



Steven V. Ley

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**Career-In-Review (CIR)**

Alessandra Polara (SJD Group)

July 6, 2007

Synthesis Literacy Group

Columbia University Chemistry

## Career Snapshot

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1945 *born in Lincolnshire*

1969 *BSc (First Class Hons) from Loughborough University*

1969-72 *Ph.D. from Loughborough University (Adv. Professor H. Heaney)*

1972-74 *Postdoc at Ohio State University (Adv. Professor Leo. A. Paquette)*

1974-75 *Postdoc at Imperial College (Adv. Professor Sir Derek H.R. Barton)*

1976-83 *Lecturer, Imperial College*

1983-92 *Professor of Organic Chemistry, Imperial College*

1989-92 *Head of Department, Imperial College*

1992-present *BP (1702) Professor of Organic Chemistry, Cambridge University*

1992-present *Head of Organic Chemistry, Cambridge University*

1993-present *Fellow of Trinity College, Cambridge University*

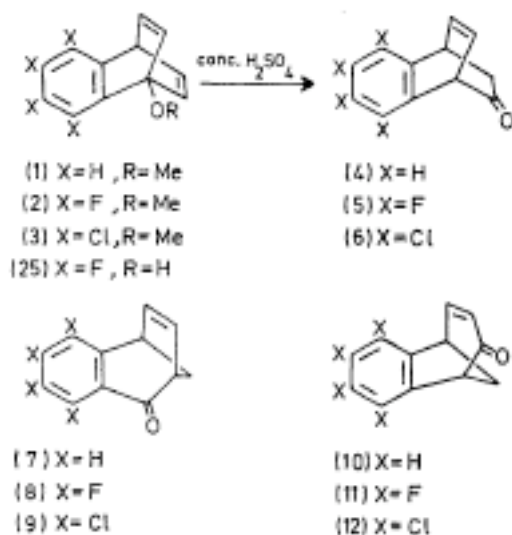
# Five Most Cited Papers (ISI Web of Science)

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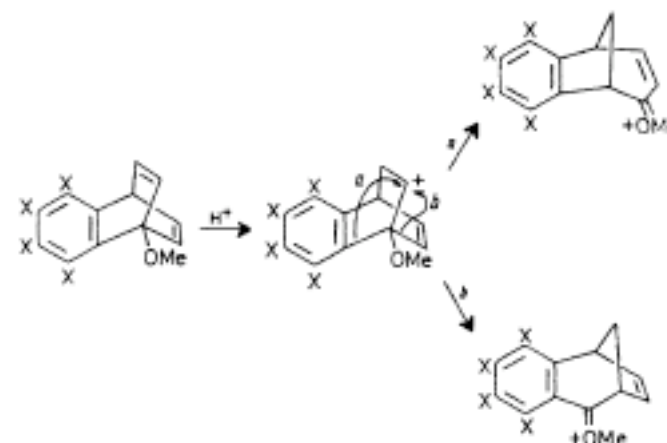
1. **LEY SV**, NORMAN J, GRIFFITH WP, et al.  
[TETRAPROPYLAMMONIUM PERRUTHENATE, PR<sub>4</sub>N<sup>+</sup>RUO<sub>4</sub><sup>-</sup>, TPAP - A CATALYTIC OXIDANT FOR ORGANIC-SYNTHESIS](#)  
SYNTHESIS-STUTTGART (7): 639-666 JUL 1994  
Times Cited: [768](#)  
[e-Link](#)
2. GRIFFITH WP, **LEY SV**, WHITCOMBE GP, et al.  
[PREPARATION AND USE OF TETRA-NORMAL-BUTYLAMMONIUM PER-RUTHENATE \(TBAP REAGENT\) AND TETRA-NORMAL-PROPYLAMMONIUM PER-RUTHENATE \(TPAP REAGENT\) AS NEW CATALYTIC OXIDANTS FOR ALCOHOLS](#)  
JOURNAL OF THE CHEMICAL SOCIETY-CHEMICAL COMMUNICATIONS (21): 1625-1627 NOV 1 1987  
Times Cited: [492](#)  
[e-Link](#)
3. **Ley SV**, Baxendale IR, Bream RN, et al.  
[Multi-step organic synthesis using solid-supported reagents and scavengers: a new paradigm in chemical library generation](#)  
JOURNAL OF THE CHEMICAL SOCIETY-PERKIN TRANSACTIONS 1 (23): 3815-4195 2000  
Times Cited: [396](#)  
[e-Link](#)
4. **Ley SV**, Thomas AW  
[Modern synthetic methods for copper-mediated C\(aryl\)-O, C\(aryl\)-N, and C\(aryl\)-S bond formation](#)  
ANGEWANDTE CHEMIE-INTERNATIONAL EDITION 42 (44): 5400-5449 2003  
Times Cited: [229](#)  
[e-Link](#)
5. MERRITT AT, **LEY SV**  
[CLERODANE DITERPENOIDS](#)  
NATURAL PRODUCT REPORTS 9 (3): 243-287 JUN 1992  
Times Cited: [180](#)  
[e-Link](#)

# PhD Work (1768-1972)

## Rearrangement Reactions of Bicyclic Systems. Part III.<sup>1</sup> Acid-catalysed Rearrangements of 1,4-Dihydro-1-methoxy-1,4-ethenonaphthalene (1-Methoxybenzobarrelene) and its 5,6,7,8-Tetrahalogeno-derivatives

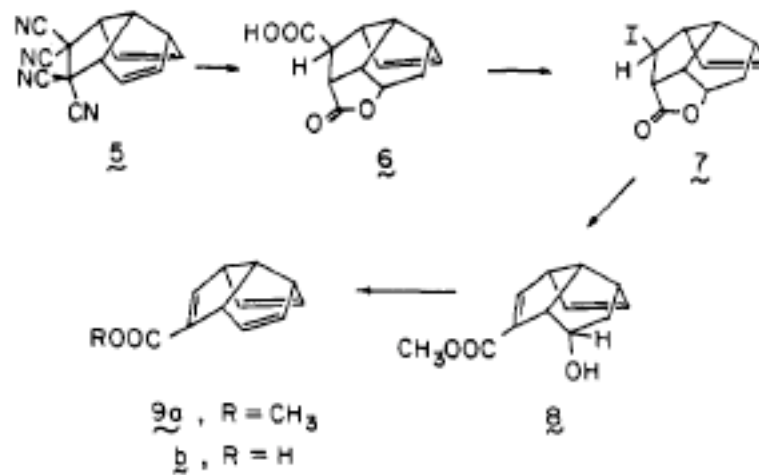
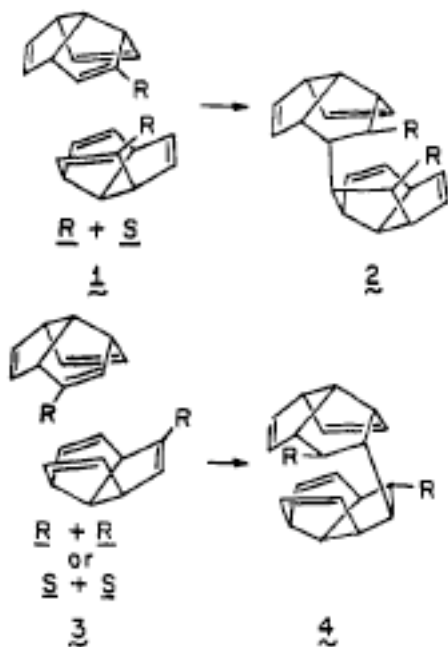


SCHEME 1



# Postdoc Work - Ohio State University (1974-1975)

## An Efficient Synthesis of (-)-Triquinacene-2-carboxylic Acid



Leo A. Paquette,\* Steven V. Ley, William B. Farnham<sup>27</sup>

Department of Chemistry, The Ohio State University  
Columbus, Ohio 43210

Received September 12, 1973

JOURNAL OF THE AMERICAN CHEMICAL SOCIETY 96 (1): 312-313 1974

# Postdoc Work - Imperial College (1974-1975)

## Regeneration of Ketones from Hydrazones, Oximes, and Semicarbazones by Benzeneseleninic Anhydride

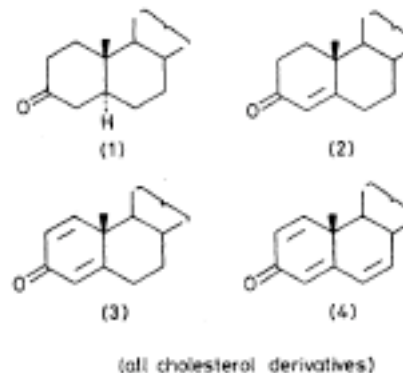
TABLE. Conversion of ketone derivatives into the parent ketone with  $(\text{PhSeO})_2\text{O}$

Derivative	Benzophenone		(1)		(2)		(3)	(4)
	% Yield <sup>a</sup>	Time	% Yield	Time	% Yield	Time		
Phenylhydrazone	90 (81)	3 h	64 (52)	10 h	57 (40)	10 h		
<i>p</i> -Nitrophenylhydrazone	56	3 days	95 (83)	10 h	57 (41)	40 h	86 (73)	96 (43) <sup>b</sup>
2,4-Dinitrophenylhydrazone	N.R.	3 days	25 (8)	24 h	3-5	40 h		
Tosylhydrazone	95 (89)	20 min	97 (87)	20 min	86 (74)	20 min		
Oxime	89 (76)	3 h	83 (60)	50 min	96 (80)	50 min		
Semicarbazone	89 (71)	2 h	83 (67)	4 h	85 (71)	4 h		
<i>NN</i> -Dimethylhydrazone	N.R.	24 h						

<sup>a</sup> Recrystallised yields in parentheses. <sup>b</sup> Isolated as the 1,2 $\alpha$ -epoxide



SCHEME



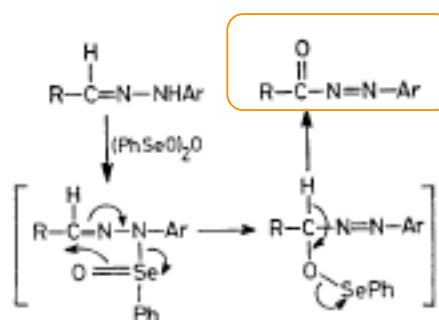
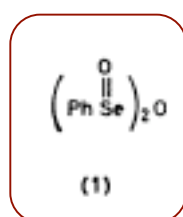
By DEREK H. R. BARTON\*, DAVID J. LESTER, and STEVEN V. LEY  
(Chemistry Department, Imperial College, London SW7 2AY)

JOURNAL OF THE CHEMICAL SOCIETY-CHEMICAL COMMUNICATIONS (13): 445-446 1977

## Oxidation of Aldehyde Hydrazones, Hydrazo Compounds, and Hydroxylamines with Benzeneseleninic Anhydride

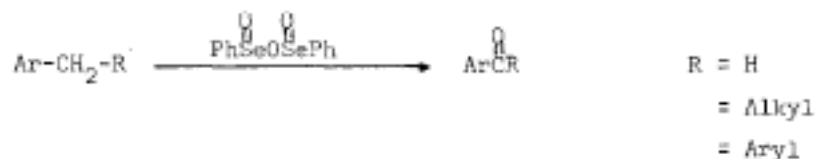
### PREPARATION OF ALDEHYDES AND KETONES BY OXIDATION OF BENZYLIC HYDROCARBONS WITH BENZESELENINIC ANHYDRIDE

*Summary* Aldehyde hydrazones, hydrazo compounds, and hydroxylamines can be readily oxidised by benzeneseleninic anhydride to afford high yields of azo- and nitroso-species.



SCHEME

Mechanistically, the acylazo-derivatives are formed via loss of benzeneselenenol from the intermediate selenenic ester (Scheme). In support of this idea, diphenyl diselenide can be isolated as the major by-product of the reaction.



By DEREK H. R. BARTON,\* DAVID J. LESTER, and STEVEN V. LEY  
(Department of Chemistry, Imperial College, London SW7 2AY)

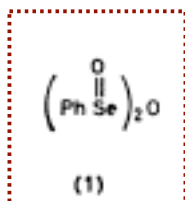
Derek H.R. Barton, Raymond A.H.F. Hui, David J. Lester and Steven V. Ley†

Department of Chemistry, Imperial College, London SW7 2AY

TETRAHEDRON LETTERS (35): 3331-3334 1979

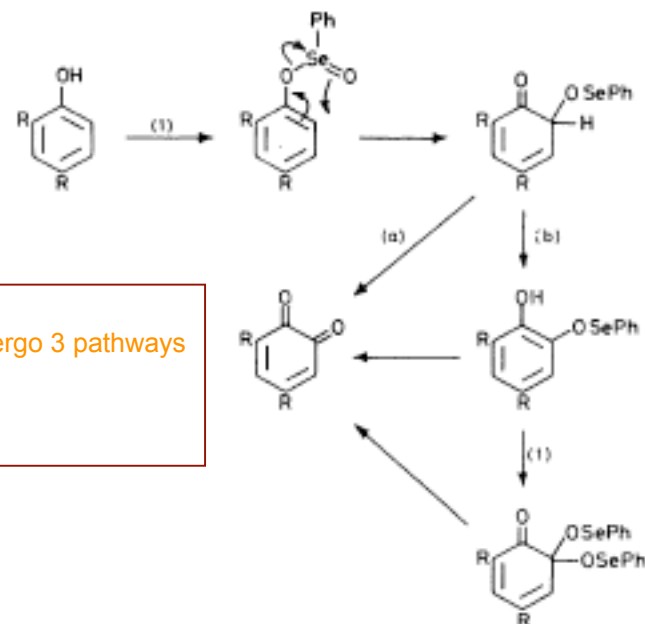
JOURNAL OF THE CHEMICAL SOCIETY-CHEMICAL COMMUNICATIONS (6): 276-277 1978

## Oxidation of Phenols, Pyrocatechols, and Hydroquinones to *ortho*-Quinones using Benzeneseleninic Anhydride



Benzeneseleninic anhydride has been used as a mild oxidising reagent to convert phenols into *o*-quinones including some examples where the *p*-position is unblocked. The method is limited to the production of *o*-quinones which are not susceptible to further reaction. Pyrocatechols and hydroquinones can also be oxidised to the corresponding quinones in excellent yield using benzeneseleninic anhydride.

ALTHOUGH *o*-quinones can be prepared from 1,2-dihydroxybenzenes (pyrocatechols) by a variety of oxidation methods, formation from monohydroxybenzenes (phenols), particularly when the *p*-position is unsubstituted, is much less common.<sup>1</sup> Indeed, the



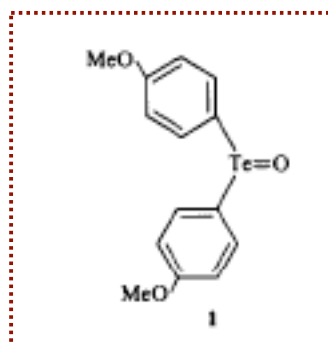
SCHEME 1

- Phenols initially react on O to form selenenyl esters  
 2,3-sigmatropic rearrangement produces the intermediate selenenyl esters which can undergo 3 pathways
- Decomposition by loss of benzeneselenenol
  - Aromatization to a p-quinone intermediate
  - Either direct reaction with Nu or via a second oxidation to an acetal derivative

By Derek H. R. Barton,\* Andrew G. Brewster, Steven V. Ley, Christine M. Read, and Moshe N. Rosenfeld, Department of Chemistry, Imperial College, London SW7 2AY

JOURNAL OF THE CHEMICAL SOCIETY-PERKIN TRANSACTIONS 1 (5): 1473-1476 1981

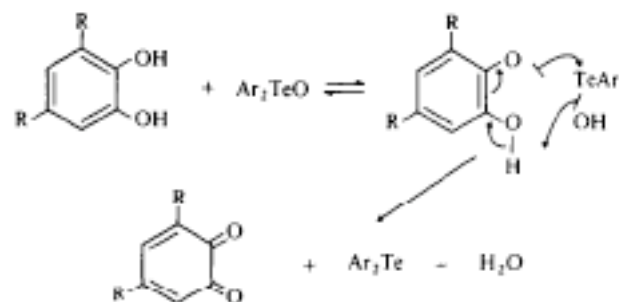
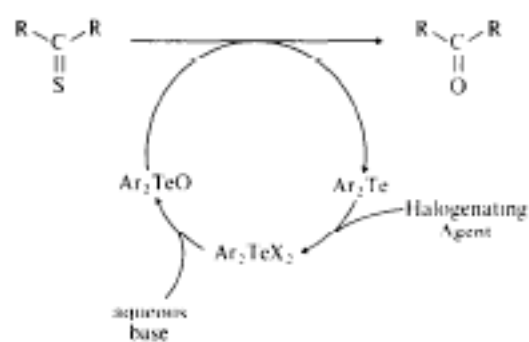
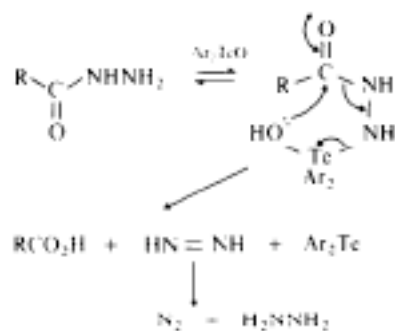
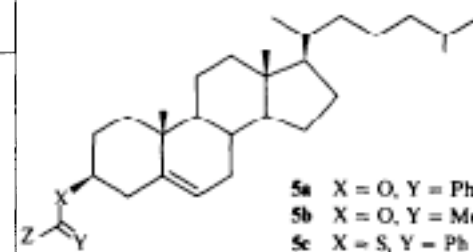
## DIARYL TELLUROXIDES AS NEW MILD OXIDISING REAGENTS†



Mild and selective reagent for phosphines  
And thiocarbonyl compounds.

Table 3.\* Oxidation of thiocarbonyl compounds at room temperature using 1,2-dibromotetrachloroethane as halogenating agent

Substrate	Eq. of halogenating agent	Eq. of tellurium species	Aqueous base	Time h	Yield %
5 (a)	1.1	(3) 0.1	10%K <sub>2</sub> CO <sub>3</sub>	116	88
5 (a)	3	(3) 0.1	10%K <sub>2</sub> CO <sub>3</sub>	23	90
5 (a)	5	(3) 0.015	10%K <sub>2</sub> CO <sub>3</sub>	88	75
5 (a)	5	(3) 0.015	20%K <sub>2</sub> CO <sub>3</sub>	20	70
5 (a)	3	(3) 0.015	20%K <sub>2</sub> CO <sub>3</sub>	80	70
5 (a)	5	(2) 0.1	20%K <sub>2</sub> CO <sub>3</sub>	26	87



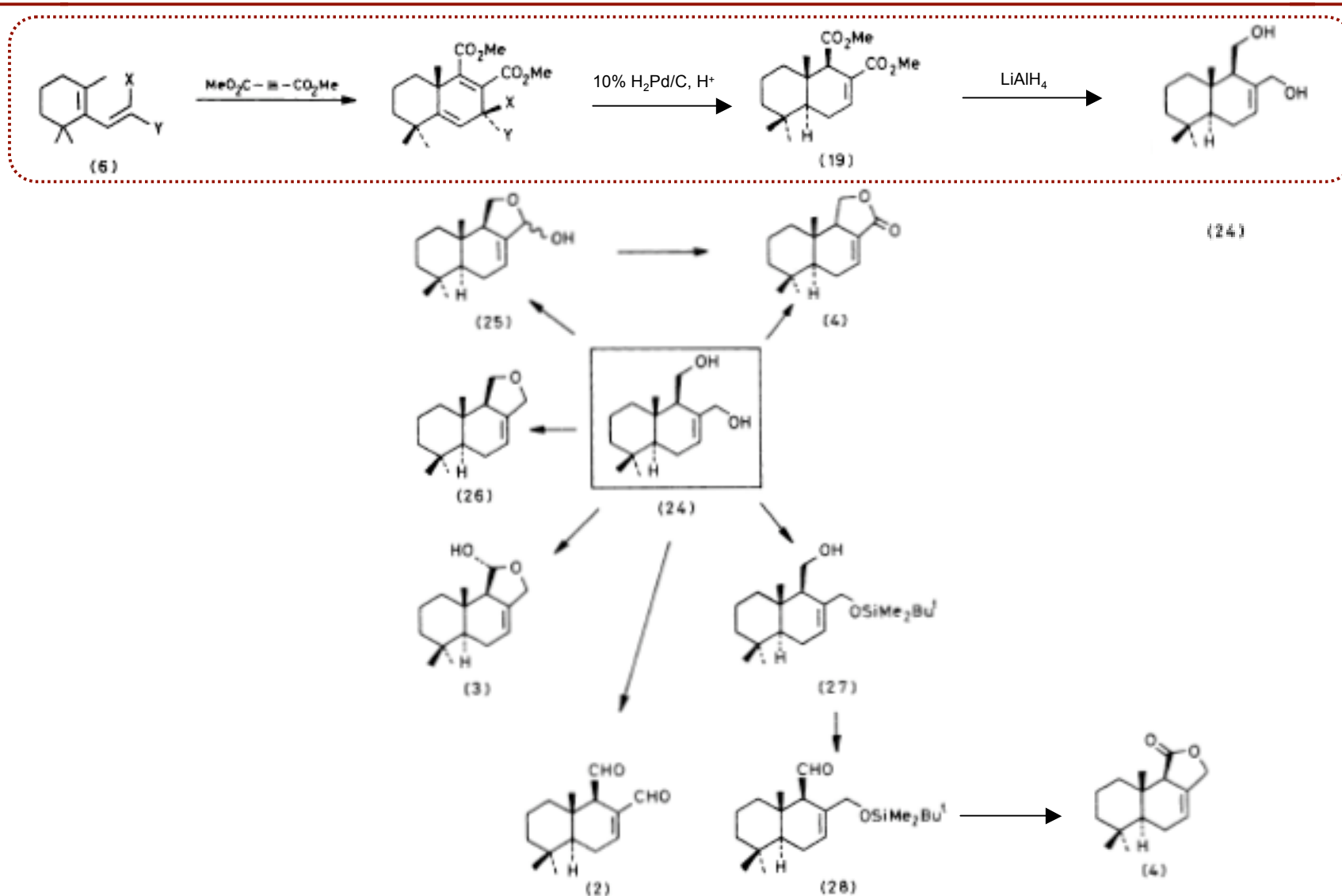
STEVEN V. LEY\* and CLIVE A. MEERHOLZ  
Department of Chemistry, Imperial College, London SW7 2AY

and

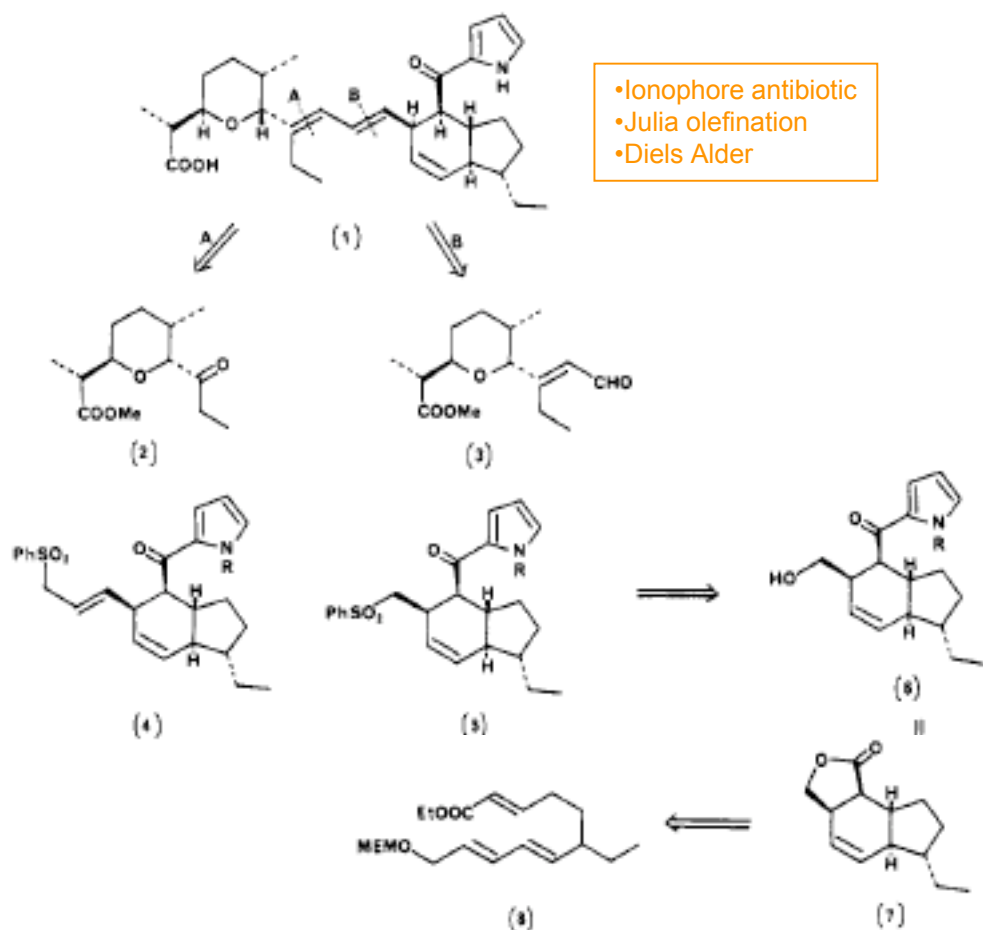
DEREK H. R. BARTON  
Institut de Chimie des Substances Naturelles, C.N.R.S., 91190 Gif-sur-Yvette, France

(Received in U.K. 7 August 1980)

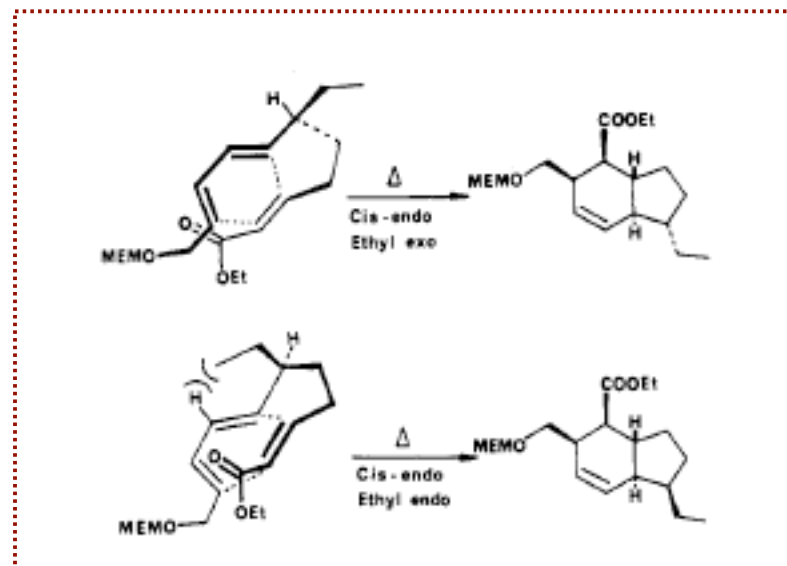
# The Diels–Alder Route to Drimane related Sesquiterpenes ; Synthesis of Cinnamolide, Polygodial, Isodrimeninol, Drimenin and Warburganal



## Total Synthesis of the Ionophore Antibiotic X-14547A (Indanomycin)



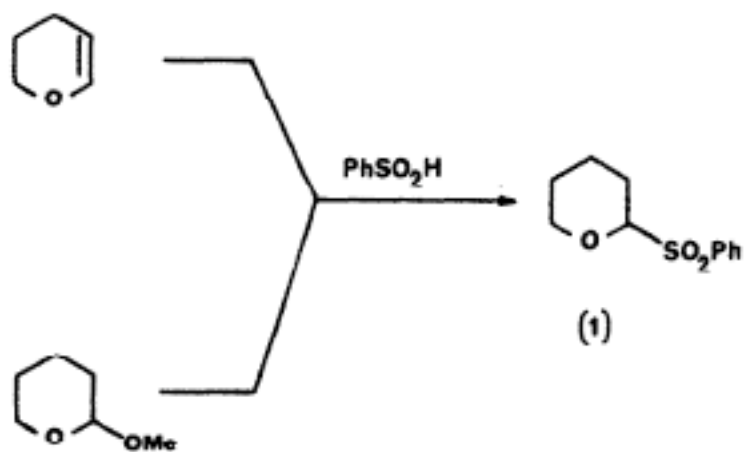
- Ionophore antibiotic
- Julia olefination
- Diels Alder



Martin P. Edwards, Steven V. Ley,\* Simon G. Lister, Brian D. Palmer, and David J. Williams

Department of Chemistry, Imperial College of Science and Technology, London SW7 2AY, United Kingdom

ALKYLATION REACTIONS OF ANIONS DERIVED FROM 2-BENZENESULPHONYL TETRAHYDROPIRAN AND THEIR  
APPLICATION TO SPIROKETAL SYNTHESIS



- Method to form c-c bond at the 2- position of cyclic ethers
- the formed enol ethers undergo acid catalysed cyclization to form dispiroketal

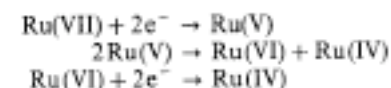
Electrophile	Product	Yield %
		71
		52
		47
		57
		79
		48



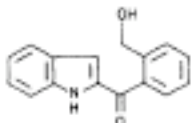
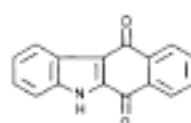
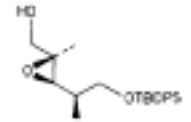
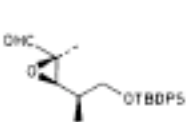
Steven V. Ley\*, Barry Lygo, Francine Sternfeld and Anne Wonnacott.

TETRAHEDRON 42 (15): 4333-4342 1986

## Preparation and Use of Tetra-*n*-butylammonium Per-ruthenate (TBAP reagent) and Tetra-*n*-propylammonium Per-ruthenate (TPAP reagent)† as New Catalytic Oxidants for Alcohols

Tetra-*n*-butylammonium per-ruthenate (Bu<sup>n</sup><sub>4</sub>N)(RuO<sub>4</sub>) and tetra-*n*-propylammonium per-ruthenate (Pr<sup>n</sup><sub>4</sub>N)(RuO<sub>4</sub>), with *N*-methylmorpholine *N*-oxide, function as mild catalytic oxidants for the high yield conversion of alcohols to aldehydes and ketones and are competitive with more conventional reagents.

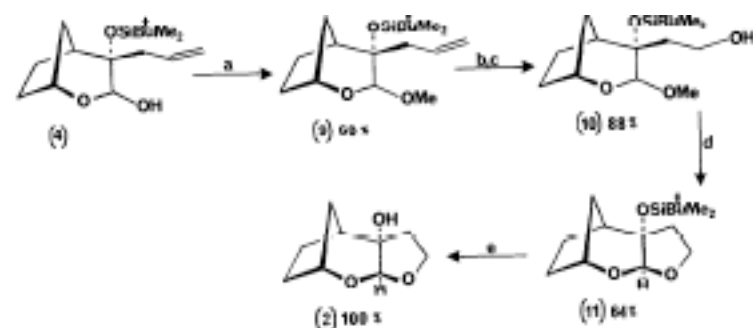
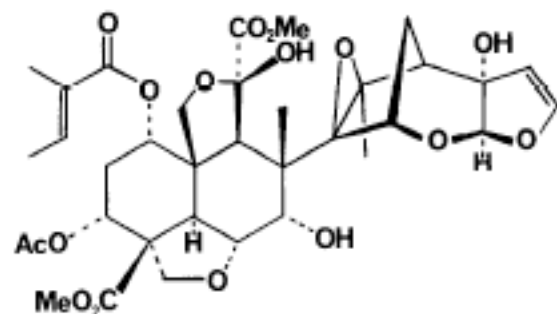


Alcohol	Product	TBAP		TPAP	
		% Yield	t/h	% Yield	t/h
<i>n</i> -Butanol	<i>n</i> -Butanal	94 <sup>c</sup>	0.8	95 <sup>c</sup>	1
Undec-10-en-1-ol	Undec-10-en-1-al	70 <sup>a</sup>	3		
Citronellol	Citronellal	75 <sup>a</sup>	5		
<i>E</i> -Cinnamyl alcohol	<i>E</i> -Cinnamaldehyde	91 <sup>a</sup>	3	75 <sup>a</sup>	5
Chrysanthemyl alcohol	Chrysanthamaldehyde	90 <sup>a</sup>	5	76 <sup>a</sup>	0.5
Benzyl alcohol	Benzaldehyde	80 <sup>b</sup>	2	71 <sup>a</sup>	0.5
<i>o</i> -Chlorobenzyl alcohol	<i>o</i> -Chlorobenzaldehyde	81 <sup>b</sup>	4		
4-Methoxybenzyl alcohol	4-Methoxybenzaldehyde			68 <sup>a</sup>	12
3,4-Dimethoxybenzyl alcohol	3,4-Dimethoxybenzaldehyde	98 <sup>b</sup>	1.5		
Piperonyl alcohol	Piperonaldehyde	89 <sup>b</sup>	3	70 <sup>a</sup>	1
Cyclobutanol	Cyclobutanone	95 <sup>c</sup>	1.1		
(±)-Menthol	(±)-Menthone	85 <sup>a</sup>	1.0		
<i>endo</i> -Norborneol	Bicyclo[2.2.1]heptan-2-one	73 <sup>a</sup>	0.3		
5 $\alpha$ -Androstan-17 $\beta$ -ol-3-one	5 $\alpha$ -Androstan-3,17-dione	96 <sup>a</sup>	6	99 <sup>a</sup>	1.5
Lanost-8-en-3 $\beta$ -ol	Lanost-8-en-3-one	86 <sup>a</sup>	6	81 <sup>a</sup>	1.5
		71 <sup>a</sup>	0.7		
		85 <sup>a</sup>	5		
				70 <sup>a</sup>	1

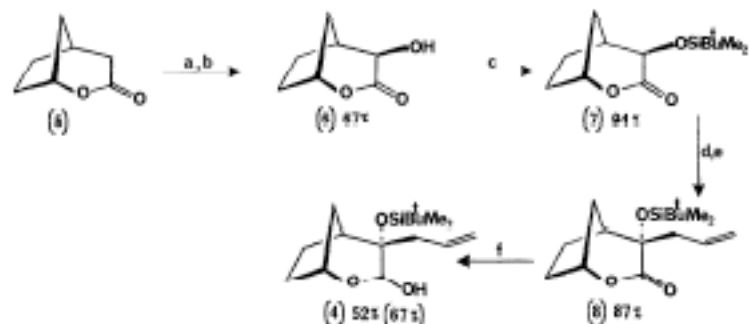
William P. Griffith, Steven V. Ley, Gwynne P. Whitcombe, and Andrew D. White  
Department of Chemistry, Imperial College, London SW7 2AY, U.K.

J. CHEM. SOC. CHEM. COMM. 1625 1987

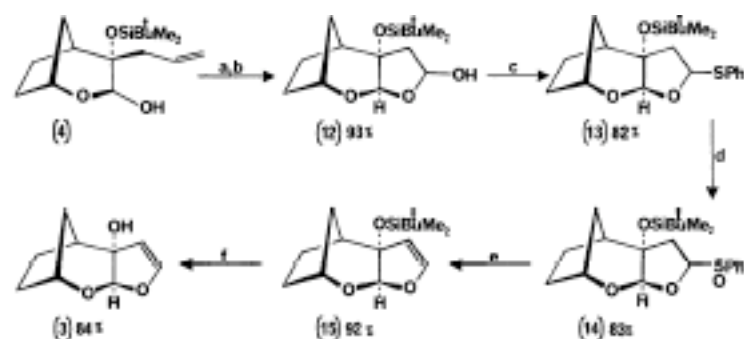
SYNTHESIS OF A HYDROXY DIHYDROFURAN ACETAL RELATED TO AZADIRACTIN:  
A POTENT INSECT ANTIFEEDANT



a)  $\text{MeOH}$ , trace  $\text{c.H}_2\text{SO}_4$  b)  $\text{D}_2$ ,  $\text{MeOH}$ ,  $-78^\circ\text{C}$  c) excess  $\text{NaBH}_4$ , RT d) trace Amberlyst 15,  $\text{MeOH}$  e) excess  $\text{tBuP}$ ,  $\text{THF}$ , RT



a) 1.1 eq.  $\text{LiAlH}_4$ ,  $\text{THF}$ ,  $-78^\circ\text{C}$  b) 1.2 eq.  $\text{MeOH}$ ,  $-78^\circ\text{C}$  to  $0^\circ\text{C}$  c) 1.2 eq.  $\text{TBDMSCl}$ , 4 eq. imidazole,  $\text{NMP}$ , RT d) 1.1 eq.  $\text{KDA}$ ,  $-78^\circ\text{C}$  e) 2 eq. allyl bromide,  $-78^\circ\text{C}$  f) 0.6M  $\text{DIBAL}$ , toluene,  $-78^\circ\text{C}$ .



a)  $\text{D}_2$ ,  $\text{DCM}$ ,  $-78^\circ\text{C}$  b) 1.1 eq.  $\text{PPh}_3$ , RT c) 1.4 eq.  $\text{PhSH}$ ,  $\text{MeCN}$ , trace Amberlyst 15, 4A sieves d) 1.1 eq.  $\text{m-CPBA}$ ,  $\text{DCM}$ , RT e) Toluene,  $\Delta$  f) excess  $\text{tBuP}$ ,  $\text{THF}$ , RT.

Steven V. Ley<sup>a</sup>, Dinos Santafianos<sup>a</sup>, W.M. Blaney<sup>b</sup>, and Monique S.J. Simmonds<sup>c</sup>.

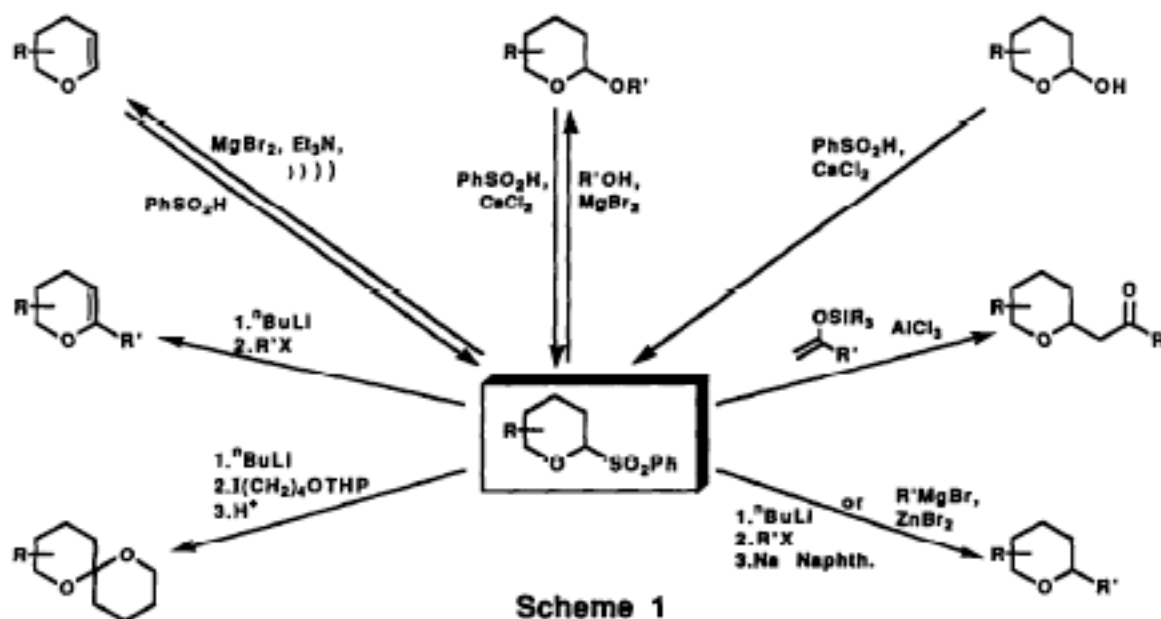
a) Department of Chemistry, Imperial College, London SW7 2AZ, U.K.

b) Department of Biology, Birkbeck College, London WC1E 7HX, U.K.

c) Jodrell Laboratory, Royal Botanic Gardens, Kew, U.K.

## SUBSTITUTION REACTIONS OF 2-BENZENESULFONYL CYCLIC ETHERS WITH CARBON NUCLEOPHILES

- Direct substitution of 2-benzenesulfonyl cyclic ethers with C-Nu
- Organozinc reagents, silyl enol ethers, silyl ketene acetals
- 6-substituted rings lead to formation of trans products.

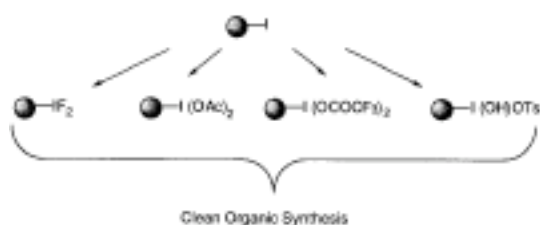


Deary S. Brown, Maurizio Bruno,<sup>1</sup> Raymond J. Davenport, and Steven V. Ley\*

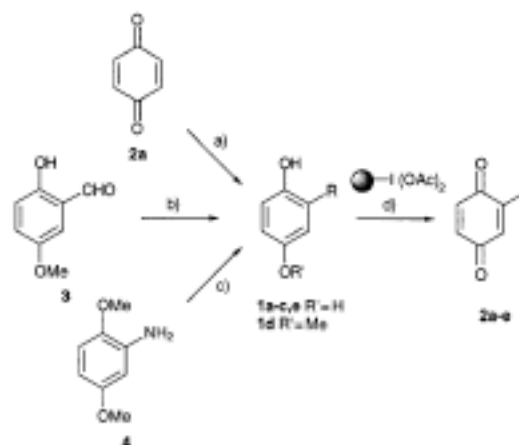
Department of Chemistry, Imperial College of Science, Technology and Medicine,  
South Kensington, London, SW7 2AY, UK.

TETRAHEDRON 45 (13): 4293-4308 1989

**Polymer-supported hypervalent iodine reagents in 'clean' organic synthesis with potential application in combinatorial chemistry**



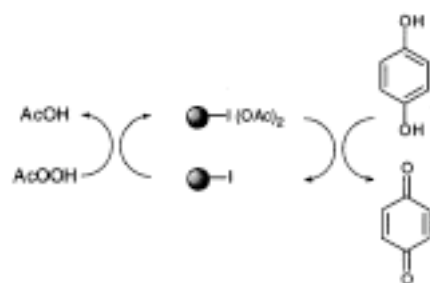
**Scheme 1** New polymer-supported hypervalent iodine reagents.



**Scheme 2** Preparation of quinones 2a-e a) PhSH (1.0 equiv.), LiCl (1.0 equiv.), HMPA, RT; b) NaBH<sub>4</sub>, 5 °C, 1 h; c) i) AcCl, Et<sub>3</sub>N, DCM, RT, 1 h; then ii) BBr<sub>3</sub>, -78 °C, DCM, 1 h; d) see note 9.

**Table 1** PSDIB oxidative reactions

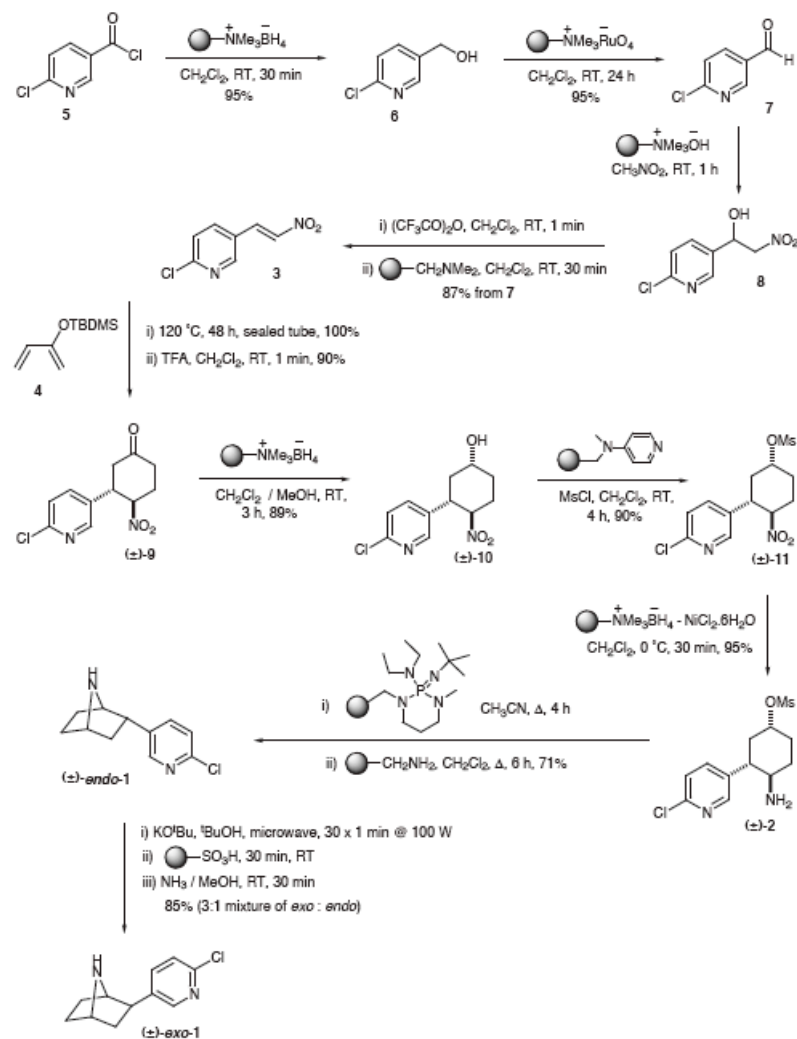
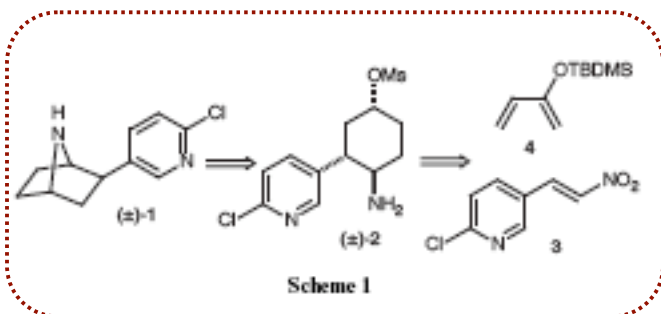
		R	Yield (%)	NMR and LC Purity (%)
2	a	H	Quant.	>95
	b	CO <sub>2</sub> Me	Quant.	>95
	c	SPh	Quant.	>95
	d	CH <sub>2</sub> OH	Quant.	>95
	e	NHAc	Quant.	>95
6	a	H	Quant.	>95
	b	4'-Cl	Quant.	>95
	c	4'-NO <sub>2</sub>	Quant.	>95
	d	2'-OMe	Quant.	>95
8	a	H	Quant.	>95
	b	4'-Cl	Quant.	>95
	c	4'-NO <sub>2</sub>	Quant.	>95
	d	2'-OMe	Quant.	>95
10	a	H	84	>95
	b	NHAc	75	90
	c	NHBoc	80	90
	d	NHFmoc	84	>95
	e	NHZ	96	>95



**Scheme 3** Regeneration and reuse of the resin.

## Synthesis of the potent analgesic compound (±)-epibatidine using an orchestrated multi-step sequence of polymer supported reagents

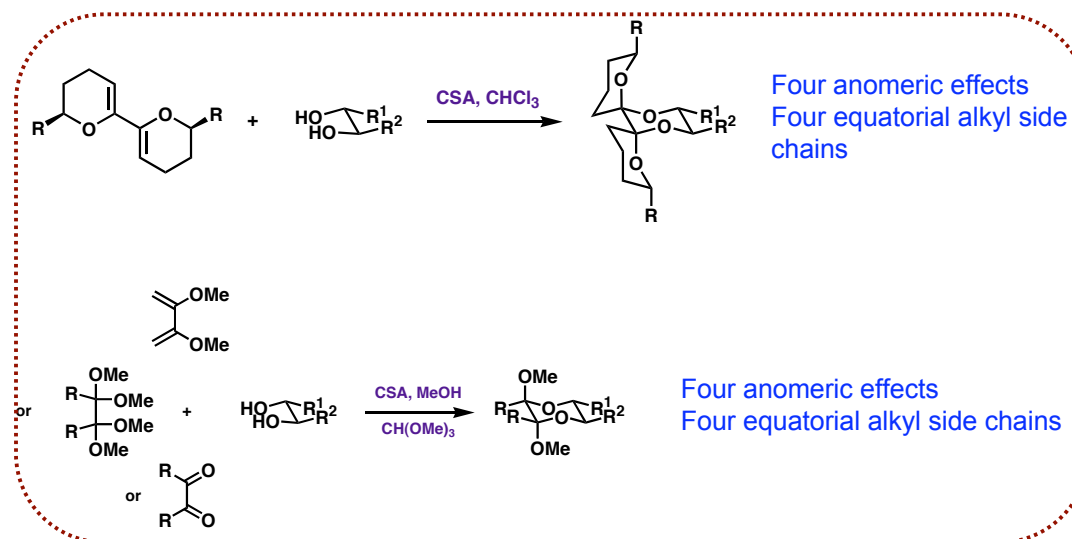
- Sequence 5-3 could be performed 1-pot by using porous pouches.
- Potent analgesic isolated from ecuadorian frog



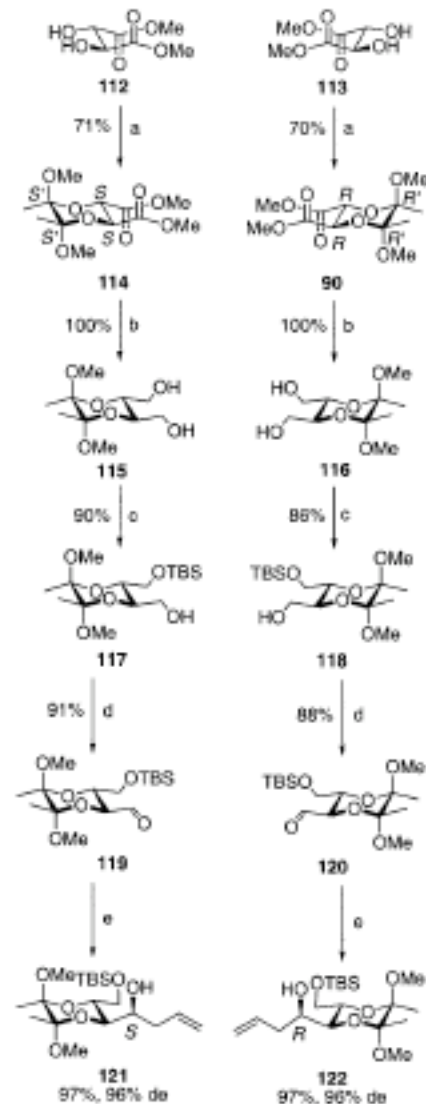
Jörg Habermann, Steven V. Ley\* and James S. Scott

JOURNAL OF THE CHEMICAL SOCIETY-PERKIN TRANSACTIONS 1 (10): 1253-1255 MAY 21 1999

## 1,2-Diacetals: A New Opportunity for Organic Synthesis



\* Reagents and conditions: (a) Butane-2,3-dione (1.2 equiv), CSA (0.1 equiv),  $\text{CH}(\text{OCH}_3)_3$  (3.0 equiv),  $\text{CH}_3\text{OH}$ , reflux, 14 h. (b)  $\text{LiAlH}_4$  (1.1 equiv), THF, 0 °C to room temperature, 0.5 h. (c) NaH (1 equiv), THF, room temperature then TBSCl (1 equiv), 2 h. (d)  $(\text{COCl})_2$  (1.3 equiv), DMSO (2.6 equiv),  $\text{CH}_2\text{Cl}_2$ , -78 °C then  $\text{Et}_3\text{N}$  (3.5 equiv), -78 °C to room temperature over 30 min. (e)  $\text{Bu}_3\text{SnCH}_2\text{CH}_2\text{CH}_2$  (3 equiv),  $\text{LiClO}_4$  (3 equiv),  $\text{Et}_2\text{O}$ , 0 °C to room temperature overnight.

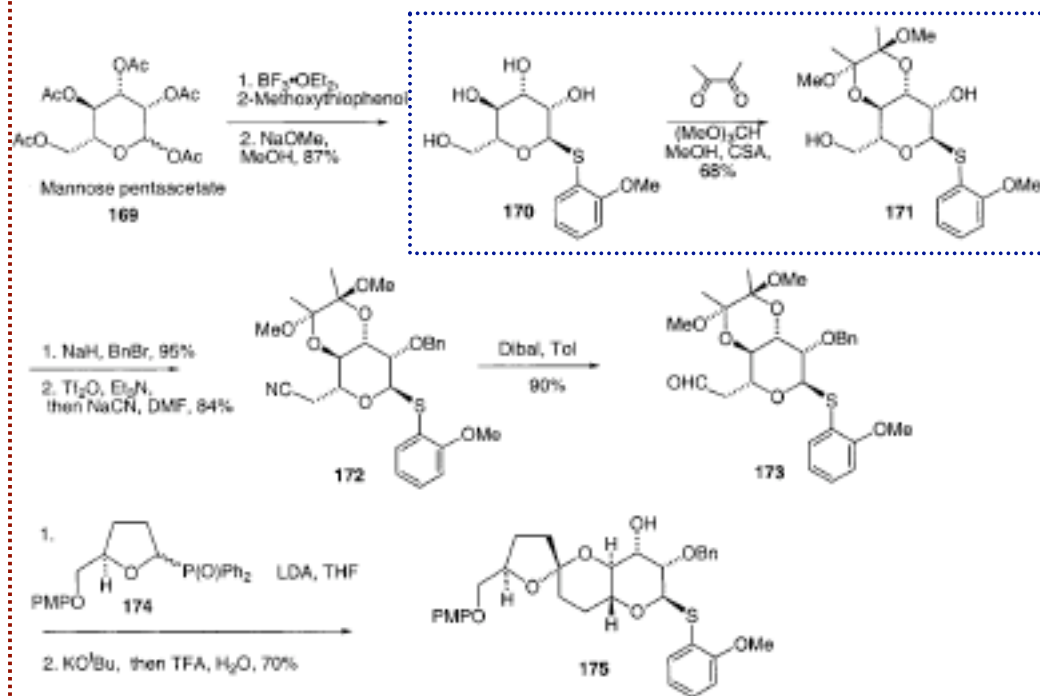
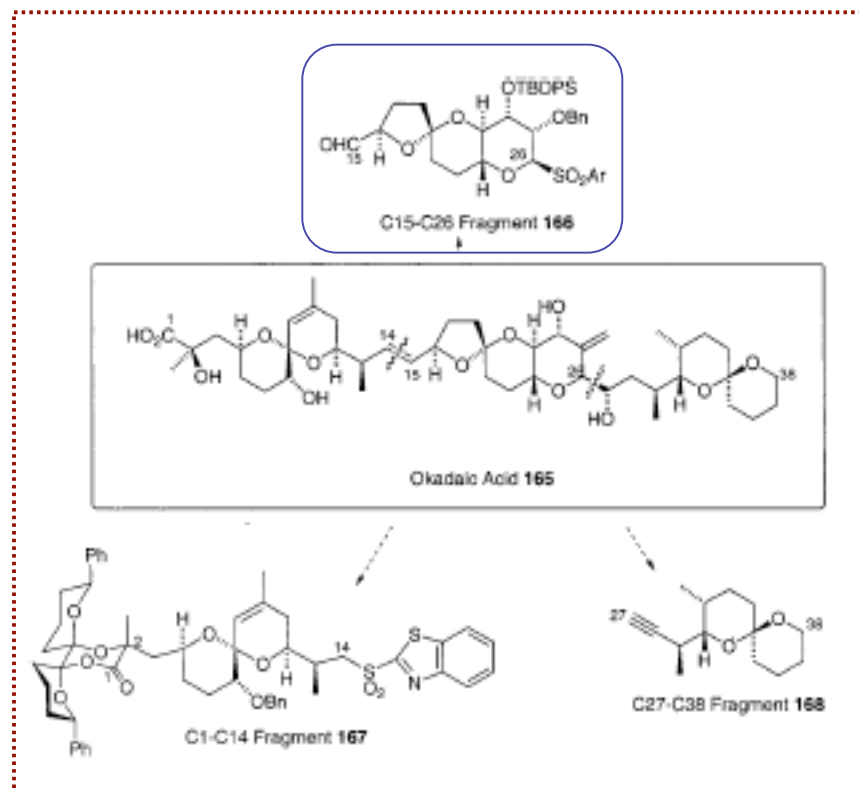


- exploit chirality embedded in the tartrate units to use it in the synthesis of polyoxygenated systems

Steven V. Ley,\* Daniel K. Baeschlin, Darren J. Dixon, Alison C. Foster, Stuart J. Ince, Henning W. M. Priepeke, and Dominic J. Reynolds

Chem. Rev. 2001, 101, 53–80

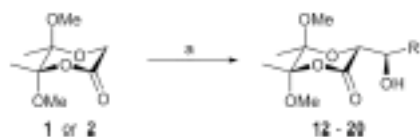
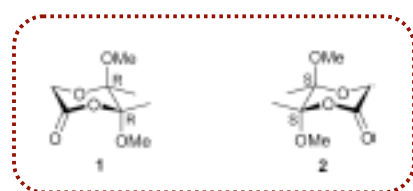
## Total synthesis of the protein phosphatase inhibitor okadaic acid



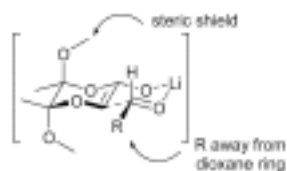
Steven V. Ley,\* Alexander C. Humphries, Holger Eick, Robert Downham, Andrew R. Ross,  
Richard J. Boyce, John B. J. Pavey and Jörg Pietruszka



**Studies on the generation of enolate anions from butane-2,3-diacetal protected glycolic acid derivatives and subsequent highly diastereoselective coupling reactions with aldehydes and acid chlorides**

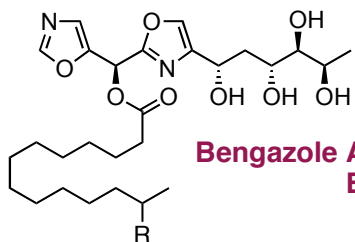


Scheme 1 (a) LHMDs (1.05 eq), THF,  $-78^{\circ}\text{C}$ , then RCHO.

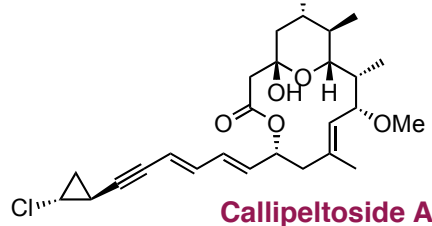
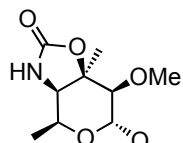


Aldehyde	Yield/%	de/%	Product
3	86	92	12
4	86	>95	13
5	89	>95	14
6	92	95	15
7	90	>95	16
8	96	>95	17
9	70	94	18
10	86	>96	19
11	60	>95	20

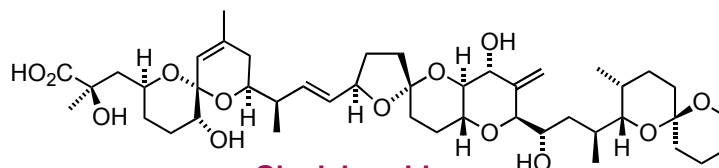
Lactone	Conditions	Product	Yield/
12	B*		47 75
13	A		48 86
14	A		49 89
15	A		50 93
16	A		51 73
17	A		52 85
18	A		53 99
19	A		54 57



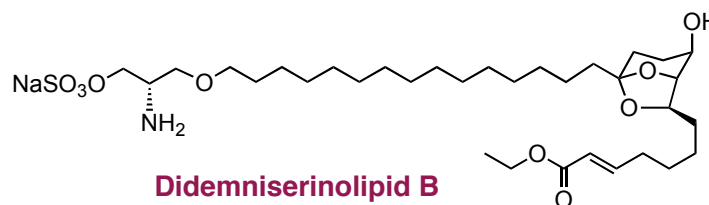
**Bengazole A (R=H)  
B (R=Me)**



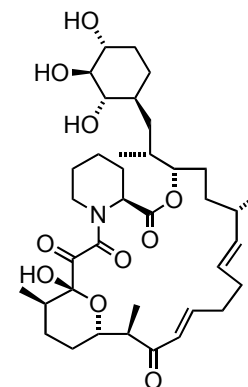
**Callipeltoside A**



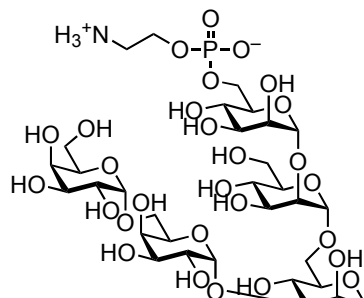
**Okadaic acid**



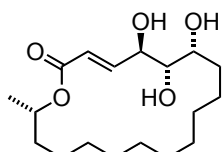
**Didemnerinlipid B**



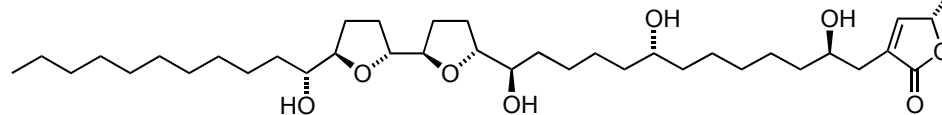
**Antascomicin B**



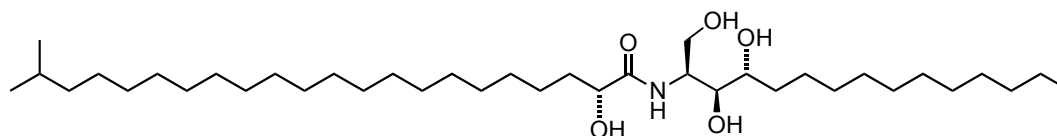
**Glycosylphosphatidylinositol  
Anchor**



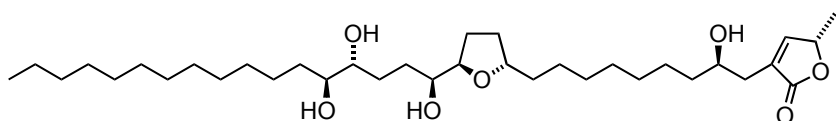
**Aspicillin**



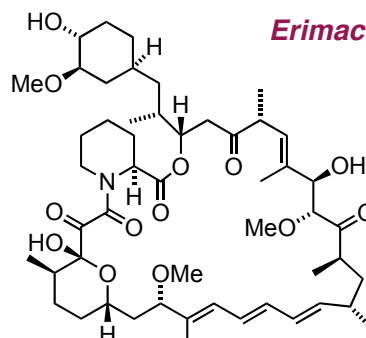
**10-Hydroxyasimicin**



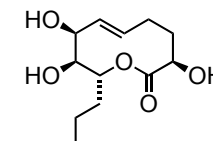
**Erimacrus isenbeckii Pheromone**



**Muricatetrocin C**



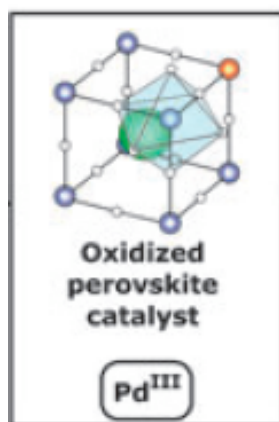
**Rapamycin**



**Herbarumin**



## Palladium-containing perovskites: recoverable and reusable catalysts for Suzuki couplings†



- Pd containing perovskites in investigation in automobile emission control
- “intelligent” as they self-regenerate under ox and red conditions, suppressing growth of Pd particles
- Investigated in Suzuki coupling reactions

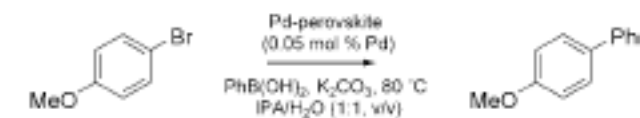


Table 1. Turnover numbers for palladium-containing perovskites.

Catalyst	TON (Pd <sup>-1</sup> )
LaFe <sub>0.57</sub> Co <sub>0.38</sub> Pd <sub>0.05</sub> O <sub>3</sub>	243,000 <sup>[32]</sup>
La <sub>0.9</sub> Ce <sub>0.1</sub> Fe <sub>0.57</sub> Co <sub>0.38</sub> Pd <sub>0.05</sub> O <sub>3</sub>	351,000
LaFe <sub>0.99</sub> Pd <sub>0.01</sub> O <sub>3</sub>	399,000
LaCo <sub>0.98</sub> Pd <sub>0.02</sub> O <sub>3</sub>	213,000
La <sub>0.9</sub> Ce <sub>0.1</sub> Al <sub>0.95</sub> Pd <sub>0.05</sub> O <sub>3</sub>	151,000
LaFe <sub>0.57</sub> Mn <sub>0.38</sub> Pd <sub>0.05</sub> O <sub>3</sub>	177,000
LaMn <sub>0.98</sub> Pd <sub>0.02</sub> O <sub>3</sub>	190,000

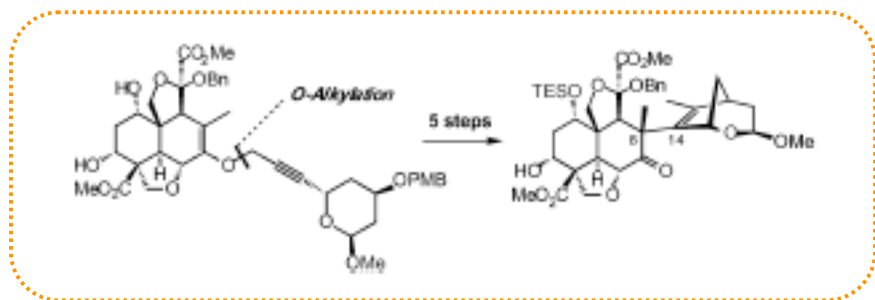
Substrate/catalyst ratio = 27000:1 (bromoanisole:perovskite) = 0.00019 mol% Pd. The reactions were run until LCMS conversion did not increase by more than 1% over 24 h (typically approx. 2 weeks). At this point conversions were estimated based on <sup>1</sup>H NMR analysis and TON calculated accordingly.

Aryl halide	Boicinic acid	Product	Base	Additive	Mol% Pd	Time/h	Isolated yield (%)
			K <sub>2</sub> CO <sub>3</sub> Cs <sub>2</sub> CO <sub>3</sub>	None None	0.05 0.0038	0.5 39	95 91
			K <sub>2</sub> CO <sub>3</sub>	None	0.05	0.5	95
			K <sub>2</sub> CO <sub>3</sub>	None	0.05	18	85
			K <sub>2</sub> CO <sub>3</sub>	None	0.05	1	89
			K <sub>2</sub> CO <sub>3</sub>	None	0.05	18	92
			K <sub>2</sub> CO <sub>3</sub> K <sub>2</sub> CO <sub>3</sub>	None TBAB	0.05 0.05	18 18	93 60 <sup>b</sup>

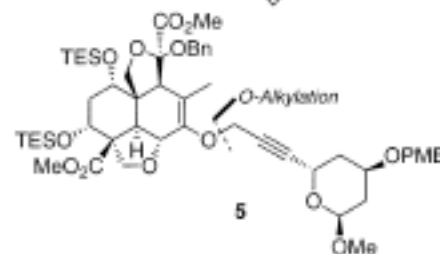
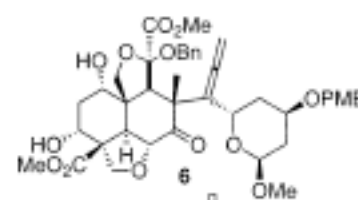
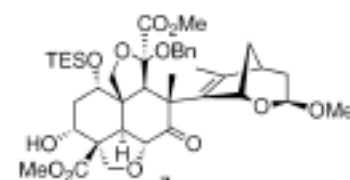
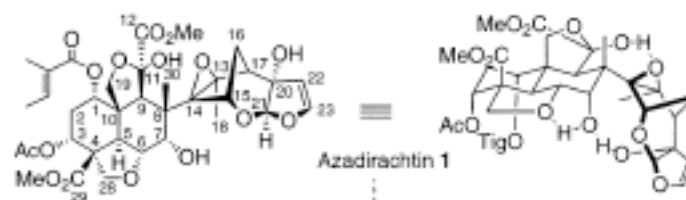
Stephen P. Andrews,<sup>a</sup> Antonia F. Stepan,<sup>a</sup> Hirohisa Tanaka,<sup>b</sup> Steven V. Ley,<sup>a</sup> Martin D. Smith<sup>a,\*</sup>

ADVANCED SYNTHESIS & CATALYSIS 347 (5): 647-654 APR 2005

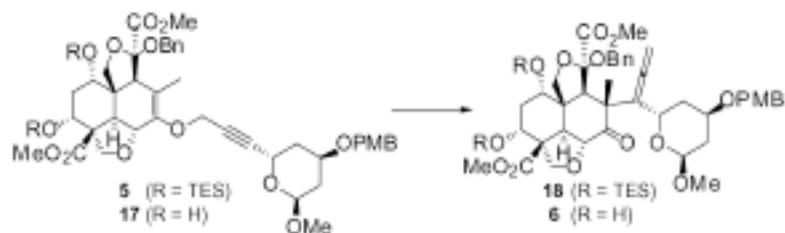
# Highly Selective Entry to the Azadirachtin Skeleton via a Claisen Rearrangement/Radical Cyclization Sequence



Scheme 1



Highly diastereoselective microwave induced Claisen rearr followed by radical cyclization allows formation of the sterically congested C8-C14 bond of azaD

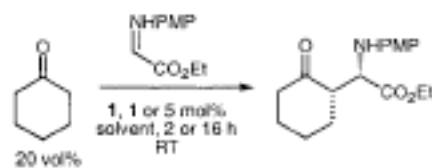
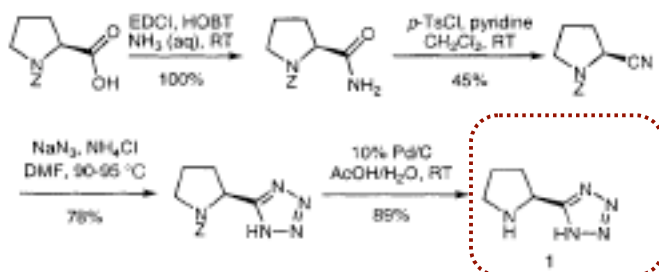


entry	subst	temp, °C	conditions	prod	yield
1	5	180	DCB, 48 h	18	7
2	5	180	DCB, <i>MWI</i> , 1 h	18	25
3	17	180	DCB, <i>MWI</i> , 15 min	6	71 <sup>a</sup>
4	17	180	DCB, <i>MWI</i> , 15 × 1 min	6	88 <sup>b</sup>

Thomas Durand-Reville, Luca B. Gobbi, Brian Lawrence Gray,  
Steven V. Ley,\* and James S. Scott

*Org. Lett.*, Vol. 4, No. 22, 2002

## 5-Pyrrolidin-2-yltetrazole: A New, Catalytic, More Soluble Alternative to Proline in an Organocatalytic Asymmetric Mannich-type Reaction



Catalyst (mol%)	Solvent	Reaction time (h)	Yield (%) <sup>a</sup>	dr <i>syn:anti</i> <sup>b</sup>	ee (%) <sup>c</sup>
1 1 (5)	CH <sub>2</sub> Cl <sub>2</sub>	2	65 <sup>d</sup>	>19: 1	>99
2 L-Proline (5)	CH <sub>2</sub> Cl <sub>2</sub>	2	0	–	–
3 1 (5)	Wet MeCN	2	49	>19: 1	>99
4 1 (5)	Wet THF	2	37	>19: 1	>99
5 1 (1)	CH <sub>2</sub> Cl <sub>2</sub>	16	70	>19: 1	>99

<sup>a</sup> Based on isolated product.

<sup>b</sup> Determined by <sup>1</sup>H NMR spectroscopy.

<sup>c</sup> Determined by chiral HPLC.

- need of proline alternative more soluble in conventional solvents
- tetrazoles are used as COOH bioisosters in med chem to improve drug solubility

Product	Reaction time (h)	Yield (%) <sup>a</sup>	Dr <i>syn:anti</i> <sup>b</sup>	Ee (%) <sup>c</sup>
6	24	74	>19: 1	94
7	8	99 <sup>d</sup>	–	>99
8	24	75	7: 1 <sup>f</sup>	95 <sup>g</sup>
9				

<sup>a</sup> Based on isolated product.

<sup>b</sup> Determined by <sup>1</sup>H NMR spectroscopy.

<sup>c</sup> Determined by chiral HPLC.<sup>10</sup>

<sup>d</sup> Reaction stopped after 24 h at 55% conversion.

<sup>e</sup> Reaction performed in acetone.

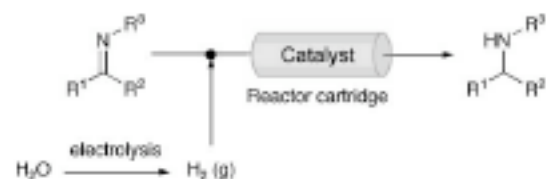
<sup>f</sup> Epimerization on the silica column led to a deterioration of dr.<sup>10,6</sup>

<sup>g</sup> Ee measured on corresponding lactone.<sup>11</sup>

Alexander J. A. Cobb, David M. Shaw, Steven V. Ley\*

SYNLETT 2004, No. 3, pp 0558–0560

## The use of a continuous flow-reactor employing a mixed hydrogen-liquid flow stream for the efficient reduction of imines to amines



Scheme 1 Continuous flow-through reduction of imines into amines.

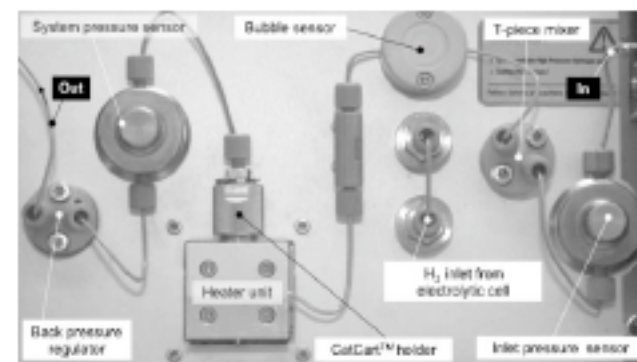


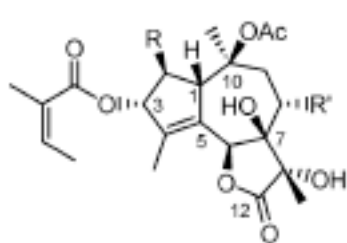
Fig. 2 H-Cube<sup>®</sup> Flow Hydrogenator front panel detail.

Table 1 Flow hydrogenation optimisation results

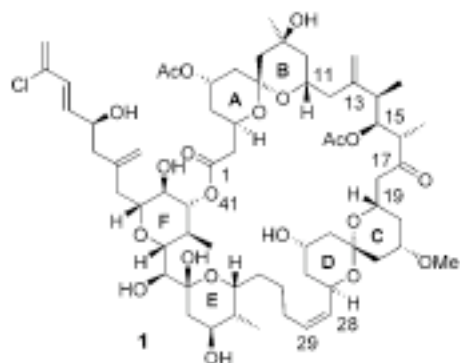
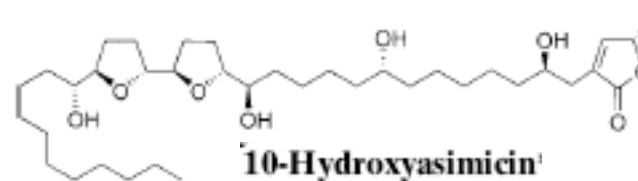
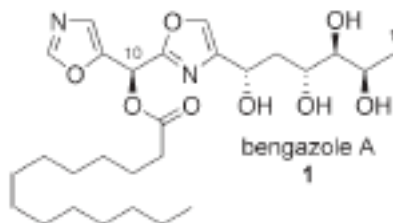
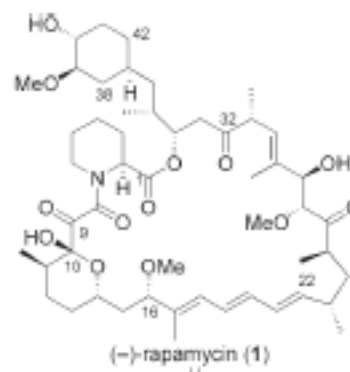
Run	Concentration/M	Flow rate/mL min <sup>-1</sup>	Injection volume/mL	Pressure/bar	Temperature/°C	Conversion (%) <sup>a</sup>
1	0.5	1	5	20	25	17
2	0.1	1	5	20	25	85
3	0.05	1	5	20	25	100
4	0.025	1	5	20	25	100
5	0.5	2	5	20	25	4
6	0.1	2	5	20	25	70
7	0.05	2	5	20	25	85
8	0.025	2	5	20	25	100
9	0.5	1	5	20	60	33
10	0.5	1	5	40	25	33
11	0.5	1	5	40	60	33
12	0.05	1	70	20	25	95

<sup>a</sup> Estimated by <sup>1</sup>H NMR analysis.

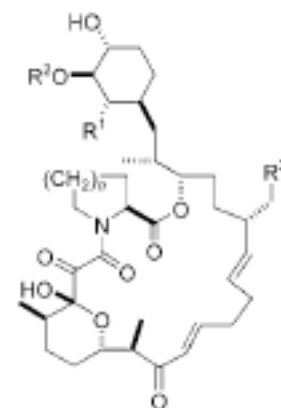
Entry	Imine	Yield (%) <sup>a</sup>	Purity (%)
1		quant.	>95
2		93	>95
3		quant.	95
4		quant.	84



**Thapsigargin (1)**  
 R = Octanoyl, R' = *n*-Butanoyl  
**Trilobolide (2)**  
 R = H, R' = (*S*)-2-MeButanoyl  
**Nortrilobolide (3)**  
 R = H, R' = *n*-Butanoyl  
**Thapsivillosin F (4)**  
 R = H, R' = Senecioyl



**Total Synthesis of Spongistatin 1:**



**Total Synthesis of Antascomicin B\*\***