Reactions of Thiophenecarbonyls with Samarium Diiodide and Their Applications

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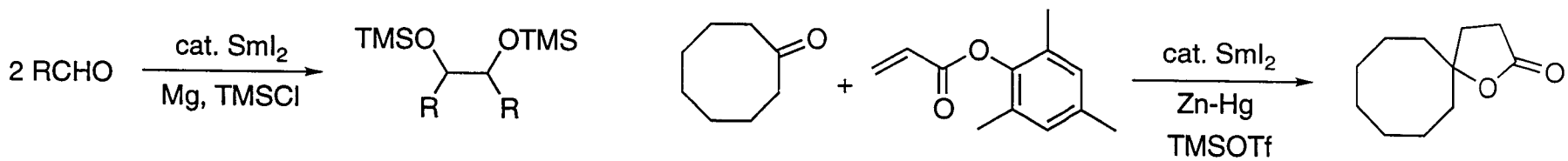
SmI_2

Advantage

- *Efficient Reductive agent (One Electron Transfer reagent)*
- *Easy Preparation*
- *Mild Condition*
- *High Functional Group Compatibility*

Disadvantage

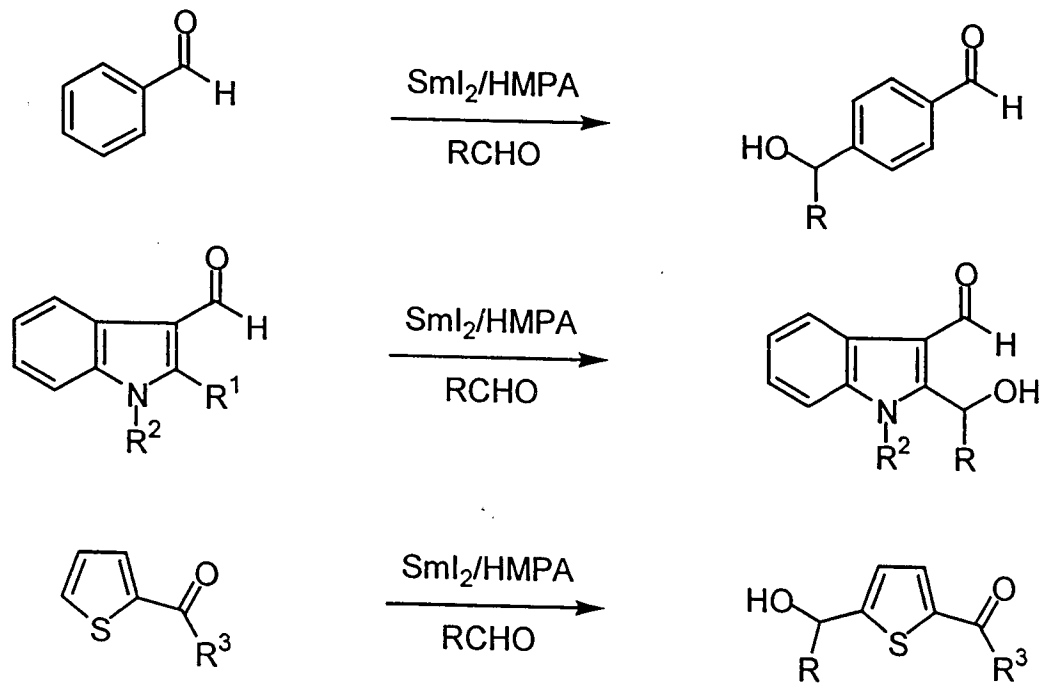
- *Expensive*
- *HMPA (Toxic)*
- *Stoichiometric*



Molander, G. A. *Chem. Rev.* **1992**, *92*, 29.
Molander, G. A. *Chem. Rev.* **1996**, *96*, 307.

Endo, T. et al. *J. Am. Chem. Soc.* **1996**, *118*, 11666.
Corey, E. J. et al. *Tetrahedron Lett.* **1997**, *38*, 2045.

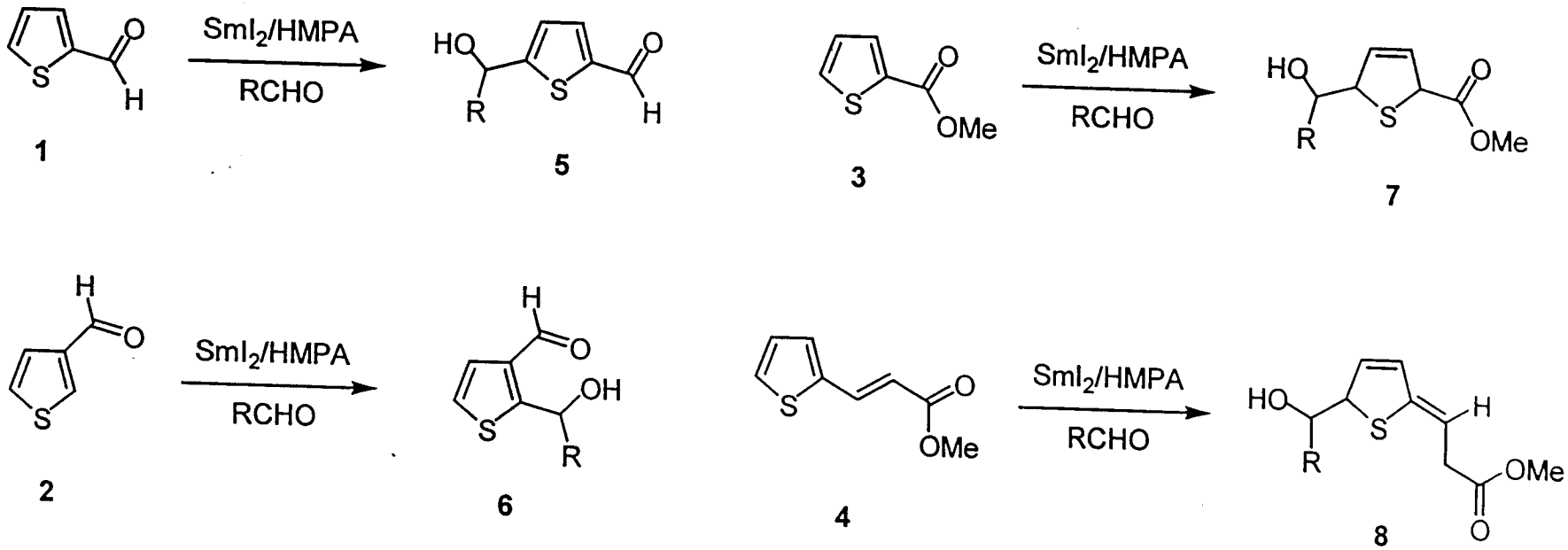
Coupling Reactions of Arylcarbonyls Mediated by SmI_2/HMPA



R= alkyl, aryl; R^1= H, CN; R^2= Me, Ms, Ts; R^3= H, OMe

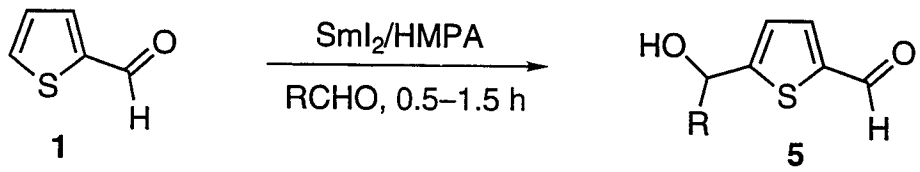
Shiue, J.-S.; Lin, M.-H.; Fang, J.-M. *J. Org. Chem.* **1997**, *62*, 4643.
Lin, S.-C.; Yang, F.-D.; Shiue, J.-S.; Yang, S.-M.; Fang, J.-M. *J. Org. Chem.* **1998**, *63*, 2909.
Yang, S.-M; Fang, J.-M. *J. Org. Chem.* **1999**, *64*, 394.

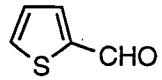
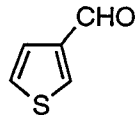
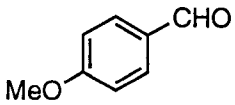
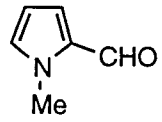
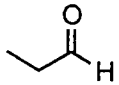
Coupling Reactions of Thiophenecarbonyls Mediated by SmI_2/HMPA



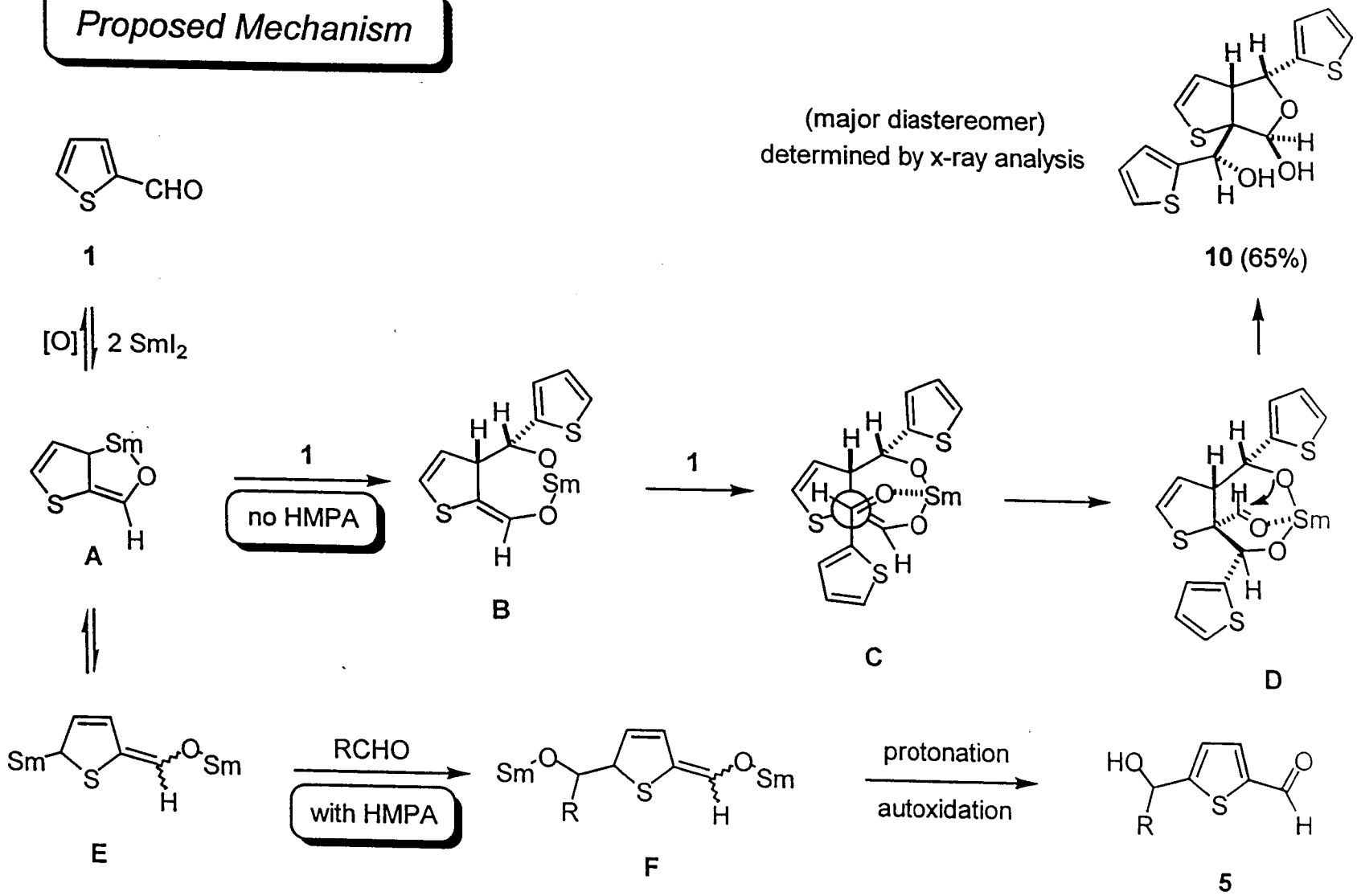
Yang, S.-M.; Fang, J.-M. *J. Chem.Soc., Perkin Trans. 1* **1995**, 2669.
Yang, S.-M.; Fang, J.-M. *Tetrahedron Lett.* **1997**, *38*, 1589.

Coupling Reactions of 2-Thiophenecarbaldehyde Promoted by SmI_2/HMPA

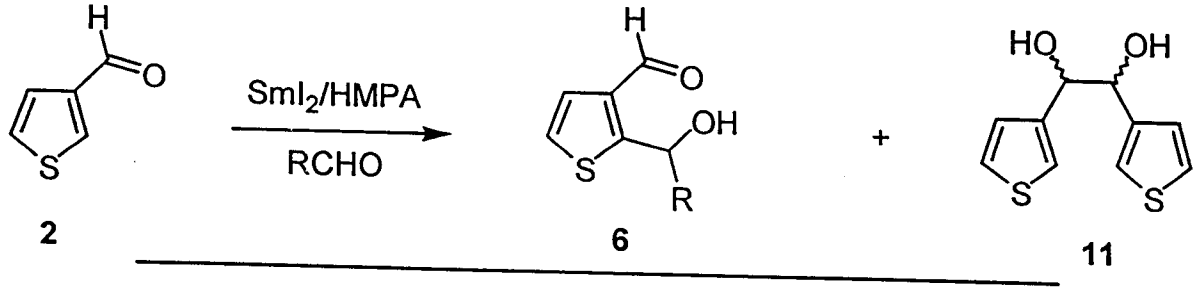


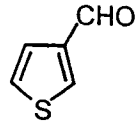
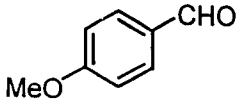
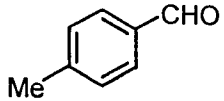
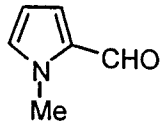
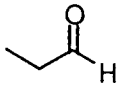
RCHO	product **5** (yield/%)
	**5a** (45)
	**5b** (49)
	**5c** (45)
	**5d** (36)
	**5a** (24) + **5e** (49)

Proposed Mechanism

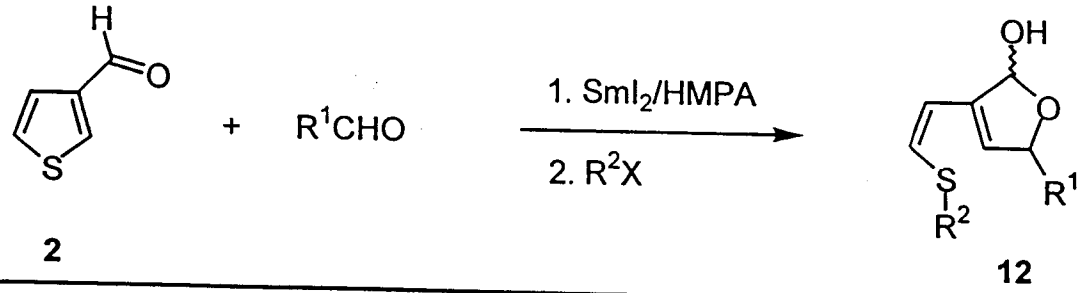


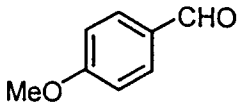
Coupling Reactions of 3-Thiophenecarbaldehyde Promoted by SmI_2/HMPA



RCHO	products (yield/%)
	**6a** (46), **11** (9)
	**6b** (43), **6a** (18)
	**6c** (37), **6a** (17)
	**6d** (21), **6a** (27)
	**6e** (43), **6a** (22)

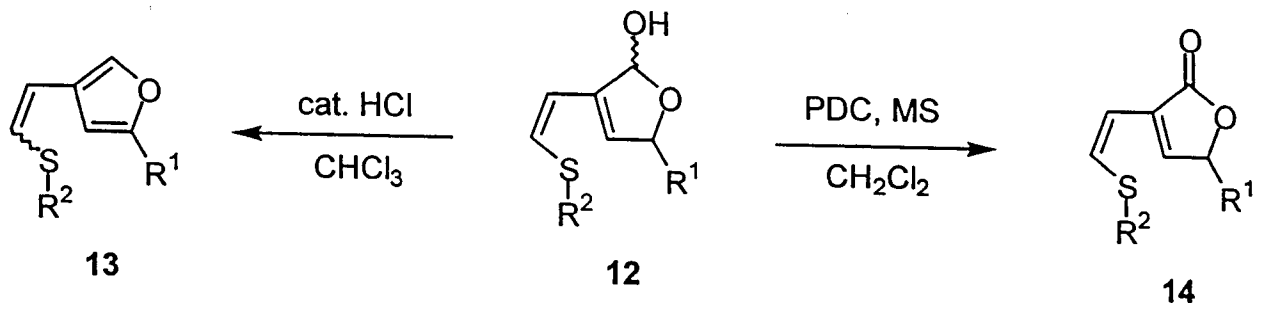
Coupling-Alkylations of 3-Thiophenecarbaldehyde Promoted by SmI_2/HMPA



R^1CHO	R^2X	products (yield/%)
2	allyl bromide	**12a** (55)
2	benzyl bromide	**12b** (65)
2	dimethyl sulfate	**12c** (29)[a]
2	methyl iodide	**12c** (74)
	benzyl bromide	**12d** (63), **12b** (22)

[a] self-coupling product **6a** (29%)

Convenient Route to Furans and Butenolides



13a (100%), R^1= 3-thienyl, R^2= benzyl

13b (100%), R^1= 3-thienyl, R^2= methyl

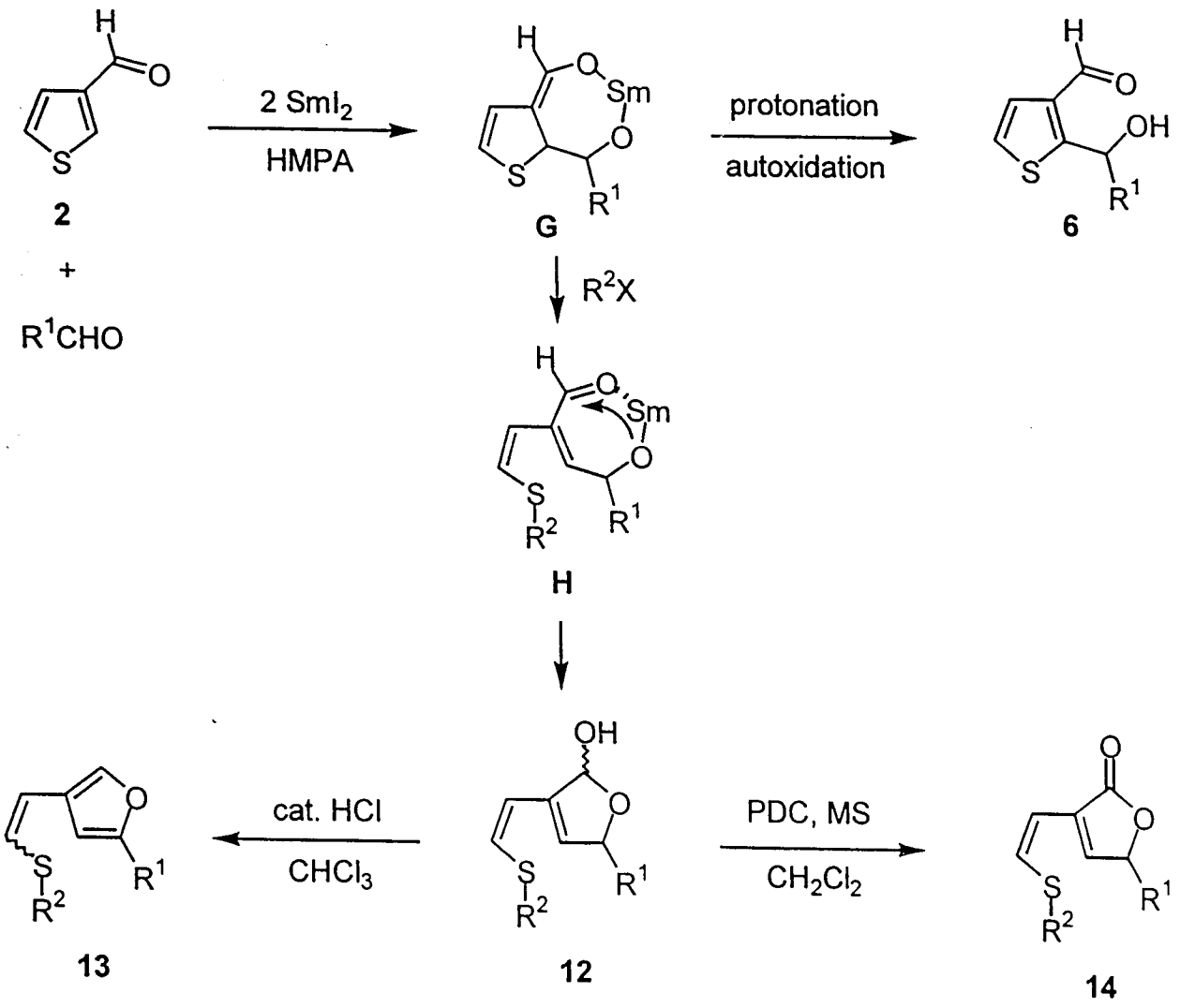
14a (77%), R^1= 3-thienyl, R^2= allyl

14b (79%), R^1= 3-thienyl, R^2= benzyl

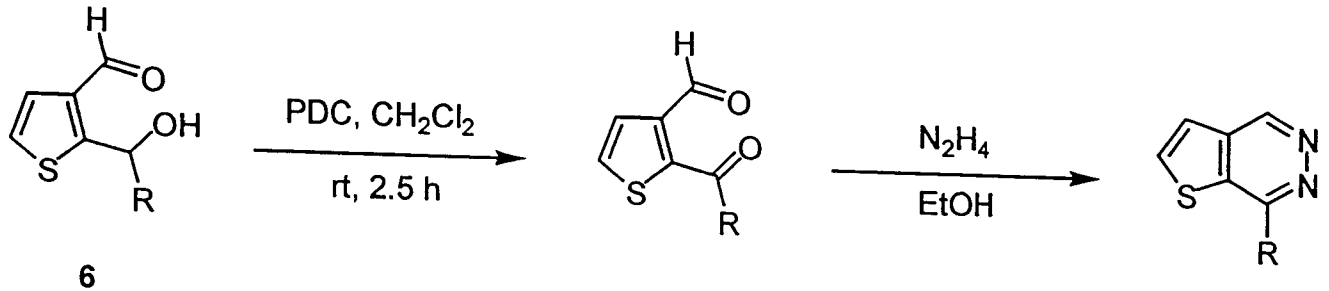
14c (82%), R^1= 3-thienyl, R^2= methyl

14d (80%), R^1= 4-methoxyphenyl, R^2= benzyl

Proposed Mechanism



Application to the Synthesis of Thieno[2,3-d]pyridazines as Sedative Agents



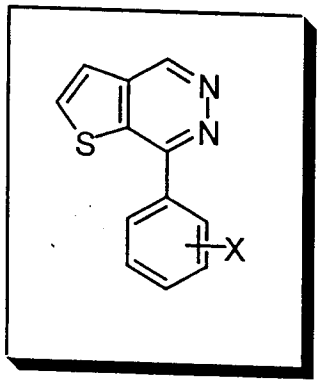
6

15a (86%), R= 3-thienyl

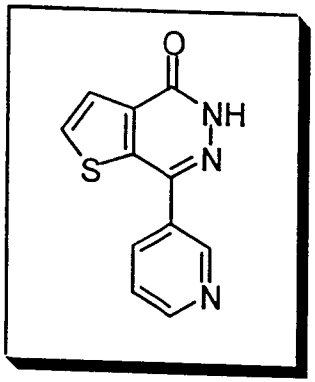
15b (85%), R= 4-$MeOC_6H_4$

16a (94%)

16b (92%)



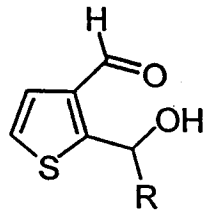
Sedative agent



antiasthmatic drug

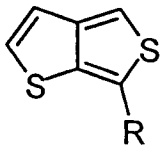
Yamaguchi, M. et al. *Chem. Pharm. Bull.* **1995**, *43*, 236.

Application to the Synthesis of Heterocyclic Analogues of 1-Arylnaphthalene Lignans



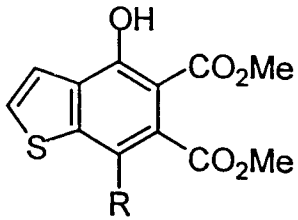
6a, R= 3-thienyl
6b, R= 4-$MeOC_6H_4$
6c, R= 4-MeC_6H_4

Lawesson's reagent
1, 4-dioxane, reflux, 3 h



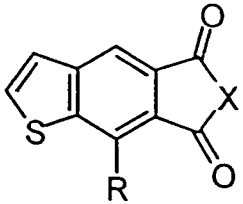
17a (85%)
17b (88%)
17c (81%)

dienophile
cat. PPTS, PhH, 1-2 h

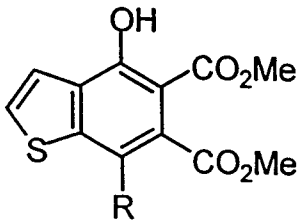


18a (91%)
18b (92%)
18c (89%)

or



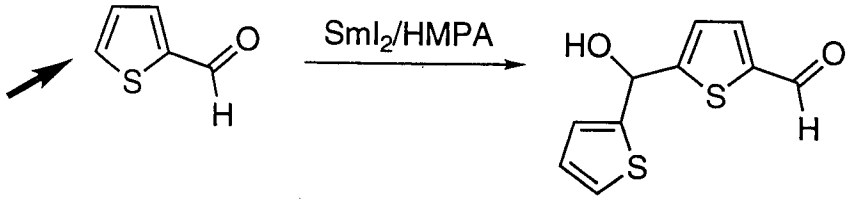
19a (89%), X= NPh
19b (92%), X= NPh
19c (94%), X= NPh
20 (67%), X= O, R= 4-MeC_6H_4

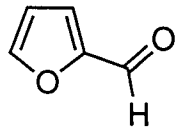


antihyperlipidemic activity

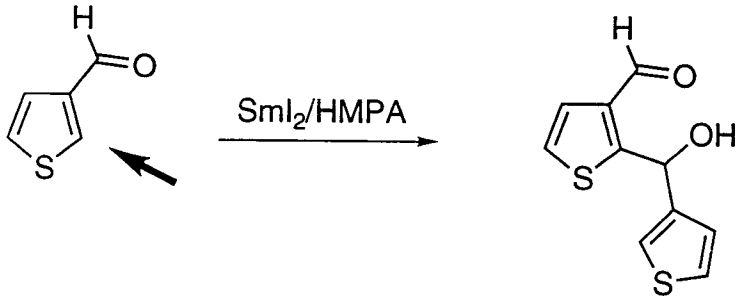
Kuroda, T. et al. *J. Org. Chem.* **1994**, *59*, 7353.
Cardwell K. et al. *J. Am. Chem. Soc.* **1988**, *110*, 2242.

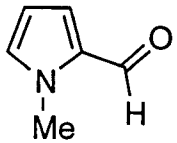
Sulfur stabilization ?



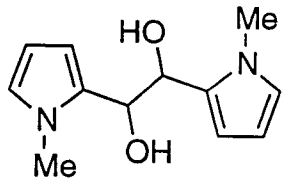


SmI_2/HMPA → messy

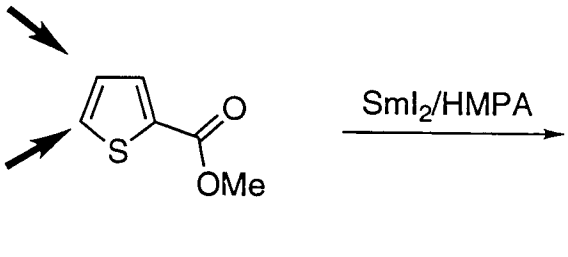




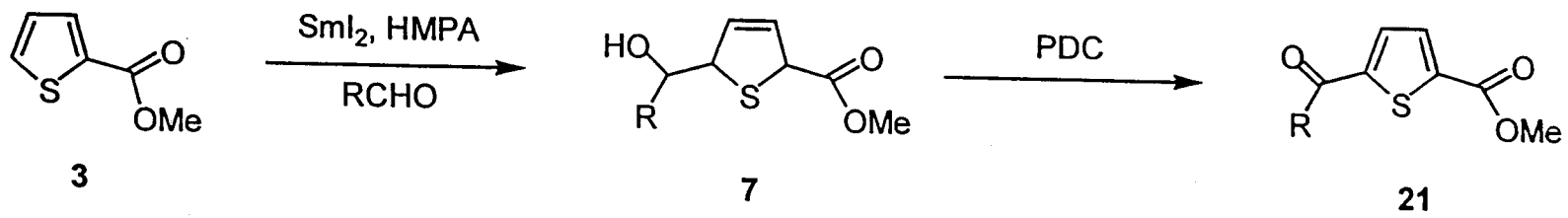
SmI_2/HMPA →

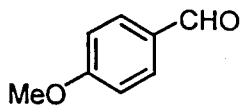
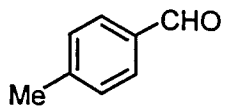
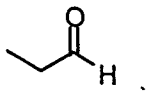
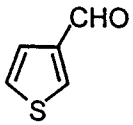


80% (dia. ratio 36:1)



Coupling Reactions of Methyl 2-Thiophenecarboxylate Promoted by SmI_2/HMPA

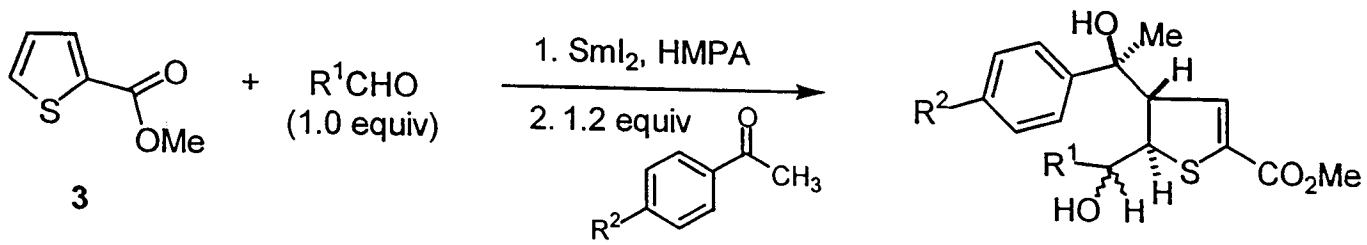


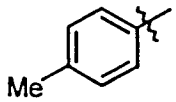
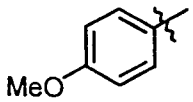
RCHO	product **7** (yield/%)[a]	product **21** (yield/%)
	**7a** (75)	**21a** (55)
	**7b** (85)	**21b** (53)
	**7c** (76)	**21c** (48)
	**7d** (67)	**21d** (45)

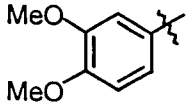
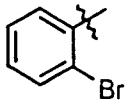
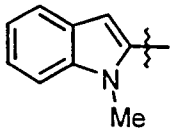
[a] four diastereomers

Yang, S.-M.; Fang, J.-M. *Tetrahedron Lett.* **1997**, *38*, 1589.

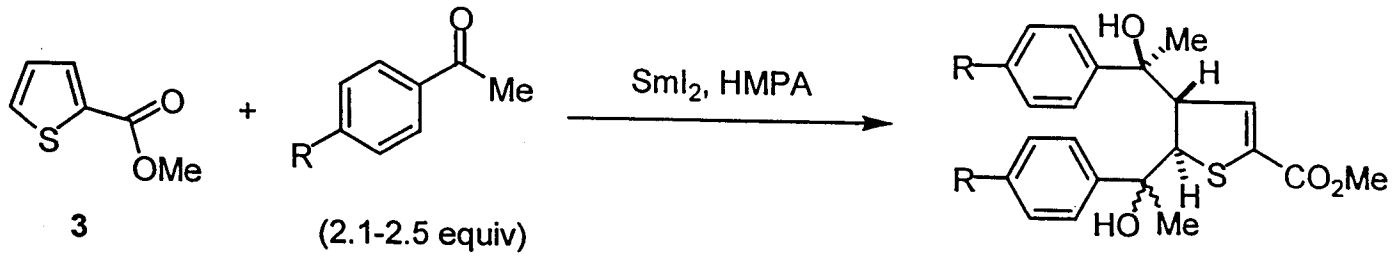
Three Component Reactions of Methyl 2-Thiophenecarboxylate Mediated by SmI_2/HMPA

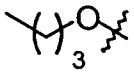
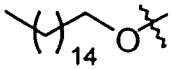
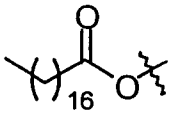


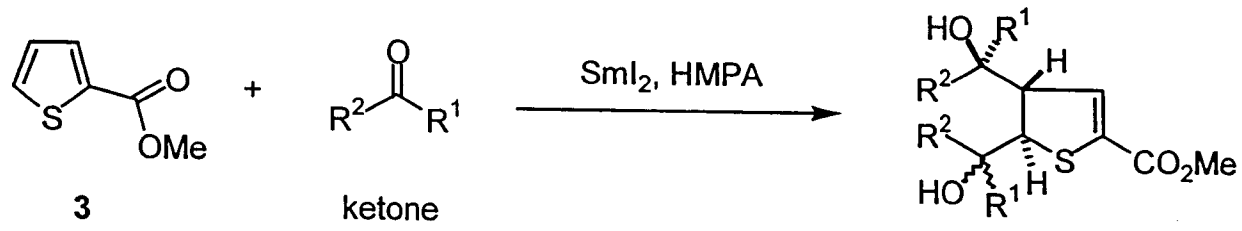
R^1	R^2	**22** (yield/%, dia. ratio)
	Me	**22a** (62, 46:54)
"	Cl	**22b** (63, 43:57)
"	OMe	**22c** (74, –)
	Me	**22d** (68, 44:56)
"	Cl	**22e** (71, 46:54)
"	OMe	**22f** (75, –)

R^1	R^2	**22** (yield/%, dia. ratio)
	OMe	**22g** (77, 45:55)
	OMe	**22h** (61, 83:17)
	OMe	**22i** (77, 63:35)

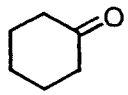
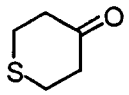
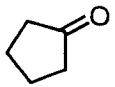
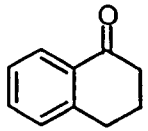
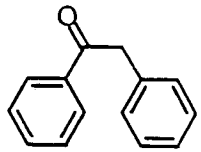
Reductive Double Electrophilic Reactions of Methyl 2-Thiophenecarboxylate



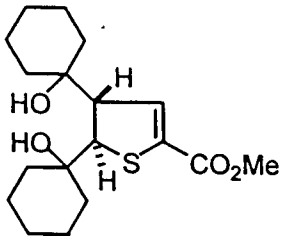
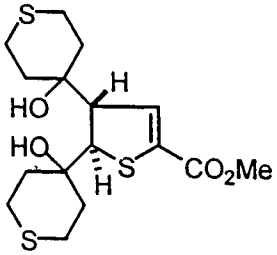
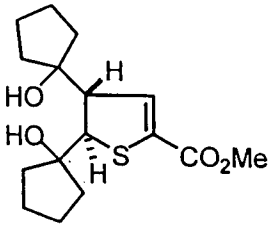
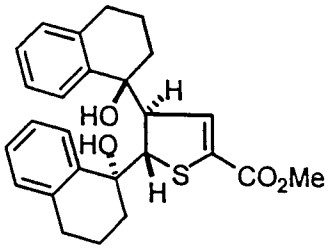
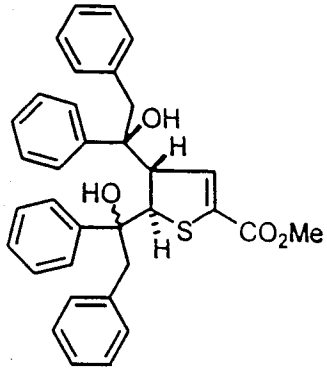
R	**23** (yield/%, dia. ratio)
H	**23a** (61, 36:64)
Me	**23b** (60, 48:52)
OMe	**23c** (67, 47:53)
Cl	**23d** (62, 46:54)
	**23e** (69, 44:56)
	**23f** (65, –)
	**23g** (58, –)



ketones:

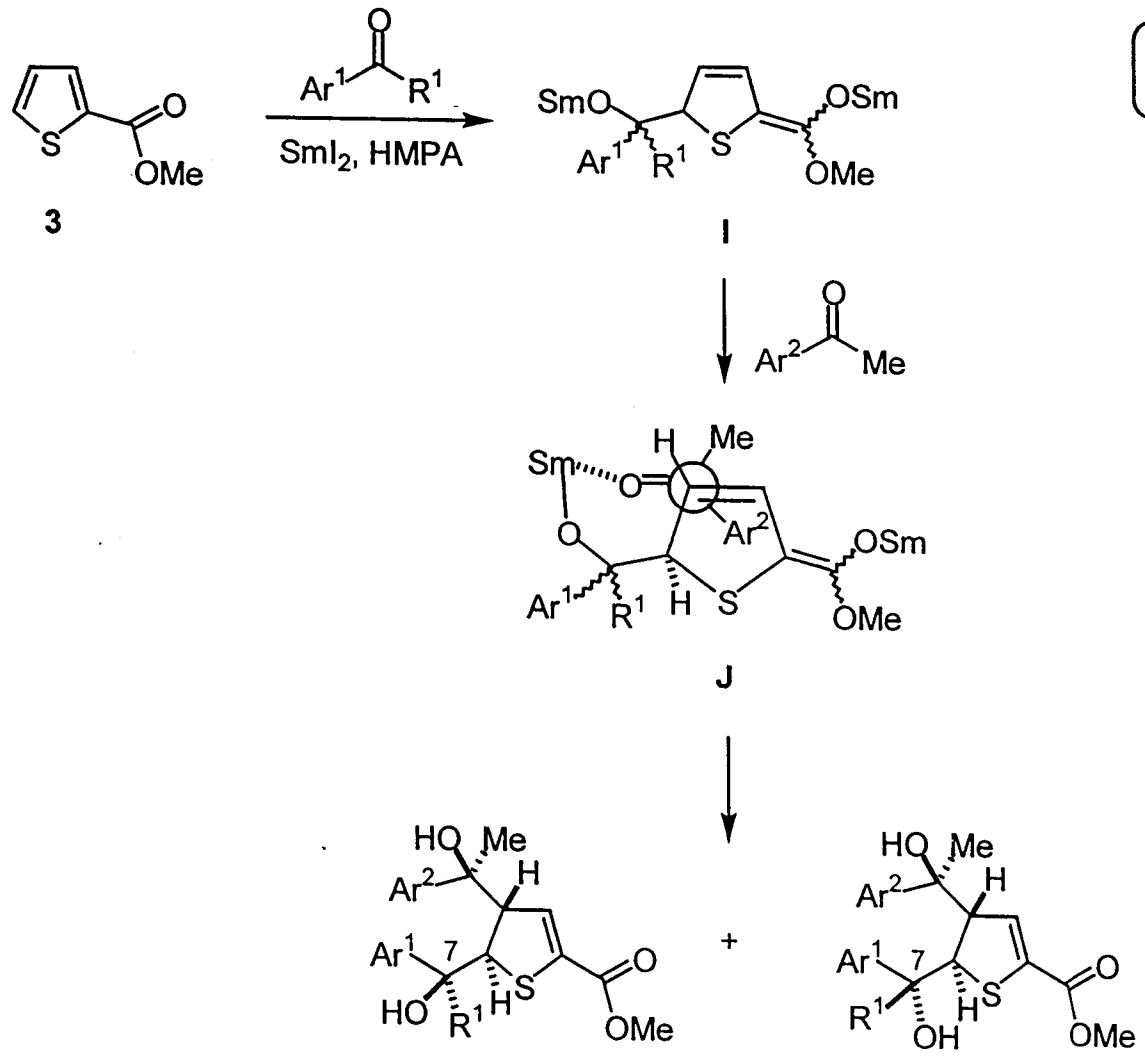
products:

24a (92%) **24b** (85%) **24c** (57%) **24d** (68%) **24e** (63%, 56:44)

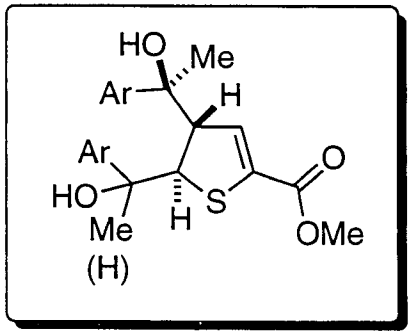
determined by x-ray analysis

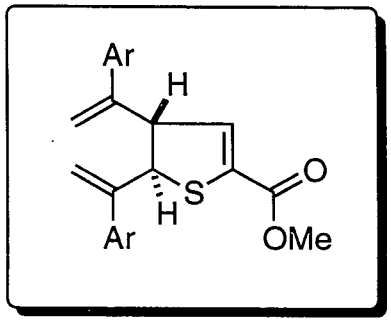
Proposed Mechanism



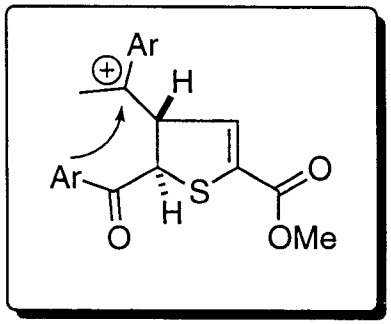
R^1= H, Me; epimers at C-7

Potential Applications



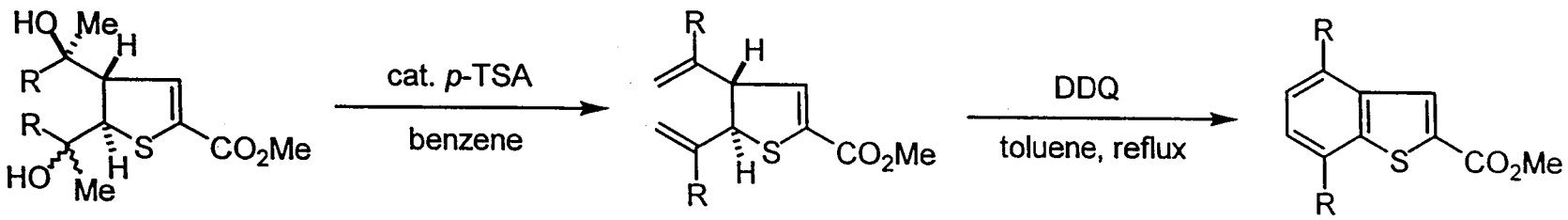


Polybenzo-fused-thiophene Compounds

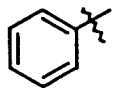
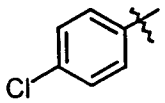
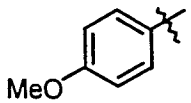
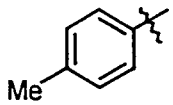


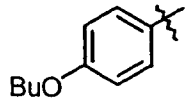
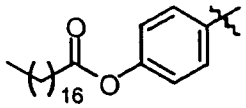
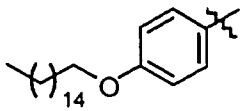
Polycyclic Compounds

Application to the Synthesis of Thieno p-Terphenyl Compounds by Sequential Dehydration and Oxidative Cyclization

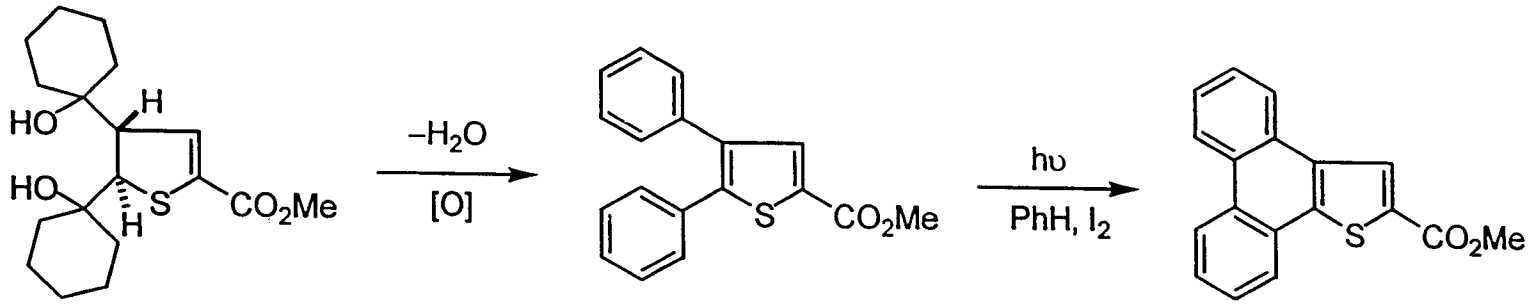


23 **25** **26**

R	**25** (yield/%)	**26** (yield/%)
	**25a** (90)	**26a** (90)
	**25b** (97)	**26b** (91)
	**25c** (95)	**26c** (59)
	**25d** (98)	**26d** (89)

R	**25** (yield/%)	**26** (yield/%)
	**25e** (93)	**26e** (29)
	**25f** (83)	**26f** (89)
	**25g** (87)	–[a]

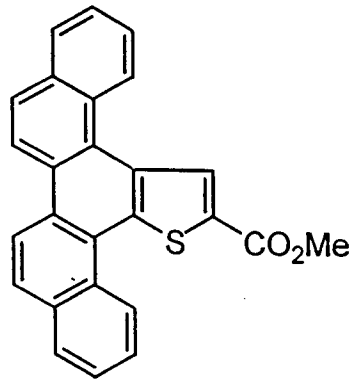
[a]decomposed



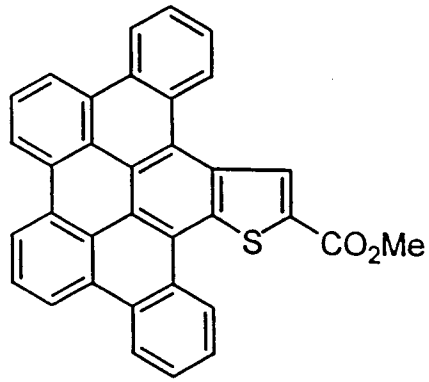
24a

27 (72%)

28 (86%)

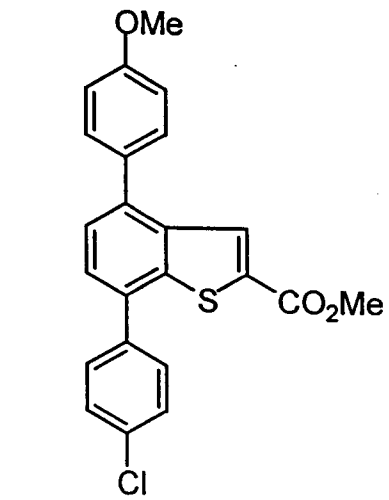


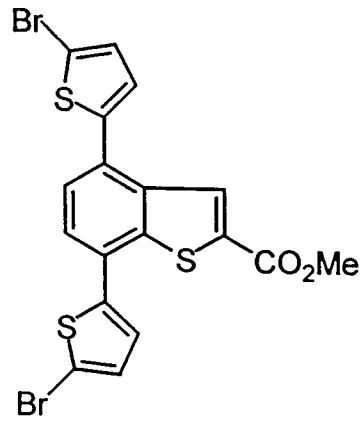
29 (81%, two steps)

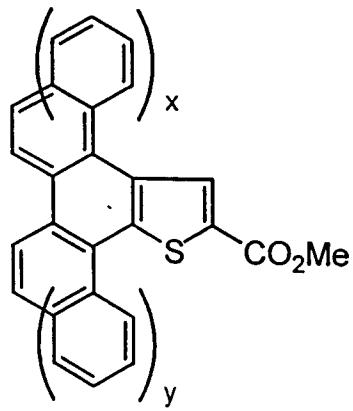


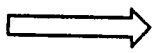
30 (62%, two steps)

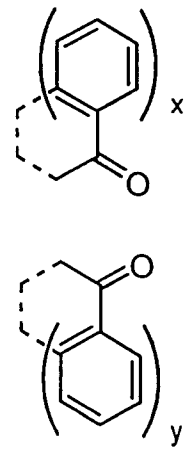
oxidative agent: $AlCl_3$, $CuCl_2$, O_2

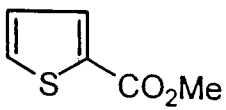

OMe
S
CO2Me
Cl


Br
S
S
CO2Me
S
Br

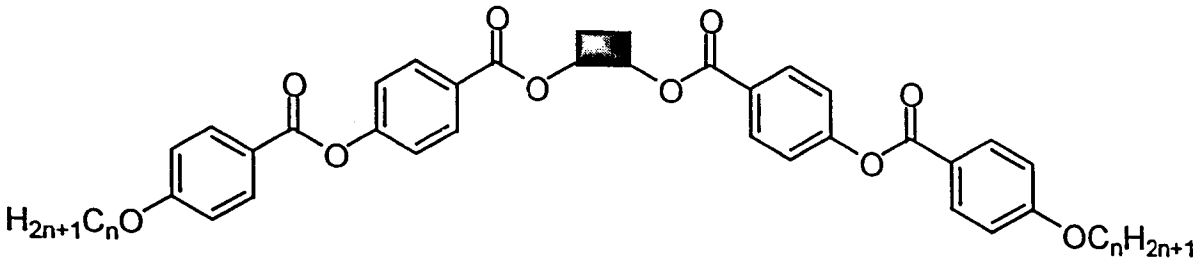

x
S
CO2Me
y

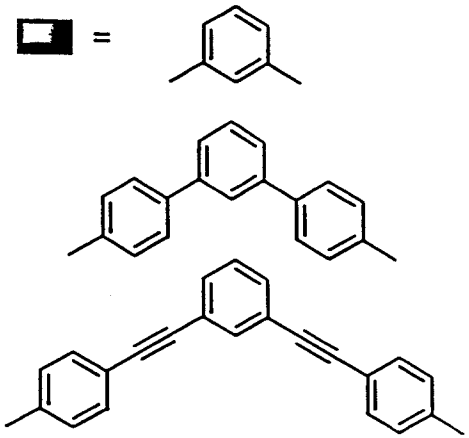



x
O
O
y


S
CO2Me

Liquid Crystals and Organic Light Emitting Diodes

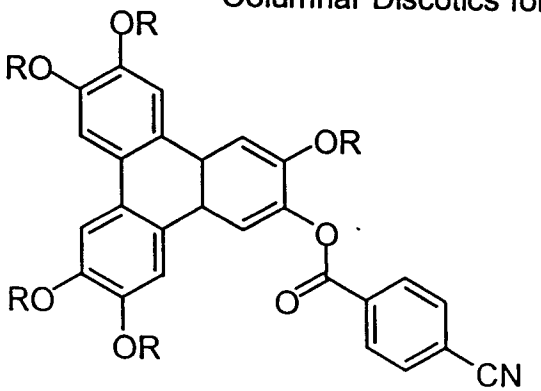


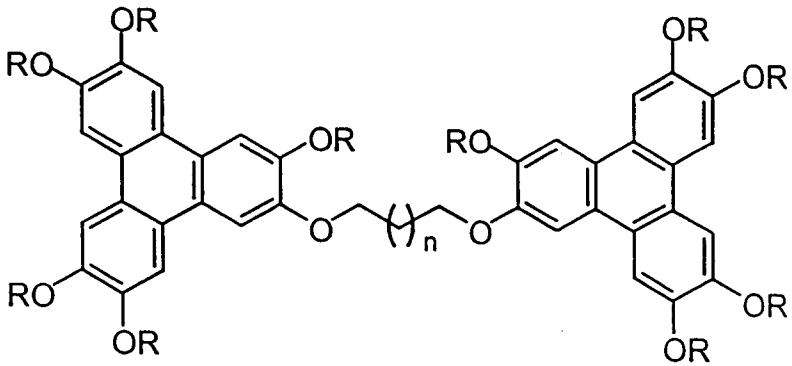


Bent-Core Liquid Crystals with Antiferroelectric Properties

Tschierske, C. et al. *J. Am. Chem. Soc.* **2000**, *122*, 1593.

Columnar Discotics for Light Emitting Diodes

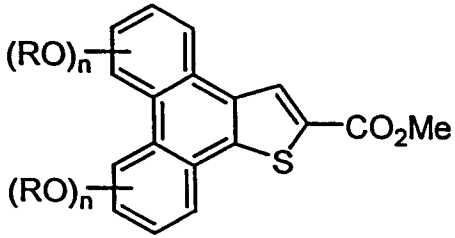


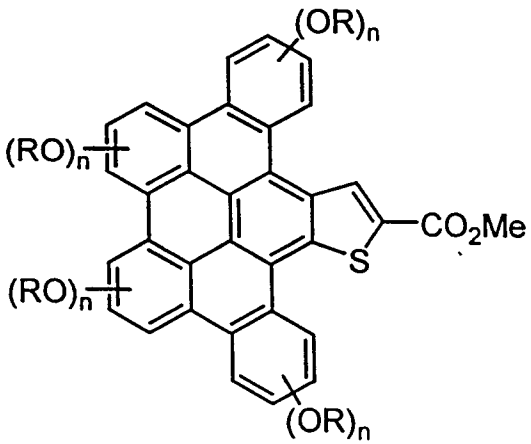


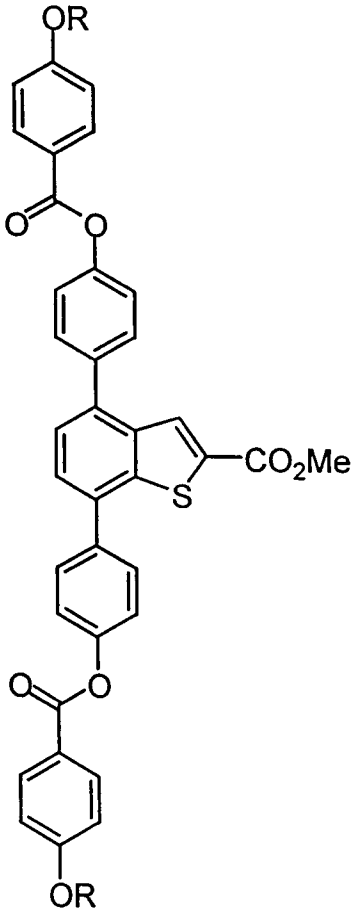
Wendroff, J. H. et al. *Adv. Mater.* **1997**, *9*, 48.

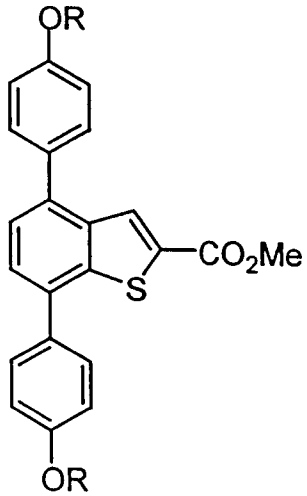
Schmidt, H.-W. et al. *Adv. Mater.* **1997**, *9*, 1031.

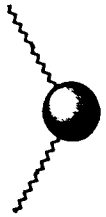
Application to Liquid Crystals or Organic Light Emitting Diodes ?



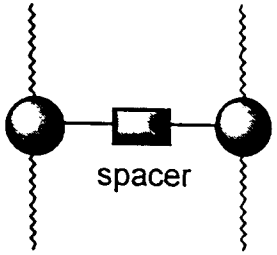




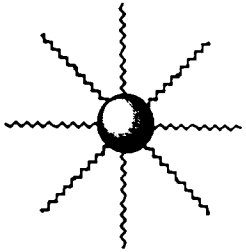




bent-type

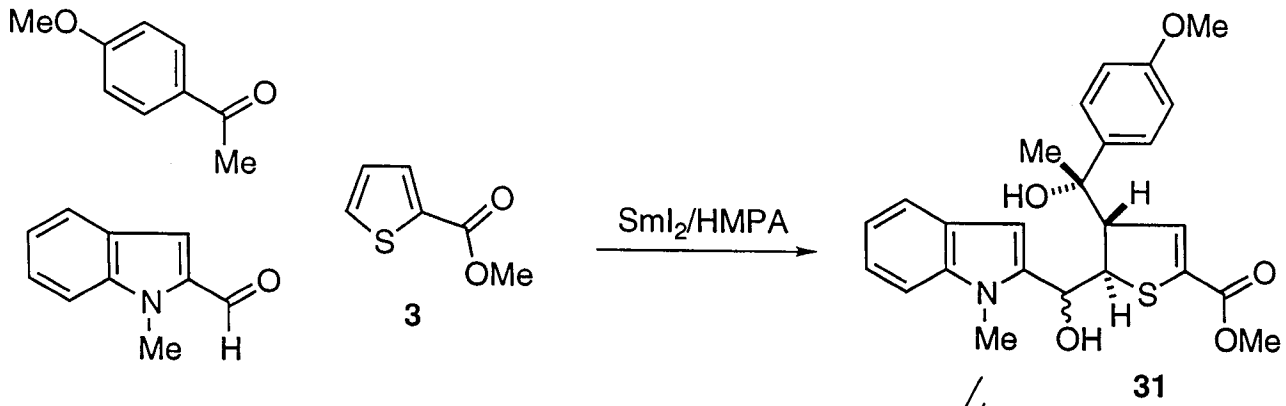


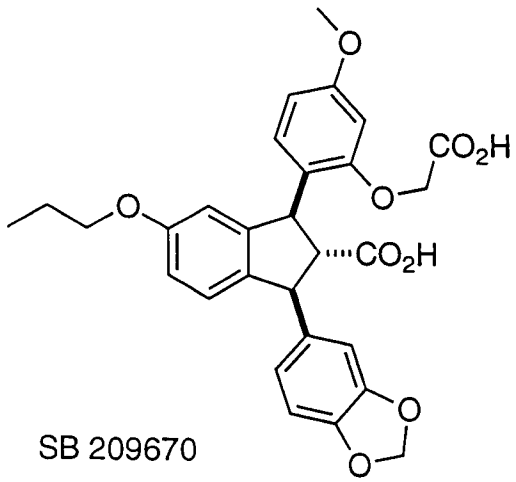
H-type



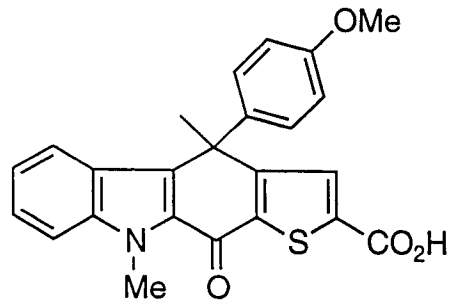
discotic-type

Application to Synthesis of Antagonist for Endothelin Receptor



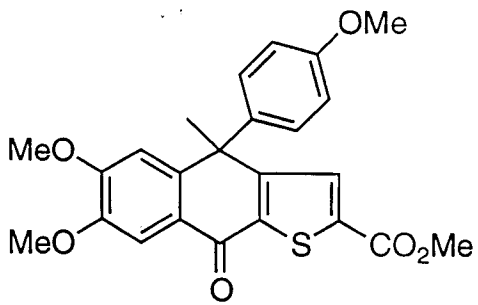


K_i (ET_A) = 0.43 + 0.09 nM
K_i (ET_B) = 14.7 + 3.0 nM



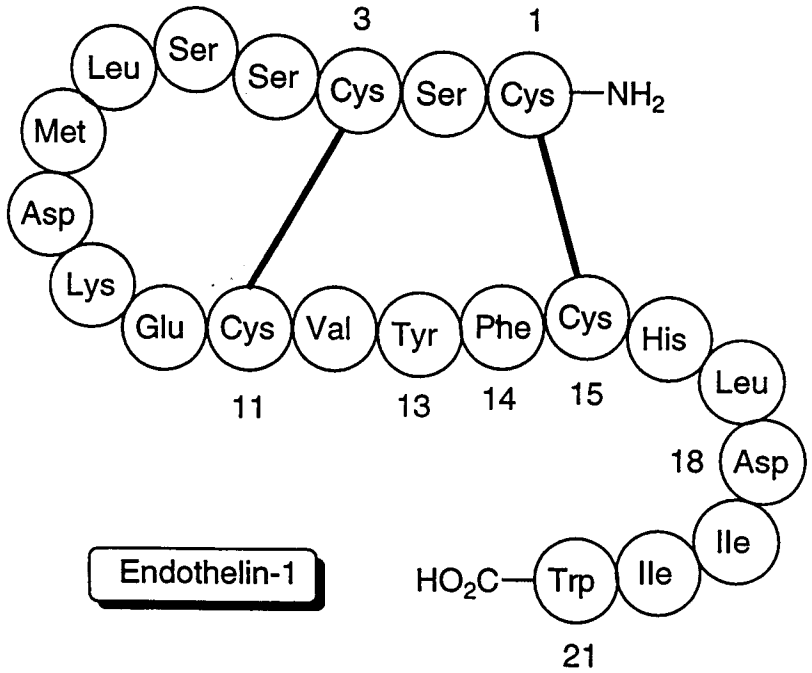
32 (56%)

IC_{50} = 1.0 μM
an antagonist for endothelin receptor

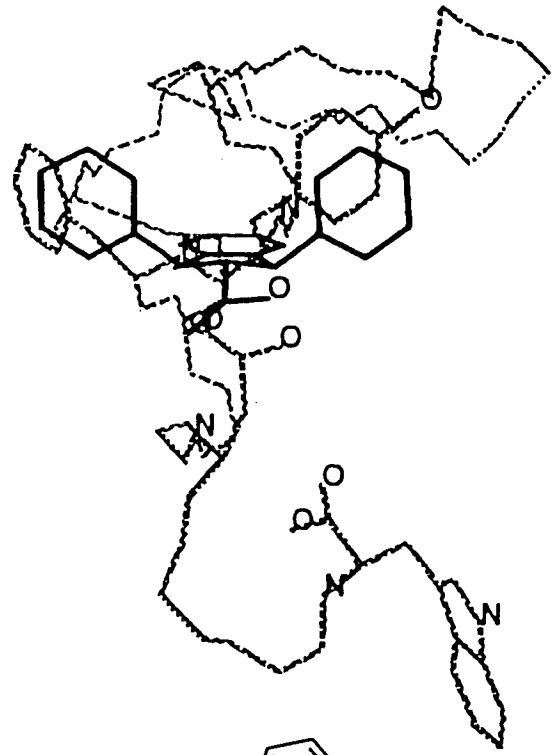


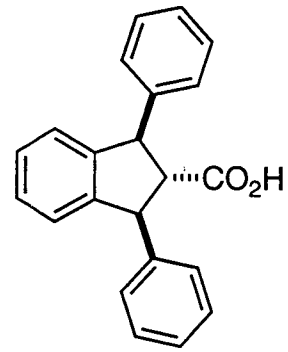
33 (58%)

Endothelin



Endothelin-1

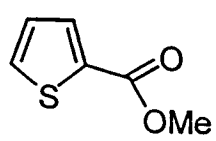




Kobayashi, M et al. *Nature*, **1988**, *332*, 411.
Elliott, J. D. et al. *J. Med. Chem.* **1994**, *37*, 1553.

trans,trans-1,3-diphenylindan-2-carboxylic acid (solid)

Conceptually Novel Approach Toward Distant Functionalization of Thiophene Moieties



3

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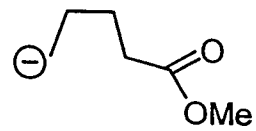
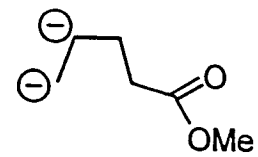
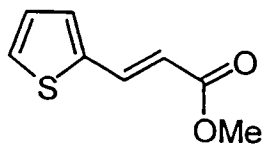


pentanoate 5-anion

or



pentanoate 4,5-dianion



4

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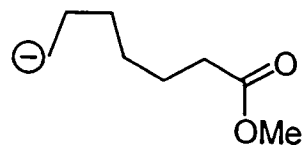
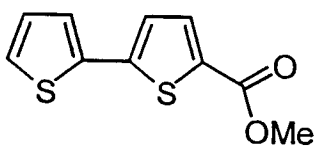
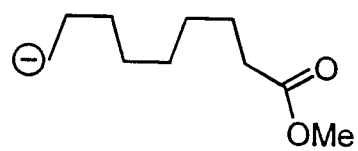


heptanoate 7-anion



40

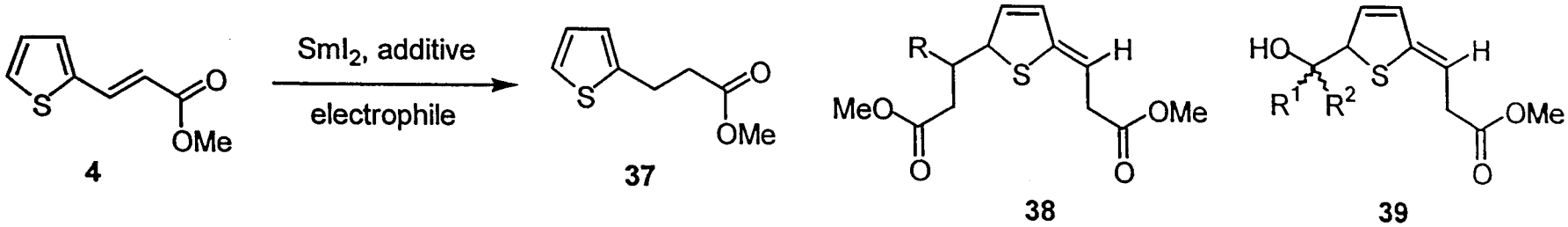
≡



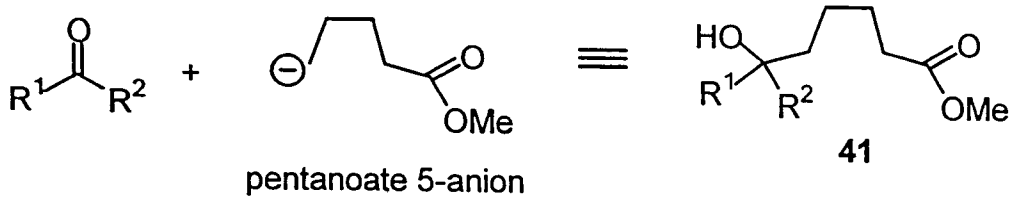
nonanoate 9-anion

Yang, S.-M.; Nandy, S. K.; Selvakumar, A. B.; Fang, J.-M. *Org. Lett.* **2000**, *2*, 3719.

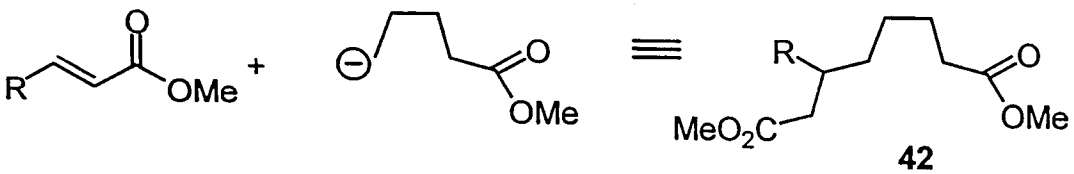
Coupling Reactions of Methyl 3-(2-Thienyl)acrylate Promoted by SmI_2/HMPA



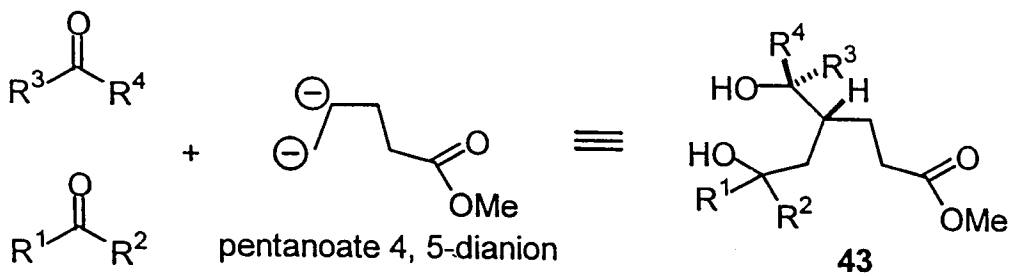
electrophile	additive	R	R^1	R^2	products (yield/%, dia. ratio)
–	none	–	–	–	polymerization
–	MeOH	–	–	–	**37** (72)
–	HMPA	2-thienyl	–	–	**38a** (67, 1:1)
$4\text{-}MeOC_6H_4CH{=}CHCO_2Me$	HMPA	$4\text{-}MeOC_6H_4$	–	–	**38b** (70, 1:1), **38a** (11, 1:1)
$4\text{-}MeOC_6H_4CHO$	HMPA	–	$4\text{-}MeOC_6H_4$	H	**39a** (78, 38:62)
$4\text{-}MeC_6H_4CHO$	HMPA	–	$4\text{-}MeC_6H_4$	H	**39b** (73, 35:65)
$CH_3(CH_2)_3CH_2CHO$	HMPA	–	$CH_3(CH_2)_3CH_2$	H	**39c** (65, 54:46)
$4\text{-}MeOC_6H_4COCH_3$	HMPA	–	$4\text{-}MeC_6H_4$	Me	**39d** (69, 1:1)



41a (72%), R^1= 4-MeC_6H_4; R^2= H
41b (68%), R^1= 6-methoxynaphth-2-yl; R^2= H
41c (60%), R^1= 4-ClC_6H_4; R^2= CH_3
41d (74%), R^1= $CH_3(CH_2)_4$; R^2= H
41e (66%), R^1= $CH_3(CH_2)_7$; R^2= H

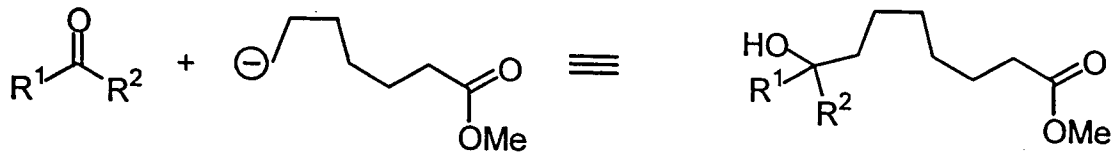


42a (48%), R = 4-$MeOC_6H_4$
42b (49%), R = CH_3



43a (73%), (R^1, R^2) = (R^3, R^4) = -$(CH_2)_5$-
43b (47%), (R^1, R^2) = (R^3, R^4) = -$(CH_2)_4$-
43c (46%), R^1= 4-MeC_6H_4; R^2= H;
R^3= 4-ClC_6H_4; R^4= CH_3
43d (45%), R^1= R^3= 4-MeC_6H_4; R^2= R^4= CH_3

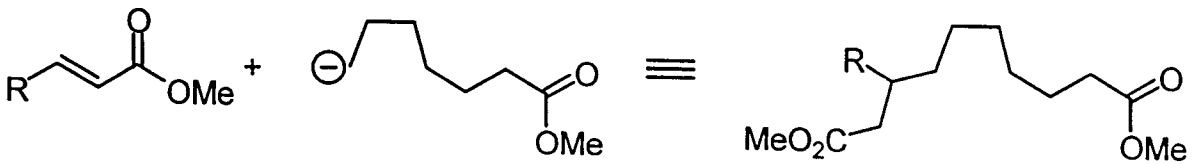
The SmI_2-promoted coupling reactions and the subsequent reductive desulfurizations with Raney nickel (overall yield of two steps)



heptanoate 7-anion

44

44a (67%), R^1= 4-$MeOC_6H_4$; R^2= H
44b (61%), R^1= $CH_3(CH_2)_7$; R^2= H
44c (43%), R^1= 4-MeC_6H_4; R^2= CH_3



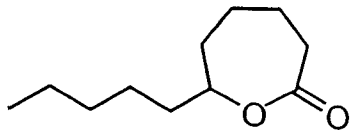
heptanoate 7-anion

45

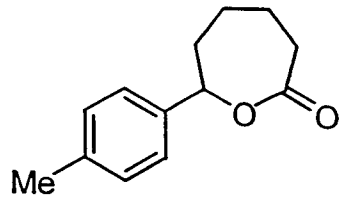
45 (58%), R = 4-$MeOC_6H_4$

The SmI_2-promoted coupling reactions and the subsequent reductive desulfurizations with Raney nickel (overall yield of two steps)

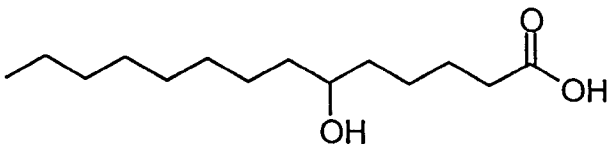
Application to the Synthesis of Biological Active Natural Products



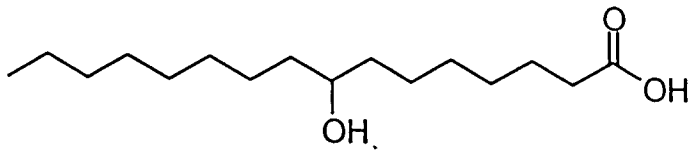
46 (68%, total yield)



47 (62%, total yield)

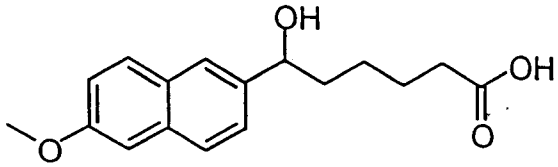


48 (three steps, total yield 63%)



49 (three steps, total yield 57%)

an inhibitory agent of spore germination

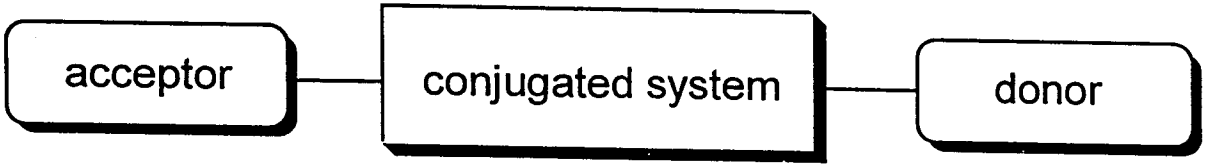


50 (three steps, total yield 65%)

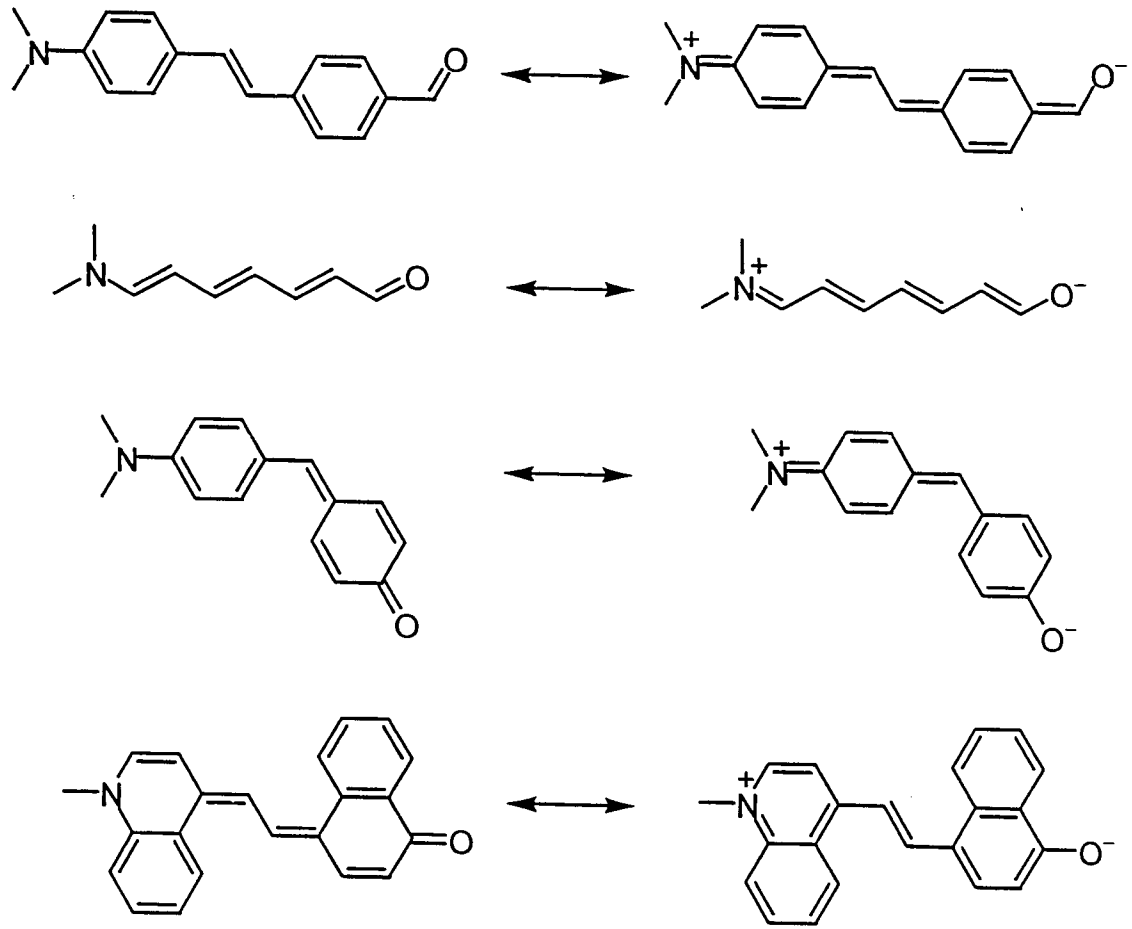
antiarthritis agent

Murray, W. V. et al. *Eur. J. Med. Chem. Chim. Ther.* **1991**, *26*, 159.
Yamane, H. et al. *Agric. Biol. Chem.* **1980**, *44*, 1697.
Mori, K. et al. *Agric. Biol. Chem.* **1984**, *48*, 2155.

Design of Organic NLO

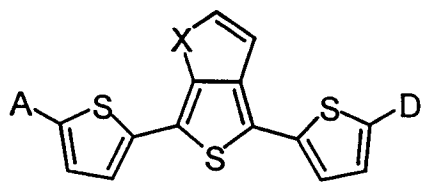


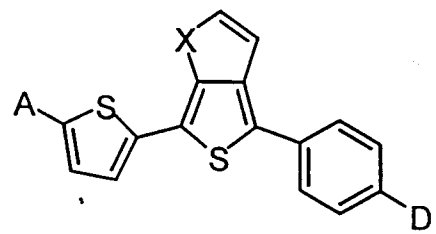
1. Donor Group
2. Acceptor Group
3. π–Conjugated Molecular Frame
4. The Type of π–Bridge
5. Transparency
6. Thermostability



Marder, S. R. et al. *Science* **1991**, *252*, 103.

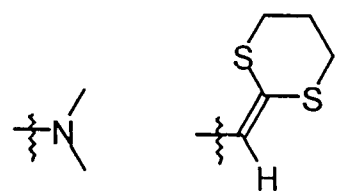
Design and Synthesis of Organic Nonlinear Optics Containing Novel Fused Bicyclic Spacer



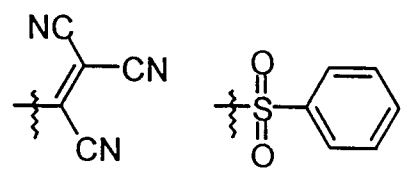


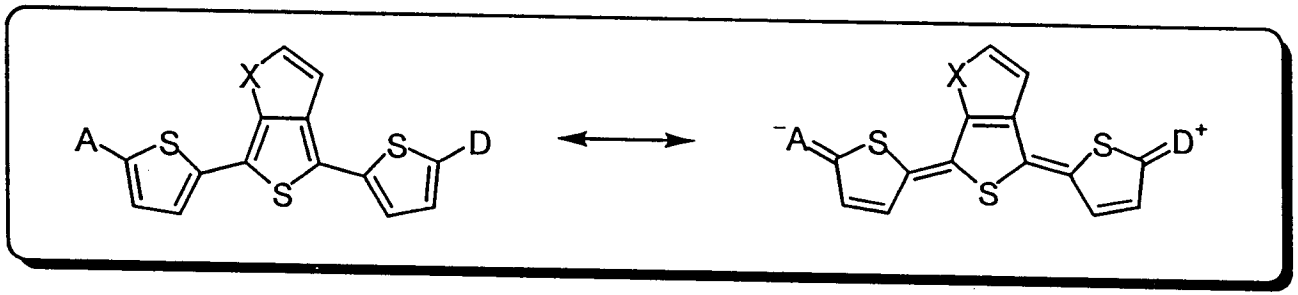
X = S, O

D = donor

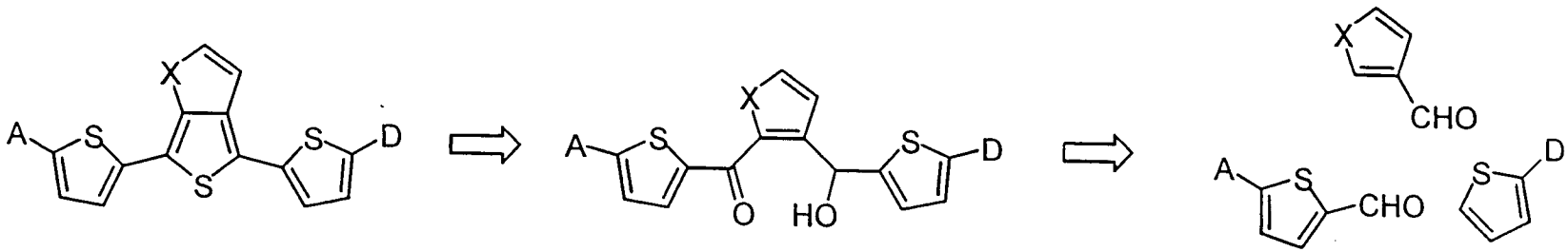


A = acceptor

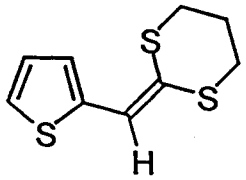




Retro-Synthetic Analysis



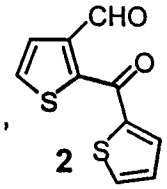
The Synthesis of Organic NLO ***5***



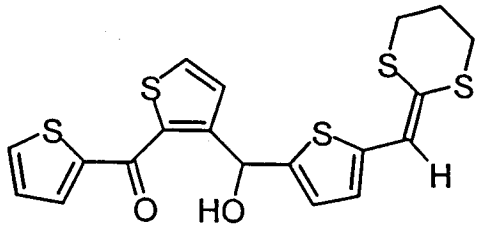
1

1. LDA, -78 °C

2. -78 °C,



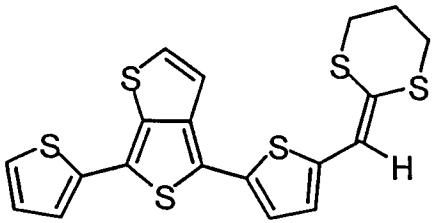
2



3 (73%)

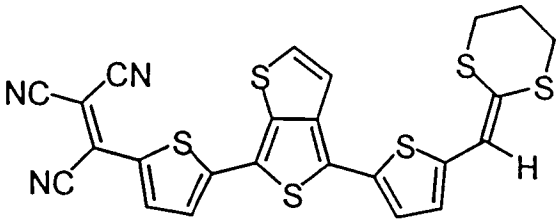
Lawesson's reagent

1,4-dioxane, reflux

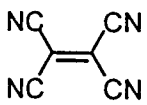


4 (94%)

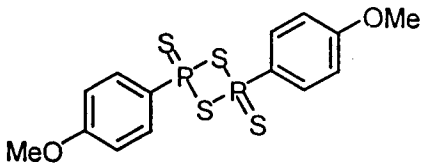
TCNE, DMF



5 (55%)

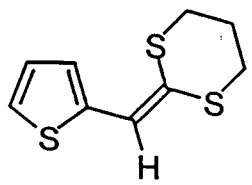


TCNE



Lawesson's reagent

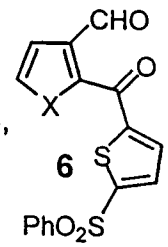
The Synthesis of Organic NLO ***8***



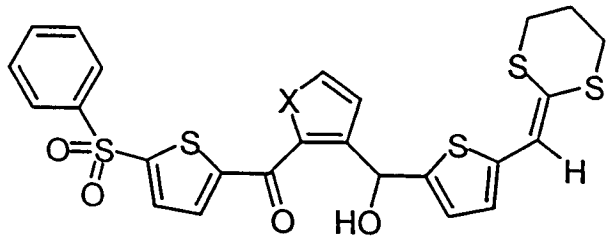
1

1. LDA, -78 °C

2. -78 °C,

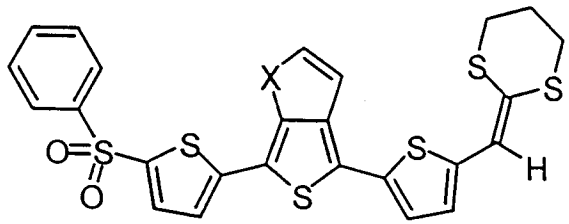


6



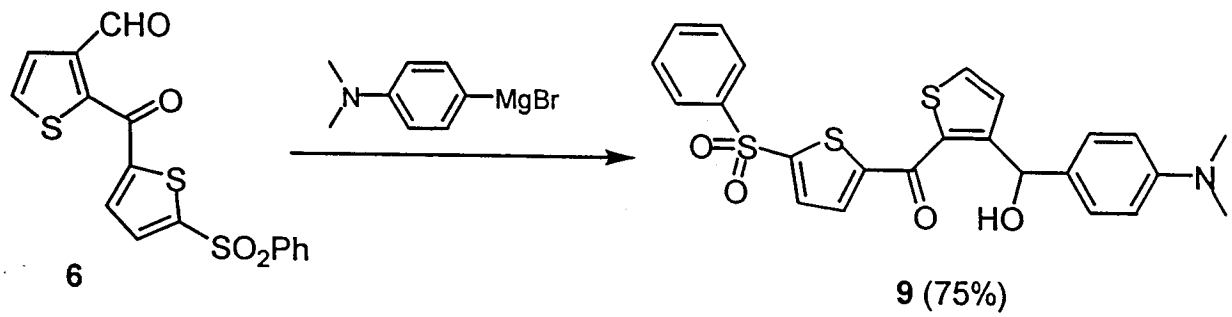
7a (72%), X = S
7b (52%), X = O

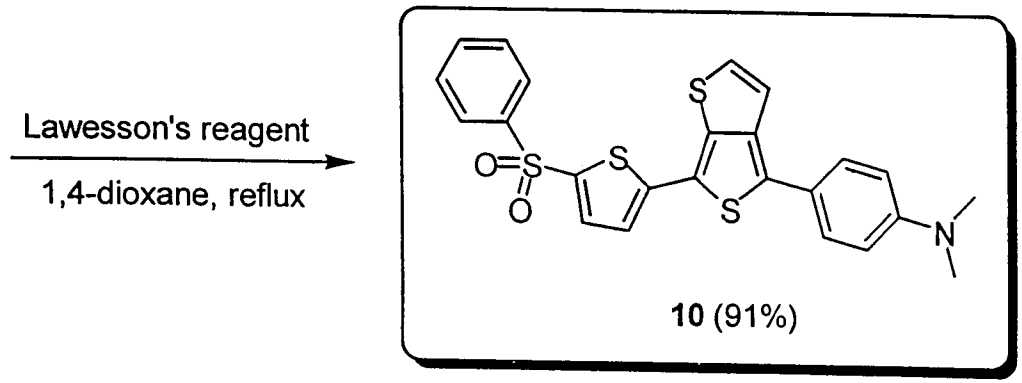
Lawesson's reagent
1,4-dioxane, reflux

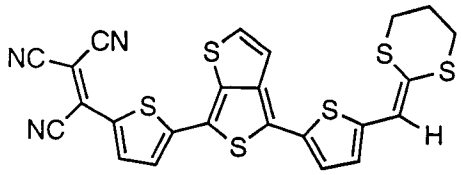


8a (89%), X = S
8b (90%), X = O

*The Synthesis of Organic NLO **10***



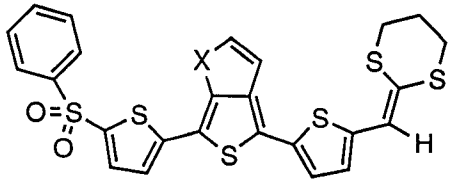




5

$\lambda_{max}^{CHCl_3}$ = 732 nm

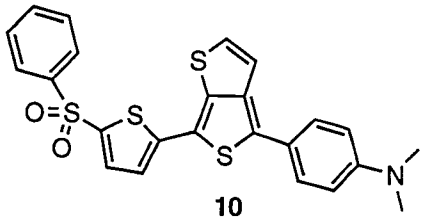
Td = 317 °C



8a, X = S
8b, X = O

$\lambda_{max}^{CHCl_3}$ = 485 nm (**8a**)

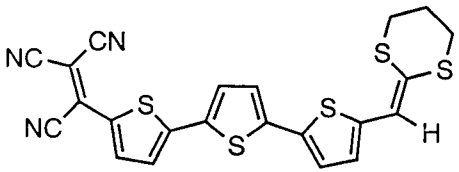
Td = 267 °C



10

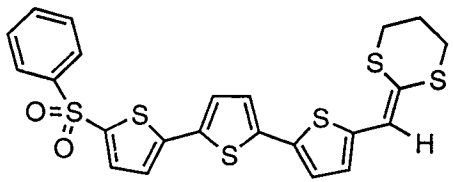
$\lambda_{max}^{CHCl_3}$ = 457 nm

Td = 267 °C



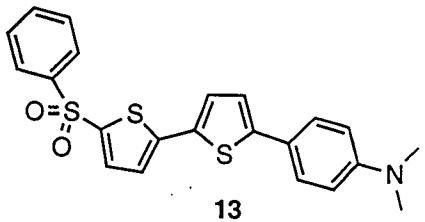
11

$\lambda_{max}^{CHCl_3}$ = 650 nm



12

$\lambda_{max}^{CHCl_3}$ = 413 nm



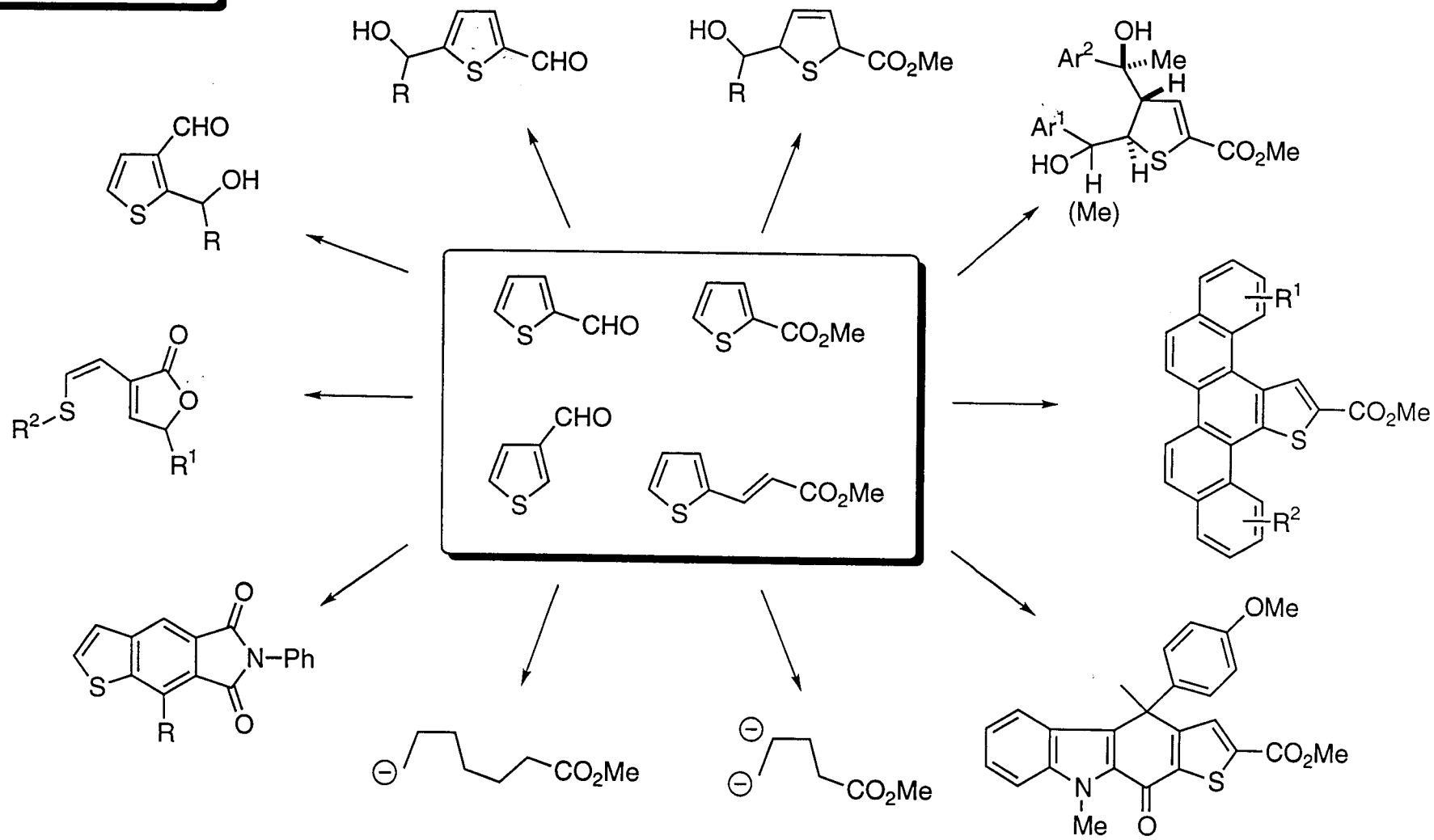
13

$\lambda_{max}^{CHCl_3}$ = 435 nm

Conclusion:

1. *The organic NLOs **5**, **8** and **10** were prepared in a simple and efficient manner.*
2. *High thermostability.*
3. *Will the second-order property of NLO be enhanced by a novel fused bicyclic spacer ?*

Conclusion


HO
R
S
CHO
HO
R
S
CO2Me
OH
Ar2
Me
H
Ar1
HO
H
(Me)
H
S
CO2Me
CHO
S
OH
R
S
CHO
S
CO2Me
CHO
S
S
CO2Me
R1
CO2Me
S
R2
O
R2
S
O
R1
O
N–Ph
S
R
O
CO2Me
CO2Me
OMe
CO2Me
S
N
Me
O

ACKNOWLEDGMENTS

National Science Council of the Republic of China

National Taiwan University

Prof. Jim-Min Fang

Dr. Sandip Kumar Nandy

Mr. Jue-Liang Hsu

Mr. Juin-Jie Shie

Ms. Ju-Hui Huang