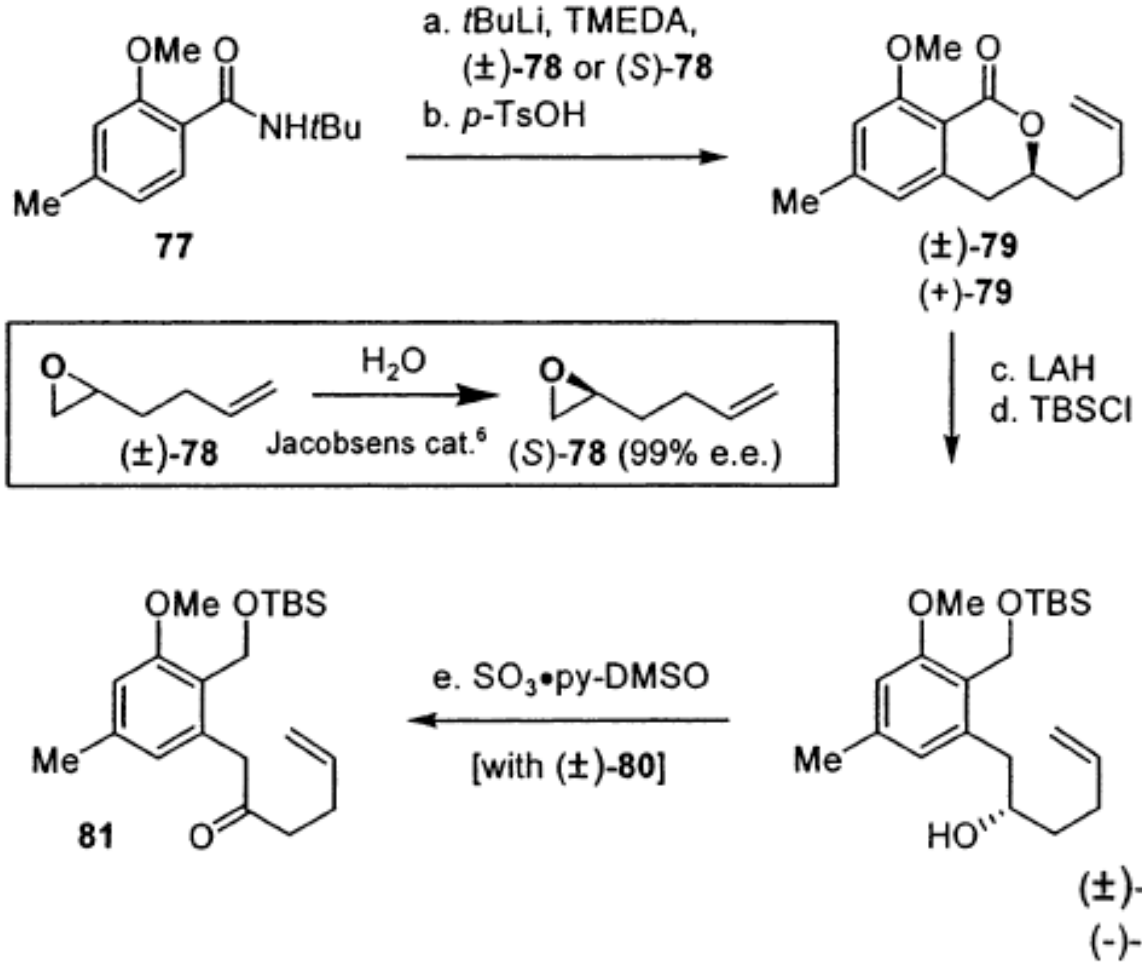
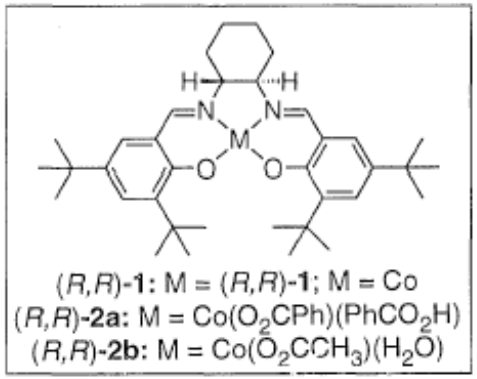


Figure 4. Retrosynthetic analysis of the hamigerans **2** and **3** based on the intramolecular trapping of a hydroxy-*o*-quinodimethane (**69** or **70**).

Synthesis of **80** via Jacobsen's Hydrolytic kinetic resolution

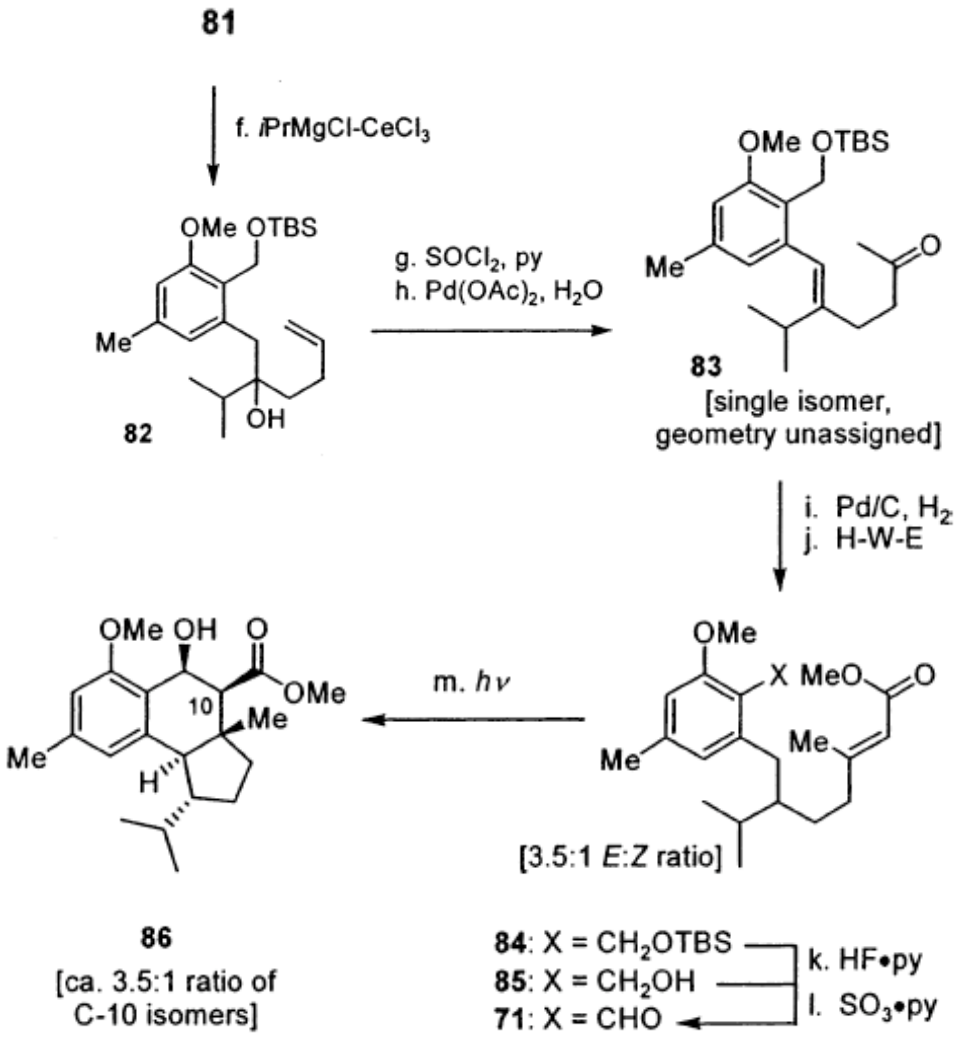
Scheme 5. Synthesis of Racemic Aldehyde **71** and Its Photocyclization to **86**[a]





Tokunga, M.; Larrow, J.F.; Kakiuchi, F.; Jacobsen, E.N. *Science* **1997**, 277, 936-938

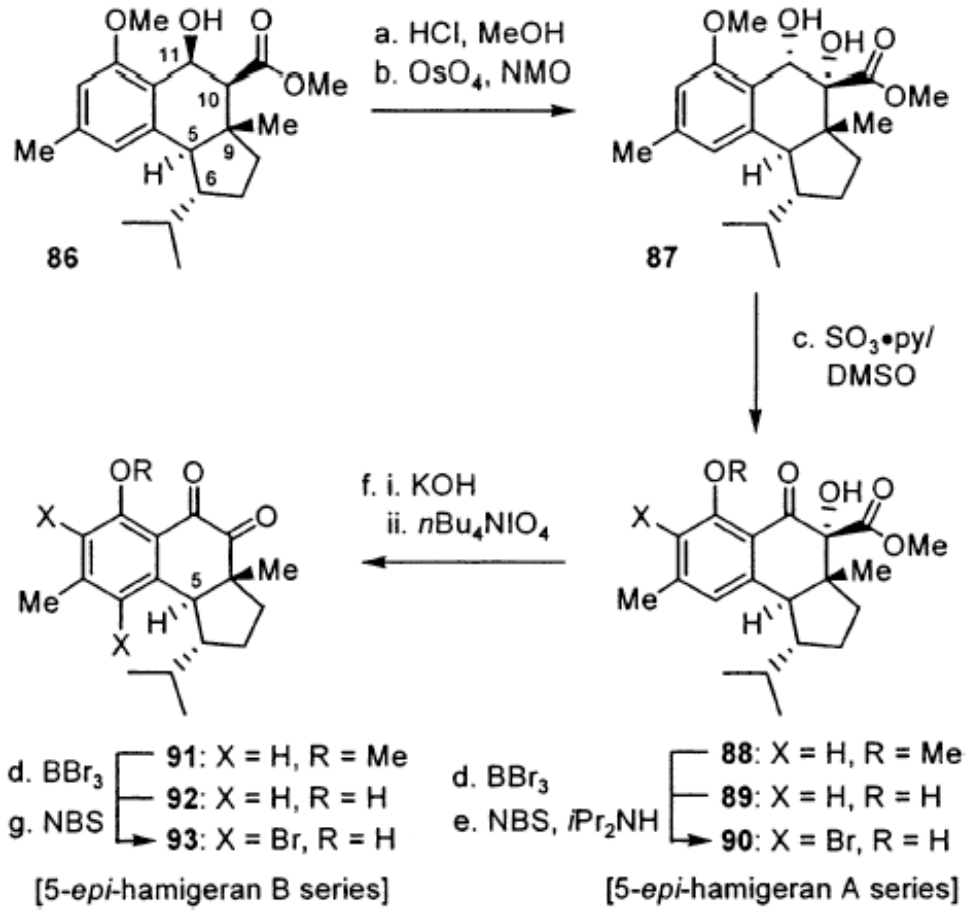
Photocyclization of **71**



[a] Reagents and conditions: (a) *t*BuLi (2.2 equiv), TMEDA (2.0 equiv), −78 to −20 °C; then (±)-**75** or (*S*)-**75** (1.0 equiv), THF, −78 to 0 °C, 2 h, 69%; (b) *p*-TsOH (2.0 equiv), toluene, reflux, 2 h, 91%; (c) $LiAlH_4$ (2.0 equiv), THF, 25 °C, 0.5 h, 91%; (d) (TBS)Cl (1.1 equiv), Et_3N (2.0 equiv), 12 h, 89%; (e) SO_3·py (3.0 equiv), Et_3N (6.0 equiv), DMSO−CH_2Cl_2 (1:1), 0 °C, 2 h, 94%; (f) *i*PrMgCl (2.0 equiv), $CeCl_3$ (2.0 equiv), −78 to 0 °C, 1 h, 94%; (g) CH_2Cl_2–py (3:1), −50 °C; then add $SOCl_2$ (10.0 equiv), −50 to −20 °C, 0.5 h, 80%; (h) $Pd(OAc)_2$ (0.1 equiv), $Cu(OAc)_2$ (2.0 equiv), DMA−H_2O (10:1), O_2 (1 atm), 16 h, 81%; (i) 10% Pd/C, H_2 (1 atm), $NaHCO_3$ (solid, 5.0 equiv), EtOAc, 2 h, 95%; (j) $(MeO)_2P(O)CH_2CO_2Me$ (3.0 equiv), NaH (3.0 equiv), THF, 60 °C, 3 h, 94% (mixture of *E*/*Z* isomers, ca. 3.5:1); (k) HF·py (2.0 equiv), THF, 25 °C, 10 min, 91%; (l) SO_3·py (3.0 equiv), Et_3N (6.0 equiv), DMSO−CH_2Cl_2 (1:1), 0 °C, 2 h, 88%; (m) *hν*, 450 W Hanovia lamp, Pyrex filter, benzene, 20 min, 91%. MOM = methoxymethyl, and H−W−E = Horner−Wadsworth−Emmons reaction.

5-epi Hamigeran A&B

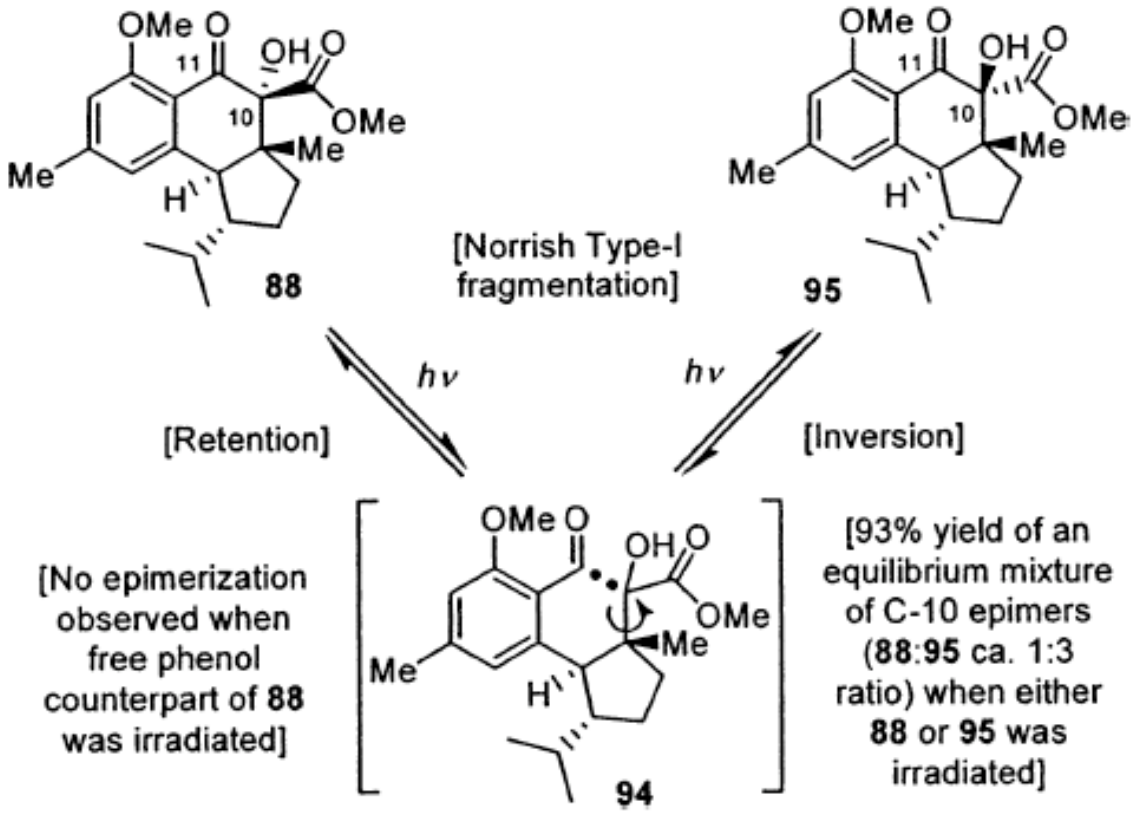
Scheme 6. Synthesis of the 5-*epi*-Hamigerans **88**–**93**[a]



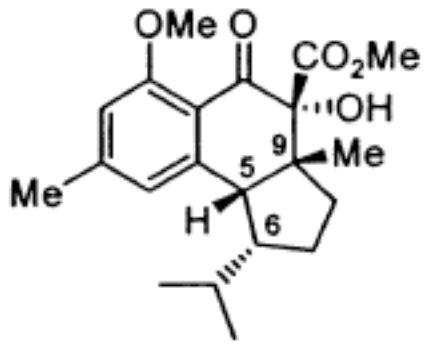
[a] Reagents and conditions: (a) 1% HCl in MeOH, 25 °C, 0.5 h, 90%; (b) OsO_4 (0.1 equiv), NMO (3.0 equiv), THF–*t*BuOH–H_2O–py (20:20:4:1), 12 h (a ca. 12:1 mixture of isomers), 92%; (c) SO_3·py (3.0 equiv), Et_3N (6.0 equiv), DMSO–CH_2Cl_2 (1:1), 0 °C, 2 h, 88%; (d) BBr_3 (10.0 equiv), CH_2Cl_2, −78 °C, 3 h, 96%; (e) NBS (1.05 equiv), *i*Pr_2NH (0.1 equiv), CH_2Cl_2, 0 °C, 3 h, 90%; (f) (i) KOH, MeOH, 70 °C, 2 h; (ii) *n*Bu_4NIO_4 (2.0 equiv), dioxane, 100 °C, 1 h, 65%; (g) NBS (3.0 equiv), DMF, 25 °C, 3 h, 92%. NMO = 4-methylmorpholine *N*-oxide, and NBS = *N*-bromosuccinimide.

Photoisomerization of Tricyle **88**

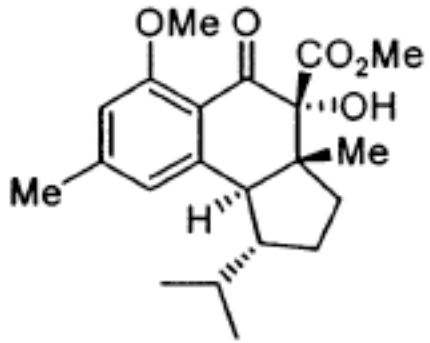
Scheme 7. Postulated Mechanism for the Photochemically Induced Isomerization (Inversion at C-10) of Compounds **88** and **95**



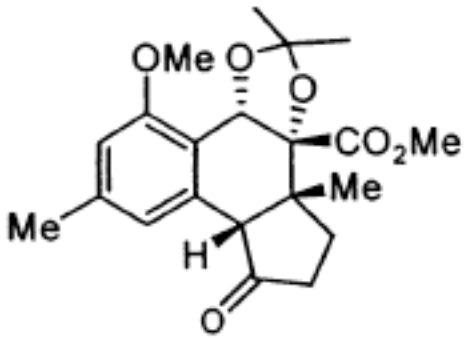
Strain Energies of Hamigerans



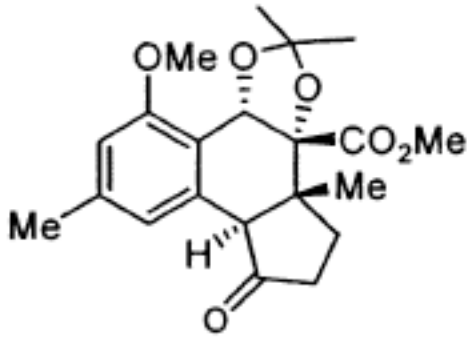
88 [natural]
19.21 kcal/mol



96 [5-*epi*-]
18.57 kcal/mol



97 [natural]
19.65 kcal/mol

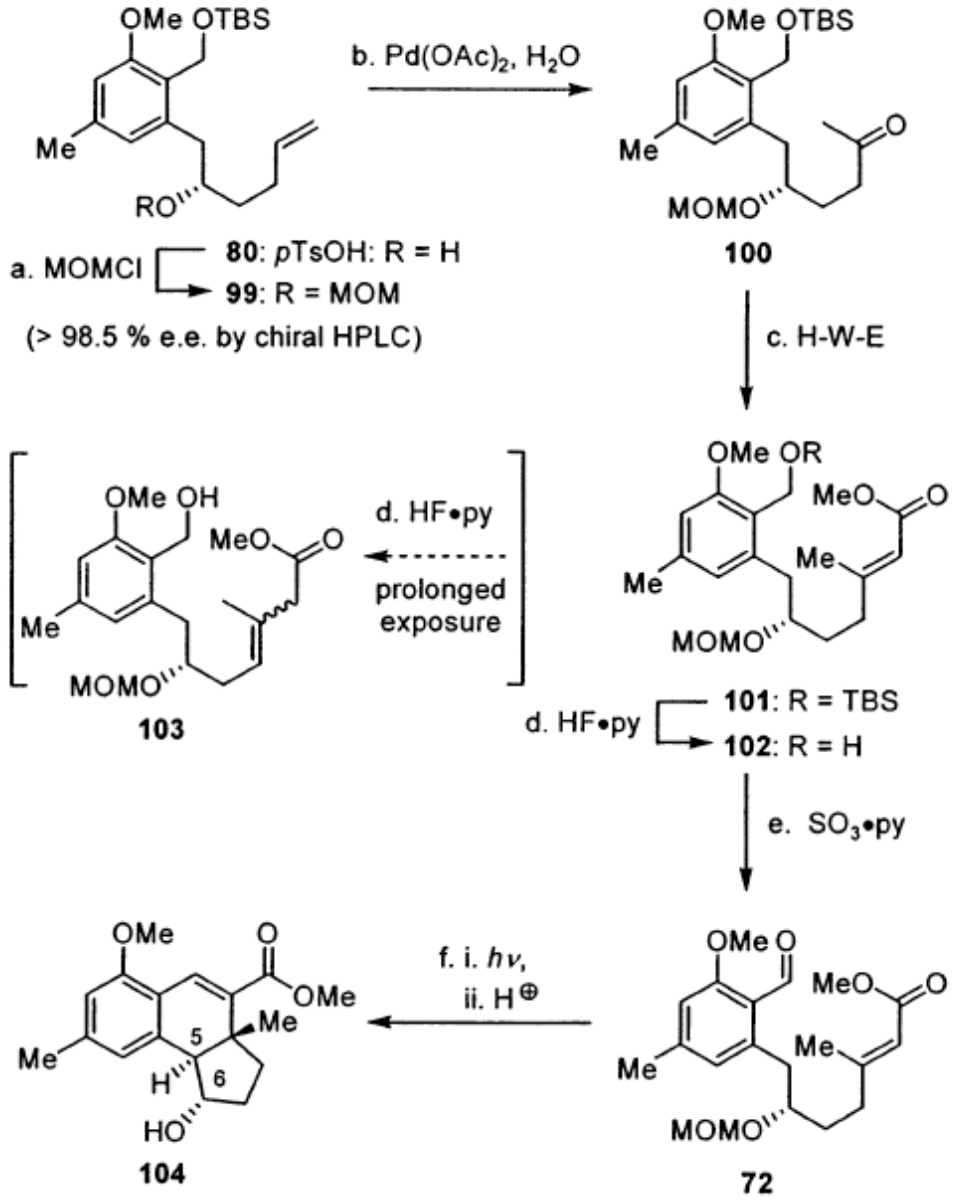


98 [5-*epi*-]
24.72 kcal/mol

Figure 5. Relative strain energies of 6,9-*cis* and 6,9-*trans* hamigeran-type structures **88** and **96**−**98**. See ref 34 for computational parameters.

Photocyclization of **72**

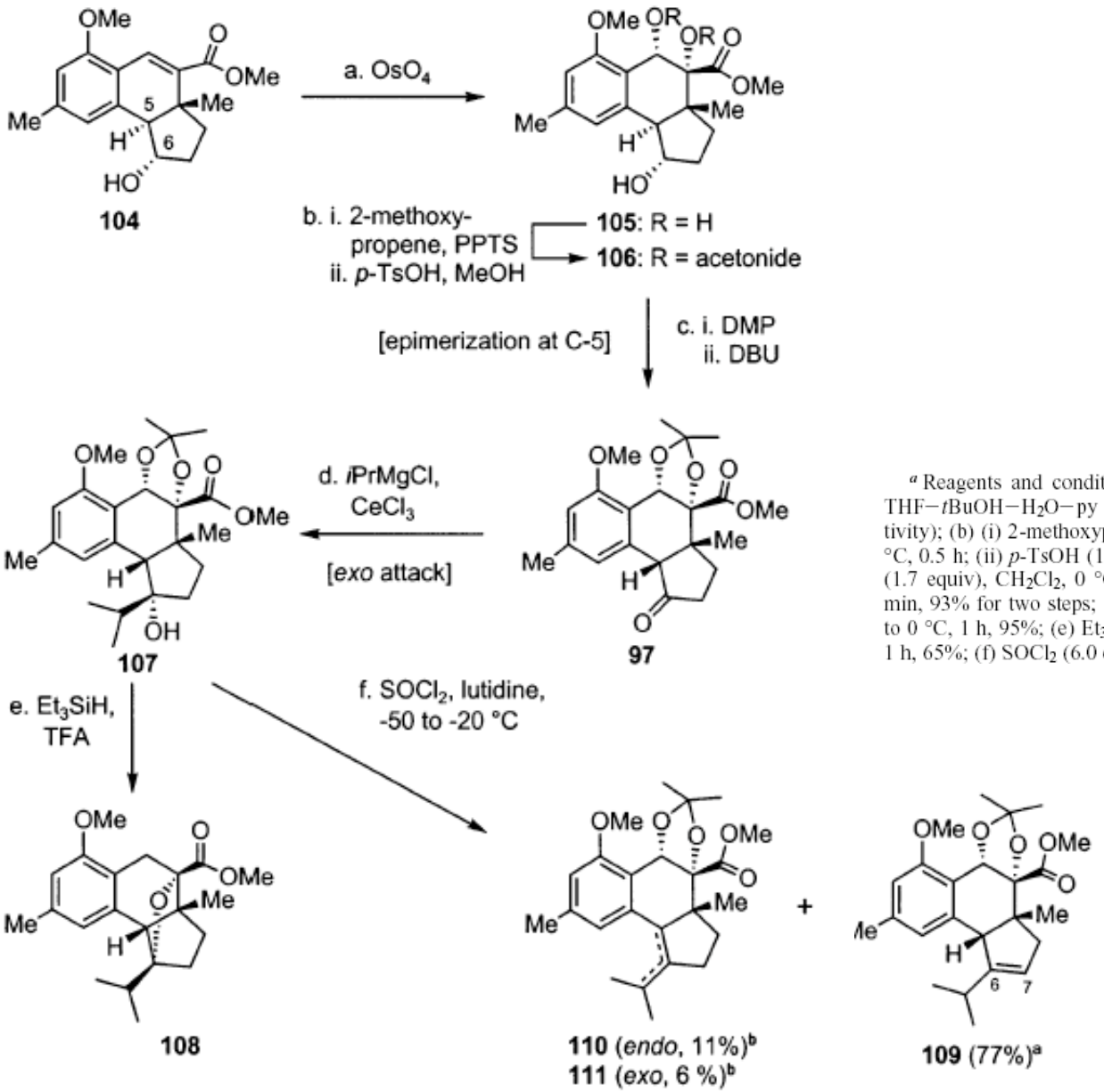
Scheme 8. Synthesis and Photocyclization of Precursor **72**[a]



[a] Reagents and conditions: (a) (MOM)Cl (2.0 equiv), iPr$_2$NEt (6.0 equiv), CH_2Cl_2, 25 °C, 12 h, 83%; (b) $Pd(OAc)_2$ (0.1 equiv), $Cu(OAc)_2$ (2.0 equiv), DMA−H_2O (10:1), O_2 (1 atm), 16 h, 81%; (c) $(MeO)_2P(o)CH_2CO_2Me$ (3.0 equiv), NaH (3.0 equiv), THF, 60 °C, 3 h, 94% (mixture of E/Z isomers, ca. 3.5:1); (d) HF·py (2.0 equiv), THF, 25 °C, 20 min, 91%; (e) SO_3·py (3.0 equiv), Et_3N (6.0 equiv), DMSO−CH_2Cl_2 (1:1), 0 °C, 2 h, 92%; (f) $h\nu$, 450 W Hanovia lamp, Pyrex filter, benzene, 25 min; then 1% anhydrous HCl in MeOH, 60 °C, 1 h, 85%.

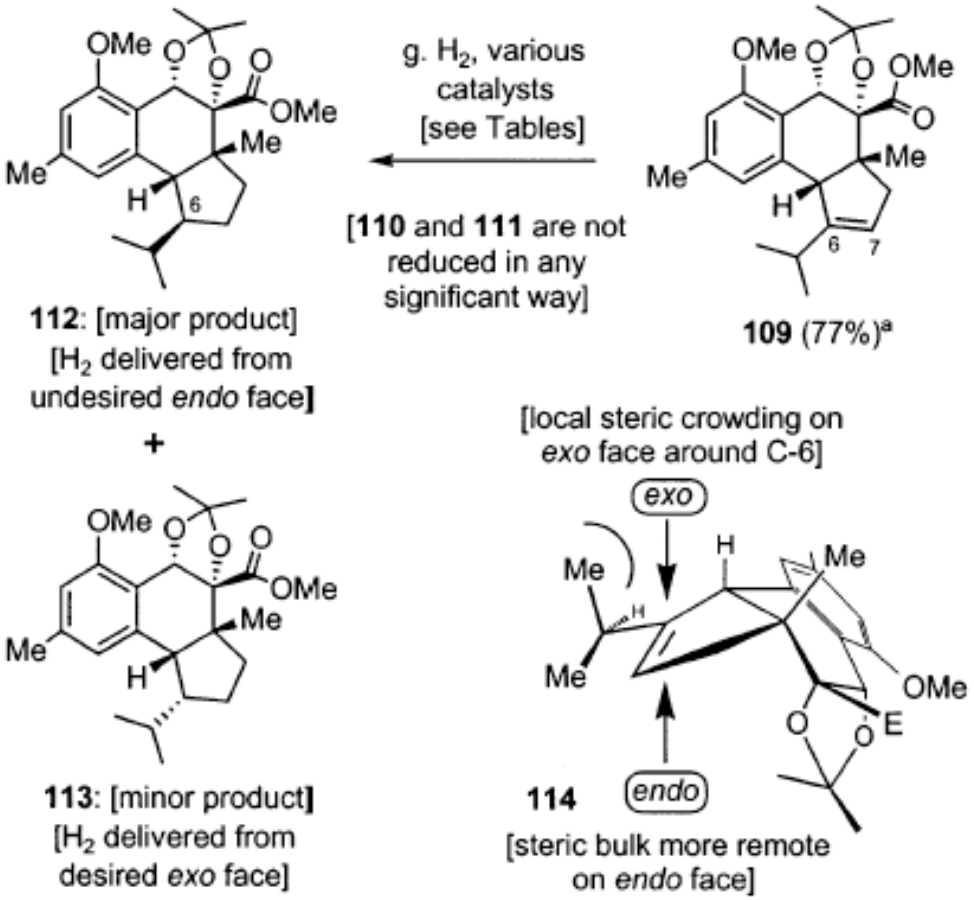
Advanced intermediate **109**

Scheme 9. Correction of the Stereochemistry at C-5 via Base-Induced Epimerization and Elaboration toward the Hamigerans **1**–**4**[a]



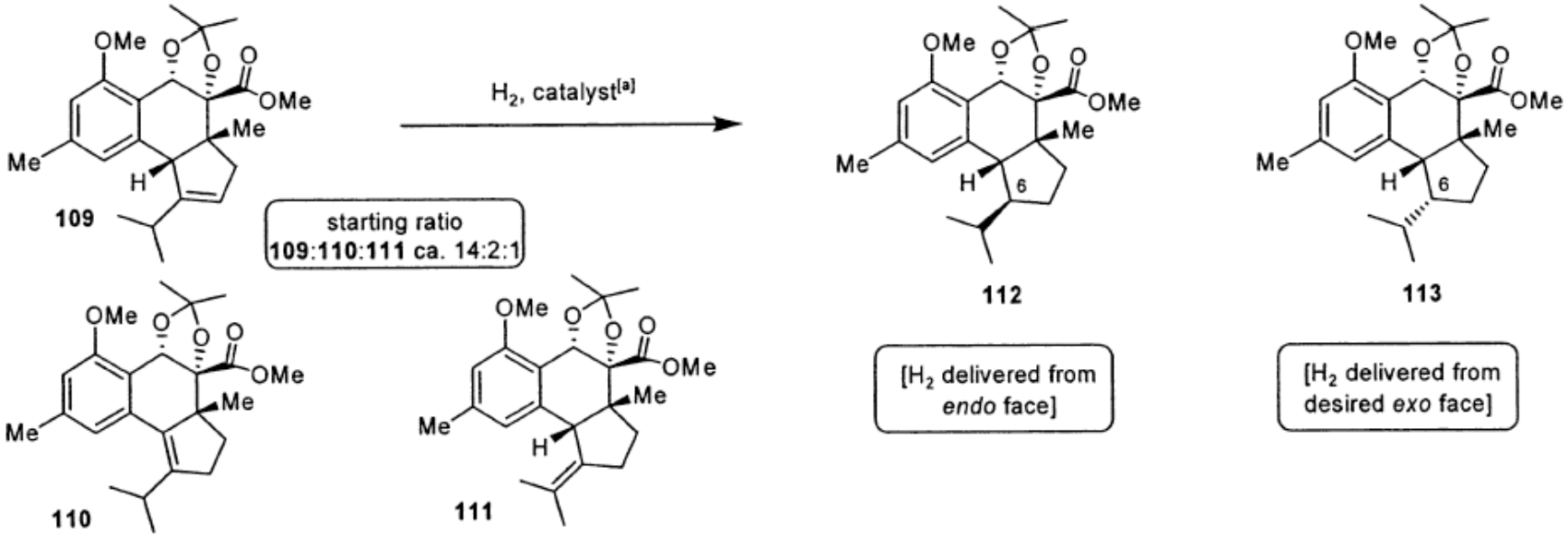
[a] Reagents and conditions: (a) OsO_4 (0.1 equiv), NMO (3.0 equiv), THF–*t*BuOH–H_2O–py (20:20:4:1), 12 h, 94% (ca. 12:1 diastereoselectivity); (b) (i) 2-methoxypropene (20 equiv), PPTS (0.3 equiv), CH_2Cl_2, 0 °C, 0.5 h; (ii) *p*-TsOH (1.0 equiv), MeOH, 0 °C, 0.5 h, 93%; (c) (i) DMP (1.7 equiv), CH_2Cl_2, 0 °C, 1 h; (ii) DBU (0.5 equiv), CH_2Cl_2, 0 °C, 10 min, 93% for two steps; (d) *i*PrMgCl (2.0 equiv), $CeCl_3$ (2.0 equiv), −78 to 0 °C, 1 h, 95%; (e) Et_3SiH (50 equiv), TFA (20 equiv), CH_2Cl_2, 25 °C, 1 h, 65%; (f) $SOCl_2$ (6.0 equiv) py–lutidine–CH_2Cl_2 (1:5:5), −50 to −20

Unexpected Endo Attack Upon Hydrogenation



Hydrogenation Studies

Table 5. Attempted *exo* Reduction of Trisubstituted Olefins **109**−**111**

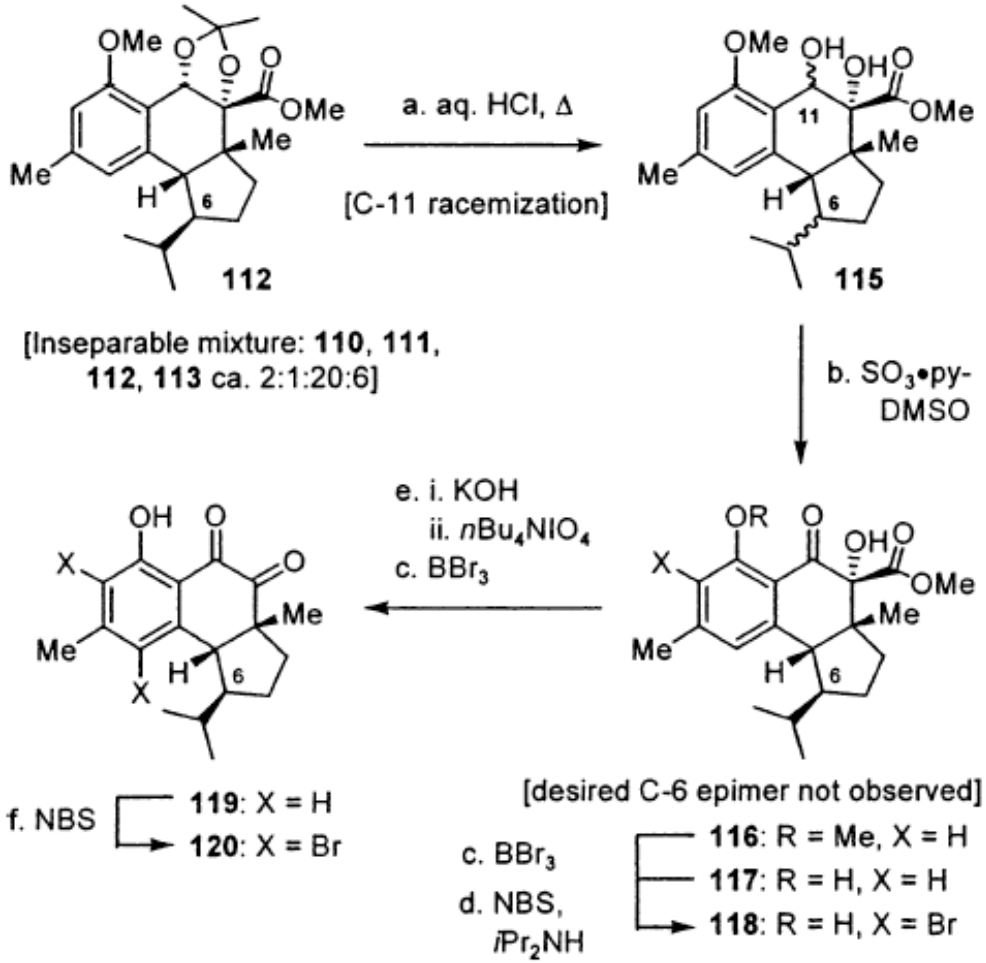


entry	conditions	product distribution by ^{1}H NMR spectroscopic analysis (%)			
		110	**111**	*endo*-**112**	*exo*-**113**
1	PtO_2, 3 atm of H_2, EtOAc, 6 h	6	3	71	20
2	$Pd(OH)_2$, 3 atm of H_2, EtOH, 12 h	24	10	50	15
3	10% Pd/C, 50 atm of H_2, EtOAc, 6 h	40	7	33	19
4	Rh−Al_2O_3, 50 atm of H_2, EtOH, 48 h	7	3	6	21
5	Rh black, 20 atm of H_2, EtOH, 48 h	negligible conversion to products			
6	$IrP(cyhex)_3(COD)(py)PF_6$, 10 atm of H_2, CH_2Cl_2, 48 h	negligible conversion to products			

[a] A mixture of olefins (**109**−**111**, 0.05 mmol) was dissolved in the indicated solvent and stirred under H_2 pressure (Parr bomb) for the indicated times, at which time the catalyst was removed by filtration and product ratios were determined by ^{1}H NMR spectroscopic analysis.

6-*epi*-Hamigerans

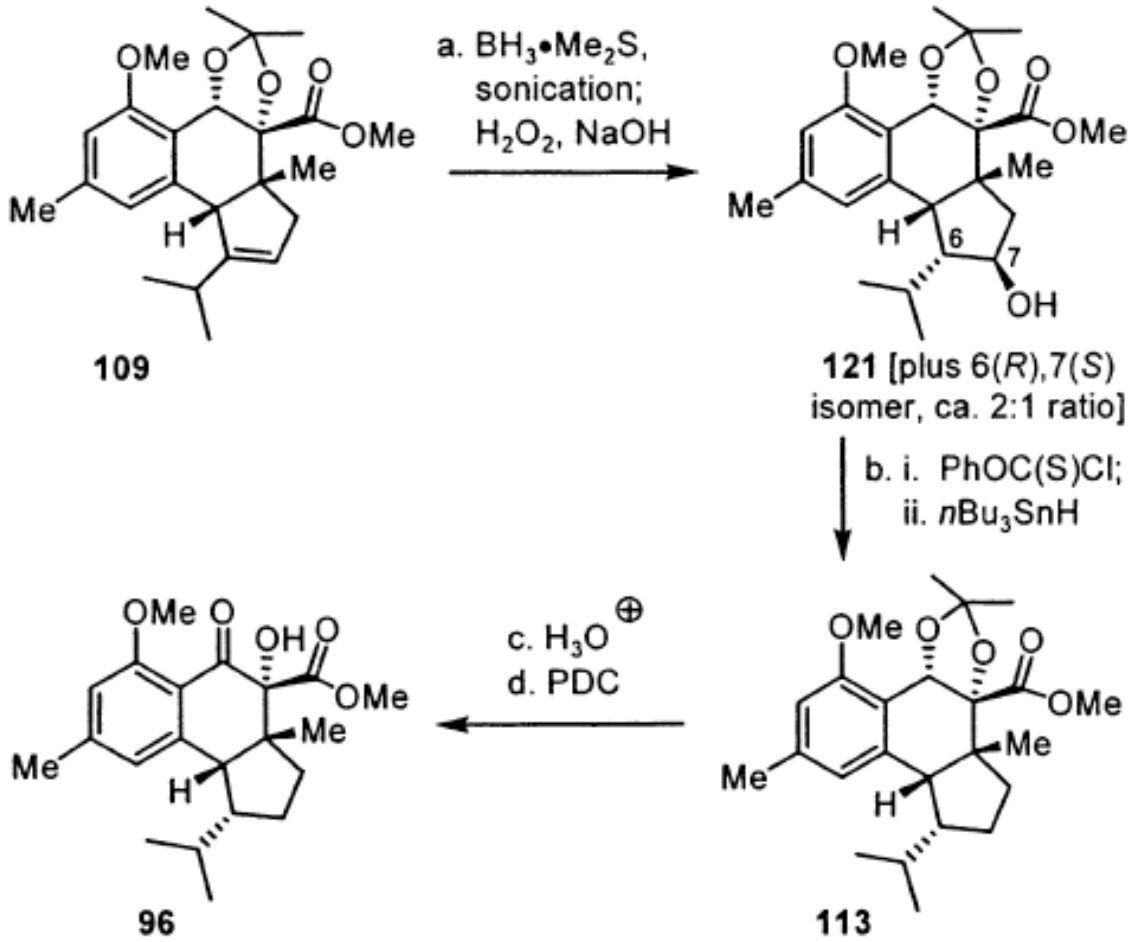
Scheme 10. Completion of the 6-*epi*-Hamigerans **116**–**120**[a]



[a] Reagents and conditions: (a) 3 M aqueous HCl–THF (1:1), 80 °C, 4 h, 70%; (b) SO_3·py (3.0 equiv), Et_3N (6.0 equiv), DMSO–CH_2Cl_2 (1:1), 0 °C, 2 h, 93%; (c) BBr_3 (10.0 equiv), CH_2Cl_2, −78 °C, 3 h, 93%; (d) NBS (1.05 equiv), iPr_2NH (0.1 equiv), CH_2Cl_2, 0 °C, 3 h, 94%; (e) (i) aqueous KOH, MeOH, 70 °C, 2 h; (ii) nBu_4NIO_4 (2.0 equiv), dioxane, 100 °C, 1 h, 65%; (f) NBS (3.0 equiv), DMF, 25 °C, 1 h, 93%.

Hydroboration to set C-6 in **121**

Scheme 11. Total Synthesis of **2** and **3**[a]



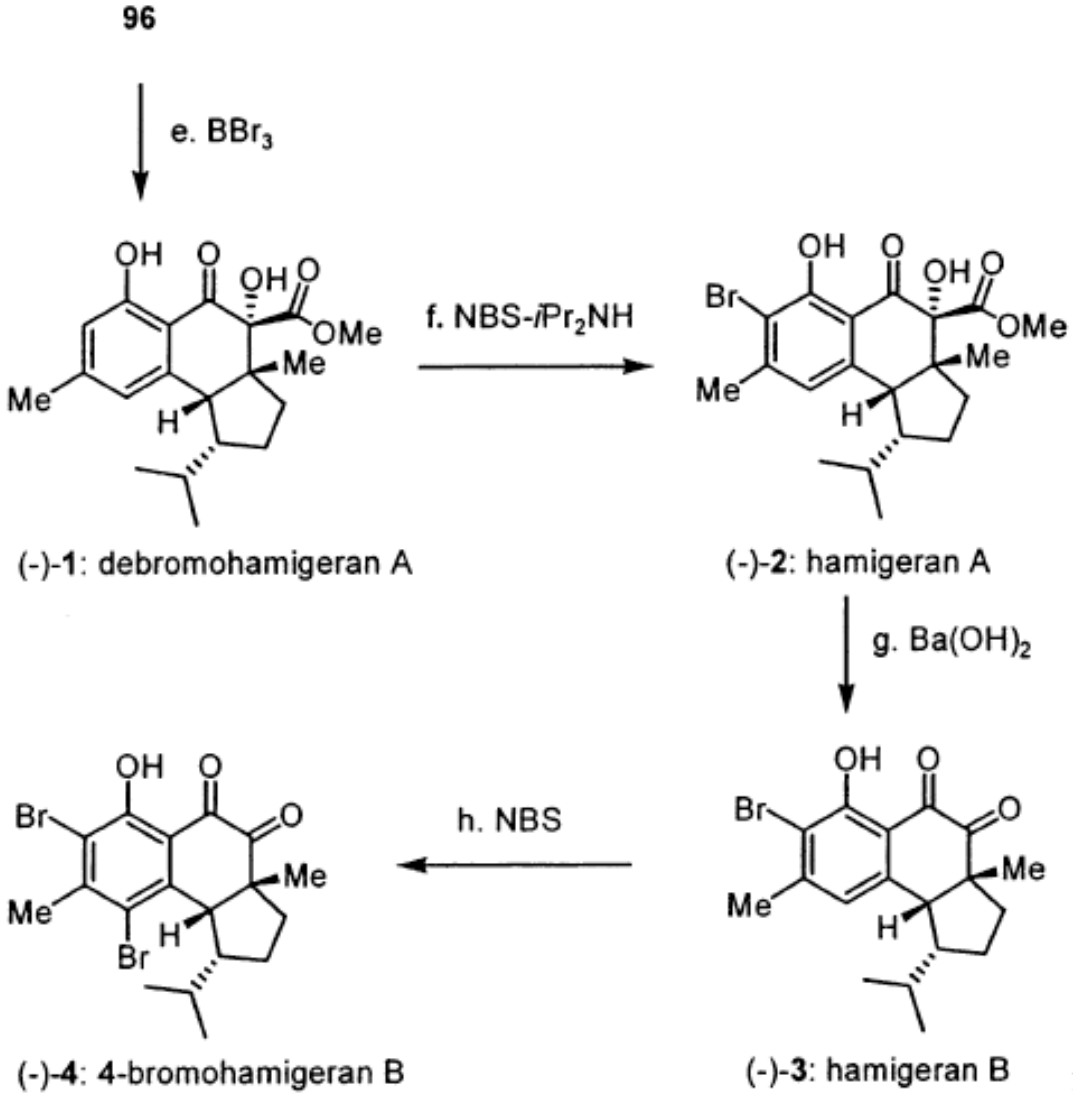
109

121 [plus 6(*R*),7(*S*) isomer, ca. 2:1 ratio]

113

96

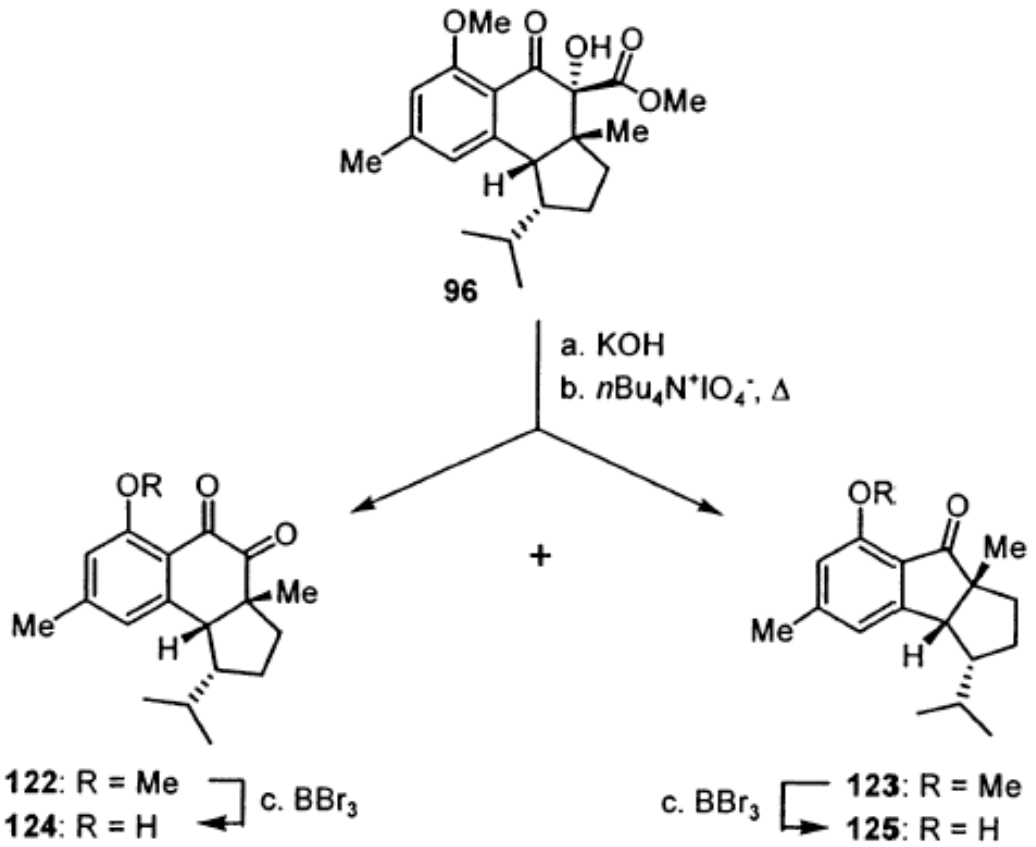
Construction of Hamigerans A and B



[a] Reagents and conditions: (a) $BH_3 \cdot Me_2S$ (40 equiv), THF, sonication, 40 °C, 8 h, 68% (a ca. 2:1 mixture of two isomers favoring **121**); (b) (i) PhOC(S)Cl (2.0 equiv), py, 25 °C, 2 h; (ii) nBu$_3$SnH (8.0 equiv), AIBN (0.2 equiv), benzene, reflux, 2 h, 64% (two steps); (c) 1 M aqueous HCl−THF (1:1), 80 °C, 1 h, 88%; (d) PDC (2.5 equiv), 4 Å molecular sieves, CH_2Cl_2, 3 h, 83%; (e) BBr_3 (10.0 equiv), CH_2Cl_2, −78 °C, 3 h, 94%; (f) NBS (1.05 equiv), iPr$_2$NH (0.1 equiv), CH_2Cl_2, 0 °C, 3 h, 95%; (g) $Ba(OH)_2$ (15.0 equiv), MeOH−H_2O (2:1), air, 25 °C, 2 h, 87%; (h) NBS (3.0 equiv), DMF, 25 °C, 1 h, 94%. AIBN = azobisisobutyronitrile, and PDC = pyridinium dichromate.

Ring Contraction of Tricycle **96**

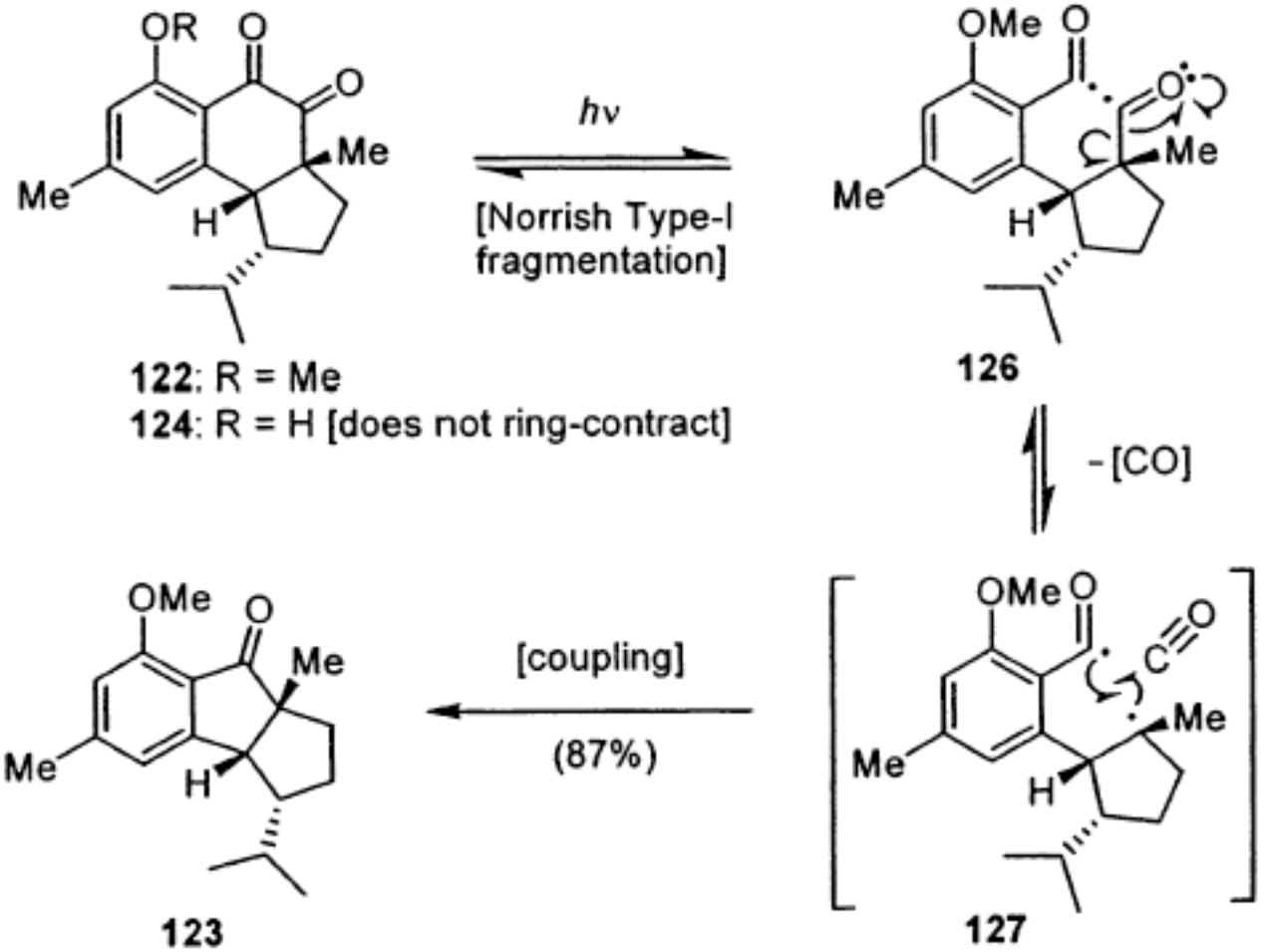
Scheme 12. Oxidative Cleavage of Hydroxy Ketone **96** to Diketone **122** and Ring-Contracted Ketone **123**[a]



[a] Reagents and conditions: (a) aqueous KOH, MeOH, 70 °C, 2 h; (b) nBu$_4$N$^+$IO$_4^-$ (2.0 equiv), dioxane, 100 °C, 1 h, varied yields (**122**, 10−50%, + **123**, 10−40%); (c) BBr_3 (10.0 equiv), CH_2Cl_2, −78 °C, 3 h, 86%.

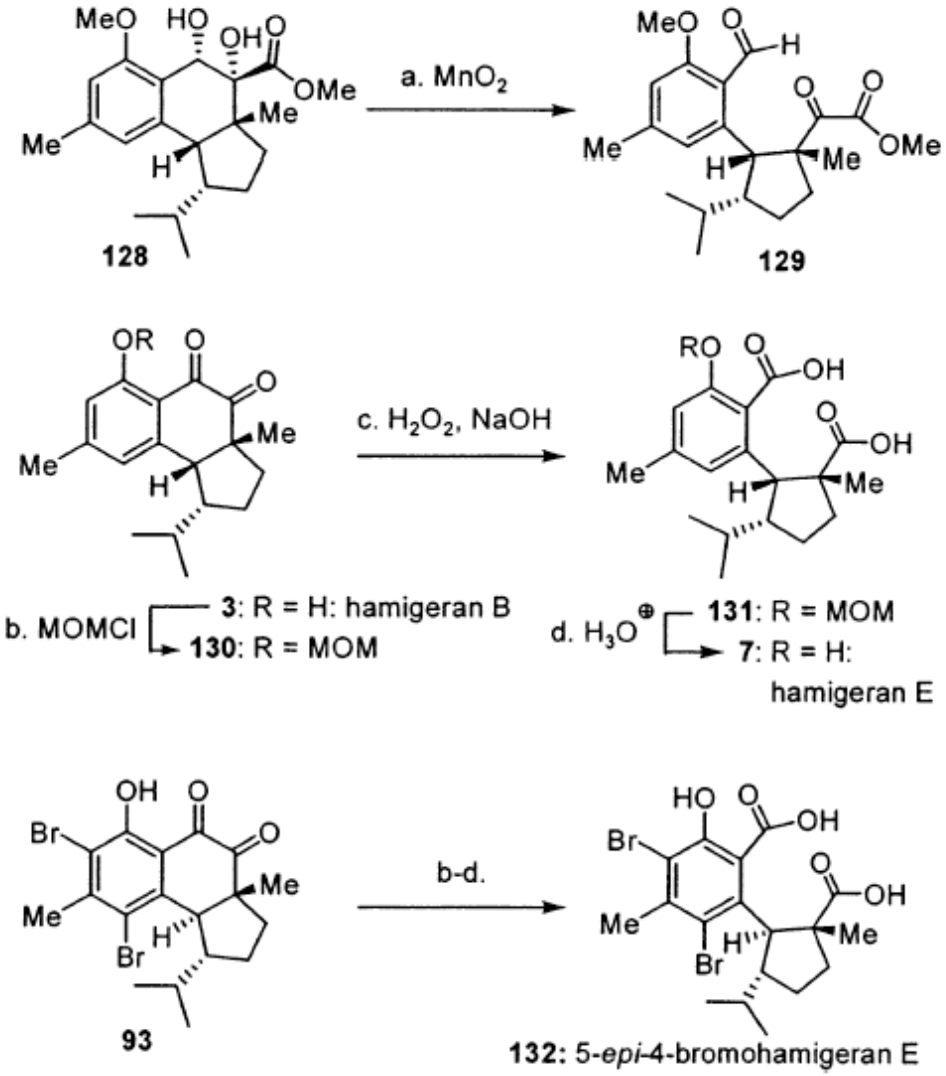
Mechanism for Ring Contraction

Scheme 13. Proposed Mechanism for the Decarbonylative Ring Contraction of **122** to **123**



Synthesis of Hamigeran E

Scheme 14. Synthesis of **7** and Related Analogues **129** and **132**[a]



[a] Reagents and conditions: (a) MnO_2 (20 equiv), CH_2Cl_2, 25 °C, 2 h, 90%; (b) (MOM)Cl (2.5 equiv), iPr_2NEt (3.5 equiv), CH_2Cl_2, 0 °C, 0.5 h, 76%, (c) 30% aqueous H_2O_2–dioxane−2 M aqueous NaOH (1:8:2), 0 °C, 10 min, 70%; (d) 3 M aqueous HCl−THF (1:1), 25 °C, 3 h, 70%.

Conclusions

- Inter and Intramolecular PEDA reactions have been developed as versatile synthetic methodologies for construction of polycyclic natural products such as Hybocarpone and Hamigerans.

- Norrish Type I fragmentation pathway led to isomerization of **88** and ring contraction leading to [3.3.0] bicyclic system **123**

- Barium hydroxide mediated cascade pathway was developed to facilitate interconversion to other members of Hamigerans

Our Approach

Alternative approach